Research governance in pharmacogenetic based drug development: why the principlist approach?

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Abstract

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The thesis will examine whether policy considerations based on the normative ethical framework of Principlism are adequate for drug development involving pharmacogenetics. In order to structure the analysis, the main research question will be based on the following three claims: (1) that the overriding deference to the principle of respect for autonomy in the current interpretation of Principlism has asserted a legacy of protectionism towards the research participant at the expense of ignoring pharmacogenetics' primary ethical issues (which are concerned with equity, fair distribution and research prioritisation); (2) that the principle of justice in Principlism requires specification, and that this principle's non-specificity may be a reason for over-compensatory application of respect for autonomy; (3) and finally, that current interpretations of Principlism represent moral values that are culturally dependant. Based on these claims, I argue that a pharmacogenetic research governance ethical framework ought to be representative of common moral values, which are culturally neutral, subscribe to a 'minimal morality', and are not based on the current precautionary approach that is entrenched in Principlism. From this main argument, I appeal to the principle of justice as fairness from Rawls's *A Theory of Justice* to provide specification for the principle of justice inherent in Principlism. As well as establish how the application of this 'minimal morality' in governance could be achieved through John Rawls's overlapping consensus, arguing that this would minimise the variability seen in regulatory decision making. I argue that greater specification of the principle of justice

would ensure that this principle could effectively be exercised to alleviate pharmacogenetics' actual ethical issues, which are not concerned with the inference of disease knowledge, as implied by ethical concerns regarding informed consent, privacy and confidentiality.

Declaration

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1. Chapter One : Introduction

1.1 Introduction

This thesis addresses the specific ethical demands that pharmacogenetics - the study of inter-individual variations in DNA sequence related to drug response - poses to research governance.

Healthcare research has become a formalised, regulated institutionalised activity, that has increased in scale and, consequently, in funding. These increases in the scale and financing of research have led to an expectation of greater accountability towards the public and private sectors of society.

In drug development, accountability (here provided by research governance) is an assured system of administration and supervision that manages healthcare research programs. Research governance provides assurances that participants and research staff are protected from research misconduct through a framework of regulatory guidelines and policies, such as the European Medicines Agency (EMEA) and, in the US, the Food and Drug Administration (FDA). These organisations have somewhat successfully governed traditional drug development[1], providing approval for the introduction of new drug treatments on the basis of efficacy and safety assessment data generalisable to a whole population generated from clinical trials.

[1] Drug development that does not have pharmacogenetic intervention,

However, with the introduction of pharmacogenetics, drugs are now based on individual genetically determined responses, presenting a situation where clinical trial data cannot be generalised for the whole population. This has raised ethical issues with regard to the distribution of the research outcomes (i.e. the resulting developed drug) to the patient population as a whole. I argue in this thesis that these ethical issues are primarily concerned with Justice.

Like any other medical technology, pharmacogenetics remains a promising field, but the realisation of its full potential in the research of new drug treatments, and in turn clinical practice, has been impeded. This is partly due to questions concerning the scope and applicability of the technology, cost-effectiveness, and clinical utility, along with the diversity of regulations concerning DNA sampling utilised in pharmacogenetic studies. Such questioning potentially hinders the procurement of robust pharmacogenetic data from required international research programmes. Also, a diversity of regulations has materialised to combat a host of controversial ethical issues related to the research process and outcomes involving human tissue sampling for DNA (i.e. genetic information). These regulations are mainly concerned with informed consent and confidentiality issues, despite other ethical issues regarding justice being apparent on a societal level. Therefore, this thesis will focus on concerns about the lack of standardisation in regulation, and its reliance on the principle of respect for autonomy. Arguments presented will examine the basis for the diversity of regulations, and will highlight that this diversity is due to the inadequacy of the current interpretation of the ethical basis of current research governance (that being the normative ethical framework of Principlism).

Thesis content

This thesis will question whether the ethical framework of Principlism underpinning current research governance is too broad a theory to deal with specific ethical justice issues for drug development involving pharmacogenetics. Arguments presented will be based on the following:

1. That there is an overriding deference to the principle of respect for autonomy, as seen in the current ethical interpretation of the management of risk.
2. The principle of justice needs to be specified when applied to genomic concerns. Its current non-specificity may be a reason for the over-compensatory application of the principle of respect for autonomy.
3. Current interpretations of Principlism represent moral values that are culturally dependent. Pharmacogenetic research outcomes have a global impact, ergo Principlism or another moral guidance framework ought to be representative of common moral values which are culturally neutral.

These claims will be presented and discussed via the following sub-arguments:

[A1] That the ethical interpretation of the management of risks (the central role of research governance) based on Principlism is subject to the presence of value-laden perceptions of risk. This is one of the reasons why there are variations of interpretation in approval outcomes by the various research governance systems.

[A2] Whether an epistemic moral framework based on what should be believed in (due to the facts) rather than what ought to be done (as in a normative framework) would be more appropriate for pharmacogenetic based drug regulation, due to value-laden risk perceptions.

[A3] That the introduction of genetic information has changed the assessment of risk-benefit in pharmacogenetic clinical trials, from one concerned with risks of harm to one of uncertainty. I therefore argue that genetic governance seems to be interpreting principles of uncertainty (using an epistemic interpretation based on value-laden perceptions of risk).

[A4] That pharmacogenetic testing in drug development is only concerned with drug-related genetic variations in genes and not with genes which determine specific diseases, as noted with clinical genetic testing.

[A5] The ethical issues that arise from pharmacogenetic interventions in drug development are more concerned with the fair distribution of pharmacogenetic outcomes such as drugs, and are therefore a matter of justice rather than autonomy.

[A6] The current interpretation of Principlism has given rise to a dogma of protectionism in research governance, manifested in the precautionary approach that is currently engaged by governance when faced with a new biotechnology.

These arguments will be presented as follows in the five main chapters of the thesis:

Chapter Two – The role of research ethics

This chapter will provide background knowledge for the proposed claims of the main argument, which considers why Principlism, above other ethical theories, has become the ethical theory of choice in research governance. It will address how normative ethical theories such as Principlism attend to the question 'How ought we to conduct our research?'; a question which is at the heart of research ethics. An analysis of the normative ethical theories employed in research will introduce the main argument of why Principlism has become the most dominant form of ethical reasoning in current drug research regulation. It will be argued that Principlism's dominance is due to two main factors. Firstly, its ease of use - the principles are general guides which can be applied to most ethical situations; and, secondly, the increasing concern for human rights in research. The concept of the common-good will also be introduced with regards to drug development. This is defined as the production of 'generalisable knowledge' (Emanuel, Wendler et al. 2000) for the improvement of health, as well as increasing the understanding of human biology.

Chapter Three – Research Governance

The role of research governance in drug development will be analysed, together with the underlying reason for the variations in governance that are seen. The analysis will focus on whether the introduction of genetic methodologies (such as pharmacogenetics) to the assessment of drugs in research has changed the role of research governance in this area. Arguments A1, A2 and A3 will be presented in the analysis. A1 will introduce the argument that the ethical interpretation of the management of risk (the central role of research governance) is one of the reasons why there are variations of interpretation in approval

outcomes by various research governance systems. A2 will analyse whether an epistemic moral framework would be more appropriate for drug regulation, meaning that data should be provided which is based on facts, rather than what ought to be done in order for the research to be acceptable and appropriate. Furthermore, this argument will be addressed by looking at how the role of healthcare governance has been affected by the introduction of genomics[2]. An affect observed and illustrated by the concept of 'Governmentality' (Foucault, 1979) . This concept was formulated by the French philosopher Michel Foucault to note the changes in power structures in governance from being a technocratic discipline with little or no input from public bodies, to being transparent, involving the public and industry. The concept of 'Governmentality' adequately explains how genomic policies are shaped by industry and general public perceptions of genetic information rather than the government, thereby ushering in the age of 'biopolitics'. Lastly, A3 looks at investigations of value-laden risk perceptions as derived from A2. This will outline why and to what extent the introduction of genetic information has altered the assessment of risk-benefit. Herbert Gottweis'[3] (Gottweis 2005a, Gottweis 2005b, Gottweis 2005c) observations will be utilised to illustrate this argument, as well as John Rawls's concept of converging influential intuitions into a coherent systematic set of normative beliefs known as 'reflective equilibrium' and its later development of 'overlapping consensus'. Concepts first introduced in *A Theory of Justice* first published in 1971 (Rawls, 1999) and later developed (mainly as overlapping consensus) in 'Political Liberalism' (Rawls, 2005), overlapping consensus will be introduced in this chapter as an ethical methodology used to show how the language of emotions (of which intuition is one), can be successfully integrated into genetic governing policy.

[2] Genomics is the study of the DNA of organisms, which includes the field of pharmacogenetics.
[3] Professor of Political Science, University of Vienna.

From this discourse, the need to establish a more appropriate normative or non-normative ethical framework for pharmacogenetic-based clinical trials will be highlighted by elucidating the appropriate moral features for regulatory assessment.

Chapter Four – The Ethical Implications of Pharmacogenetic drug development

Clarification on the role of pharmacogenetics in the area of drug development will be covered in this chapter.

The chapter will first highlight the need for an agreed definition of pharmacogenetics to clarify the aims of this biotechnology for the relevant agents, to minimise the misconceptions of its role in research. Defence of the requirement for an agreed definition will lead to an analysis of what the benefits of pharmacogenetics are to particular agents (such as the patient and industry), and, in turn, how this affects research governance. I will also elaborate on the way in which pharmacogenetics is employed in the drug development process, particularly in the area of the clinical trial (an area of research which utilises human participants). A4 will establish the argument that pharmacogenetic testing in drug development is only concerned with drug-related genetic variations, and not specific disease genes. In providing clarity on the role of this biotechnology as a risk assessment tool with relevance to clinical trials, the actual ethical issues will become apparent.

The latter half of the chapter will then focus on the aspects of pharmacogenetics which are utilised as risk assessment tools, thus introducing the argument (A5) that the ethical issues that would arise from pharmacogenetic interventions in drug development should be concerned

more with the fair distribution of pharmacogenetic outcomes. In my arguments on the actual ethical issues, I will note that they are primarily a matter of justice, due to the stratification of the research participant population into genetic groups. This argument will be defended by developing the argument (A4) introduced earlier on in chapter four, through noting that ethical issues should include the equitable distribution of research knowledge and research priorities, rather than simply the inference of disease knowledge (as implied by concerns regarding informed consent, privacy and confidentiality). Ethical implications in notably well-researched areas of pharmacogenetic drug development will be illustrated, in order to provide a defence for the main argument of whether Principlism exercised in pharmacogenetic research governance provides an adequate ethical underpinning for the resolving of the following issues: research prioritisation; division of patients into sub-groups; clinical trials and the returning of genetic information.

Lastly, a critique of the current market-driven approach of patent rights in drug development will be undertaken, in order to further illustrate the failings of the current interpretation of Principlism. This critique will highlight the fact that these failings have led to inequalities of access to pharmacogenetic outcomes among economically diverse nations, and ultimately to the individual, (rather than autonomy-based) breaches to research participants. From this discourse, a proposal will be made. This is that the ethical implications for pharmacogenetic research outcomes are primarily concerned with the inequity of distribution, and so require a moral framework which takes into account social responsibility concerned with beneficence (the balancing of benefits against risk and costs, or, in other words, solidarity) and justice.

Chapter Five – The Application of Principlism in Pharmacogenetic Research Governance

A review of the evolution of regulatory and ethical guidelines based on the normative ethical framework of Principlism will be conducted, prior to analysis of argument A6 (which is concerned with the precautionary approach to research governance). The pertinent ethical codes and guidelines that are utilised in drug development involving human participants (such as the Nuremberg Code, The Declaration of Helsinki, and The Belmont Report) will be reviewed. This review will provide background information about how these codes are currently employed in the research governance of pharmacogenetic-based clinical trials. It will then consider how they have evolved into more specific pharmacogenetic guidelines, such as the position paper on the terminology in pharmacogenetics by the Committee for Medicinal Products for Human Use (CHMP)(CPMP 2002), and the report 'Pharmacogenetics: ethical issues' by the Nuffield Council on Bioethics (Nuffield Council on Bioethics, 2003). A critique will be presented on Good Clinical Practice (GCP), the formalised international quality standard utilised in drug development research governance. GCP epitomizes the industry's considerations on what ethics is, and how research governance appears to be exercised at an ethical level. The review of these guidelines and policy documents will highlight the significance of argument A6, which states that the current interpretation of Principlism has given rise to a dogma of protectionism in research governance. In addressing this argument, Rosalind Rhodes's article ''Rethinking Research Ethics' (Rhodes, 2005) will be critiqued, as it presents a view of how this dogma has occurred, and puts forth an agreement about the existence of protectionist policies in research. However, a counter-argument will be presented that notes that her assessment is flawed, particularly in the area of the prioritizing of informed consent. It will be noted that such a flawed assessment does not provide clear moral criteria

for the ethical conduct of clinical research, but instead creates further confusion about the role of autonomy in research ethics.

Chapter Six – Rawls's 'Overlapping Consensus': a possible way forward?

In this chapter, argument A5 (that the required ethical approach to address ethical breaches concerned with justice rather than individual liberty should be based on the fairness and distribution concerns evident in pharmacogenetic-based clinical trials) will be defended. Furthermore, it will be argued that such an ethical approach should not, in essence, be culturally dependant, but should instead subscribe to a 'minimal morality' as put forth by Tuija Takala[4]. Defined as an approach which takes into account both reasons and emotions in order to formulate regulations that strike some sort of balance between 'everyone's sense and sensibilities in bioethical decision making (Takala, 2003). My argument will develop into the claim that, if such an ethical approach features Rawls' overlapping consensus (a method that seeks to find a balance between considered judgements and intuitions of particular cases, providing an approach which enables decision making in a pluralist context with different stakeholders who often endorse different or possibly conflicting cultural and moral frameworks), then multi-layered regulations required for pharmacogenetic drug development will give rise to consistent moral guidance. The global theme of governance's remit required for pharmacogenetic-based drug development will also be continued in this chapter's examination of the need for ethical guidelines that transcend cultural boundaries.

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The analysis of the argument will primarily be concerned with an overview of how justice is applied in healthcare contexts in order to provide a background for how justice is viewed in healthcare and, consequently, in clinical research. A critique of the concept of justice will be conducted by reviewing the basic requirements and principles that constitute distributive justice in order to highlight the definitional framework of this concept. The concepts from Susan Cozzens' work on assessing justice models in science and technology policy will be applied, as they emphasize the requirement of achieving 'the common good'(Cozzens, 2007). Furthermore, an evaluation of the utilization of David Thomasma's established rules (Thomasma, 1997b) will be conducted in order to provide worthy moral guidelines when setting up a 'global research ethics framework'. These rules, which are not necessarily culturally dependant, take into consideration the pursuit of the 'common good' as one of the aims of research ethics. Here I argue that the acknowledgement of the common good in pharmacogenetics research allows for the production of more effective drug treatments, or more insight into treatment options for conditions that seriously impair autonomous and social functioning, without unfairly placing the burden of research participation on those who are unable to benefit from these knowledge outcomes. Furthermore, I will address how appealing to the societal value of research within a socioeconomic context as exampled by Thomas Pogge's Health Impact Fund and the Global Fund promotes research committed to the common good by addressing the issue of research prioritisation as highlighted in chapter four.

My argument will develop into the claim that the principle of justice as fairness as exercised in the Rawlsian method of overlapping consensus would provide the appropriate moral guidance system for pharmacogenetic ethical issues. I will propose a possible application of the

Rawlsian Justice model to pharmacogenetic research governance. This can be done by utilising from Rawls's the principle of justice as fairness and overlapping consensus as a coherent systematic framework of normative beliefs (a feature of genetic governance discourse as discussed in chapter three) into a proposed procedural–substantive model for regulatory policy decision making in pharmacogenetic research governance. Furthermore the development of such a moral guidance system into a procedural approach i.e. a method of decision-making given unresolved moral disagreements as put forth by Daniels and Sabin (Daniels, Sabin 2002) will be defended.

Discussions on these concepts will highlight the equal primacy of social justice in pharmacogenetic research ethics – interpreted as fair distribution of pharmacogenetic research outcomes – with that of the principle of respect for autonomy.

Conclusion

This research considers the features required for a universal moral theory, which may be multi-layered in approach, and can be applied to the regulation of pharmacogenetic clinical trials. By presenting the case that there is room for further harmonisation and clarity of regulatory frameworks that govern this technology in terms of the ethical basis of governance, this thesis forms the basis for a critical evaluation of whether Principlism alone can still be the predominant ethical framework for pharmacogenetic research governance. It is my ultimate intention to argue for the ethical evaluation of pharmacogenetic drug development in terms of a Justice -based model within recognised ethical parameters, and not just based on choice and need.

Therefore, recommendations for policy concerned with promoting social responsibility or the 'common good' in pharmacogenetic-based drug development will be proposed, to ensure that ethical considerations in pharmacogenetic clinical trial regulation shift their focus from the protection of specific groups (such as the research participant), to the function of ensuring that research is undertaken with reasonable risks and benefits to the community (global or otherwise). Such a recommendation would highlight that an ethical framework that considers research participation for the common good makes certain that the benefits of research are equally shared amongst populations. This in turn will promote international research governance policies of universal worth, which strive to either achieve equality or reduce inequality.

Finally, this thesis intends to encourage the regulatory research community to be confident in considering the moral value of research outcomes again, instead of falling back into a protectionist mode of protecting the vulnerable that has arisen since the mid 1940's. The emergence of an ethical framework focused on ensuring justifiable research outcomes - rather than just the protection of the 'vulnerable' research participant - will minimise opposition to the introduction of this new technology in drug development, especially if the research participant is active in assessing the considerations of risk.

2. Chapter Two: The Role of Research Ethics in Clinical Research

2.1 Introduction

Ethics in research tends to address the fundamental question: 'How ought we to conduct our research?' to which you might add, in the context of clinical research; 'in order to ensure the interests of society or the researcher do not override those of the individual participating in the research'. To address this question, normative ethical theories are appealed to. These are theories that prescribe, imply or explain certain standards (norms) of conduct that are considered justified or required to ensure research participants are not put at more than minimal risk of harm by participating in research. Therefore, the normative ethical theory of Principlism will be critiqued in this chapter, especially with regards to how it has become the dominant normative ethical framework applied to clinical research. My analysis will centre on how this normative theory has become prevalent due to the challenges of applying other theories in the clinical research context. Moreover, I will introduce the argument that a normative ethical theory for pharmacogenetic-based clinical research should also promote the pursuit of 'the common good' in research, rather than being concerned solely with providing modes of conduct to ensure non-exploitation of the research participant. In this context, the 'common good' refers to the requirement of pharmacogenetic-based clinical research to produce 'generalisable knowledge' regarding drug responses, with the aim of improving health by developing diagnostics for drug response and/or increasing understanding of human biology.

Therefore, section 2.2 will provide an analysis of the main ethical approaches that could be considered for pharmacogenetic-based clinical research, and will highlight why Principlism is

used widely in research governance. The latter will be analysed further in section 2.3. In section 2.4, an introduction to the argument for how the pursuit of the common good could be considered as important as Principlism in the moral underpinning of pharmacogenetic research governance will be scrutinised.

2.2 Research Ethics in Drug Development

In relation to clinical research (particularly drug development), research ethics has focused on safeguarding individuals from either harm or a failure to respect their autonomy. However, research ethics is not merely concerned with ensuring individuals are protected from exploitation and other forms of harm; it also considers factors external to the study process, such as whether a certain piece of research should be conducted in the first place, or what should be done with the findings once the research is complete. This part of research ethics contemplates the moral and methodological aspects of research that may manifest as tensions. This section outlines the main ethical concepts that could be used to alleviate these 'tensions', focusing on why Principlism has been given prominence in pharmacogenetic-based clinical research.

2.2.1 Ethical Tensions

So, what are these ethical tensions and how do they arise? In the context of ethical decision making in clinical research, such tensions arise when the exercising of research ethics occurs at the expense of the medical care ethic. Since clinical research is similar to medical care in that they are both performed by physicians within clinical settings, they often use comparable

diagnostic and treatment interventions. Tensions surface due to conflicts surrounding the aims of the medical care ethic, which is to promote the well-being of individual patients by considering that the potential benefits of diagnostic and therapeutic measures prescribed to patients outweigh the risks. This is known as the duty of therapeutic beneficence (Litton, Miller 2005), as opposed to the clinical research setting, which may utilise techniques and procedures to test scientific hypotheses that sometimes do not aim to benefit the individual research participant (Litton, 2006). Therefore, it is unsurprising that tensions emerge when physicians act as investigators in clinical research. This is due to the fact that, in an investigative capacity, physicians who undertake research do so without knowing if the intervention being examined will be beneficial.

The medical care ethic is regarded as the 'goal' of a physician who aims to provide the best medical care for individual patients. Such a goal is governed by the ethical principles of respect for well-being; namely, beneficence (the ethical duty to promote the health of patients or at least provide palliative treatment), and non-maleficence (the ethical duty to cause no harm based on the 'Hippocratic Oath'). Both principles provide ethical justification for the medical risk to which a patient is exposed by rationalising the prospect of compensating medical benefits (Rhodes, 2005). However, it has been noted that strict adherence to the medical care ethic would make research impossible. This is because interventions in research would be considered prohibitive, as the risks posed to subjects are not outweighed by the benefits to them individually (Litton, Miller 2005; Rhodes, 2005, p.21). Therefore, in order to enable the physician (as an investigator) to overcome tensions regarding the ethical principle of respect for well-being in the context of clinical research, or the presumed difficulty of

exercising beneficence within the clinical research setting (Miller, Brody 2003), the physician is required to be in a state of equipoise or clinical equipoise. This is a state of genuine uncertainty, expressed by the physician, as to whether one treatment option in a clinical trial is superior in order to avoid violating his/her therapeutic obligation to the patient as a research participant. Therefore, the following ethical considerations for research protocols have been established to ensure research adheres to an ethical framework (in this case, Principlism), regardless of whether or not the therapeutic obligation (as the duty of therapeutic beneficence is sometimes referred to) is upheld:

1. Have 'social, scientific or clinical value' that justifies exposing subjects to potential harm.
2. Must have scientific validity - the research must be methodologically rigorous.
3. Must select participants fairly, on the basis of scientific objectives and not, for example, because of vulnerability or privilege.
4. Must minimise the risks to individual participants, and yield potential benefits to those participants and/or society that outweigh or are proportionate to the risks.
5. Must be reviewed and approved prospectively by a committee of independent and qualified evaluators.
6. Must be conditioned, to the greatest possible extent, on the voluntary and informed consent of participating subjects.
7. Must ensure enrolled participants are shown respect, which includes protecting their privacy, monitoring their well-being and providing opportunities to withdraw from the research project (Litton, Miller 2005).

The framework outlined above is based on the ethical principles established in the Declaration of Helsinki (practical interpretation of Principlism) in relation to the rights, safety and well-being of patients. More information on how this framework (as the minimal risk standard) and the Declaration are employed will be provided respectively in chapters three and five. This framework is generally considered necessary and sufficient by regulatory bodies for making clinical research ethical (Emanuel, Wendler et al. 2000), and is further enshrined in GCP (Good Clinical Practice) guidelines, which are the pharmaceutical industry's practical interpretations of ethical guidelines. Furthermore, the framework's requirements are regarded as universal, albeit with a caveat that they must adapt to health, economic, cultural and societal conditions, as well as the technological conditions in which clinical research is conducted (Emanuel, Wendler et al. 2000, p.2072). However, in spite of this, I argue in chapter three that in the context of pharmacogenetics-based clinical research, this framework is not workable when it comes to considerations on subject selection, informed consent and privacy (as noted in points 3, 6 and 7). Since this framework does not provide explicit guidelines for dealing with the interdependent qualities of pharmacogenetic information, which focus on the distribution of research knowledge and research prioritisation and are a matter of the principle of justice, and become apparent as a result of the stratification of research participants into genetic groups. Rather, the framework provides explicit guidelines for ethical issues surrounding privacy, confidentiality and discrimination. These are concerns of the principle of respect for autonomy, which I will argue in chapter four as important considerations for instances in which pharmacogenetics is used as a tool for disease susceptibility. To which I will highlight that, in drug development, pharmacogenetics is used as a risk assessment tool

(as a diagnostic aid), thereby providing information directly related to a participant's likely response to a specific medicine, and not the presence of a disease.

2.2.2 Main Ethical Concepts

Ethical theories provide the basis for justifying specific ethical decisions, such as the pursuit of the common good, which will be argued later in this chapter as an ethical decision that should be at the forefront of pharmacogenetic research ethical decision making. Moreover, ethical theories are helpful in practical situations, such as the aforementioned 'tensions' and when faced with difficult issues; in these circumstances, it can be helpful to review the issue in light of various ethical theories. Allowing for the application of an ethical theory to an ethical issue is a helpful means of creating a framework of justifications for decisions and actions made in light of these theories, and is preferable to using a step-by-step procedure or formula (as in an algorithmic approach). In the next section, I argue that this approach has been observed in the application of Principlism. Suffice to say, ethical theories in research ethics do not rely on a scientific justification basis in application.

As mentioned previously, the main ethical approaches in clinical research (which have been appealed to for the ethical justification of decision making) tend to be based around normative ethics. These ethical theories involve arriving at moral standards that regulate right and wrong conduct. The most predominant ethical theories in clinical research are either consequentialist, duty-based or principle-based theories. I will now provide a brief outline to support why

Principlism – a principle-based theory - has become the theory of choice in pharmacogenetic research governance.

Consequentialist Theories

Consequentialism is a collection of moral theories, of which utilitarianism is the most important in research ethics. Central to consequentialism is the idea that the morally right action is that with the best foreseeable consequences. In other words, an action is right only if it promotes the best consequences.

Under utilitarianism, our actions should maximise utility (defined in terms of happiness, maximization of goods valued by rational persons or preference satisfaction) for the greatest number of people. Utilitarianism also values actions based upon utility-maximizing consequences (Loue 2000, p.61). It is a 'person-neutral' theory of ethics, whereby an agent's own happiness counts for no more (and no less) than that for any other person. Therefore, this theory is neither self-centred nor bound by self-interest. Consequently, research under utilitarian ethics is considered justified if there is a strong likelihood that it would contribute to improvements in the human condition, either as research participants or future patients. However, a criticism of this type of thinking is that it may not always be possible to quantify risks or benefits in such a clear-cut manner, in order to determine whether or not a project should proceed (given ethical or regulatory approval) (Schüklenk 2005, p.6). This is because it is not possible to measure the key components of utilitarianism, such as happiness and preference-satisfaction (or similar), in a single measure. Moreover, it has been argued that

utilitarianism appears to condone immoral acts if they maximise utility; therefore, greater importance is placed on outcomes, rather than intentions, in the ethical evaluation of actions. An example of this is the continuation of a high-risk trial, which has been denied ethical approval, but succeeded in demonstrating a correct hypothesis that resulted in the production of quality of life, health-improving or life-saving drugs (Loue 2000, p.63).

Duty-based Theories

Duty-based moral theories, which are sometimes called 'deontological' (from the Greek *deon*, meaning duty), are ethical theories that focus on duties, rather than consequences, in relation to ethics. Central to these theories is the belief that there are certain acts which are wrong in themselves, regardless of their foreseeable consequences. Actions are considered to be right not by looking at consequences, but by exploring the nature of the actions. For example, one duty might be that we must not lie to one another. In deontological thinking, it may be wrong to tell a lie even if the consequences of doing so would yield a better outcome compared with the consequences of telling the truth.

For deontological theories to be practical, the morally-relevant duties must be specified in such a way that:

'*…we should be able to derive a set of absolute duties by way of utilising pure reason. The motive for our action matters: it should always be that we want to act ethically and that we act the way we act, because it is our moral duty to do so…'*(Schüklenk 2005, p.5)

Therefore, duties that are specified are phrased or cited as acts; such as, not lying, not violating various rights, (like the right not to be killed, injured, or coerced) and not imposing certain sacrifices on someone as a means to an end.

The German enlightenment philosopher Immanuel Kant introduced the duty-based ethical theory, and developed maxims to tell us what we ought to do. The categorical imperative is central to Kant's moral philosophy. This is an absolute non-negotiable rule (as agreed by a hypothetical community of rational people), which transforms a rule into a moral rule. The Categorical Imperative was postulated in three different ways, known as maxims. The first maxim noted that a moral principle has to be a principle for all. The second maxim stresses the liberal principle that people should not have their individual freedom compromised for some other end, particularly for the good of society. In other words:

'...do not treat other people as mere means to your ends...'

(Korsgaard, 1992)

In this maxim, the word 'mere' is crucial because, in many everyday transactions, we use others as a means to our own ends; for example, we use doctors as a means of restoring our health. What is meant by using someone *as mere means* is trying to get him or her to do things for our own purposes, which they would not choose to do if they were fully informed. We do not manipulate the doctor if they are carrying out their job voluntarily, but it is possible to manipulate others by deceiving them, which is one aspect the maxim tells us we must not do. Lastly, the third maxim, which notes that we must always treat any other person '*to your ends',* is more obscure; what does it mean to say we should treat someone '*to your ends'*? A

modern Kantian interpretation is that we should not merely respect others as rational persons with aims and purposes of their own, but that we should also make some attempt to help others to achieve some of those aims (Green, 2001). In clinical research, such a maxim provides the ethical basis for obtaining informed consent, the process where competent research participants agree voluntarily to take part in a research project once they are provided with sufficient information, including the risks and benefits of the research project. Therefore, the research participant has a stake in the research objectives, and is not being utilised solely for the researcher's purposes (Schüklenk 2005, p.5).

A modern interpretation of an aspect of deontology, which I will argue to be of prime importance with regards to the research participant, is demonstrated in John Rawls's *A Theory of Justice* (Rawls, 1999). His theory was an account of distributive justice (how money and goods should be distributed between people in a society), formulated by considering which society we would choose behind a 'veil of ignorance' (see section 6.3.3). In other words, the derivation of ethical principles by rational persons who had no information about the particular person or persons they represented. Rather, they make choices based on their goals and preferences. Conversely, Kant determined his ethics by considering what rational people would consistently choose, regardless of their individual desires, preferences or goals. I will discuss Rawls's account of distributive justice later on in the thesis, and demonstrate how it can work in combination with Principlism to provide a more robust ethical underpinning for pharmacogenetic research governance.

Principle-based Ethics

Utilitarianism and duty-based ethics are abstract moral theories, and in resolving ethical issues, it is not always necessary to consider moral theory at that level of abstraction. Therefore, a number of principles pertinent to many situations in medicine, and endorsed as important in the noted moral theories, have been identified and applied when there is an ethical problem. The most notable principlist ethical framework is that of Tom Beauchamp and James Childress, whose book '*Principles of Biomedical Ethics'* (Beauchamp, Childress 2009) first appeared in 1979. This has been refined and reworked continually over the years in response to objections, so that it is now inclusive of features of the moral world that it had, initially, ignored. This resulted in an influential principle-based theory designed to help clarify key moral issues. Central to this theory is the existence of governing principles that declare obligations. The four principles identified are: respect for patient autonomy; beneficence (the promotion of what is best for the patient); non-maleficence; and justice. Principlism is the term often used to refer to the theory of four standard, or *prima facie,* principles. *Prima facie* moral duties 'at first sight' (duties which are understood by reference to what we should do if no other such duties were present) were introduced by W D Ross (Snare, 1974). Ross noted that in any specific situation where there is a clash between different duties, we must decide in light of the circumstances whether it is morally more important to follow one duty or another; this is a matter of judgement. There is no ranking of duties, and the truth of a moral principle or duty is known by understanding and thinking about the principle in relation to a particular situation. Furthermore, our moral intuitions assist us in recognising the *prima facie* duties (Snare, 1974), and ethical conflicts are seen to arise when two such duties come into conflict. For example, what should one do if the only way not to betray someone is by lying? To

address this conflicting situation, one must distinguish between actual moral duty and *prima facie.* Therefore, *prima facie* principles can be overridden by other, weightier, competing concerns. In other words, they are not absolute.

Thus, ethical theories provide the basis for justifying specific ethical decisions. For clinical research, the ethical theories that are appealed to are more practical principle-based theories, such as Principlism, since these theories are not abstract and are 'easy to use'. However, it has been identified that the central focus of these theories is to ensure the interests of society, or the enthusiasm of the researcher, do not override those of the individual. This core focus has existed to the detriment of appealing to the common good in the application of the new technology of pharmacogenetics in clinical trials. In the final section of this chapter, I will introduce the argument that the requirement of appealing to the common good is as important as ensuring the safety of research participants. But first, more detail will be provided on how and why Principlism became the most dominant form of ethical reasoning in clinical research.

2.3 Research Ethics and Principlism

Modern research ethics were borne out of recognition of the core principles centred around the priority of individual rights and welfare over society's interest in pursuing medical knowledge (Kimmelman, 2005); namely, the *prima facie* principles of Principlism. In this thesis, the theory of Principlism (as according to Beauchamp and Childress) will be outlined in order to highlight some of its shortcomings in its current interpretation as the research ethics theory for the governance of pharmacogenetics-based clinical research.

Principlism is noted as a set of considered judgements on universal morality in healthcare (Beauchamp, Childress 2009, p.25). In this, universal morality is a collection of very general norms to which everyone who is committed to morality subscribes (Herissone-Kelly, 2011). In the setting of clinical trials involving human participants, these considered judgements or core principles emphasise respect (of autonomy) for a person to choose whether or not to participate. These principles also stress the importance of beneficence (the acknowledgment and acceptance of the constraints and potential risks by participants), and justice, that some vulnerable persons should not be considered as a participant for a trial unless under strict conditions to protect them (Salek 2002, p.72). Derived from the principled approach of the Nuremberg Code and Belmont Report, and further developed by the Declaration of Helsinki (Loue 1999, p.58) (all of which will be discussed in greater detail in chapter five), Principlism was one of the first contemporary attempts to ground a method of bioethical decision-making in something other than an abstract moral theory. The idea was that, despite disagreement about moral and religious theories, we could all agree on certain principles. All one had to do was identify the 'universal morality', and extract a set of middle level principles. Universal morality is not a singular morality, but a set of standards of action or rules of obligation that are applicable to all persons in all places. These standards judge human conduct (Beauchamp, Childress 2009). Examples of these universal norms include: do not kill; tell the truth; and do not steal. Furthermore, the notion of international human rights has been noted as an example of a universal norm.

Principlism was one of the first notions of morality without a theory (i.e. a theory or method of resolving bioethical issues without relying on a foundational moral theory), and intends to

provide general rules or recommendations to a number of specific cases, based on 'what is the right action' in any particular medical situation. It is not the only moral framework available for such a purpose, but it is one that clearly addresses the individual (Thomson 1999, p.123); i.e. rights-based morality.

Rights-based morality has increased in consideration since World War Two, due to the enhanced concern for human rights. Moreover, alongside rapid advances in technology, there has also been an increase in the rejection of the attitude that healthcare providers have sole authority over healthcare provision. This has impacted more noticeably on the lives of those in Western society and has resulted in notions of personal autonomy, as reflected in Principlism. However, as clinical research and practice continue to develop (as in the case of pharmacogenetic drug development), it must be recognised that an unreflective approach to Principlism (an approach that accepts the principles as a given without inquiring into the deeper reasoning and theories that ground them) may be unable to cope with or identify complex and unknown future ethical problems.

Principlism was first identified by the Belmont report, which noted three basic principles, identified as

…general judgements that serve as a basic justification for the many particular ethical prescriptions and evaluations of human action…

(Jonsen, Veatch et al. 2000).

The principles identified were:

- Respect for persons - 'The principle…divides into two separate moral requirements [1] the requirement to acknowledge autonomy, and [2] the requirement to protect those with diminished autonomy'
- Beneficence - expressed as two general rules of beneficent actions; '[1] do not harm; and [2] maximise possible benefits and minimise possible harms.'
- Justice – '…equals ought to be treated equally'.

(Beauchamp, Childress 2009)

Since the Belmont report, Principlism has been further developed into a 'four principle approach', particularly by Beauchamp and Childress in the USA, whose account of Principlism is the most utilised ethical framework for clinical trial ethical regulation.

Beauchamp and Childress's four principles are:

- Respect for Autonomy - '…a norm of respecting the decision-making capacities of autonomous persons…'
- Non-maleficence – '…a norm of avoiding the causation of harm…'
- Beneficence – '…a group of norms for providing benefits and balancing benefits against risks and costs…'
- Justice – '…a group of norms for distributing benefits, risks and costs fairly…'

These principles aim to act as general guides for healthcare professionals facing ethical issues when treating their patients. These general guides, from which specific rules or judgements can be made, are derived from a universal morality (rather than having a philosophical or

theoretical derivation). The notion of a universal morality has yielded a number of criticisms with regards to the universality of the framework, which has been described as 'distinctly American in character' (Holm, 1995). Furthermore, Soren Holm[5] goes on to state:

'...it should come as no surprise that the content of this theory will be influenced by its basic premises, and therefore influenced by the morality and culture of the society from which it originates...'(Holm 1995, op cit 31)

It should be noted that the premise of the four-principles approach is based on shared morality in a specific society, and that these 'specific societal premises' make light of the claim of the four-principles approach as a universal morality theory. This raises the question that, in order to establish a universal morality theory, an internal set of norms must be evident that are considered acceptable cross-culturally. This has not been apparent for the principles of respect for autonomy, beneficence, non-maleficence and justice, which have been criticised as being too individualistic, rights focused, rationalistic and narrow in their understanding of religious and cultural frameworks, in addition to not being globally acceptable (Herisson-Kelly 2003, p.76; Clouser, Gert 1990). For example, the principle of beneficence is:

'...only operative if it can be discharged without significant risk...'

(Holm 1995, p.334)

This implies that in order to act beneficently, we are requesting:

'...something which is beyond the capability of most moral agents...'

[5] Professor of Bioethics , The University of Manchester

(Holm 1995, p.334)

Therefore, to act beneficently, one must note that an element of self-sacrifice is required. This is considered an unpopular undertaking for our individualistic, rights-based society. Furthermore, the principle of respect for autonomy (again, regarded as 'universal') is actually not found in Buddhist cultures, due to this philosophy's metaphysical assertion of 'non-self'. In Western culture, we understand autonomy as freedom[6] or self-determination; that is, determination by one's self. However, in Buddhist cultures, if there is no conception of 'self' then freedom needs to be understood differently. They note that the greatest freedom comes from losing self-preoccupation and assuming responsibility for all things; not only immediate family, but also the community and beyond. This does not mean that the four principles or ethical principles per se must be consistent with the religious perspective of the country in which the research will be conducted, but it should acknowledge those features of existence and culture that unite human beings, without overruling the very real differences. Features that are not necessarily culturally dependent but are inherent in the global ethics framework developed by David Thomasma[7], which, I argue in chapter 6, should be considered for pharmacogenetic research governance. Since this ethical framework maintains the considerations of the pursuit of the 'common good' as one of the aims of research ethics.

[6] Freedom is a crucial issue for the sense-of-self because it understands the basic problem of a lack of autonomy. Throughout the ages, Western civilisation has pursued questions of free will and liberty, to the extent that the pursuit of freedom might be considered a dominant myth of modernity. For example, starting with the Greek "emancipation" of reason from myth, then since the Renaissance, there has been progressive religious freedom (the Reformation), then political freedom (the English, American, French revolutions), followed by economic freedom (the class struggle), racial and colonial freedom, and most recently sexual and psychological freedom (psychotherapy, feminism, gay rights, deconstruction as textual liberation, etc.). Each of these endeavours has succeeded each other for the ultimate stake inherent in all of the right of the self to determine itself. Excerpt taken from Loy, David. 1993. "Indra's post-modern net."(Loy 1993)

[7] Editor Emeritus *Theoretical Medicine & Bioethics*

Prima facie principles (developed by Ross and mentioned in section 2.2) refer to how a principle is binding unless it conflicts with another moral principle (Beauchamp, Childress 2009, p.33). An example of the *prima facie* nature of principles is observed in a situation where research is permitted on anonymous human tissue. Such tissue may have been stored for some time, and the link between identifying the donor and stored material is often non-existent. The tissue could be a by-product of surgical interventions (e.g. frozen serum), used without the individual's consent (an application of respect for autonomy). The principle of respect for autonomy is overridden by the principle of beneficence, where the research in question benefits other patients[8].

It is understood that if the principles are interpreted and weighed sensibly, they provide an adequate response to all major bioethical concerns anywhere in the world (Takala, Häyry 2007). However, there is a problem with this perception of *prima facie*, which has given rise to the criticism that the four principles lack *'...explicit decision rules...'*(Holm, 1995), since they are interpreted in different ways. A criticism further noted by Raanan Gillon[9] is as follows:

'...Here we can all agree, for the approach has never claimed to provide such a decision mechanism, and some sort of justifiable decision procedures are badly needed...'

(Gillon, 1995)

[8] However, this does not apply to genomics research, where the samples have not been completely anonymised, and can, therefore, be traced back to the patient.

[9] Emeritus Professor of Medical Ethics at Imperial College, London

Beauchamp and Childress agree with these criticisms, but go on to argue that no successful theory exists that can provide such a decision procedure. Moreover, they further note that,

'…we see disunity, conflict, and moral ambiguity as pervasive aspects of the moral life. Untidiness, complexity, and conflict are unfortunate features of communal living, but a theory of morality cannot be faulted for a realistic appraisal of them…'

(Beauchamp, Childress 2009, p.107).

The universal morality of the principles are described by Gillon as:

'…a common set of moral commitments, a common moral language and a common set of moral issues…'(Gillon 1994)

This was adopted by Beauchamp and Childress, and incorporated into later editions of the *Principles of Biomedical Ethics*. There was also the concern that, by taking these four principles collectively, we might account for any dilemmas encountered by a healthcare professional. However, as a result of the criticisms levelled at the principles, Beauchamp and Childress introduced the processes of specification and balancing to enable the principles to be more applicable to practical situations.

Specification was introduced as a method of resolving conflict between the principles, as Beauchamp and Childress noted that

…when moral conflicts occur, specification supplies an (ideal) of repeated coherence testing and modification of a principle or rule until the conflict is specified away…

(Beauchamp, Childress 2009, p.32)

In other words, this involves specifying a principle in such a way that only one principle can be applied to a particular situation; thereby resolving any potential conflict. Indeed, Paul van Diest, a Professor of Ontological Pathology, argues that the principle of 'solidarity' (beneficence) is more important than the right of self-determination (respect for autonomy) over discarded material (van Diest 2002, p.648).

Therefore, for specification to occur, it needs to be justified and not based on arbitrary or biased principles. Beauchamp and Childress note that specifications are justified:

'…only if it is more coherent with the whole set of relevant norms than any other available specification…' (Beauchamp, Childress 2009, p.31).

However, when specification fails to resolve conflicts between principles, the balancing of norms is employed.

Balancing is the overriding of one principle or norm by another, and is similar to Ross's account of *prima facie* obligation; that the principles are binding unless overridden by competing obligations. This implies that we have to apply balancing on a case-by-case basis in order to decide which principle is the most important.

As with specification, balancing is controversial, as noted by Beauchamp and Childress:

'... [Balancing] is a process of justification only if adequate reasons are presented ...'
(Beauchamp, Childress 2009, p.34)

They highlight that the following conditions must be met to justify the overriding of one principle by another, thus reducing the amount of intuition involved in the decision-making process:

1. Better reasons can be offered for acting on the overriding norm than the infringed norm.
2. The moral objective justifying the infringement has a realistic prospect of achievement.
3. No morally preferable alternative actions can be substituted.
4. The form of infringement selected is the least possible, commensurate with achieving the primary goal of the action.
5. The agent seeks to minimise the negative effects of the infringement. (Beauchamp, Childress 2009, p.39)

Yet, the process of overriding and balancing will not be able to determine which moral norm is overriding in some cases; consequently, intuitive judgements and subjective weightings are unavoidable.

The specification and balancing of the four principles substantiates the use of moral intuitions in Principlism as a function of 'intuitive apprehension and intuitive reflection' (Quante, 2002); basically, this is a way of qualifying the intuitions or 'considered judgments (Beauchamp, Childress 2009, p.20). This highlights the argument that principled ethical reasoning is based 'upon an a-rational core' (Tomlinson, 1998), an appeal to 'moral common sense' (Tomlinson 1998), and a methodology that delivers different intuitions due to the subjective nature of 'common sense'. In other words, judgements are balanced based on intuition, such as subjective reasoning (which is based on mere feeling), a feature prevalent in genomics research governance. This substantiates the realisation of the presence of mental dispositions in regulatory decision-making, especially in genomics research governance a point to which I will argue further in chapter three.

The way in which the balancing and specification of the four principles is applied to pharmacogenetic-based clinical trials is illustrated by the case of population biobanks, which hold research participants' genetic information. Here, the concept of the research participant as genetic information tests the focus of the person as a separate identity 'whose interests - and records - can neatly be separated from those of their families' (Kaveny, 1999), due to the fact that some genetic information by nature is shared. The well-established principles of non-maleficence and beneficence are put into conflicting situations when returning genetic research results to participants. It is perceived that deciphering the genetic code may pose the risk of eroding a participant's privacy. For example, some variants of the genetic code that predicts drug responses may also be a marker of disease predisposition (e.g. the apolipoprotein E4 allele, known to influence responses to cholesterol-lowering drugs (statins) are also

associated with an increased risk of Alzheimer's disease). If such information were to fall into the hands of employers or insurance companies (and this is possible, since the debate continues about whether these parties should be given rights to assess genetic data), stigmatisation of the participant could occur. However, such fears can be more or less laid to rest due to regulations in the US, specified by the *Genetic Information Non-discrimination Act 2008*(US Congress, 2008). This legislation prohibits the use of genetic information by insurers or employers. The European Union took similar steps towards regulation in 2003, with the policy document *Genetic information and testing in insurance and employment; technical, social, and ethical issues* by the European Society of Human Genetics (Godard, Raeburn et al. 2003). However, no formal law has been passed to date. In such situations where public policy positions in Europe and the US are based on the balancing of principles, it is an assertion of 'moral common sense', which is employed, providing subjective reasoning for ethical dilemmas. Nevertheless, such an approach to taking feelings into account in bioethical decision making, has been proposed by Tuija Takala[10], who supports the argument that bioethics should consider both reasons and emotions in order to formulate regulations that strike a balance between 'everyone's sense and sensibilities (Takala, 2003). Takala calls this setting a 'minimal morality', which can be accepted in a pluralistic society. What this 'minimal morality' could comprise remains to be seen, but the principles of respect for healing and respect of dominion (the non-objectification of matter and persons to such an extent that both become objects for manipulation) as advocated by David Thomasma[11] and featured as part of the basis of his global ethical framework would be a good starting point (Thomasma, 1997) and will be critiqued further in chapter six.

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[11] Editor Emeritus *Theoretical Medicine & Bioethics*

Principlism, the ethical 'theory' of choice in current clinical research ethics, derives from the abstract moral theories of consequentialism, and duty-based moral theories. Its ease of use is due to the approach of the principles as general guides, which can be applied to most ethical situations. The introduction and employment of aspects of specification and balancing help make this theory more malleable. Principlism has proved popular as a rights-based morality framework due to increased concern for human rights. In the healthcare setting, such concern is represented by the informed consent process (the practical application of the principle respect for autonomy). This principle has become an indelible component of medical ethics, dictating the appropriateness of the conduct of health care professionals towards their patients. Furthermore, respect for autonomy has emerged as the guiding principle in current ethical discourse, and its normative and emotional appeal now goes largely unquestioned, apart from the criticism of the questionable universal appeal of this ethical principle. The significance of this view of autonomy has been reflected equally in law and regulation with regards to the research participant. In later chapters, I will argue that this has presented a dogma of protectionism in policies towards research participants, rendering other issues of ethical assessment within research as secondary, such as justice, efficacy, risk, and considerations of performing clinical trials for the common good. This argument will be addressed further in chapter five, in relation to how Principlism is currently applied to pharmacogenetic research governance. However, the main focus of the thesis will be concerned with whether Principlism in its current interpreted form is adequate or requires further detailed specification of its principles to resolve ethical issues that arise in pharmacogenetic-based clinical trials.

2.4 The Common Good

One must note that the goal of clinical research is to answer a scientific question, with the aim of producing 'generalisable knowledge' for the improvement of health, and to increase understanding of human biology (Emanuel, Wendler et al. 2000). This is known as the common good. I argue that pursuing the common good in this context is also an important normative justification factor in pharmacogenetic research. Pharmacogenetic outcomes, such as drugs and genetic information, are public goods, and are not the preserve of the individual [research participant]. However, in order to secure such knowledge and outcomes, research participants are often placed at risk of harm for the benefit of others. Furthermore, clinical research has the potential to exploit research participants, since they can be perceived inevitably as being 'used'. However, this 'use' and risk of harm can be accepted if ethical requirements for clinical research aim to minimise the possibility of exploitation, by ensuring that research participants are not being used without their knowledge and consent, whilst they contribute to the common good. Furthermore, such 'use' is regarded as acceptable if research participants have a realistic opportunity to derive direct benefits from the outcome of the research projects in which they are involved (De Castro, Sy 2001). Therefore, in addressing how the common good in clinical research can be served, one also needs to discuss how the ethical requirement of non-exploitation of research participants can still be adhered to.

There are four basic notions of the term 'common good' (Sulmasy, 2001): aggregative common good; the common common good; the supersessive common good; and the integral common good. The aggregative common good is the aggregate sum of all the goods of all the individuals in the social unit. It is aggregative because it sums up the individual goods and is

popular in cost-effective analysis. The common common good refers to goods we hold in common, such as air and water. The supersessive common good is believed to override all of the individuals who constitute the community, where the individual good of a few people becomes the common good of all, such as in an oligarchy or junta. Finally, the integral common good is the kind of good that comes explicitly from mutual human interaction and cannot be divided into equally aggregative parts. This is considered the most traditional sense of the common good where being in a community of relationships with other human beings is a good in itself, and the adoption of this notion of the common good into pharmacogenetic research governance will be argued in this thesis.

The integral common good, herein known as the 'common good', is concerned primarily with the needs and interests of society as a whole, rather than only individual persons, their interests, or their needs. It is not the sum of individual goods, but rather a good worth pursuing in its own right. It is bound by the individual good rather than against it, since the individual usually flourishes in the context of a healthy wider community (Peterson-Iyer 2008, p.46). Such an interpretation of the common good is communitarian[12] in outlook, in which individuals are a part of communities and this creates commitments. These are embedded in a multitude of social bonds and dependencies. Individuals can still pursue their own interests, but only in light of contributing to the realisation of the common good (Hoedemaekers, Gordijn et al. 2006).

[12] Communitarianism is a social philosophy that maintains that society should articulate what is good (Etzioni 2006).

In healthcare, the common good follows this communitarian definition, since it focuses on members of the larger community, rather than individual choice. An example of the common good under this interpretation would be guaranteed universal access to basic healthcare. In the context of pharmacogenetics research, which focuses on developing diagnostics for drug response or individually-customised drugs, the research participant contributes to the research project by contributing their data, not only for gain of better treatment outcomes for themselves as individuals, but collectively for their genotype or 'genetic community'. Moreover, due to the research leading to more effective diagnostics and drug interventions, this reduces the number of diseased persons and benefits society in terms of savings in healthcare costs. Furthermore, the common good can be served in the development of new or more effective drug treatments for diseases that seriously impair individual autonomous and social functions, such as Alzheimer's disease or Malaria. This could not be the case for clinical research, on the other hand (whether it may or may not involve pharmacogenetic information), which focuses on performance enhancement, or conditions with only a minor disease burden.

2.5 Conclusion

The role of current research ethics in clinical research is to ensure ethical standards are maintained, by providing justified norms of conduct on what ought to be done. Furthermore, I also note that for pharmacogenetics-based clinical trials, this role should also extend to what ought to be done to pursue the common good in research.

The ethical theories that are appealed to for the justification of ethical decisions in clinical research are the more practical, principle-based theories, such as Principlism, which has become the most dominant form of ethical reasoning in current drug research regulation. This is due to Principlism's ease of use - that of an approach of the principles as general guides which can be applicable to most ethical situations.

In the next chapter, I will look at how Principlism is applied through the vehicle of research governance in drug development. The focus of the chapter will be on the main thesis question of whether the principles can be effective in resolving ethical issues that arise in clinical trials involving genetic information.

3. Chapter Three: Research Governance

3.1 Introduction

While the previous chapter established the reasons why Principlism is used widely in research governance, this thesis will now turn to explore what research governance for pharmacogenetic-based clinical trials actually comprises. The main focus of the argument will be on whether the current precautionary approach of governance is appropriate for such clinical trials.

Research governance is the mechanism of regulation in research. It ensures the accountability of assured systems of administration and supervision which manage healthcare research programs (Shaw, Boynton et al. 2005). Governance is not the responsibility of any single institution or individual, but rather a system of supervision and administration exercised at regional, national and international levels. For example, in the European Union (EU), governance provides codes of practice, national and European law, alongside professional standards and values. For the UK, research governance is provided by the Research Governance Framework (RGF) (Department of Health, 2005), which is based on the EU Directive on Good Clinical Practice (2005/28/EC) (EMEA, 2005), and incorporates requirements of the *Medicines for Human Use (Clinical Trials) Regulations 2004* (UK Government, 2004) (MHRA, 2010b). The latter regulation controls how research is conducted to ensure the safety and efficacy of a medicinal product for human participants. Furthermore, the RGF sets out the responsibilities of individuals and organisations involved in research, including researchers, research ethics committees, local authorities, and pharmaceutical and other industries.

In many countries, different research governance systems have been established, with varying remits and agendas based on their specific social, healthcare and research environments. This has given rise to professional codes and guidance, which vary widely within and across countries. These variations have caused problems, such as delays in setting up clinical trials for participating countries following a common protocol, for example. Furthermore, these distinctions in national governance of research protocols have been found to have the potential to stifle the emergence of innovative technologies (Halffman, 2005), (Epstein,2008) .

The sections of this chapter will address the underlying reasons for differences in governance, as well as the expectations of research governance in traditional drug development. I will also explore whether this changes once pharmacogenetics is introduced. The thesis will argue that variation in research governance is due to the ethical interpretation of the management of risk – the central role of research governance - and this will be discussed in section 3.2. This section will establish the concept of governance in healthcare, and how governance has a precautionary nature in managing the concept of risk with particular regard to drug development. Section 3.3 will examine further how governance is employed in a precautionary approach to research, which one could argue is not appropriate for pharmacogenetic clinical trials. In section 3.4, I will argue how the landscape of governance has changed with the introduction of genomics in drug development, from being one concerned with the language of scientific evaluation (that is, of risk evaluation) and precaution, to being concerned with the language of emotions, which is linked to uncertainty. Section 3.5 will develop further the argument on how the interpretation of the principles of uncertainty is an epistemic interpretation based on value-laden perceptions of risk. Herbert Gottweis's observations on

this conversion (Gottweis, 2005b) will be used to illustrate this discourse. Furthermore, John Rawls's theoretical concept of reflective equilibrium will be mentioned as a method for showing how the language of emotions can be utilised as a method for arriving at the content of required principles of an ethical guidance system. This will lead to the introductory analysis of Rawls's concept of overlapping consensus a latter procedural development of reflective equilibrium that is more appropriate for the successful integration of 'principles of uncertainty' within genetic governing policy.

From such discourse, background information will be provided for the establishment of the main argument's primary and secondary claim; of the overriding deference to the principle of autonomy (as seen in the current ethical interpretation of the management of risk); and the non-specificity of the principles in particularly the principle of justice in Principlism. All of these may have contributed to the shrouding of the main aims of research governance for research protocols involving pharmacogenetics, as well as the variability of governance.

3.2 Role of Research Governance

This section will discuss firstly the mechanism of research governance within the healthcare context, in order to provide a background to the evolution of clinical trial governance. Then, discussions will be concerned with the management and interpretation of risk of harm, which is pivotal to research governance in relation to clinical trials, regardless of whether pharmacogenetics is integrated within the drug development process.

3.2.1 Concept of governance

The concept of governance is concerned with rule-making, and was initially associated with the nation-state government (Bunton, Petersen 2005, p. 4). However, the term 'governance' has become concerned with systems of rule relating to all levels of human activity, from family relations to international organisations; thereby acknowledging that the world is influenced and structured by these interdependent systems, rather than by state rule alone (Rosenau, 2000). Governance takes into account the activities of other mechanisms and strategies of command, and this may manifest in the form of goals, directives and policies. However, these mechanisms and strategies focus more on the role of organisational networks at local, national and international levels and across societal divides, than on hierarchical and authoritarian rule[13]. An example of this has been seen in the West in the latter half of the 20th century, where public sector reform resulted in national government functions being transferred to lower regional levels, as well as supranational organisations. A further instance is observed in healthcare, where there has been a redistribution of responsibility from state healthcare systems to private service providers and individuals (who are expected to manage their own health by making careful choices and reducing lifestyle risks, which is a form of self-governance). Such an illustration has led to healthcare regimes, which have sought to encourage the empowerment of communities to have a role together with local and international bodies in maximizing health. This has resulted in governance in health being considered in broad terms of encompassing social systems, as well as the conduct of the individual's life through self-governance. This gives rise to what has been regarded as the

[13] Rosenau, in *Governance in the twenty-first century,* prefers the use of the concept of control or steering mechanisms to replace the notion of command. Such concepts provide focus for the central purpose of governance.

emergence of 'Good' governance for health. In this context, the 'Good' is interpreted in the ethical sense of utilitarianism (holding that an action, or in this case guideline, is right only if it produces the best outcome), or as complying with health guidelines that maximise welfare (Ott, 2010). Integrated public health policies that have arisen from such 'good' governance have been effective for increasing the health of the population, rather than just the health of individuals, especially amongst disadvantaged and vulnerable groups (Bunton, Petersen 2005, p.5).

3.2.2 The management and interpretation of risk of harm

In all aspects of drug development, governance is considered that which ensures high quality research and the maintenance of public confidence. This is achieved through the vehicle of risk assessment, a principled judgement that has created a tension between conducting 'good' governance based on maximising the production of the best outcomes, and governance concerned with the acceptability of the risk of the research project. Risk is associated with potential knowable harm, and risk assessment involves the identification, evaluation and estimation of the levels of risk in any given situation, in addition to making comparisons between standards that determine acceptable levels of risk (Risk Assessment, 2010). Furthermore, risk is concerned with the anticipation of the consequences of research, and the impact of the researcher's actions. How risk is managed in research is influenced by the surrounding social and political environment. Such influence has led to differences in national and local styles of regulation and review (Rikkert, Lauque et al. 2005). Currently, the review of clinical trials involves the interpretation of intricate legislation, and assessment of the

potential benefits of clinical projects in terms of knowledge gained in proportion to the potential physical and or psychological harm it might cause.

In the context of drug development, risks are interpreted as the probability that harm will be caused to a research participant (where harm refers to adverse events concerned with drug inefficacy or toxicity, as well as the consequences of genetic variation). In these instances, risks are most often interpreted in terms of calculation, measurement, probability and the prediction of adverse events (which are untoward medical occurrences in patients due to the administered medicinal product), rather than notions of fate or chance (Shaw and Barrett, 2006).

In this context, risk is associated with mathematics and statistical probability (Drummond, 2000, p. 177). When risk is interpreted as probabilities of harm, it is an example of an approach derived from our rational post-enlightenment view of the world, where potential harm is assessed using mathematical judgement to weigh up the potential risks and benefits (Shaw, Boynton et al. 2005). However, these judgements continue to be value driven, since they are based on the interpretation of scientific evidence regarding the risk of harm to research participants. Moreover, they are influenced by high-profile events that may provide cause for government or professional intervention. For instance, the Alder Hey organ retention scandal, which was evidentially within the legal and ethical codes of the time, resulted in changes in the way surgical and autopsy tissue are stored. This was a direct consequence of the controversial and high-profile debates it triggered (Shaw, Barrett 2006, p.14).

Furthermore, the concept of risk is historically and socially located, in that different people perceive it in various ways across diverse societies. Consequently, managing risk requires judgement and interpretation, while good[14] governance, as perceived by regulatory authorities, provides a framework for action rather than being prescriptive. A framework based on structures and systems for assessing the risks of harm potentially inherent in research studies is undertaken as a process of review by governance bodies. These regulatory bodies ensure the risk of harm is proportionate to the potential benefit (represented in the risk-benefit assessment). They consider the concept of risk in terms of the physical, moral and emotional harm related to the drug interventions, associated tests and monitoring procedures encountered during a clinical trial. Therefore, the primary regulatory goal of pharmaceutical regulations is to promote and protect public health by fostering access to medicinal products and devices with a favourable risk-benefit ratio (Rid, 2014).

Furthermore, the scientific assessment of risk as probabilities of harm is preferred, since it is recognised that scientists understand issues in terms of scientific feasibility and risk; therefore, regulation is only justified if directed at a specific risk (Black 1998). These dissimilar views from regulatory bodies and the industry on risk assessment in clinical trial regulation are often a source of contention (Kielmann, Tierney et al. 2007). However, this can be bridged by facilitating the integration of scientific objectivity and the non-scientific view (some aspects of the regulatory body view), through recognising the different rationalities of both approaches (Black 1998, p.652). This integration would be facilitated by regulators or indeed bioethicists, who would translate the different rationalities of both parties by acting as interpreters. In doing

[14] Here, 'good' is regarded in a functional rather than in an ethical context, as in adhering to the proposed guidelines.

so, they would be able to facilitate the negotiation of regulation and its integration (Black 1998, p.660). It has been suggested that addressing the mutual incomprehension of both parties through this interpretive approach would be contrary to the ethos of an intergrationalist approach. But recognition of how both parties understand, identify and address issues should be acknowledged in the interpretation (Black 1998, p.660). How this would be achieved remains the subject of some debate and is a central challenge to regulation. But the proposal of Norman Daniel's[15] and James Sabin's[16] '*Accountability for reasonableness'* (Daniels, Sabin 2002) as a possible approach will be examined in chapter six.

Nonetheless, in drug regulation, the scientific assessment of risk is represented by the risk-benefit assessment and has as its ethical basis the Principlist ethical framework discussed in chapter two, which ensures that moral duties are upheld in research. This risk-benefit assessment consists of a four step model: (1) hazard identification; (2) exposure assessment; (3) dose-response analysis; and (4) risk characterisation (Goldstein, 2005).

1) Hazard identification (where a hazard is defined as anything that could cause harm, as opposed to risk, which is the probability that harm will be caused by the hazard) is based on the toxicological principle of identifying the hazards of new chemicals through pathological and physiological evaluation such as animal studies.

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2) Exposure assessment, which takes into account the concept of exposure efficiency. This relates exposure to source emissions by calculating the extent of eventual human uptake of material released from a source.
3) Dose-response analysis, where the extrapolation of data from animal to human studies, and high dose to low dose effects is central. Moreover, the use of biological markers which link exposure with effect, particularly in the context of human susceptibility; thereby providing a potential mechanism for linking dose with response.
4) Risk characterization, which takes into account risk communication and management, and it is here that risk perception is integrated into risk assessment.

(Goldstein, 2005)

But, before risk assessment begins, guidelines are required to outline how the four-step risk-assessment is performed. These policy guidelines help establish this uniformed approach in clinical trials; thereby providing an advantage to research of replacing default assumption and extrapolative approaches with actual data, thus leveling the playing field for stakeholders involved in the outcome of risk assessment (Goldstein 2005, p.151). In the current climate of bringing new drugs to market, this approach to risk assessment is seen as standard and known as the minimal risk standard or best interest standard, whose ethical basis is rooted in Principlism (Kopelman, 2004).

3.2.3 The minimal risk standard

The minimal risk standard, or best interest standard, as a normative approach provides moral guidance to regulatory and ethics committees on how research ought to be conducted, by

assessing potential harm that could arise in clinical trials. It is not applied universally to all research, but it is pivotal for risk assessment in paediatric research and studies involving vulnerable populations or where subjects are unable to consent. Discussions about this standard will illustrate the need for a consistent standard of risk assessment (which is not subject to value-laden assessment) for national and international studies that can be utilised by review boards (regulatory and ethical), investigators and the public.

Minimal risk of harm in a study is a normative judgement that includes assessing the probability of physical and psychosocial risks, such as stigmatisation, breaches of confidentiality and threats to privacy. Furthermore, since risk-benefit evaluations combine qualitative descriptions, quantitative estimates and other perceptions, it is inevitably a rather imprecise and heavily value-laden assessment.

The term 'minimal' risk is defined by the US federal regulations as when the:

'*Probability and magnitude of harm or discomfort anticipated in the research… [is] not greater in and of… [itself] than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests'*

45CFR 46.102(i) (OHRP, 2006)

In a traditional clinical trial, the minimal risk standard considers the following potential harms:

1) To the participant
    a) The participant's rights

i) Entry into a trial without full informed consent

ii) Failure to act on a participant's request to withdraw from the trial

iii) Failure to protect the privacy of participants

b) To the participant's safety

i) Hazards of the intervention; i.e. adverse drug reactions (both expected and unexpected)

ii) Likely risk/benefit ratio of the intervention(s) in the study population

iii) Hazards of the assessment methods (e.g. biopsy, x-ray)

2) To the integrity of the trial

a) Due to the completion of the trial – recruitment and follow-up

b) Due to the reliability of the results, based on:

i) Study power[17]

ii) Major violation of eligibility criteria

iii) Fraud

iv) Randomisation procedure

v) Outcome assessment

vi) Completeness and accuracy of other data

vii) Adherence to the protocol[18]

(Baigent, Harrell et al. 2008)

[17] A statistical term based on calculating the number of research participants required to demonstrate an effect of the treatment at a certain magnitude(Sim, Wright 2002)

[18] Via following the set guidelines as set out in MRC/DH joint project to codify good practice in publicly funded UK clinical trials with medicines. Workstream 4:Trial Management and Monitoring. http://www.ct-toolkit.ac.uk/__data/assets/pdf_file/0007/35962/monitoring-procedures-workstream.pdf

If the risk of harm is considered minimal for all categories, then governance bodies such as ethics and regulatory committees are more inclined to provide approval for the research (or speed up the approval process). If the research contains more than a minimal risk, greater protection of the research participants' rights and welfare is required, regardless of the study's benefits. There has been a wide variation in how these risk categories have been interpreted and understood by research governance bodies. This variation has raised concerns about whether the minimal risk standard is fulfilling its moral and social obligations; such as, respect for the partcipant's rights and welfare (Kopelman 2004, p.352) and championing efficiency and social utility (Petersen, 2012).

3.3 Precautionary Regulation

In this section, I will argue that governance has been dominated by protectionist policies, which are unable to fulfil the role of providing adequate governance when applied to pharmacogenetic-based drug research. This argument is based on the reasoning that such protectionist policies are based on the precautionary principle, which interprets broadly any uniquely new activity as prohibitive, and seems to be the default principle of regulatory bodies when faced with a new biotechnology.

The precautionary principle was originally intended for policy makers faced with environmental issues, such as marine pollution. It has become the ideological vehicle for the risk assessment industry and, as such, is very general. Its contribution to governance is that the regulation of new products or technologies assumes them to be hazardous unless proof can be provided otherwise, by engaging in a form of risk assessment acceptable to regulatory bodies

(Salter, Jones 2002). The imposition of this principle on regulators and legislation gave rise to further litigation in the US, and an increase in the cost of assessing risk in regulation in Europe (manifested in penal terms). Furthermore, the evaluation of risks became dictated by belief and an absence of scientific rules of evidence. This served to fuel public anxieties, which have the potential to halt progress of a technology at any time (Scruton 2004).

Definitions of the principle have been found to be vague and confusing; thereby facilitating inconsistent interpretation (Lierman, Veuchelen 2005; Cohen 2001; Engelhardt Jr., Jotterand 2004). For example, the 1998 Wingspread Statement provided a definition of the principle, in which it interprets any activity as prohibitive:

> *'...when an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically...'*
>
> (Lazzarini, 2001).

In 2000, the European Commission provided the following definition:

> *'...where preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen for the Community...'* (Lazzarini, 2001)

This demonstrates that the principle could be used to hinder technological progress, due to its potential prohibitive stance and extreme variability in interpretation. This can be noted in the Italian government's justification of preventing the sale of GM food by taking literally the following line:

> *'...no human technology should be used until it is proven harmless to humans and the environment...'*
>
> (Cited from the European Commission 2000, communication on the principle Lazzarini 2001).

In turn, this replaced scientific standards with unsubstantiated claims and burdened innovators with the impossible requirement to prove positive benefits in the absence of any possibility of harm. Such a situation has called for a definition in the EU, which views the precautionary principle as a risk regulation instrument that permits the adoption of preventative measures in the face of scientific uncertainty (Khoury, 2010). However, despite this lack of clarification, the current definition, as given below, implies that a technology should not be released, or continue to be released, into an environment until there is compelling evidence that it will not cause harm (Abraham, 2002). Moreover, the burden of proof is placed on demonstrating that the technology does not inflict serious short-term or long-term damage on those who would like to introduce or maintain it.

The Precautionary Principle as defined by UNESCO is as follows:

When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm. Morally unacceptable harm refers to harm to humans or the environment that is

- *threatening to human life or health, or*
- *serious and effectively irreversible, or*
- *inequitable to present or future generations, or*
- *imposed without adequate consideration of the human rights of those affected.*

The judgement of plausibility should be grounded in scientific analysis. Analysis should be ongoing so that chosen actions are subject to review. Uncertainty may apply to, but need not be limited to, causality or the bounds of the possible harm.

(Weiss, 2007)

In the context of pharmacogenetic-based clinical trials, it would be the regulatory authorities and stakeholders who would select test options, such as the level of reported adverse drug reactions (ADRs - an indicator of whether a drug was safe and efficacious) most sensitive to the hazards and damages selected; thereby ensuring the detection of potential risks. Risks may be interpreted as the probability that harm will be caused to a patient, which, in this context, refers to drug inefficacy or toxicity (ADRs). In pharmacogenetics, these risks are consequences of the addition of genetic factors, producing harm attributed to genetic variations in genes which are responsible for drug-metabolising enzymes, drug receptors, and

drug transporters. They are inherently unknown and arise from the complex pathways of drug metabolism and gene interaction (Severino, Chillotti et al. 2003).

These chosen test options are then analysed by quantitative assessments (i.e. risk - benefit assessment), such as the minimal risk standard based on the following judgements (Engelhardt Jr., Jotterand 2004):

a) Whether the drug is effective at low doses, even with insufficient controlled trial data; for example, analysis is made by extrapolating beyond the available controlled clinical trial data to utilizing data on the clinical experience of the use of a drug.

b) Whether the safety data analysis is acceptable, basing further judgement on the analysis of 'unique' configurations of the data, such as comparing 'low' dose medication X to 'high' dose medication Y, rather than normal constructs of clinical trials, which tend to utilise the construct of like with like 'low' dose medication X to 'low' dose medication Y.

c) Whether the clinical trial safety data should override other safety data that is not obtained necessarily from the stakeholder. For example, data obtained from spontaneous reporting systems (SRS) from the FDA database in the US, or the Yellow card system in the UK.

d) Whether there is adequate data to support the drug's effectiveness.

e) Whether warning signals, like ADRs from SRS or yellow card, should be included, due to the fact that, sometimes, the drug is administered at higher doses and for longer than expected, giving rise to SRS similar in profile to ADRs reported from earlier clinical

trials of the drug. These earlier clinical trials investigate the optimum conditions of a drug and tend to include the higher drug doses and longer treatment regimes.

Recently, the precautionary principle has been applied to medical issues and has been interpreted in two ways: as a normative, action guiding principle (as in Principlism) characterised by what it urges decision makers to do; and as an epistemic (belief-guiding) principle, characterised by what it urges us to believe. A precautionary approach to risk assessment depends on the political prioritisation of public safety over and above some of the commercial interests of pharmaceutical companies; thus, it is linked to the socio-politics of technology assessment (Abraham, 2002).

Suffice to say, the precautionary principle is exercised by allowing reasonable responses to credible and immediate threats in the absence of what would otherwise be sufficient information. Furthermore, the minimal risk standard's value-laden content is belief dependent, albeit by 'experts', suggesting that the precautionary principle that is exercised in drug regulation has an epistemic interpretation. This provides information on what should be believed in (due to the facts), rather than what ought to be done, in order for the research to be morally acceptable; thereby, suggesting whether an epistemic moral framework would, in general, be more appropriate for drug regulation

3.4 Genetic Governance

This section will debate whether value-laden perceptions of risk, i.e. epistemic interpretations, need to be taken into account in pharmacogenetic-based drug regulation. The discussion will concentrate on how the introduction of genetics has changed the landscape of governance, from being concerned with the language of scientific evaluation, to assessing belief states. Additional analysis will demonstrate how the introduction of genetics has further entrenched the change in governance from a top-down approach with government determining policy, to a bottom-up approach determined by the public and other agents such as industry. The argument taken by this thesis will call on the French philosopher Michel Foucault's concept of 'Governmentality', which is concerned with government as conduct (problems of self-control, guidance for the family and for children, management of the household, directing of the soul) and not just management of the state or administration (Lemke, 2002). This concept refers to how the state exercises control over, or governs the body of its populace and provides a better understanding of the relationship between changing forms of knowledge and power.

The introduction of genomics into public perception has presented an image of humankind as being determined by genes. This is known as *genetic determinism*, whereby genes alone define all aspects of an individual. For example, the genetic testing of embryos may indicate an increased risk of a trait, but such analysis does not tell us what traits the embryo would have as a person. This is because genetic diseases are generally caused by the interaction of many genes (known as *polygenic*), rather than the defect of a single gene (monogenic). Furthermore, environmental factors play a crucial role in whether a trait or condition is expressed. Moreover, the more complex the interaction of genes and environment, the less likely a correct

prediction of a disorder becomes. In addition, another popular public perception of genes is that they are considered objects of manipulation and transformation (Gottweis 2005a, p.197); thereby presenting the notion of scientists as 'Playing God'. Such perceptions of genomics have created inaccurate observations of the goals of current genomic technologies. Inaccurate meanings have emerged as a result of DNA being identified with the self-understandings of the human person, provided for by both the classical world and the Christian tradition. Meanings and beliefs argued as a by-product of the cultural understanding of genetics and that have, in turn, determined how such biological material is utilised (Krueger, 2002).

For governance, this means that the traditional reliance upon technocratic networks to provide the scientific identification of hazards and determination of risks for policy formation and implementation is currently an insufficient mechanism for legitimising the risk assessment process (Lemke, 2004). Therefore, governance is altering its stance by seeking methods of engagement with the public and non-governmental organisations in human genetics. Regulation of a biopolitical nature has ushered in the 'biopolitical age', bringing forth laws about genetic equality that outlaw discrimination based on one's genetic makeup (Salter, Jones 2002). Such biopolitics are an example of Foucault's '*Governmentality'* of emerging forms of knowledge and practice, which is regarded as an indicator of the rules and rationality of neoliberal democracies.

3.4.1 Foucault's Governmentality

The concept of *Governmentality*, as conceived by the French philosopher Michel Foucault, will be drawn upon in this section, since it explains aptly how genomic policies are shaped by

industry and the general public, rather than the government. Apparently, the age of 'biopolitics' has revealed flaws in the application of Principlism in research regulation (Winickoff, 2003). Foucault's concept of governmentality, which he defined as the 'art of government', refers to government not only being linked to politics of the State, but also considers different forms of control, such as social-control and biopolitics (Foucault, 1979) . The State (according to Foucault) is concerned with moving on from a territorial administrative function and refers to the way in which people are taught to govern themselves, shifting power from a central authority, like a state or institution, and dispersing it among a population. This 'art of government' directs the purpose of government towards the welfare of the population, entailing the care and control of the population (Miller, 2008).

Foucault noted the close relationship between ethics and governance, in that ethical judgement is implicated in the formation of the self and citizenship. He argues that individuals govern themselves through; 'self-care, self-examination and self-discipline, training and exercise' (Lemke, 2002). Therefore, governance relies on political strategies focused on regulating all aspects of human life in a given population. An example of this is the Universal Declaration on the Human Genome and Human Rights adopted by UNESCO in 1997. This declaration established rights-based regulatory criteria, which recognised how human genetics research (and associated industries) should be conducted (Salter, Jones 2002, p.328). This implemented regulations based on the tracking and management of risk, which, in the field of drug development, is the prediction of potential adverse drug reactions. However, this has resulted in the establishment of global or super-national systems for regulating potential risks, such as the Committee for Medicinal Products for Human Use (CHMP) and the European Agency for

the Evaluation of Medicinal Products (EMEA). These transnational governance organisations provide a system of multi-level governance, which consists of multi-tiered governmental and non-governmental, geographically overlapping structures. This moves political negotiation from a local (public) to a transnational level (Gottweis, 2005c), which, in turn, ushers in a drugs regulation system ruled by judgements from experts who are well protected from public scrutiny. For drug development involving genetic information (such as pharmacogenetics), it is questionable whether this can be politically contained similarly within an established regulatory arena that relies heavily on technocratic closed and non-transparent procedures, given the cataclysmic shifts in the neighbouring regulatory territories of food and agriculture (Salter, Jones 2002, p.327).

Public perception of genetics has introduced an element of determinism and reductionism in governance. This has been proven as changing governance from having a top-down approach (with the government determining policy for the 'good' of research) to a bottom-up approach that involves the public and other agents. In the field of drug development, governance has returned to being a technocratic discipline, with little or no input from public bodies. However, the introduction of pharmacogenetics in drug assessment may bring forth public challenges to policy recommendations, especially if these policies are viewed in the current deterministic light.

3.5 The Concept of Uncertainty

In this section, I will argue how the introduction of genetics has changed the landscape of governance, from one that is concerned with the language of scientific evaluation and precaution, to focusing on the language of emotions. I will also argue how governance is observed as interpreting principles of uncertainty (value-laden perceptions of risk, or epistemic interpretations), rather than principles of a normative precautionary nature, which are concerned with the assessment of risk. I will refer to Herbert Gottweis's observations on governance (as changing from risk perception to uncertainty in this genetic era (Gottweis 2005b)).My argument will first cite John Rawls's ' theoretical concept of reflective equilibrium, a methodology for showing how the language of emotions can be utilised to arrive at the content of required principles of an ethical guidance system. Then I will introduce Rawls's procedural development of reflective equilibrium, the concept of overlapping consensus, which will be fully discussed in chapter six. From these discussions, an initial assessment will be made of the application of the normative framework of Principlism prevalent in current research governance. Such an assessment will make known the relevant moral test options or features of the regulatory assessment of pharmacogenetic-based clinical trials. In making these features known, I aim to highlight the requirement of appropriate moral guidelines for consideration in drug research governance involving genetic information.

3.5.1 Pharmacogenetic profilng and risk assessment

Traditional pharmaceutical products, i.e. those not generated from pharmacogenetic intervention, do cause unavoidable harm. Such harm is due to the drug either not producing the desired therapeutic effect, or causing an undesired ADR. Such dangers appear to be tolerated by society, as the alternative would be to remove the drug from the market; thereby denying all potential benefits for patients who are willing to accept the risks. Therefore, unpreventable ADRs are legally deemed to be no one's fault, and viewed as the unfortunate but necessary cost of scientific uncertainty (Lindpaintner, 2002). If you note that the criterion of accepting ADRs is the high level of certainty of the drug's benefits, this demonstrates how other risk assessments based on a beneficent or utilitarian basis are favoured over the minimal risk standard; i.e. where the benefits are apparent and there are no real alternatives (Giroux, 2005). However, since pharmacogenetics in drug development is still in its infancy with regard to marketable products, this premise is challenged by the perception of a condition of low certainty. Very few marketable benefits have been produced, which begs the question; why accept the risks? For example, in the regulation of stem cell research, a biotechnology which is also in its infancy, the use of embryos for research and therapy poses a problem for regulatory risk assessment. The basis of this 'problem' is the perceived moral value placed on embryos, fuelling the arguments about whether the research is ethical. The embryo used in research is a means to an end[19], which goes against deontological norms. This gives credence to a prohibitive stance to such research, which is further perpetuated by the fact that the

[19] The embryo is perceived as an actual or potential human being entitled to special protection, rather than as a pure biological entity. A key factor in accepting or rejecting this line of research.

'fruits' of this research are not currently accessible. However, allowances have been made for certain aspects of stem cell research, such as cell nucleus replacement, as there is an argument that this particular line of research is necessary as it is the only way to obtain knowledge about a disease.

The stem cell research scenario provides an example of an approach to formulating a decision about whether a line of research should be deemed 'necessary'. Decisions are made based on the strong consequentialist argument of the moral imperative to reduce human suffering (Holm, 2002). This illustrates how policy can be formed in areas where the following factors are in place: agreement about the value of the goal of research; scientific uncertainty about whether this research can achieve its goal; and disputes about the ethical evaluation of the research (Holm 2002, p.507).

Pharmacogenetic profiling of patients can be used as a potential risk assessment parameter; however, as genes do not act in isolation and drugs are often involved in complex metabolic pathways in the cell (before they are converted to active or inactive forms, which determine the drug's effectiveness and safety profile), unknown inherent risks will arise. Therefore, pharmaceutical products derived from pharmacogenetic technology will not lose their risk-producing profile. Furthermore, since the product potential has not been fully realised, the inherent uncertainties of this new technology may not be acceptable. In other words, it is difficult to apply the minimal risk standard to this technology due to the numerous

uncertainties. These are argued to be due to the 'nature'[20] of genetic information, and are apparent in the following areas of the minimal risk standard:

1) To the participant:
    a) The participant's rights:
        i) Entry into trial without fully informed consent - intentional non-disclosure due to the limitlessness timeframe and information which can be obtained from a tissue sample; whereby the research participant never fully receives the total 'picture' on what the research project is undertaking
        ii) Failure to act on a research participant's request to withdraw from the trial – due to anonymisation; it may be impossible to withdraw data since there are no traceable identifiers
        iii) Failure to protect the privacy of research participants - Further non-disclosures due to the controversy of revealing sensitive health information unbeknown to the subject, possibly to third parties
    b) To the research participant's safety:
        i) Hazards of intervention i.e. ADRs, expected and unexpected – due to polygenic effects of the drug
        ii) Likely risk/benefit ratio of the intervention(s) in the study population
        iii) Hazards of assessment methods (e.g. biopsy, x-ray).

[20] A 'nature' which is based on the 'uniqueness' of genetic information known as 'genetic exceptionalism', rather than the objective relations of this information among genomes, genes, individuals, persons and species (Ross 2001, Lazzarini 2001).

2) To the integrity of the trial:
    a) To the completion of the trial – recruitment and follow-up
    b) To the reliability of the results
        i) Study power
        ii) Major violation of eligibility criteria
        iii) Fraud
        iv) Randomisation procedure – may not be applicable due to increased predictability of the drug, or due to research participants with known genomic profiles for drug efficacy will be used. Unethical to have someone on placebo or a known lesser acting pharmacogenetic drug
        v) Outcome assessment
        vi) Other data – completeness and accuracy
        vii) Adherence to the protocol (Baigent, Harrell et al. 2008).

This illustrates that, with regard to the research participant, the minimal risk standard would be difficult to apply due to the implications of genetic information; therefore, it may not be an adequate form of risk assessment for this technology. Subsequently, another standard must be found; primarily, to satisfy regulatory quantitative measures. Such a standard should not necessarily be subjected to value judgements or intuition. The presence of these mental dispositions or attitudes, which are both unreliable and reliable, has led to various interpretations of the minimal risk standard and, in turn, the inconsistent application of ethical and regulatory assessment and subsequent approval.

3.5.2 Rawls's Reflective Equilibrium and Overlapping Consensus

Intuitions are mental dispositions that are considered reliable indicators of corresponding normative truths, or propositions about which mental states are correct or rational (Wedgwood 2006, p.70). As beliefs, intuitions differ from value judgements, which are evaluative beliefs based directly on emotions and due to this emotional aspect value judgements can be considered to be unreliable (Wedgwood 2006, p.78). In looking at intuition there is no way to distinguish between reliable and unreliable mental dispositions, but as beliefs, these mental dispositions can be revised by utilizing John Rawls's ' epistemological theory of reflective equilibrium' (Daniels, 1979). Reflective equilibrium is a process of mutual adjustment of principles and considered judgements. It is essentially a three-step process whereby one (1) identifies a group of considered judgments about justice, for example, (intuitions about justice that strike one as relatively secure, such as that slavery and religious persecution are unjust), (2) attempts to explain and justify these considered judgments by discovering what (relatively more abstract) principles of justice can serve as their foundation, and (3) addresses any lack of fit between the principles one has arrived at and considered judgments about justice other than the group from which one started. Rawls's notes that

'…it is an equilibrium because at last our principles and judgements coincide and it is reflective since we know to what principles our judgement conform and the premises of their derivation…'

(Rawls, 1999, p.20)

Through this approach, we collect as many intuitions as possible and fit them into a coherent systematic set of normative beliefs. These beliefs receive their outline from normative propositions that can be explained. Normative propositions, which cannot be explained, are rejected; thereby giving rise to a coherent overall set of normative beliefs. The rejecting of normative propositions is based on empirical psychological explanations, which cast doubts on the reliability of the proposition.

Reflective equilibrium succeeds if the initial intuitions are sufficiently reliable, and if further reflection on them would lead closer to the truth. Therefore, the approach seeks to stimulate coherence between moral judgements, principles and background theories, and takes into account the moral judgements of the agents involved in regulation; thereby leaving room for critical reflection on these judgements (van Zwart, 2010). This Rawlsian method does not focus on one single comprehensive doctrine to provide guidance for moral dilemmas, but seeks to find a balance between intuitions, general principles and theories. These considered intuitive judgements therefore, rest on factual inquiry, comparison of consequences, and mid-level rules, systematic derivation from general moral principles is excluded.

Rawls's 'overlapping consensus' is considered to be a less demanding development of reflective equilibrium. It is less demanding because individuals who take part in the process do not have to go through an exhaustive and searching process of reflection in order to test their judgements. The fact that they have reached agreement constitutes the principal test of their conclusions.

The idea of an overlapping consensus was to develop a concept of justice, which could be agreed by all, by recognising the permanent plurality of incompatible and irreconcilable moral frameworks (Doorn, Neelke 2010). Rawls's notes two main points about the idea;

The first

'...is that we look for a consensus of reasonable (as opposed to unreasonable or irrational) comprehensive doctrines...'

The second

'...the public conception of justice should be, so far as possible presented as independent of comprehensive religious, philosophical, and moral doctrines...' (Rawls, 2005, p.144).

How overlapping consensus could provide a way of moving towards a consensus on regulatory matters, about which we may be intuitively divergent as suggested in the next section, will be discussed in more detail in chapter six.

3.5.3 The Concept of Uncertainty in regulatory assessment

In the meantime, the presence of these mental dispositions has led to variability in regulatory assessment, as addressed previously. A variability that has arisen in the management and interpretation of the risk of harm, due to influences from the surrounding social and political environment. These differences, which have been magnified further due to the introduction of genomics in research, emphasise shifts in the language of scientific evaluation towards the weighing up of belief states, as stated in Herbert Gottweis's article *Governing genomics in the 21st century: between risk and uncertainty* (Gottweis, 2005b). This provides further

explanation on how governing styles have been influenced by the introduction of genomics; whereby the focus of human risk scenarios has shifted from one of concern for the external technological risks of genetic engineering for humans (i.e. are genetically modified organisms hazardous to humans), to the management of internal body risks through genetic technology (i.e. how can health risks be managed by genetics) (Gottweis 2005b, p.183).

Gottweis stated that this shift has given rise to the language of emotions, and a refocus from appealing to reason, to other levels of argumentation concerned with the language of compassion and empathy. As seen with patient advocacy groups and public inquiries, tools of 'compassion and empathy' are becoming standard policy instruments, which serve the purpose of linking genomics with society through a language of reflection.

This language of reflection is a tool used primarily in the political arena to convey uncertainties or lack of sureness. Uncertainty is encapsulated in the precautionary principle (meaning that it is concerned with holding back what cannot be assessed) (Gottweis 2005b, p.187), and emerges from situations of incomplete scientific information. With pharmacogenetics, the risks are inherently unknown because of the complex pathways of drug metabolism and gene interactions. Therefore, a standard based on the concept of uncertainty would be more appropriate for regulatory quantitative measurement, especially for pharmacogenetic-based drug development, because the concept of uncertainty is a prevalent feature of any new technology, and is more widespread than the concept of risk (Gottweis 2005b).

Uncertainty can be observed as minimising the importance of statistical and expert models of risk management and an absence of agreement, an example of which is cited in Gottweis's article, which notes the following effect of the utilization of uncertainty in policy for BSE[21]:

> *'…The effort to 'manage' the sensitive issue of BSE triggered a shift toward a new mode of governance, in which openness and transparency were key commitments. The British Food Standards Agency (FSA) was created following the BSE-crisis. It was designed to introduce elements of deliberative governance, transparency, openness, argumentation, reciprocity and authenticity in a concrete setting and to deal with widespread distrust in the existing procedures. The rise of new sites of policy-making also offered new opportunities to cultivate capacities for self-rule and generate multiple spaces within which self-rule can develop…'*
>
> (Gottweis 2005b, p.188)

Furthermore, Gottweis makes the comment that in genomic policing:

> *'…These[genomic] policies are presented as difficult decisions, which demand caution, deliberation and credibility, but also compassion; the decisions cannot be taken lightly, and they should only take place under the guidance of trustworthy people and institutions that command respect and authority. The style of these policies is decentralized; there is no centre for these new argumentative strategies that emerge in a variety of locations, from patient groups to government ministries…'*

[21] Bovine spongiform encephalopathy (BSE), known commonly as mad cow disease, is a fatal neurodegenerative disease (encephalopathy) in cattle that causes a spongy degeneration in the brain and spinal cord.

(Gottweis, 2005b, p.189).

In this context, uncertainty is articulated as emotional discourse, whereby emotions are a form of social action. This gives rise to the mobilisation of ethical expertise and governmental bodies, which employ a new genre of discourse that places emphasis on trust and proof of credibility.

Therefore, in using the concept of uncertainty to assess harm, we would be appealing to the essence of the precautionary principle, which speaks of society not waiting until it knows all of the answers before attempting to protect against significant harm. In employing the concept of uncertainty, we would be implying that the benefits of a technology are assumed to outweigh its risks; unless there is compelling evidence that serious harm would be done. The burden of proof would fall on those who believed that the technology was unsafe, implying that the test options selected would highlight the benefits of the technology rather than the hazards. Consequently, if we are looking to perform pharmacogenetic-based clinical trials with poorly understood consequences - and we have no more than quantitative outcome estimates - we should perhaps be circumspect about these trials. There is a possibility of them generating conditions with no precedent in the natural universe.

3.6 Conclusion

This chapter has established that the introduction of genomics in governance has given rise to the general public and industry shaping genomics-related policy-making. This has led to the entrenchment of a global (or at least a super-national) system of regulating the potential risks

connected to such new technology; hereby, such regulation is based on the minimal risk of harm in research projects. This is a precautionary approach, and could be restricting for the development of this technology. Furthermore, this category of risk management, despite being perceived as calculable, has been demonstrated as being value driven or influenced by belief states. Moreover, this has yielded variability in regulation and interpretation. However, the presence of these value-laden risk perceptions have presented considerations as to whether they should be taken into account when setting up robust regulatory mechanisms, especially in the assessment of genomic technologies such as pharmacogenetic drug development regulation.

In examining an example of a risk-assessment methodology, such as the minimal risk standard, it was found to be inadequate for providing information on what ought to be done in research involving pharmacogenetic information. However, as a methodology based on 'measurement of utility', it does provide facts that indicate in what we should believe. Indeed, since it has been established that the risks are still present but are inherently unknown in pharmacogenetic research outcomes, attention has been paid to the perspective that uncertainty is a prevalent concept in this type of research. Subsequently, risks still need to be assessed for pharmacogenetic-based clinical trials. However, in a way, that allows the selection of moral test options or features for regulatory assessment, thereby highlighting the benefits of this technology, rather than the hazards. A possible test option for consideration is Rawls's 'overlapping consensus' a procedural development of 'reflective equilibrium', since it contemplates certain aspects of mental dispositions. A further reason for considering Rawls's approach is that its presence in governance as overlapping consensus would encourage agents

to consider the benefits of this technology, by providing a platform for the adequate balancing of benefits against hazards. Furthermore, by appealing to the concept of uncertainty through overlapping consensus, we would again focus on the benefits of a technology rather than the risks; unless there is compelling evidence that serious harm could be done. Those who believed that the technology was unsafe would have to tackle the burden of proof, and this would help to establish credibility and trustworthiness in research governance, rather than governance resorting to a defensive stance.

4. Chapter Four: The Ethical Implications of Pharmacogenetic Drug Development

4.1 Introduction

Before I introduce the argument concerning the ethical issues that are apparent in pharmacogenetic drug development, further information will be provided about what is pharmacogenetics, and why there is an interest in this biotechnology. Therefore, section 4.2 will address the need for an agreed definition of pharmacogenetics, in order to clarify the aims of this biotechnology to relevant agents, and minimise the misconceptions of its role in drug development. Section 4.3 will establish the benefits of this biotechnology to particular agents (such as the patient and industry), focusing on the possible motivations and interests of these agents which could affect research governance. Section 4.4 will address how pharmacogenetics is integrated into the drug development process, particularly in the area of the clinical trial (an area of research which utilises human participants). Information in this section will highlight how pharmacogenetic tests in drug development are only concerned with drug-related genetic variations, and not specific disease genes. This in turn will contribute to the general argument in the latter half of this chapter, which looks at why results from pharmacogenetic testing do not have the same ethical concerns for informed consent, privacy and confidentiality as genetic tests relating to susceptibility genes or carrier status. My argument here will be concerned with how ethical issues which arise from risk assessment pharmacogenetics occur due to the fact that the outcomes of pharmacogenetics (i.e. drugs) give rise to ethical issues that operate at a general level. In other words, pharmacogenetics introduces a new domain of information (Møldrup 2002, p.34). As noted in the preceding

chapter, the concept of information (in this case genetic information) puts forth potential ethical issues concerned with informed consent, privacy and confidentiality, due to the 'public' nature of this information (Gostin, 1995) . In the latter half of this chapter, it will be argued that this premise is true only when pharmacogenetics is employed in the same way as a genetic screening tool for disease susceptibility. This section will also address the argument that pharmacogenetic's ethical concerns are more attributed to matters of justice, especially when pharmacogenetics is employed as a risk assessment tool.

Section 4.5 will debate the oft cited ethical issues concerned with informed consent, privacy, confidentiality and discrimination, which have been attributed to pharmacogenetics in the literature. This will lead to further discussions on the relevant ethical implications of drug development outcomes when pharmacogenetics is utilised in clinical trials. I will term these ethical implications as actual, to distinguish them from perceived claims for the purpose of this discourse. In this section, it will be argued that the apparent ethical issues are a result of the stratification of the research participant population into genetic groups, giving rise to ethical issues concerned with the equitable distribution of research knowledge and research priorities, rather than inferences of disease knowledge as implied by concerns regarding privacy and confidentiality.

To address this argument, this section will discuss the ethical implications of concern in the following areas. These areas have been highlighted in pharmacogenetic-specific research governance guidelines, such as the position paper on terminology in pharmacogenetics by the

Committee for Medicinal Products for Human Use (CHMP)[22] (CPMP, 2002), and the report *Pharmacogenetics: ethical issues*, by the Nuffield Council on Bioethics (Nuffield Council on Bioethics, 2003), which will be discussed further in chapter five.

- Research prioritisation – the targeting of disease areas, which have a high economic return as opposed to societal need.
- Division of patients into sub-groups – due to genetic profiling, giving rise to stratification of the patient population according to genotype. This ushers in the aspect of 'orphan' populations (groups of patients with a rare genetic profile where there is no drug available), and the possibility of entrenching further existing inequalities in healthcare based on race or ethnicity.
- Clinical trials and the returning of genetic information – potential misuse and misunderstanding of the clinical relevance, scientific validity and clarity of this information by the research participant, as well as international research programs. These create concerns surrounding the distribution of research outcomes between rich and poor countries.

The analysis of the actual ethical issues that arise with this biotechnology will contribute to the thesis by enabling the development of an appropriate ethical framework for research policy, or at least appropriate moral points to consider. It will be argued that moral guidelines should still be based on the Principlism framework but with the principle of justice specified preferably by

[22] When the CHMP was formerly the Committee for Proprietary Medicinal Products (CPMP)

an egalitarian Justice model such as Rawls's , and that such an ethical framework should recognise the pursuit of the common good.

This discourse will introduce the argument that ethical issues arising from pharmacogenetic interventions in drug development are more concerned with the fair distribution of pharmacogenetic outcomes (such as drugs), and are therefore a matter of justice and not autonomy. It will also introduce the argument that pharmacogenetic tests in drug development are only concerned with drug-related genetic variations in genes, and not with genes which determine specific diseases, as noted with clinical genetic testing. From this, the central argument of the inadequacy of the current ethical guidance gained from Principlism will become apparent.

4.2 A Definition of Pharmacogenetics

Pharmacogenetics is generally known as the study of inter-individual variations in DNA sequences related to drug responses; its role in drug development is to create less hazardous drug treatments, and find new drug treatments. This section will address the requirement for a recognised definition of pharmacogenetics, as a definition of pharmacogenetic terminology is apparently yet to be universally clarified.

An attempt was made by the EMEA, which proposed the following terminologies for usage in clinical trials (CPMP, 2002):

Pharmacogenetics is the study of inter-individual variations in DNA sequence related to drug response.

Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development.

These initial definitions were proposed to facilitate communication between regulatory authorities, ethics committees, investigators, and research participants, and have been fully adopted by the prominent UK policy initiative, *Pharmacogenetics: Ethical Issues* by the Nuffield Council of Bioethics Nuffield (Nuffield Council on Bioethics, 2003). This will be discussed further in chapter five. This policy document has greatly contributed to establishing the current ethical view of pharmacogenetic's role in clinical trials. Since this initiative, the following further definitions of pharmacogenetics and pharmacogenomics have been put forth, again with regard to clinical trials (European Medicines Agency (EMEA) 2007):

Pharmacogenetics (PGt) is a subset of pharmacogenomics (PGx) and is defined as:
The study of variations in DNA sequence as related to drug response.

Pharmacogenomics (PGx) is defined as:
The study of variations of DNA and RNA characteristics as related to drug response.

These definitions have been adopted by the U.S. Department of Health and Human Services Food and Drug Administration (FDA), and are encapsulated in Good Clinical Practice (GCP) guidelines (Food and Drug Administration (FDA), 2008). However, only those agents (namely the industry and regulators) who have knowledge of and follow GCP know of these definitions. Outside of industry and regulatory bodies, there is still no universally accepted definition. Instead, the terms pharmacogenetics and pharmacogenomics tend to be used interchangeably. Despite this situation, there is emerging consensus on the differences between the two terms as follows:

- *Pharmacogenetics*
    - Differential effects of a drug – in vivo – in different patients, dependent on the presence of inherited gene variants.
    - Assessed primarily genetic (SNP)[23] and genomic (expression[24]) approaches.
    - A concept to provide more patient/disease-specific health care.
    - *One drug-many genomes (i.e. different patients)*
    - *Focus: patient variability*

- *Pharmacogenomics*
    - Differential effects of compounds – in vivo or in vitro – on gene expression, among the entirety of expressed genes.
    - Assessed by expression profiling.

[23] The single nucleotide polymorphisms (SNPs) are a specific pair of nucleotides observed at a single polymorphic site. They are considered as 'tools' which indicate sites on the genome where variability occurs.
[24] Genomic expression approaches concerned with disease targeting not disease susceptibility

- A tool for compound selection/drug discovery.
- *Many "drugs" (i.e., early-stage compounds) – one genome [i.e., "normative" genome (database, technology platform)]*
- *Focus: compound variability* (Lindpaintner, 2002).

An accepted definition of terms would help to cement an understanding of this biotechnology in drug development for all. Such a consensus between these terms is further substantiated by the industry, which tends to use the following working definitions:

'...pharmacogenetics refers to people including gene identification and "right medicine for the right patient". Pharmacogenomics refers to the application of tools including, but not limited to, the functional genomics toolbox of differential gene expression, proteomics, yeast two-hybrid analyses, tissue immuno- and histopathology, etc...'(Roses, 2000)

Nonetheless, this follows the initial CHMP (CPMP, 2002) definitions – which will also be discussed further in chapter five. These have formed the basis of prominent policy guidance documents for industry and regulatory bodies' definitions, and hold up quite well with the above consensus:

<u>Pharmacogenetics definition</u>

- CHMP; inter-individual variability
- General Consensus; focus on patient variability

Pharmacogenomics definition

- CHMP; variability of expression of individual genes in drug response.
- General Consensus; focus on drug effects on gene expression.

Consequently, these definitions will be utilised throughout this thesis, especially as neither term has a definitive definition. The term pharmacogenetics will be the pejorative term as it is considered to be the primary 'tool' of pharmacogenomics.

I note that the advantage of having a clear definition of what pharmacogenetics is will contribute to the clarification of the actual ethical impact of this biotechnology on drug development. Furthermore, in highlighting an actual workable definition, and the apparent ethical issues of pharmacogenetics, the focus would fall on pharmacogenetic's true aim of revealing a drugs' effect on gene expression. This would allow a better understanding from governing bodies of the remit of pharmacogenetics in research protocols.

4.3 Why the interest in Pharmacogenetics?

The potentially positive outcomes of improved drug safety and efficacy (as advocated by the industry) have attracted great interest from the media and public. In this section, the use of pharmacogenetics in producing safer and more efficacious drugs (and the central aim of pharmacogenetics, which is the minimizing of undesirable medical effects) will be addressed. This section will cover what the 'promises' are to the agents concerned, such as the public and industry, and the potential implications of these promises to research governance. Promises are, for industry, concerned with decreased drug development costs due to the streamlining of

clinical trials, and the resurrecting of drug compounds which were abandoned because of their safety profile. As an aside, this means further financial benefits to the health service, due to less wastage in drug prescribing, and the avoidance of the clinical consequences of detrimental drug effects.

4.3.1 Promises for the patient

A drug is rarely effective and safe for all patients. A physician has to determine the dose of a drug by compromising between 'not being too high' and 'not being too low'. This variability has been shown to be an important (if not a leading) indicator of therapeutic failure, and a major risk factor represented by an adverse drug reaction (ADR) in individuals or a subpopulation of patients. So what are ADR's? An ADR is the consequence of a variety of factors, including the inherent pharmacological action of the drug, patient physiology, inappropriate prescribing and poor patient compliance. An ADR, as defined by the World Health Organisation (WHO):

'...in the general medical and pharmacological fields, denotes a toxic physical or (less commonly) psychological reaction to a therapeutic agent. The reaction may be predictable, or allergic or idiosyncratic (unpredictable).In the context of substance use, the term includes unpleasant psychological or physical reactions to drug taking...' (Babor, Campbell et al. 1994)

The ADR is seen as a major problem in drug development and clinical practice (Meyer, 2002) and in the US, serious adverse drug reactions are noted to be the fourth and sixth leading

causes of death in hospital patients (Lazarou, Pomeranz et al. 1998). In the UK, it has been estimated that approximately 7% of patients are affected by ADRs, and one in ten of all NHS bed days are used by patients with ADRs, costing approximately £380 million a year. In cancer chemotherapy, ADRs are estimated to increase overall hospital costs by 1.9% and drug costs by 15% (Marsh, McLeod 2004). Furthermore, the drugs most frequently associated with ADRs are diuretics, opioid analgesics, and anticoagulants. In conclusion, approximately one in seven hospital in-patients experience an ADR, which is a significant cause of morbidity, increasing the length of the stay of patients by an average of 0.25 days per patient admission episode (Davies, Green et al. 2009). These figures highlight that the current regimen of 'one dose fits all' may not be ideal for patients, or cost effective for the health service.

Until the thalidomide disaster focused the attention of governments and doctors on what produces ADRs to drug treatment, research into what caused ADRs was predominately concerned with epidemiology, and the mechanisms involved in producing ADRs to various medications. This resulted in the notion that ADRs were caused by the interaction of both environmental and genetic influences (Meyer, 2002). Today, however, the focus is on genetic factors, and how these factors explain the predisposition of certain individuals to developing ADRs to drugs, rather than from environmental influences.

Therefore, ADRs are an indication of the effectiveness of drug therapy. Still, it must not be forgotten that other factors could also produce lack of drug efficacy in an individual patient, such as the nature of the disease (e.g. an infective microorganism, which is resistant to a prescribed antibiotic). Furthermore, factors such as the inherent pharmacological action of the

drug, patient physiology, inappropriate prescribing and poor patient compliance may contribute to an unsatisfactory outcome of drug therapy. Despite these factors, there sometimes remains no clear reason as to why in some patients, conventional doses of appropriate medications are ineffective. This is where the expectations of pharmacogenetics come in. Pharmacogenetics provides a physician with the ability to determine the factor of the underlying genetic cause of variable responses. This in turn aids the accurate prescribing of the right drug to the right patient, at the right time. In order to enable this objective, pharmacogenetics must be integrated within the drug development process.

4.3.2 Promises for the Industry

For the industry, the 'promise' or expectation is the unique 'selling' point of pharmacogenetics potential 'candidate gene approach' to discovering novel targets, which are protein products not necessarily concerned with disease risk that can be used as drug targets. These targets are then used as molecular diagnostic tools (a type of risk assessment testing) to individualise and optimise drug therapy, eventually replacing the 'one-size-fits-all' paradigm of current clinical practice and drug development. Medicines arising from this risk assessment testing would give rise to medicines for subsets of patients based upon their pharmacogenetics – the concept of personalised medicine (Christensen, 2002). A prediction that each of us may one day have a bar code that identifies our genotype (which would help with healthcare decisions) has ushered in the 'designer drug' concept in pharmacogenetics (Koch, 2012).

Another possible advantage is that pharmacogenetics offers the opportunity for the streamlining of the drug development process. At present, it costs approximately $800 million

to develop a new drug, and up to 15 years to get from target identification to regulatory approval. 75 per cent of this cost can be attributed to target failures[25] along the way, but with the introduction of genomics i.e. pharmacogenetics and pharmacogenomics, this amount could be reduced to $500 million, with approximately 15 per cent of time saved (Tollman, Guy et al. 2001).

Also, the selecting and recruiting of participants by genotype could increase the success of clinical trials (Alcalde, Rothstein 2002). Usually, research participants are categorized by their race and ethnicity, but such an approach has come under criticism due to questions regarding the validity and appropriateness of race-based categorisation in research, especially when race is considered a social and not a biological construct (Rothstein, Epps 2001). This point will be discussed in section 4.6, along with the implications of the use of 'race' in research initiatives.

The approach of pharmacogenetics to pharmaceutical research creates the idea of a bright future for medicine, with the creation of drugs which are safer and more effective. Developments in pharmacogenetics have focused on how individual genotypes[26] may impact on drug metabolism, response, adverse effects and clinical outcome. These developments have shown that pharmacogenetics may have a substantial impact on the drug development process; particularly the following areas, which will now be briefly addressed: (1) drug safety, (2) market segmentation, (3) differentiation and (4) the concept of personalised medicine.

[25] The late attrition in drug development of drugs which have been found to have intolerable or unacceptable risk profiles.
[26] Genotype – a sequence of nucleotide pair(s) found at one or more polymorphic sites in a locus (location on the chromosome or DNA molecule corresponding to a gene or physical or phenotypic feature) on a pair of homologous chromosomes (chromosomes derived from father and mother) in an individual.

Drug Safety

It is perceived that the use of pharmacogenetic techniques will prevent or limit adverse events by preventing drug exposure to affected genetically defined subgroups. This could affect drug development in two ways. Firstly, by rescuing drugs from unmarketable status which have created adverse drug reactions (ADRs), and whose dose-related toxicity is linked to a genetic variant in a drug metabolising enzyme

In such instances, diagnostic screening tests could be developed to identify patients who are at risk of particular ADRs. For these patients, the drug would then not be given, or would at least be prescribed at an altered dose, thereby remaining a therapeutic option in low risk groups (Ginsburg, Konstance et al. 2005). Secondly, pharmacogenetic assessment could be used in the post marketing of drugs to assess safety issues. Currently, once a drug has been marketed, physicians report possible ADRs to the manufacturer or the regulatory authority (MHRA, 2010c) (via the Yellow card scheme in the UK)[27]. However, this scheme is susceptible to underreporting, thereby delaying the recognition of ADRs of a drug (Holtzman, 2003).

Market segmentation

Current medical practice bases disease recognition on a collection of clinical signs and symptoms i.e. clinical phenotype, which is very subjective and incurs a high level of inaccuracy. Yet, our understandings of disease processes are increasing, due to causative biological systems (for example, we know that hypertension is the outcome of underlying

[27] The Yellow card scheme is run by the Committee on Safety of Medicines (CSM) and the Medicines and Healthcare products Regulatory Agency (MHRA) - a government agency which is responsible for ensuring the efficacy and safety of medicines and medical devices. The scheme is used to collect information from health professionals and patients on suspected adverse drug reactions (ADRs).

pathophysiologic mechanisms such as sodium re-absorption or rennin-angiotensin system). The industry could produce pharmacogenetic-based drugs, which target these underlying processes rather than the clinical phenotype. The financial implications of such a strategy will not be discussed here, but suffice to say, it has its critics, who are worried that the implications of segmentation could cause a reduction in sales and revenue (Christensen 2002, Tollman, Guy et al. 2001, Ginsburg, Konstance et al., 2005) (Pharmacogenomics-based drugs give hope to pharma industry. 2008), due to the costs of research and development. However, a smaller market based on identifiable patients likely to respond to a drug, together with decreased costs in drug development, would potentially (Ginsburg, Konstance et al. 2005, p.2333):

i. Increase the rate of adoption of the drug.
ii. Identify further patients who would not have been candidates for the drug but were tested positive.
iii. Increase drug compliance due to improved efficacy.

Differentiation

Pharmacogenetics challenges the current pharmaceutical industry 'block buster' business approach model. This model targets therapies to the broadest population that might benefit, relying on statistical analysis of this population's response to predict therapeutic outcomes in individual patients. Block buster's being medicines with peak annual sales in excess of 800 million GBP and usually address the general population or large subsets of it. This model encourages the 'me too' (drugs which are chemically related to the prototype) product, which have the advantage of rapid development and improved clinical benefits over the original

drug, giving rise to market exclusivity. With pharmacogenetics, companies would have a broader product portfolio with smaller drug brands, rather than the blockbuster approach (Service, 2004). Products would be clearly differentiated by specific genotype, thereby providing a sustained competitive advantage. Rather than the current situation of not-so-innovative me-too drugs, which are developed based on the argument that these drugs offer an improvement on the efficacy of the prototype, Pharmacogenetic-based drugs would show different qualities mainly due to different profiles of adverse effects, and would be effective in patients resistant to the prototype, also they would improve compliance in long-term treatment, and potentially be less expensive than the prototype (Garattini, 1997).

The Concept of Personalised Medicine

Currently, drug therapy is targeted to the broadest patient population. Patient groups are considered to be homogenous, and are treated as such, regardless of potential disparities in drug response. At present, pharmacogenetics has focused on the monogenic (single gene) traits of the genetic polymorphisms[28] that influence drug metabolism. This current state of one-drug-one-gene will eventually develop into one in which multiple genetic (polygenic) determinants of drugs effects will be defined and used to individualise drug therapy.

Pharmacogenetics' potential is in discovering novel targets that can fall into two categories: those that identify disease–related genes, and those that are protein products that can be used as drug targets. For drug development, the latter category is of prime importance. However,

[28] Genetic polymorphisms - DNA sequence variations on the human genome

both these targets could be used as molecular diagnostic tools to individualise and optimise drug therapy, eventually replacing the 'one-size-fits-all' paradigm of current clinical practice, and thereby creating the concept of personalised medicine for subsets of patients, based upon their pharmacogenetics.

Therefore, pharmacogenetics has attracted great interest and expectation due to its 'promises' of improved drug safety and efficacy. This represents a big benefit for the public as a whole, as well as industry, due to the health-economic implications of pharmacogenetics. However, despite these benefits, the development of pharmacogenetic tests for existing drugs or new drug compounds is currently quite slow (Garrison Jr, Austin 2006), but is on the increase (Shin, Kayser et al. 2009). The reason for this is not entirely due to the ethical implications of this biotechnology (which will be covered later in this chapter), but is also because of industry perceptions of poor financial viability due to market fragmentation and litigation concerns from unforeseen detrimental medical occurrences (Cuticchia, 2009).

4.4 Drug Development and Clinical Trials

As previously mentioned, the industry's interest in pharmacogenetics is for developing new-targeted therapies (personalised medicine), the development of diagnostic tests to already licensed medicines (i.e. genotyping patients before treatment), and improving the process of drug discovery and development. This section will discuss the latter application of pharmacogenetics in the drug development processes, particularly in the area of the clinical trial. The intention of this information is not just to provide background for pharmacogenetic's actual role in drug development, but to shed light on why information from pharmacogenetic

testing does not have the same implications for privacy, confidentiality and discrimination as genetic tests relating to susceptibility genes or carrier status. This section will illustrate how pharmacogenetic tests are only concerned with drug-related genetic variations and not specific disease genes, and how the genetic testing aspect of pharmacogenetics has led to misconceptions of its actual function.

A traditional clinical trial programme with any new drug passes through the following four main strategic phases which begin after drug discovery (pre-clinical research), and continue until market approval (usually after phase III):

- **Phase I:** Initial safety trials on a new medicine. An attempt is made to establish the dose range tolerated by healthy volunteers for single and for multiple doses. Phase I trials are sometimes conducted in severely ill patients (e.g. in the field of cancer) or in less ill patients when pharmacokinetic issues are addressed (e.g. metabolism of a new antiepileptic medicine in stable epileptic patients whose microsomal liver enzymes have been induced by other antiepileptic medicines).
- **Phase IIa:** Pilot clinical trials to evaluate efficacy (and safety) in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented.
- **Phase IIb**, sometimes referred to as pivotal trials, which are well controlled trials to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent the most rigorous demonstration of a medicine's efficacy.

- **Phase IIIa**: Trials conducted after efficacy of the medicine is demonstrated, but prior to regulatory submission for drug approval. Clinical trials are conducted in patient populations for which the medicine is eventually intended. Phase IIIa clinical trials generate additional data on both safety and efficacy in relatively large numbers of patients, in both controlled and uncontrolled trials. These trials often provide much of the information needed for the package insert and labelling of the medicine.
- **Phase IIIb**: Clinical trials conducted after regulatory submission of a new drug application (NDA) for the US, for example, or other dossier, but prior to the medicine's approval and launch.
- **Phase IV:** Studies or trials conducted after a medicine is marketed to provide additional details about the medicine's efficacy or safety profile. Different formulations, dosages, durations of treatment, medicine interactions, and other medicine comparisons may be evaluated. New age groups, and other types of patients can be studied. Detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors are an important aspect of many Phase IV studies. If a marketed medicine is to be evaluated for another or new indications, then those clinical trials are considered Phase II clinical trials.

In general, pharmacogenetic testing is integrated into the earlier phases of drug development such as Phase I and II, to assess the effect of genetic variation. It is used to ensure that research groups contain a balance of relevant genotypes, and that the later phases of trials, such as Phase III and Phase IV, can be targeted to good responders. As a risk assessment tool,

it is concerned with genes that code for proteins that modulate the following processes[29], which are known to vary in a population or individual (McCarthy, 2000):

- amount and rate of medicine absorption
- rate of drug metabolism and elimination
- drug concentration at the drug target
- variation at the drug target, e.g. differences in the number of receptors or receptor morphology
- second messenger mechanisms[30]

These variations have an effect on an individual's response to a medicine, and are attributed to single nucleotide polymorphisms (SNP) profiles (a form of genome variation). These SNPs correlate to a specific response to a treatment, as identified in Phase II trials. They help with selecting research participants most likely to benefit from the treatment in Phase III trials, thereby allowing typically large Phase III studies to be smaller and more efficient (Shi, Bleavins et al., 2001).

4.4.1 Pharmacogenetics: a risk assessment tool

As noted in the previous section, pharmacogenetics is used to exclude drugs where there is a wide variation in response according to common genotypes. Its application is as a stratification

[29] Otherwise known as the drug pharmacodynamics which are concerned with the desired effects of a drug i.e. whether someone responds or not; and the drug pharmacokinetics, which are concerned with the course of the drug from intake to elimination

[30] Molecules that relay signals from receptors on the cell surface to target molecules inside the cell, in the cytoplasm or nucleus (e.g. Adrenaline).

tool, argued to be not dissimilar to other laboratory tools or tests, such as drug concentration monitoring and liver enzyme analysis. Moreover, these are tests which provide information directly related to a participant's likely response to a specific medicine (Renegar, Rieser et al, 2001).

With the introduction of pharmacogenetics in phase I clinical trials, dose escalation could be performed separately on cohorts of research participants of a relevant SNP. Phase II trials would determine the SNP profiles to be used to identify research participants who show efficacy for a particular drug, or even to identify adverse events. This tests the hypothesis that a certain polymorphism might result in greater efficacy and or less toxicity. Indeed, test populations of research participants would be categorised in order of respondents versus non-respondents, or tolerant versus intolerant patients. All such categories could be used to fathom a genetic signature that might be of use in future trials.

The use of these SNP profiles would lead to drug approval limited to patients of that SNP profile, giving rise to segmented drug markets which are based on stratification of patient groups, potentially defining some groups as 'untreatable' or 'difficult to treat'. This has brought forth the argument that pharmacogenetics ushers in new inequalities based on genetically defined groups, where potentially some groups could be screened out of the drug's development during Phase II, giving rise to an 'orphan population' (i.e. individuals with very rare disorders lacking in treatment options). However, orphan medicine legistration in Europe and the US has attempted to address such inequalities, and has encouraged pharmacogenetic based research and development in the orphan markets by providing incentives under the EU

Orphan Medicinal Products Regulation (141/2000) (Ceci, Felisi et al. 2002) and the US Orphan Drug Act (amended in 2005) (Grabowski, 2005) (Koch, 2012) .

Pharmacogenetic Phase III studies could confirm the hypotheses generated from Phase II trials, by utilising research participants who have been pre-screened and have a favourable predictive pharmacogenomic profile. This in turn will enrich the research population, thus avoiding those research participants with unfavourable pharmacogenomic profiles, and in effect allowing for a smaller, faster and less expensive trial. Furthermore, pharmacogenetic assessment could be used in Phase IV trials, in the post marketing setting of drugs, to assess safety issues. Here, patients who have received prescriptions could have blood spots stored on filter paper in an approved location. As ADRs are documented, DNA could be extracted from these blood spots for patients with particular drug-related ADRs, and compared with well-matched patients who took the drug but did not experience an ADR. The abbreviated SNP profile for these ADRs could then be added to the SNP profile of the drug to provide further information on efficacy (Roses, 2000).

As noted previously, pharmacogenetics has focused on the monogenic (single gene) traits of the genetic polymorphisms that influence drug metabolism. This current state of one-drug-one-gene will eventually develop into one in which multiple genetic (polygenic) determinants of drugs effects will be defined and used to individualise drug therapy. However, at the moment, this ‘one-gene-one-test’ situation has put pharmacogenetic analysis in the same class as genetic disease susceptibly testing, which is arguably inaccurate.

4.4.2 Pharmacogenetic analysis – A form of genetic disease susceptibility testing?

By discussing the validity of the argument regarding the pharmacogenetic test and the clinical genetic test having different ethical concerns, one can develop the antithesis that if pharmacogenetic genotyping does indeed become a medical diagnostic tool for the clinician, it may be subjected to the same ethical concerns as clinical genetic testing (van Delden, Bolt et al. 2004). To aid this argument, one needs to examine how misconceptions of the aims of pharmacogenetic analysis arose.

In current literature, there is a suggestion that breaches of privacy, confidentiality and discrimination are of equal ethical concern for both pharmacogenetics and clinical genetic testing (Rothstein, 2003). A possible reason for this may be due to the fact that both pharmacogenetics and clinical genetic testing use presymptomatic genotyping, and this application has well documented ethical concerns, including breaches of privacy, confidentiality and discrimination. However, it must be noted that pharmacogenetic (presymptomatic) genotyping is not primarily a diagnostic approach. It is performed to identify phenotypic variation in the reaction to therapeutic substances. This provides information about risk to adverse drug reactions, and the genetic information provided only highlights genetic characteristic information on the medicinal response. Therefore, no collateral information on family members concerning any genetic disease is made available. Nevertheless, this has been disputed on the basis that some of this genetic information is hereditary (Netzer, Biller-Andorno 2004).

Pharmacogenetic analysis does indeed require a form of genetic testing to help assist in both accurate risk/benefit outcomes of drug response, and increasing understandings of the molecular basis of disease. But, the main objective of genetic testing utilised in pharmacogenetics is to provide understandings of the probability or possibility of observing a specific therapeutic response of genes or genetic markers to a drug. This is in contrast to genetic testing for disease prognosis and diagnosis (disease genetic testing), the objective of which is to identify causative gene mutations or polymorphisms for disease susceptibility genes, which, although they alter the risk of disease, may have no effective interventions. Bearing these distinctions in mind, one would assume that any moral concerns arising from both pharmacogenetic analysis in drug development and disease genetic testing would be of a distinct nature or magnitude. However, from the literature that can be gathered, there are no distinct ethical concerns particularly attributed to the objectives of pharmacogenetic analysis, and as previously mentioned in this section and in chapter two, the ethical concerns attributed to disease-related genetic testing are mainly cited as follows:

- Possibility of discrimination and stigmatisation
- Loss of privacy
- Loss of confidentiality

Furthermore, a number of articles discuss pharmacogenetic analysis as a tool of potential in disease susceptibility testing (to be known henceforth as susceptibility testing) (CPMP 2002; Alcalde, Rothstein 2002; Garrison Jr, Austin 2006). But, genetic testing for disease susceptibility is also known as predictive genetic testing, and tests asymptomatic persons for

future health problems. In susceptibility testing, genetic material is analysed to identify particular mutations or polymorphisms that increase the probability of disease development. It is different from disease diagnostic testing, since it is used to identify risks in those without symptoms; disease diagnostic testing is used to confirm diagnosis in those who are ill. In susceptibility testing, biological variation is directly disease-related, and of pathological importance. The differential response to a drug is therefore related or matched to the presence or prominence of the pathological mechanism it targets in different patients, i.e. the molecular differential diagnosis of the patient. This implies that the drug is only appropriate for those patients who carry the clinical diagnosis, where the dominant molecular cause of contributing factors of the disease match the mechanism of action of the drug in question. For example, Herceptin (Trastuzumab), a humanised monoclonal antibody which acts against the HER-2-oncogene[31] Herceptin breast cancer treatment, is prescribed based on the level of HER-2 oncogene expression in the patient's tumour tissue, and patients with a high expression of HER-2 protein (her-2 oncogene) are prescribed the drug (Marsh, McLeod 2004). Differential diagnosis at this level provides a refined diagnosis, and a prerequisite for choosing the appropriate therapy (Christensen, 2002). This is an example of a genetic polymorphism influencing disease risk and drug response. An indication of the possible overlap of pharmacogenetics and disease genetics which gives rise to ethical implications for pharmacogenetics (Ginsburg, Konstance et al. 2005, Garrison Jr, Austin 2006, Burris, Gostin 2002) in identifying the target as the disease itself. But it must be noted that the target identified is only one of a number of contributing factors of the disease (which tends to be polygenic) and not necessarily the disease itself.

[31] Over expression of HER-2 oncogene, a breast cancer marker, is associated with rapid tumour growth, increased risk of recurrence after surgery, poor response to conventional chemotherapy and shortened survival.

Furthermore, the perceived overlap of genetic testing with pharmacogenetic analysis may be a factor in the misapprehension of what the actual ethical issues of this biotechnology are. As noted from Figure 1, which summarises how the phrase `genetic testing' is used as a general term to cover different types of genetic analysis (which actually have quite distinct ethical implications). This indicates that current policy for clinical trial regulations may be based only on the disease-orientated nature of genetic testing, and not on taking into account the risk assessment nature of genetic testing predominant in pharmacogenetic analysis.

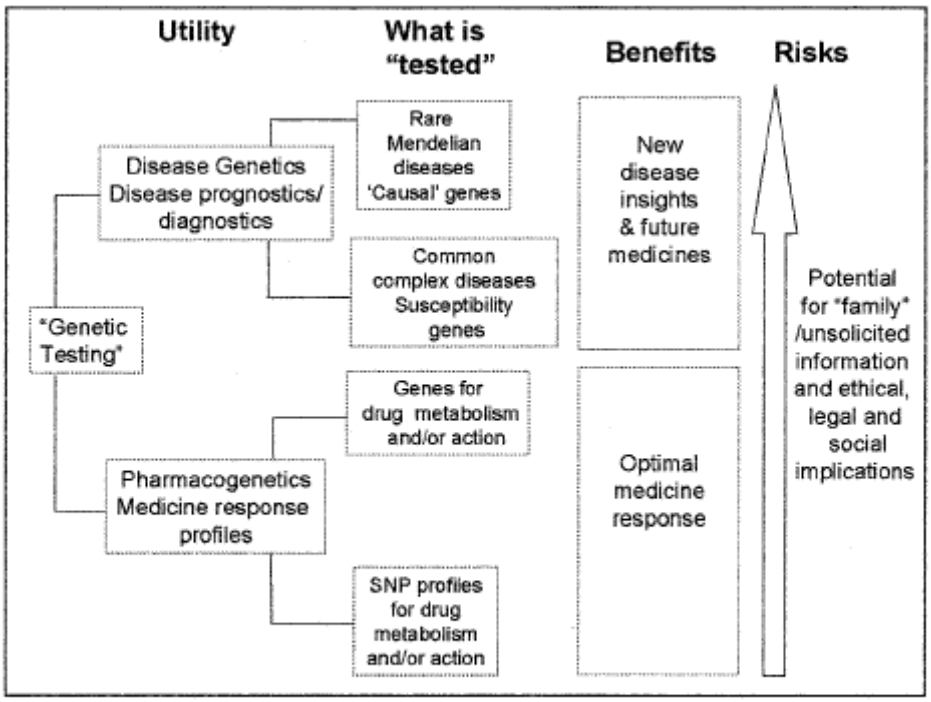

Figure 1; 'Genetic testing' is used in a number of different settings.
(McCarthy, 2000)

Clarity in the area of pharmacogenetic analysis has been sought by a number of policy guidelines, such as the CHMP guidelines on pharmacogenetics (CPMP, 2002), which gave us the CHMP working definitions for pharmacogenetics and pharmacogenomics (to be discussed

further in chapter five). In this policy, one of the aims was to distinguish pharmacogenetics from the area of genetic testing for disease, as well as to address the different levels of ethical concern apparent within pharmacogenetics analysis. The noted concerns centre on the fact that the outcomes of pharmacogenetics and pharmacogenomics, i.e. drugs, give rise to issues that operate at a general level. This differs from disease genetic testing outcomes, which tend to operate at a personal level, where the individual is the main focus. In other words, due to the therapeutic and genetic-specific nature of pharmacogenetic analysis, drugs based on pharmacogenetic information become public genetic information markers of an individual's genetic predisposition. Therefore, issues of stigmatisation, discrimination and fair distribution of pharmacogenetic benefits become more apparent.

So, the idea of pharmacogenetic testing being a form of genetic testing has contributed to the current confusion about pharmacogenetic testing in clinical trials. This has resulted in the incorrect categorisation of pharmacogenetic analysis in drug development research governance. The implication of this incorrect perception, I argue, is the misrepresentation of ethical issues for pharmacogenetics, which are concerned with pharmacogenetics as a tool for disease susceptibility testing, rather than as a risk assessment tool.

4.5 Perceived Ethical Issues

This section will analyse the oft-cited ethical issues for pharmacogenetics employed in drug development. These are ethical issues which are concerned with breaches of the principle of respect for autonomy in Principlism, such as informed consent, privacy and confidentiality. It is hoped that from these discussions, this thesis will illustrate that although breaches of the

principle of autonomy give rise to issues in the areas of informed consent, privacy and confidentiality, this is only apparent when the notion of the self is as the 'autonomous individual'; a concept which has given rise to a liberal, individualistic model of the self which is dominant in the rights-based morality of Principlism (Rhodes, 2010). However, this concept of the 'autonomous individual' is challenged by the fact that genetic information is not solely individual information, as disclosure of genetic information (indirect information) from an individual also exposes information about others with similar genetic profiles. Therefore, drug development pharmacogenetics provides 'indirect' information on the probability of observing a therapeutic response of genes to a particular drug, further substantiating that this is different to disease genetic testing, which provides direct information on disease susceptibility.

4.5.1 Issues of Informed consent

Informed consent—a concept that for decades has stood for the protection of individual choice regarding medical treatments or research—begins to break apart in pharmacogenetic drug development. The practical application of the principle of respect for autonomy is informed consent. Informed consent is important for providing reasonable assurance that a research participant has not been deceived or coerced into taking part in research. Ethical breaches of informed consent arise when genetic information or data is gathered and stored for testing purposes. Genetic data from tissue samples which are stored and utilised for future drug or genetically-based disease research are used for potentially a number of research purposes, many of which unrelated to the original purposes for which the data was gathered. Therefore, potential breaches of the following elements of informed consent become evident:

I. *Threshold Elements (Preconditions)*

1. Competence (to understand and decide)
2. Voluntariness (in deciding)

II. *Information Elements*

3. Disclosure (of material information)
4. Recommendation (of a plan)
5. Understanding (of 3. and 4.)

III. *Consent Elements*

6. Decision (in favour of a plan)
7. Authorisation (of the chosen plan)

(Beauchamp, Childress 2009, p.145)

From the *Threshold Elements,* the increased commercial value of human tissue and financial gain to be made in pharmacogenetics could potentially have undue influence on the cooperation of research participants. From the *Information Elements,* intentional non-disclosure due to the limitlessness timeframe and information, which can be obtained from a tissue sample, means that the research participant never fully receives the total 'picture' of what the research project is undertaking. Furthermore, how can a research participant be 'informed' of the risks and benefits of participation when scientists and clinicians themselves may not be aware of all the potential uses of the genetic information gathered? Also, an element crucial in any valid transaction is the understanding of that information; in other words, the manner and context in which the information is provided. This influences the

adequacy of understanding, and can be done by using appropriate terminology, presented in an unbiased manner, with encouraging questions for ascertaining what the research participant understands. However, the relative understanding in the scientific and medical community of the implications of pharmacogenetics research is still quite low, and information provision is lodged with industry, so the industry's perspective is by default put before participants in current pharmacogenetics research, which could be perceived as a bias.

Therefore, for the research participant involved in pharmacogenetic clinical trials, ethical issues arising from breaches of the elements of informed consent are apparent and still relate to the individual. However, protecting the individual is not the only consideration, since the research participant is no longer conceived as an individual existing in an isolated moment in time, but rather as a concrete historical person (Peterson-Iyer, 2008), whose genetic information will stretch forward in time and be of use to future others.

4.5.2 Issues of privacy

The use and consequent disclosure of genetic information has brought to the forefront issues concerning the protection of privacy. The concept of privacy has a number of definitions; in epistemology, privacy is defined as:

'...being known to, or knowable by, only one person…'

(Bullock, Trombley et al. 1999, p.686)

Defined as an ethical right, privacy is the ability to control who has access to us and to information about us, as well as our ability to create and maintain different sorts of social relationships with different people. In this context, social relationships are those being between two people such as relationships between friends, between husband and wife or even between an employer and employee (Rachels, 1975).

In a genetic context, it is defined as:

> *'...Limited access to a person, the right of an individual to be left alone, and the right to keep certain information from disclosure to other individuals…'*
>
> (Rothstein 2003, p.198)

This definition includes the right of an individual to decide to receive certain information from a third party, as well as to share information with others. Privacy defined in this context is concerned with keeping information safe, and is noted as a legal right.

Privacy is recognised in the Universal Declaration of Human Rights (Hulstead, Goldman, 2002), and is a constitutional foundation for the concept 'the right to know'. When individual 'A' is said to have a right to know about her own or somebody else's genetic constitution, this can mean at least three different things:

1. 'A' has no duty to remain ignorant.
2. Others have a duty not to interfere with 'A's' quest for information.

3. Somebody has a positive duty to assist ‘A’ in her quest for information (Häyry, Takala 2001).

Similarly, when individual ‘B’ is said to have a right not to know about his own or somebody else’s genetic constitution, this can mean that:

1. ‘B’ has no duty to know.
2. Others have a duty not to inform ‘B’ against his will.
3. Somebody has a positive duty to assist ‘B’ in remaining in ignorance.

The issue of a subject’s right to know (or not know) is linked in part to the concept of autonomy, since an element of disclosure is required, which is provided through informed consent. However, as previously mentioned, the function of informed consent in research involving genetic information is subject to breaches of this required disclosure, due to the controversy of revealing sensitive health information. Also, further breaches need to be considered in pharmacogenetics clinical trials, such as the limitlessness timeframe of information, which can be obtained from a tissue sample.

However, realistic expectations about the information pharmacogenetics provides must be paramount, as analysis of a broad set of genetic markers may only show that a genotypically-defined subgroup of patients with a certain disease have a higher probability of responding in a certain way to a certain drug. Therefore, pharmacogenetic analysis can be likened to the assessment of blood pressure, where raised blood pressure is an accepted risk factor for

cardiovascular disease, but does not imply that the patient will definitely suffer a specific cardiovascular event. This is also seen in genetic susceptibility testing. Individuals make requests for specific tests, believing that the tests will reveal their possible risk of developing a disease. For example, in Alzheimer's disease, individuals request tests for the polymorphisms APDE and PSI (gene for apolipoprotein and Presenilin respectively, whose presence indicates a risk of developing Alzheimer's disease). These tests are not predictive, and are currently limited to those who already have symptoms of dementia (Benner, Shobe 2003, p.259).

Therefore, the pharmacogenetic-based clinical trial provides information on risk, which is considered to be less than risks associated with genetic research for disease genes, due to the fact that patients already have the diagnosed disease at entry or already have an available drug for treatment. Moreover, the genetic information obtained is limited to the association between a gene, i.e. SNP, and reaction to a particular drug or class of drugs. It is used only for genotyping for inclusion to a trial, and is not applicable for research for new therapeutic targets. Hence, the overall risk is considered to be lower than genetic research for disease genes, but is perceived to be high due to the associations with genetic information.

4.5.3 Issues of confidentiality

Privacy has already been defined in the genetic context, as a right for certain information to be kept from disclosure to other individuals. Confidentiality is considered to be

'... the right of an individual to prevent re-disclosure of sensitive information that was disclosed originally in the confines of a confidential relationship...' (Rothstein 2003, p.198).

In looking at confidentiality issues, we are examining the issue of ownership, where it could be said that an individual owns their own genes (Chadwick, 1998). Such ownership calls into question the fact that genetic relatives share these genes, and this can further question an individual's right to confidentiality, especially where this information might affect the reproductive decisions of others. This interrelatedness is a platform for the involvement of communitarianism, a social philosophy that maintains that society should articulate what is good and in turn, should acknowledge the 'common good' by focusing on members of the larger community rather than the individual. However, since pharmacogenetic data in the drug development context does not provide collateral information, confidentiality should not be a major concern.

Principlism puts the individual in focus through the principle of respect for autonomy, in which breaches of Principlism are interpreted in terms of autonomy violations, bringing the language of individual rights to the fore. However, this individualism is challenged in genetic considerations, due to genetic information not being solely for the individual. Therefore, informed consent, privacy and confidentiality concerns are still apparent for pharmacogenetics, but only of the same magnitude as disease genetic testing when employed in the same way as a genetic screening tool for disease susceptibility. But it has been established that pharmacogenetics is employed as a tool in clinical research for risk assessment, and not disease susceptibility. Such risk assessment is more concerned with highlighting and conferring the benefits of the outcome of research. Therefore, the next section will show what pharmacogenetic's actual ethical issues are in relation to risk

assessment. It will be argued that these actual ethical issues are a matter of justice and not just autonomy, since they are concerned more with the fair distribution of research outcomes.

4.6 Actual Ethical Issues

In this section, I will argue that, due to the stratification of the research participant population into genetic groups, the apparent ethical issues in pharmacogenetic-based clinical trials are concerned with the equitable distribution of research knowledge and research priorities, rather than inference of disease knowledge (as implied by concerns regarding informed consent, privacy and confidentiality). In order to justify my argument, the following areas will be considered, which are of great importance in pharmacogenetic drug development: research prioritisation, division of patients into sub-groups and clinical trials, and the returning of genetic information. From such an analysis of the ethical implications of these areas, I will be able to analyse further if Principlism in its current execution in research governance is adequate.

4.6.1 Research prioritisation

I argue in this subsection that pharmacogenetics will create issues in research prioritisation if introduced into the current market-driven approach of drug development, as epitomised by the drug patent process. A governmental process which provides exclusive rights (sole production of the drug) to a holder for a designated period of time, typically 20 years. I claim that such an approach will lead to inequalities of access to pharmacogenetic outcomes between economically diverse nations and individuals.

As noted in section 4.4, the use of pharmacogenetics in drug development initially starts with the search for protein products that can act as drug targets, i.e. discovery genomics. But in discovery genomics, genomic identification does not provide information on a gene for a disease, but instead provides a collection of genes, which code for a protein that can act as a drug target. However, certain disease specific genes may also code for proteins which can act as drug targets, indicating the overlap between pharmacogenomics and disease genetics. It has been estimated that there are 10,000 novel protein targets for potential drugs (Hanke, 2000). If you consider that 500 targets have been discovered in the last 30 years from thousands of laboratories throughout the world, then to follow-up on this large number of protein targets would incur huge expense and immense operational efforts, especially if traditional clinical trial methods were used. Therefore, prioritisation of research becomes an issue when considering which diseases or genotypes to target first. From the 1393 new chemical entities marketed between 1975 and 1999, only 16 were for diseases such as tuberculosis, malaria, leishmaniasis, and trypanosomiasis, which affect millions of people each year in resource-poor settings with underdeveloped health care systems (Trouiller, Olliaro et al. 2002). Yet it is noted that 'frequently' occurring disease fields such as cancer and cardiovascular are producing the initial drug discoveries (Trouiller, Olliaro et al. 2002, p.2191). This is because these areas are able to recoup the development costs incurred from their target market, i.e. the industrialized world, where these diseases tend to be prevalent (Plump, Lum 2009). Nonetheless, with pharmacogenetic drug development, common genetic variants within an overall population will be the overarching fields of interest to industry, since they will be those which have the largest market potential.

Patent rights currently create a temporary monopoly for the inventor firms, enabling them to charge prices for their innovations that are many times higher than the marginal cost of production. These high returns are to recoup the incurred research and development (R&D) costs, and to further fund future R&D initiatives. However, two situations are conferred from this pricing strategy; firstly, patents tend to price some users out of the market and secondly, patents compel innovation-enabling drug companies to protect their investments in R&D (Outterson, 2009).

The patent system was set up to encourage innovation and knowledge for the benefit of society, by creating privacy rights to protect inventors from others using their innovations at no cost. However, it has encouraged the development of 'me-too' medicines - medicines with a low index of innovation (a drug that is structurally very similar to already known drugs, with only minor differences), that produce small health improvements in a large number of people, giving rise to better financial rewards than developing innovative medicines that produce major improvements in a smaller number of people (Oprea, Braunack-Mayer et al. 2009, p.311). This is due to the cost-effectiveness view of pharmaceutical research; where governance of health technology assessment usually involves an evaluation of the incremental cost-effectiveness of the new therapy, compared to alternative treatments for the disease in question. Therefore, patent rights, due to their financial attractiveness, are instrumental in the market failure of the undersupply of pharmaceutical innovations (Sonderholm, 2009a).

Moreover, the current patent system diverts industry research from the health needs of low-income countries, whose economies cannot secure sufficient financial returns, to recoup

industry investment in the research. This impedes both health gains and economic development for both low-income and high-income countries, due to the subordination of global and national health and economic needs to commercial interests. This is expressed as the competition in the market between companies attaining high market shares for their products via the registration of patents in different global jurisdictions, fostering a low market incentive to develop innovative, effective and affordable drugs.

Therefore, the current prioritizing of research is based on the measurement of payback of the research, burden of the disease or technology, and estimate of welfare losses (Claxton, Sculpher 2006). However, such a market-driven logic in R&D which considers research as a means for changing clinical practice needs to be shifted towards a needs-driven logic, based on societal value. Research based on societal value would promote research committed to the common good.

So, the private sector must do more. There is currently an imbalance between private-sector rights and obligations under international agreements. The public sector—i.e. the main buyer of pharmaceuticals—provides the private sector with patent incentives for innovation, but has little say over the research agenda (as discussed in Section 3.4), which highlights that the field of drug development is more of a technocratic discipline with little or no input from public bodies. A neglected-disease research obligation would require industry to reinvest a percentage of pharmaceutical sales into neglected disease research and development, either

directly or through public programmes, such as a global fund, which will be critiqued further in chapter six.

Therefore research outcomes such as drugs would be ethically reviewed by governance in light of how they contribute to social responsibility, with a focus on promoting health and economic freedom and avoiding discrimination. This would contribute to the promotion of collective health and economic rights in all countries through the recognition of global social justice, which has yet to occur within the current system of just providing humanitarian assistance to vulnerable countries.

4.6.2 Division of patients into sub-groups

As noted in section 4.3, the pharmacogenetic profiling of drugs has the potential to produce orphan populations or sub-groups. I will argue in this subsection whether pharmacogenetics would further entrench existing patterns of inequality and discrimination i.e. increase social risk, and whether this would be morally permissible. Furthermore, the meaning of 'race' in research will be discussed, since this concept epitomizes the injustices of inequality and discrimination, which threaten to burden this research.

With personalised medicine, research participants would be chosen according to genetic makeup for a clinical trial. However, as noted in the previous sub-section, industry will target common genetic variants within an overall population, since they have the largest market potential. From such stratification, there will always be a sub-group or 'orphan population' (a patient group with a rare genetic profile where there is currently no pharmacogenetic-based

drug available) due to this target group being too small and therefore considered non-profitable in the current market climate[32]. For this group, the bulk traditional drug available would be prescribed.

Due to this aspect of subdivision of the patient population, the development of pharmacogenetic based drugs has been noted to be analogous to the development of orphan drugs[33], where it is envisaged that appropriate policies for pharmacogenetics would be realised from the understanding of the characteristics of the economic and policy impact of orphan drugs (Boon, Moors 2008). In the introduction of the *Orphan Drug Act 1983* (US) and the *EU Orphan Drug Regulation 2000*, orphan drugs had the beneficial effect of allowing faster approvals of these drugs to the market, due to the registration of such drugs being based on reduced clinical trial sizes, the acknowledgement of the life-threatening nature of these diseases and the lack of alternative effective treatments. Such a realisation of these factors would contribute to alleviation of the issue of equity of access to pharmacogenetic-based drugs. This would aid the development of smaller economical markets and therefore increase pricing to recoup R&D costs (van Delden, Bolt et al. 2004, p.312; Smart, Martin et al. 2004, p.328). Furthermore, if pharmacogenetics leads to more efficient clinical trials, as noted in Section 4.4, then it is foreseen that lower development costs would be expected; hence, an overall decrease in pricing, especially if the current patenting system was reviewed in line

[32] Assumptions are made if the drug is developed according to the current patenting system.
[33] Orphan drugs are medicinal products for rare diseases which are defined as life-threatening or chronically debilitating such as cystic fibrosis and phenylketonuria, which affect less than 2000 individuals in a given population (Europe US). They are labelled as "orphan" because drug companies are not interested in 'adopting' them as markets for new products.

with this pharmacogenetic expectation. As stated by Steve Burrill, CEO of Burrill & Co (a private merchant bank focused exclusively on life sciences companies):

> *'People used to equate rare diseases with small markets and small margins…But small markets don't necessarily translate to poor economics.*
>
> (Goodman, 2001)

This statement noted a change in thinking in relation to the development of orphan drugs, which can be attributed to the pharmacogenetic drug market where orphan populations can be focused upon to produce monopolistic niche markets. If regulated in the same way as orphan drugs (as in put through a fast tracked registration system according to therapeutic need and with reduced development times), a beneficial model system for understanding 'neighbouring indications' could be considered. Therefore, due to this 'beneficent' aspect of the orphan population, it could be morally permissible to have such sub-groups, if pharmacogenetic products were developed and registered in the same mode as for orphan drugs. This is because the development of drugs based on the orphan model would not be subjected to the value-based, cost-effective models of R&D assessment, which would hinder development[34].

However, pharmacogenetic testing is still a matter of probability, which still puts some patients at risk from suffering adverse events whether they are in the general or orphan population. This raises the question: how much weight should pharmacogenetic information be given in the treatment decision process? It also highlights the issue of discrimination due to

[34] Since the development of orphan drugs for rare diseases is considered to be expensive due to the small number of patients who would be eligible for treatment.

inappropriate denial of treatment because of genetic categorisation. When first analysing the question regarding the weight of pharmacogenetic information, we need to consider that treatment decisions tend to involve other factors such as patient condition, cost–benefit of the treatment and therapeutic alternatives. However, with the probabilistic nature of pharmacogenetics, refusal of treatment becomes problematic, especially when there is a weak genetic association and no therapeutic alternative. Since it cannot be guaranteed that the drug can be safely used in such patients or that they would benefit from such therapy, this raises the possibility of inappropriate denial of treatment due to their genetic categorisation. Professional judgements are still required for interpretation of patient categorisation and treatment options, emphasising liability issues for the clinicians and industry due to the responsibility of patient treatment outcomes and expectations. Liability issues of increased risk of inappropriate off-label prescribing could be minimised if further obligations to these groups were sanctioned to improve post-marketing surveillance, and stiffen professional sanctions against inappropriate off –label use.

Despite this, the study of rare conditions or 'orphan' conditions merits scientific study, since these conditions can provide medical insights and potential drugs for common conditions, as they are generated from single gene alterations. For example, patients with breast cancer may be subdivided into several (small) groups with different genetic profiles, giving rise to drugs targeted to these profiles, as well as providing further information on the nature of the disease, as illustrated by the breast cancer drug Trastuzumab (marketed as Herceptin). Herceptin was licensed for use in the UK in 2000 and is used to treat end-stage breast cancer in women

whose tumours produce too much of the protein HER2. Prior to treatment, the tumour tissue is tested to assess its HER2 status, and around 30% of patients are eligible for treatment.

The categorisation of individuals into particular sub groups may give rise to circumstances of stigmatisation and social discrimination. An individual could be perceived as difficult to treat if they did not fall into a known treatment category, or where genetic stratification results in a clinically relevant difference such as a disease risk or prognosis. Such secondary information has social implications, as it is relevant to third parties such as the family, and prompts further questions about who could or should obtain test results and under what circumstances. Therefore, in the revelation of secondary information, pharmacogenetic information should be treated as a form of genetic test.

These new categories of stigmatisation and social discrimination beg the question: have existing patterns of stigmatisation and social discrimination, such as ethnic or racial categories, become more entrenched with the genetic understanding of drug responses? In addressing this question, the use of the concept of race in research will be deliberated, as will the impact of genomics on this concept and its ethical implications. References will be made to Joon –Ho Yu's[35] article *Race-based medicine and justice as recognition: exploring the phenomenon of BiDil* (Yu, 2009), which provides a refreshing outlook on this well cited example of a potential 'race-specific' drug.

It has been noted that:

[35] Senior Fellow at the University of Washington School of Medicine, Dept. Pediatrics, Div. Genetics

'...pharmacogenetic information may alleviate, or it may entrench existing inequalities in healthcare based on race or ethnicity…'

(Smart, Martin et al. 2004, p.335)

This statement is based on the problem of using race as a factor in medicine, i.e. race-conscious medicine, where public funds for treatments and research and development are based on race. The approval and marketing of BiDil is an example of 'racially profiled' (Smart, Martin et al. 2004) prescribing. This discourse will only outline the BiDil controversy in order to provide a background of how race could be used in pharmacogenetic research. However, it will be argued that the BiDil case will not necessarily become the norm for the way that pharmacogenetic-based drugs are introduced to the market, since one notes that the BiDil case is a symptom of health disparities. It could be further argued that drugs developed using pharmacogenetic techniques may actually have the possibility to eliminate racial disparities in health, as mentioned in Joon –Ho Yu article's opening statement:

'...in the United States, health disparities have been framed by categories of race. Racial health disparities have been documented for cardiovascular disease, cancer, diabetes, HIV/AIDS, and numerous other diseases and measures of health status. Although such disparities can be read as symptoms of disparities in healthcare access, pervasive social and economic inequities, and discrimination…' (Yu, 2009)

However, the case of BiDil gives rise to controversy, due to the idea of demographically targeted treatment that could potentially result in the provision of better medical care for particular populations, but not for others.

The drug BiDil was approved in 2005 by the US Food and Drug Administration (FDA) for the treatment of heart failure in patients who identified themselves as African Americans. Approval of the drug was based on the statistical re-review of the original V-HeFT trials (the Vasodilator-Heart Failure Trials), and a later A-HeFT (African American Heart Failure Trial). Evidence that the drug was effective in this group of patients was noted in the first V-HeFT trials and a race –specific methods patent was applied to treat heart failure in African Americans. This resulted in the A-HeFT obtaining further information on this drug in the African American population (Jordan, 2008). Corresponding evidence for the drug's effectiveness in other self-identified racial groups, i.e. 'Whites' and 'Hispanics', was not made available at the time of approval. Also, it should be noted that BiDil did not result from pharmacogenetic research, but from the re-examination of statistical data. However, it has been stated that BiDil encouraged the use of pharmacogenetic technology to concentrate on the coding for racial phenotypes (Yu, 2009).

Nevertheless, the way that human difference has been conceptualised (such as in the concept of race) and used in health-disparities research has had profound moral consequences. The appreciation that there were continuing and widening disparities among black and white Americans in a number of diseases led to the enactment of the NIH (National Institutes of Health) *Revitalization Act of 1993*. This legislation required that all NIH-sponsored phase III

clinical trials include minorities and women in sufficient numbers, so that a valid subset analysis could be done (Shavers, 2007).

Yet with the introduction of genetic science, it has been shown that all humans are 1 per cent different from one another in terms of genetic structure, and only 15 per cent of this relates to race (Rothstein, Epps 2001). From this 15 per cent, intragroup variation is more predominant than intergroup variation, thus rendering the idea of a racial group as a homogenous race as obsolete. Bearing this in mind, in relation to BiDil, it would be an overgeneralisation to state that all African Americans would respond positively to BiDil. In subsequent pharmacogenetic analysis of BiDil response, individuals of a West-African descent have been shown to respond positively, but this does not indicate that persons from other African descents would also respond positively. Therefore, defining BiDil as an African American drug ignores the genetic breadth of African Americans. However, despite this information, African American community leaders capitalized on BiDil, using the opportunity to bring attention to African American health issues, even running the risk of inaccurately portraying race as biological. Such a portrayal has been strategic in affirming the use of race to ultimately transform the process of drug development, through a strategy based on a demand for justice (based on Nancy Fraser's bivalent theory of justice on asserting a demand for justice) and not just consequentialist benefit. Fraser's theory asserts that there are two types of injustice, based on misrecognition and maldistribution, which are rooted in cultural domination (subjection to alien standards of judgement) perpetuated by economic systems (Lovell, 2007). In the BilDil case, the affirmation of racial labels in the short term was used to seek recognition for a

disparity of health distribution. Therefore, this embraced the rhetoric of difference and emphasised the approach of different social groups harbouring different genes.

For that reason, in pharmacogenetics research, the study of difference occurs at the DNA level, and variation at the genetic level puts forth new categories for comparison across human populations based on molecular difference, and not phenotypes such as race. Such interpretation would minimise the potential for unequal access to resources and opportunities based on racial or cultural lines. Therefore, research initiatives which overlook the fact that census categories used as descriptors of difference are indeed political, and instead confer the idea that these categories are scientifically meaningful would be rendered obsolete (such as the epidemiological studies funded by the National Institutes of Health (NIH), which insist on the representation of minority groups to demonstrate representation of the population) (Lee, Mountain et al. 2001, p. 67). A disciplined focus on patterns of genetic variation, which is not influenced by prior racial categorisation of research participants, is therefore required to avoid reinforcing the destructive notion that biological races exist, in order to gain fuller understanding of health disparities (Lee, Mountain et al. 2001).

4.6.3 Clinical trials and the returning of genetic information

As noted earlier, pharmacogenetic screening of research participants to enable the linking of their responses to the tested drug would generally be performed in the early phases of research, such as Phase I. Such screening would reveal information about whether a research participant was a responder or non-responder to the drug, i.e. reveal information about whether they are difficult to treat with a given drug therapy. This sub-section will argue that results

from a clinical trial which note this information should be returned to participants on a benefit to risk basis, based on the following criteria (Renegar, Webster et al. 2006) derived from the minimal risk standard utilised in research governance;

- Clinical relevance
- Privacy and Confidentiality
- Competency of persons returning the results

Clinical relevance

Genetic information can be worrisome or even psychologically harmful, due to its perceived deterministic nature and potential implication for future healthcare. The decision on whether and how to return results must therefore consider the interests of the research participant, and balance this against the realities of the research results, which are, in fact, exploratory genetic results (exploratory information), which have not yet reached the point of general clinical acceptance (Renegar, Webster et al. 2006, p.31). In general, genetic research results are a broad category of information that include both validated and non-validated, highly and poorly predictive, probabilistic, and deterministic data. In drug development trials, genotypic information is often not readily interpretable, and even results that are widely recognised among geneticists do not necessarily lead to clear clinical interpretations (due to low or incomplete penetrance of the genotype), or practical implementation for patients. Also considerations must be made for the practicalities of expecting investigators to maintain contact with research participants, perhaps for extended periods of time, for the purpose of

offering participants access to updated information. A sensible solution is required for investigators, the industry, and regulators with regard to the limitations of access to information to the research participant.

Privacy and Confidentiality

There are potential risks and benefits which need to be considered in terms of the receiving of results. Research participants should appreciate that most genetic research is undertaken to benefit society and not just individuals. Disclosure of individual genetic results, possibly negating the research setting's confidentiality safeguards, may disadvantage the participant if such information is misused. As noted by the CHMP guidelines on pharmacogenetics which will be critiqued latter in section 5.4 (CPMP, 2002), the research participant's clinical trial record is an important component of data for submission to regulatory authorities, which should be made accessible to the authorities to validate the evidence that is reported. Furthermore, this record may link a clinical outcome to a particular type of patient. Therefore, the use of data from a study involving anonymised samples might not be acceptable for the submission of a claim, since regulatory bodies would not be able to include such anonymised information due to the mere fact of not being able to trace the phenotypic features of this information.

Competency of persons returning the results

Due to the fact–laden content of pharmacogenetic information, persons (usually the doctor as investigator) who are responsible for providing this data to participants, should be able to communicate the data in a manner (and at a level) which is informative and appreciative of the participant's social and psychological standing. According to philosopher and bioethicist Julian Savulescu, a rational, non-interventional, and paternalistic manner should be employed, to avoid being just fact-providers (Savulescu, 1995). This means the doctor actually takes on the paternalistic role, and makes judgements on what information provided is in the best interest of the participant, while rejecting the idea that the participant cannot seek any further information if they so wish.

Therefore, as the body of data on genotype-phenotype associations grows, the international research community, in partnership with key stakeholders, must be prepared to reach a consensus on when and how genetic research information (with all of the appropriate qualifiers and caveats to place it in a proper context), should be made available to research participants who desire it. Factors such as scientific validity, clinical relevance, and clarity of information provided to recipients need to be considered, as well as measures for maintaining confidentiality and preventing discrimination.

It has been shown that the ethical issues of pharmacogenetics are more concerned with the equitable distribution of research knowledge and research priorities than inference of disease knowledge, as implied by ethical concerns regarding privacy, confidentiality and discrimination, which have been the main focus of research governance policy. Furthermore, the persistent references (as gathered from the literature) to these implied ethical concerns for

pharmacogenetics illustrate how Principlism has entrenched concerns and increased perceptions of unethical research for this technology, in terms of research participant liabilities.

4.7 Conclusion

Pharmacogenetics has attracted great interest because of the expectations of improved drug safety and efficacy. The main advantage for industry is providing the potential for more economical and faster (smaller) clinical trials. I have asserted that the role of pharmacogenetics in drug development is to act as a risk assessment tool for the production of more effective medicines with minimal adverse effects. This is achieved by using genetic information about patients, to maximise therapeutic benefits and minimise harmful side effects by prescribing drugs targeted to genomic patient populations. The nature of this technology has the potential to decrease drug development costs. However, in producing these benefits, pharmacogenetics would create subdivisions according to genotype in the patient population, ushering in the 'cherry picking' of 'valuable' subsets of the population for a clinical trial. Subsets where efficacy is likely to be proved, or less likely to be susceptible to ADRs. This also introduces the consideration that certain subsets would become economically 'valuable' to industry or governments.

As a risk assessment tool, pharmacogenetics gives rise to ethical issues concerned with conferring benefits of the outcome of research such as the fair distribution of research outcomes, (i.e. justice) rather than autonomy, due to the stratification of the research participant population into genetic groups.

Therefore pharmacogenetic drug development ethical issues are concerned with equitable distribution of research knowledge and research priorities, rather than inference of disease knowledge. Suggesting whether the current interpretation of Principlism exercised in pharmacogenetic research governance provides an adequate ethical underpinning for the resolving of these issues? In the next chapter, this question will be addressed.

5. Chapter Five: The Application of Principlism in Pharmacogenetic Research Governance

5.1 Introduction

The central question for this thesis is: why the Principlist approach for research governance in pharmacogenetic-based drug development? Preceding chapters have focused partly on answering this question, in addition to determining the adequacy of the current interpretation of Principlism in research governance of pharmacogenetics research in resolving the ethical issues arising from this research. Chapter two answered the question to some extent through the critique of why Principlism was considered over other notable ethical frameworks in drug research regulation. The chapter concluded that Principlism was selected due to its ease of use, as the principles were regarded as general guides that could be applied to most ethical situations. Furthermore, I noted that Principlism, being an ethical framework that is entrenched in rights-based morality, better serves concerns for human rights in healthcare, which is an important feature of current research governance.

In chapter three, I argued that the exercising of human rights concerns occurs mainly through the practical application of the principle of respect for autonomy as the informed consent process, as well as the management of risk through risk assessment standards such as the minimal risk standard. Chapter four introduced the argument of whether Principlism provided adequate ethical guidance for the resolving of pharmacogenetics' actual ethical issues. This argument will be developed fully in this chapter by critiquing the pertinent ethical codes and guidelines utilised in drug development involving human participants and applied currently to

pharmacogenetics drug development. This critique will focus on whether the exercising of Principlism through these approaches has rendered as secondary other issues of ethical assessment within research, such as justice.

Consequently, section 5.2 will analyse how Principlism, through the dominant ethical medical guidelines of the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report, became the ethical framework of choice for research governance. The formalised international quality standard of Good Clinical Practice (GCP) will be critiqued in section 5.3, since this is a prominent example of how current research governance is exercised at an ethical level in drug development. Section 5.4 will be concerned with the application of pharmacogenetic-specific guidelines, such as the position paper on the terminology in pharmacogenetics by the CHMP (CPMP, 2002), and the report *Pharmacogenetics: ethical issues* published by the Nuffield Council on Bioethics (Nuffield Council on Bioethics, 2003). This will lead to section 5.5, 'Protectionism as Dogma'. Here, I will summarise my argument on the ethical interpretation of the management of risk, which is based on Principlism (as discussed in chapter three). I will argue that the current interpretation of Principlism's overriding deference to the principle of autonomy, namely the practical application of the informed consent process, has rendered this principle to merely a protective 'tool' for the research participant. In addressing this argument, I will be appealing to Rosalind Rhodes's article *Rethinking Research Ethics* (Rhodes, 2005), since it presents a view of how this deference to the informed consent process may have arisen. From the presentation of this argument and review of current influential guidelines and policy documents utilised in pharmacogenetic research governance, I aim to demonstrate that

the current interpretation of Principlism is not sufficiently specific for providing adequate guidance in the area of justice concerns for pharmacogenetic-based research governance.

5.2 Ethical Codes and Guidelines

Ethical codes and guidelines in medical research and, consequently, clinical trials, emerged as a result of atrocities to which research participants were subjected. This section will discuss how the various dominant ethical medical guidelines, such as the Nuremberg Code, the Declaration of Helsinki and the Belmont Report, were developed and eventually embraced Principlism as the ethical framework to protect the research participant.

5.2.1 The Nuremberg Code

A war crime gave rise to the most influential and widely quoted ethical code for biomedical research involving human participants; a code based on protection of the vulnerable from exploitation in research. This was known as the Nuremberg Code (National Institutes of Health, 1949).

The Nuremberg Code (herein referred to as 'The Code') was the first international document to advocate voluntary participation and informed consent (Shuster, 1998). The document emerged from the US Military tribunal in the 1946-7 that was convened to investigate the atrocities of human experimentation performed during the Second World War. This was the first international research ethical guideline, and was intended to ensure that participants in medical research and research in general should not be vulnerable to abuse. The code was

established to address ethical breaches surrounding the notion of autonomy, such as autonomous choice. It stressed that it is important:

> *'...to respect autonomous agents [by] acknowledging their right...to make choices, and to take actions based on their personal values and beliefs...'*
>
> (Loue 1999, p.103)

The Code (see Appendix (i) and summarised below) comprises 10 clauses that must be met to justify the involvement of human participants. These clauses describe the need for the protection of research participants from injury or death, with relation to autonomy rights:

1. Must have voluntary consent of the human participant.
2. Experiments should yield fruitful results for the good of society.
3. Experiments should be based on animal trials, with results that justify the experiment.
4. Experiments should be conducted to avoid unnecessary physical and mental injury.
5. No experiment should be conducted to where death or injuries will reasonably occur.
6. Degree of risk should never exceed the humanitarian importance of the problem.
7. Preparations should be made to protect research participants against possibilities of injury, disability, or death.
8. Experiments should only be conducted by scientifically qualified persons.
9. Research participants should be allowed to end participation in the experiment at any stage.

10. Scientists in charge must be prepared to end the experiment, if a continuation is likely to result in injury, disability, or death.

The first clause or principle is considered the most important and an ethical necessity, not only in research[36], but also in medical treatment:

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

[36] Pappworth. M.H., 'Ethical Principles' in Human Guinea Pigs- Experimentation on Man' (Routledge & Kegan Paul Ltd, 1967), 188. Maurice Pappworth's book was the major catalyst for change in ethics and regulation in biomedical research in the 1970s. He suggested a code of principles for human experimentation -a precursor to Principlism and basis for current clinical research regulation based on equality: valid consent; prohibited research participants; previous animal experiments; experimenter's competence; proper records.

The purpose of the Code was to merge Hippocratic ethics[37] and the protection of human rights into a single document (Shuster, 1998). However, it has been argued this combination is usually unsuccessful in research ethics, due to the non-interventionist and reflective nature of the 'Hippocratic' physician who sides with life, and pledges

> *'...to help or at least to do no harm...'*
>
> (Shuster 1998, p.974)

With Hippocratic ethics, consideration of the patient's autonomy is not a requisite, unlike the physician's autonomy, which is required in order to act in the patient's best interest.

However, the Code replaced physician-centred Hippocratic ethics with research participant-centred human rights. Hippocratic ethics were concerned with a physician's pledges of benefiting patients on a case-by-case basis according to the physician's ability and judgement (Veatch, Mason 1987). It has been noted that such considerations do not take into account medical care allocation amongst patients, since the physician focuses on one patient at a time. Hence, the Hippocratic Oath does not mention platitudes for issues concerning distribution, justice and rights to healthcare (Veatch, Mason 1987).

The Code requires the physician as a researcher (commonly known as the investigator in drug development) to protect the life and welfare of research participants (principles 2 through 8 and 10), declaring that research participants must assert their autonomy to protect themselves

[37] Hippocratic ethics are concerned with a physician's pledges of benefiting patients on a case by case basis according to the physician's ability and judgement (Veatch, Mason 1987).

through informed consent and the right to withdraw from the study (principles 1 and 9) (Shuster 1998, p.975). Therefore, the research participant's autonomy becomes as important as that of the investigator.

This eventual merge of Hippocratic ethics and human rights into a single code aimed to dissuade people from the temptation of subordinating the research participant's rights to the will of the investigator, whilst retaining the beneficent view of the investigator (Hippocratic physician-researcher) towards the welfare of their research participants. The Code was also the first research ethical guideline to recognise and provide core principles in relation to individual rights. However, the subordination of the rights of research participants to the investigator's will did become evident, especially when research was perceived as extremely important, promising results that could substantially improve the care of future patients. When this kind of research was contemplated, efficiency and the perceived need to obtain prompt answers to significant research questions have been known to overwhelm the rights and welfare of research participants.

An apt illustration of this was observed with the Tuskegee Syphilis experiments, conducted between 1932 and 1972 (Curran, 1973). These experiments were performed prior to the existence of an effective treatment for syphilis, but ended long after effective antibiotics were available. Hundreds of black sharecroppers with late-stage syphilis were never told from which disease they were suffering, or of its seriousness. Instead, they were left to deteriorate in ignorance, albeit with the prospect of 'free' medical care. This was deemed necessary for collecting data on the conflicting effects of the disease on blacks and whites (the theory being

that whites experienced more neurological complications from syphilis, whereas blacks were more susceptible to cardiovascular damage), in addition to observing the natural course of the disease.

Therefore, due to the probable oversights inherent in the Hippocratic Oath, the Code was not considered as relevant to the physician-as-researcher, who rationalised that experimental work was treatment 'benefiting' patients (Shuster, 1998). Furthermore, it became apparent that the Code was deemed relevant only to Nazi doctors and their associated atrocities; consequently, it was ignored for 20 years after its inception (Horner, 1999). Moreover, the Code was apparently unconcerned with providing guidance on the burgeoning ethical issues surrounding the distribution of healthcare resources, use of research participants, privacy, community responsibility and truthfulness (Griffin, O'Grady 2004).

5.2.2 The Declaration of Helsinki

The Declaration of Helsinki (DoH) (see Appendix (ii)) superseded the Code and was adopted initially by the World Medical Association in 1964. As a result of a number of notable criticisms (which will be discussed in this section), and the burgeoning core ethical principles, as noted in the Belmont report (which now constitute Principlism), the DoH published in June 1964 has undergone a number of revisions. The most recent of these were made in October 2013.

The DoH emphasised the role of physicians in conducting medical research involving human research participants, in addition to medical research on identifiable human material or identifiable data, as cited in the introduction:

1. *The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data*

   (World Medical Association, 2008)

Furthermore, stringent requirements for the minimal risk standard[38] criteria were provided, which were applicable to incompetent research participants. However, this raised questions on the scope of informed consent for competent research participants, especially when granting permission to conduct vaccines research on children (Williams, 2008). These (and many other) major criticisms of the DoH, outlined below, became apparent and led to numerous revisions;

- The criticism of the omission of a review mechanism for researchers' (both investigator and non-physician researcher) actions.
- The criticisms concerned with the distinction between therapeutic clinical research (research that provides treatment benefiting the patient-research

[38] The minimal risk standard is sometimes known as the 'best interest standard'; considered to be a guide to select what most informed, rational people of good will would regard as maximising net benefits and minimizing net harms for less competent research participants (Kopelman, 1997).

participant) and non-therapeutic clinical research (research which is purely scientific, without direct therapeutic value) on healthy participants[39], apparent in the following DoH Articles 31 and 32:

31. *The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value, and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.*

32. *The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:*

    - *The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists.*
    - *Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option*

(World Medical Association, 2008)

[39] A category of voluntary research participant prevalent in phase I clinical trials.

This implied that therapeutic research is justifiable, since it benefits patients, and that non-therapeutic research was also tenable due to its social benefit; i.e. it has the well-being of society in mind. This suggests that procedures are legitimate if performed for the good of persons in general, rather than the patient or society.

The criticism regarding the lack of a review mechanism for researchers was triggered by reports of commonplace serious abuses of research ethics, which led to the first revision of the DoH in 1975 (Williams, 2008). This amendment added the requirement of an independent review committee for the advance review of all research projects, and the prerequisite of adhering to the DoH for the publication of results.

5.2.3 The Belmont Report

During the Thalidomide disaster in 1962, it was revealed that the drug marketed as a mild sleeping pill that was safe for pregnant women to take, caused thousands of babies worldwide to be born with malformed limbs. As a direct consequence, all previous research legislation was consolidated to ensure stricter controls on drug testing, marketing and advertising. Furthermore, the ethical principle of respect for autonomy through the practical requirement of patients to provide 'informed consent' became mandatory before participating in drug studies. All these sanctions created a formal regulatory structure, ensuring that legislation was adequately and fully implemented (Griffin, O'Grady 2004). The introduction of the *Medicines Act* (1968) in the UK, and the US the *National Research Act of 1974*, led to the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (1974-1978). Work from this Commission was then revised and

expanded on by the Department of Health and Human Services (HHS) in order to formulate the Commission's report: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, named the Belmont Report.

Published in 1979, the Belmont Report was charged with identifying the ethical principles for governing research involving human research participants, and the formulation of appropriate guidelines. It defined a principle as:

> *'...a general judgment that serves as a basic justification for the many particular prescriptions for and evaluation of human actions…'*
>
> (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (US), 1979)

Principlism was first identified by the Belmont Report as:

> *'...general judgments that serve as a basics justification for the many particular ethical prescriptions and evaluations of human action…'*
>
> (Jonsen, Veatch et al. 2000).

The three principles identified were:

- Respect for persons – *'The principle…divides into two separate moral requirements [1] the requirement to acknowledge autonomy, and [2] the requirement to protect those with diminished autonomy'.*
- Beneficence - expressed as two general rules of beneficent actions; *'[1] do not harm; and [2] maximise possible benefits and minimise possible harms'.*
- Justice – *'...equals ought to be treated equally'*

(National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (US), 1979)

The report took the position that research involving human participants must not violate any universally applicable ethical standards, but should acknowledge the application of the ethical principles. For example, for individual autonomy and informed consent, cultural values needed to be taken into account, whilst, simultaneously, the ethical principle of respect for persons needs to be adhered to. This is quite a challenge for international research ethics, as biomedical research is conducted in a multicultural world with a multiplicity of healthcare systems that vary considerably in terms of standards. This situation has fuelled the argument of moral relativism, whereby ethical statements (not necessarily these principles) can be regarded as true for the members of one society or culture, but false for those of another (Bullock, Trombley et al. 1999, p.743). Moreover, an argument has been raised about whether it is realistic for these principles to be universally recognised (Beauchamp, 2004), especially when such focus is placed on the features of differences, such as culture, religion, and ideology (to name but a few). However, it has been noted that, if focus could be reoriented to

recognising in these features aspects that unite humans whilst acknowledging the differences, this would indeed move research ethics towards attaining universality (Razis, 1990) and achieve coherent and effective research governance. I argue this point further in chapter six, in a critique of a global research ethic framework as proposed by David Thomasma (Thomasma, 1997). A moral framework that subscribes to a minimal morality which takes into accounts both reasons and emotions that are not culturally dependant, providing additional guidance for international research governance.

Despite the issues raised on moral relativism and universality, Principlism was enshrined in the Belmont Report, and clearly became an ethical guideline for applying ethics to medicine, through the authoritative academic text of the first edition of the *Principles of Biomedical Ethics* published in 1977. In this source, Principlism consisted of the following: (1) norms intrinsic to medical practice that guide determinations of what the best action is in medicine; (2) the fundamental ethical principles; autonomy, beneficence, non-maleficence, and justice, that should guide ethical action in medicine; and (3) moral judgements for certain situations based on the application of these principles noted in (2) (Emanuel, Wendler et al. 2000).

Today, Principlism has evolved, as noted in the seventh edition of Principles of Biomedical Ethics (Beauchamp, 2013), from a singular deductive approach of applying medical ethics 'principles', to one that reflects common practice. In other words, progression has been made towards a:

'"... [universal] morality theory" by which the four principles are elucidated and justified…'

(Emanuel, Wendler et al. 2000).

However, this new direction has attracted criticisms regarding whether Principlism contains the correct values for a 'universal morality' theory, having 'no decision procedure' (Charles, 2003) due to a mismatch of ethical theories. This has led to the criticism that Principlism lacks specific guidance on applying the principles, due to the perception of their *prime facie* nature, and the potential for different interpretations. Furthermore, the notion of a universal morality has raised a number of criticisms, with regards to the universality of the framework, which has been described as 'distinctly American in character' (Holm, 1995). Due to the premise of the four principles approach being based on the shared morality of a specific society (i.e. US), and in order to establish a universal morality theory, an internal set of norms considered acceptable cross-culturally must be evident.

Therefore, current clinical research governance arose from historical abuses and misapprehensions of research participants and researchers respectively. This caused moral decision making for the ethical conduct of research to be concerned with the safety and rights of the research participant. Principlism fits neatly into this requisite, mainly because of the principle of respect for autonomy, interpreted as the concept of informed consent, which is considered to be the cornerstone of research ethics. However, it is crucial to remember that for research to be regarded as ethical, all principles within Principlism must be subscribed to, even if the willing, fully informed cooperation of the research participant is gained.

5.3 Good Clinical Practice

At an ethical level, drug development research governance is exercised through the quality standard, Good Clinical Practice (GCP)[40]. By adhering to GCP, regulators and the industry believe they have conducted clinical trials in an ethical manner. Compliance with GCP should provide public assurance that the rights, safety and wellbeing of trial participants are protected.

This quality standard arose in the 1960s, due to widespread concern amongst members of the medical profession, the scientific community, regulatory authorities, and the general community about the safety and control of investigational drugs and the clinical research process, following the Thalidomide disaster in 1962 . This gave rise to the Kefauver-Harris Amendments in 1962 in the US, which established procedures for the clinical evaluation of drugs that required assurance of informed consent of the research subjects, and required reporting of adverse drug reactions. Consequently, the entire regulatory system was re-shaped in the UK. A Committee on the Safety of Drugs (CSD) was launched in 1963, followed by a voluntary adverse drug reaction (ADR) reporting system (Yellow Card Scheme) in 1964. The DoH, introduced in 1964, provided ethical underpinning of GCP by acknowledging the principles of Principlism for medical research involving human subjects. It was a major landmark in recognising GCP as a standard for drug development (Abraham, Grace et al. 2009). Therefore, how GCP interprets Principlism in the Declaration will be discussed in this section. Furthermore, I will argue that there is no emphasis on GCP of serving the common

[40] Also referred to as ICH GCP, ICH referring to The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, however for the purposes of this discourse the term GCP will only be used.

good (i.e. of promoting generalised knowledge or providing specific guidance to justice concerns), particularly in the area of pharmacogenetic research governance.

GCP processes and procedures set out responsibilities for key organisations and individuals, including funders, researchers, organisations employing researchers, and healthcare organisations (Shaw, Petchey et al. 2009). These responsibilities are formalised under the EU Directive 2001/20/EC, whereby all clinical trials performed in drug development in the European Union are required to be conducted under this directive (European Parliament, 2001) and, therefore, this standard. The directive acts as a form of governance which is administrative in nature, concerned with regulating potential risks in clinical trials.

The following definition of GCP is given in Article 1, Clause 2 from the directive (implemented in 2004 which governs clinical trials conducted in the UK):

> *'...a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects…'*
>
> (European Parliament, 2001)

Therefore, the principles set out in GCP broadly cover the protection of clinical trial participants and the scientific approach in design and analysis. GCP is encapsulated in guidelines from the International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use, including:

- ICH Harmonised Tripartite Guideline - Guideline for good clinical practice E6 (R1); adopted by the regulatory bodies of European Union, America and Japan. The document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and regulatory bodies. It covers all aspects of monitoring, reporting and archiving of clinical trials and associated essential documentation (ICH, 1996).
- ICH Topic E 8 - General Considerations for Clinical Trials; describes principles and practices and sets out the general scientific principles for the conduct, performance and control of clinical trials. The guideline addresses a wide range of subjects in the design and execution of clinical trials, and development strategy for new medicinal products (European Medicines Agency, 1997).

In the UK, the legislation *The Medicines for Human Use (Clinical Trials) Regulations 2004* (SI 2004 no. 1031) (MHRA, 2004) implements the EU Clinical Trials Directive through the regulatory body, The Medicines and Healthcare Products Regulatory Agency (MHRA). This legislation replaces the clinical trials component contained within the 1968 *Medicines Act*.

Despite this background, GCP has been regarded as

> *'…rather [a] dry set of regulatory procedures, not a substantive and authoritative ethics document…'*
>
> (Rennie, 2009)

and is considered lacking in moral judgement (Kimmelman, Weijer et al. 2009). The reasoning behind such opinions could be due to GCP's notable focus on regulatory harmonisation rather than the expression of ethical commitments. Examination of both GCP and the DoH by Kimmelman et al (Kimmelman, Weijer et al. 2009, p.37) noted the following ethical issues, which are present only in the Declaration, and not in GCP guidelines:

- *Investigators to disclose funding, sponsors, and other potential conflicts of interest to both research ethics committees and study participants*
- *Study design to be disclosed publicly (e.g., in clinical trial registries)*
- *Research, notably that in developing countries, to benefit and be responsive to health needs of populations in which it is done*
- *Restricted use of placebo controls in approval process for new drugs and in research done in developing countries*
- *Post-trial access to treatment*
- *Authors to report results accurately, and publish or make public negative findings*

Such omissions have led to concerns about whether GCP confers adequate protection of research participants in international research, especially when GCP is referred to in isolation from the DoH (Kimmelman,Weijer et al. 2009). Since the Declaration does seem to cover concerns of inequality and social justice applicable to research conducted in populations of low socioeconomic backgrounds (Rennie, 2009), further derivation of these opinions could be attributed to the GCP being established by the International Conference on Harmonisation.

This consisted of voting members from the USA, the EU and Japan, and contrasts with the Declaration established by the World Medical Association, which include 85 worldwide national medical societies.

GCP contains the ethical underpinnings of Principlism, as enshrined in the Declaration. The core principles of Principlism, which appeal to the respect for autonomy, prevention of harm, promotion of benefit, and justice, provide an ethical dimension to GCP. These principles are considered to inform the duty of care that a researcher owes to research participants, as well as the duty that a research institution or sponsor owes to both participants and researchers (Shaw, Boynton et al. 2005). However, it is fair to say that the key requirement of these core ethical principles is to ensure that the importance of the research objective is in proportion to the inherent risk to the participant. Therefore, GCP adheres to a core role of governance; managing risk of harm.

Thus, by acting in accordance with GCP, researchers are regarded as appealing to the core ethical principles expressed in Principlism. Where the 'Good' in GCP is an operative term, it is not concerned with the term 'the integral common good' (as noted in section 2.4), but the general good. Through the requirement of research risk being justified and proportionate to its benefit to society as well as providing the belief that no research participant should receive less than the prevailing standard of care, as quoted in section 4.3.2. from GCP, as follows:

> *'...During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The*

investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware…'

However, this highlights that GCP is not absolute and unquestionable, rather it is a working guideline for decision making for all agents involved in the conduct of clinical trials. This guideline should perhaps be open to questioning in specified cases (Viens, 2008).

In summary, all clinical trials are governed on a national and international scale, in which all research governance adheres to GCP (Good Clinical Practice). GCP guidelines ensure that:

- Clinical trials should be conducted in accordance with the ethical principles as stated in the DoH (practical interpretation of Principlism).
- The rights, safety and well-being of patients are most important.
- Trials are scientifically sound and described in a clear, detailed protocol.
- Investigational products are manufactured, handled, and stored according to Good Manufacturing Practice (GMP) – an industry standard which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use. GMP is concerned with both production and quality control

(MHRA, 2010a)

By complying with GCP, regulators and the industry believe they have conducted clinical trials in an ethical manner. Therefore, compliance with GCP provides public assurance that the rights, safety, and wellbeing of trial participants are protected. There is no emphasis on GCP

for promoting the common good; i.e. to promote generalised knowledge or specific guidance for justice concerns, such as the prioritising of research projects (in the case of pharmacogenetic clinical trials). Instead, GCP focuses predominantly on the principle of respect for autonomy and whether this situation (which will be discussed in greater detail in the next section) is evident for policies that specifically govern pharmacogenetic-based clinical trials.

5.4 Pharmacogenetic Research Regulation Policies

The influential guidelines such as the *Position Paper on the Terminology in Pharmacogenetics* by the CHMP (CPMP, 2002), and the report *Pharmacogenetics: ethical issues*, published by the Nuffield Council on Bioethics (Nuffield Council, 2003), will be critiqued. Particular attention will be paid to whether the outlook of these policies is protectionist.

5.4.1 Committee for Medicinal Products for Human Use (CHMP)

The CHMP has proposed a number of position papers for the use and handling of pharmacogenetic tests in clinical trials. The first notable position paper *Position paper on terminology in Pharmacogenetics* (EMEA/CPMP/3070/01), published in 2002[41] (CPMP, 2002), outlined an agreed set of working definitions for terminologies and procedures used in Pharmacogenetics research. This paper was further updated and incorporated into ICH GCP in 2007 as the position paper *ICH Topic E 15: Establish definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories*

[41] When the CHMP was formerly the Committee for Proprietary Medicinal Products (CPMP)

(CHMP/ICH/437986/2006) (CHMP, 2006). The aim of these papers was to further facilitate clarity in communication between regulatory authorities, ethics committees, investigators and research participants involved in pharmacogenetic research. This was achieved by presenting a definition of terms proposing appropriate levels of protection for the privacy of the research participant, when describing how results and samples will be used in pharmacogenetic clinical trials. Discussions in these papers were centred on privacy and confidentiality implications of the donor subject when affected by the five methodologies proposed. Furthermore, discussions were based on the following: assessment of the implications of subject withdrawal of their sample from the study; return of information to the subject or subject's physician; involvement of a subject's sample in future clinical investigations, and use of data for regulatory purposes. The five methodologies defined for the handling and collection of genetic samples and data are as follows:

Identified samples and data are those labelled with personal identifiers such as name, initials or social security number.

Single-coded samples and data are those whereby single specific codes of randomly picked numbers/letters are assigned and can only be traced or linked back to the research participant. The investigator stores the connecting code of the sample to the individual's data, separating the research participant's identity from the results of the pharmacogenetic analysis.

Double-coded samples and data, which have a unique second number. The link between the clinical study research participant number and the second number is unbeknown to the investigator. It is possibly maintained by the sponsoring organisation or an external entity such

as a governmental agency or qualified third party not involved with the research (as in legal, quality assurance, and clinical statistics).

Anonymised samples and data are double-coded and labelled with the unique second number. The link between the first and second code is deleted after the genetic and clinical information has been obtained. These may also be previously single-coded samples where the single code key is destroyed, or even formerly identifiable samples where the name/identifier is removed.

Anonymous samples and data are those that do not have any personal identifiers or identification of the research participant from the time the sample was collected, and no direct link exists between the sample and donor. Such anonymous samples may contain population information; for example, the samples may come from research participants with diabetes. However, there is no additional individual clinical data that might permit the identity of the research participant to be traced.

These papers went on to observe that identified and single-coded categories are treated similarly to those acquired in medical practice, and provide a low level of privacy protection. The sample and the data generated can be traced directly to the research participant; thereby enabling easy retrieval of the sample, in the event of the research participant wishing to withdraw from the study. Moreover, the traceability of the sample origins helps facilitate feedback of research results to the research participant. However, this raises questions about the confidentiality of stored data and the lack of privacy. As outlined in the definition of the double-coded category, the guardianship of the key to the second code by a third party provides more adherence to privacy, as the information is accessed only under certain

conditions, such as a medical emergency. Nevertheless, this must be made clear to the research participant through informed consent.

With the anonymised category, and due to the deletion of the second key, privacy of the individual is fully maintained since it is no longer possible to link the individual to their samples or data. However, the data's usefulness is debatable due to the fact that pharmaceutical companies must allow audit and review of all their clinical trial data by regulatory bodies, for the basis of libel claims.

Therefore, the coding of samples and genetic data in pharmacogenetic clinical trials was regarded as the preferred mechanism for ensuring subject confidentiality and potential feedback, as noted by the recent report from the Nuffield Bioethics Committee (which will be discussed fully in the next sub-section):

> *We consider that to protect the privacy of participants in research, the greatest degree of anonymity should be imposed on samples, compatible with fulfilling the objectives of the research*
>
> (Nuffield Council 2003, p.34, 3.36)

The implication is that full anonymisation of genetic samples acquired during a clinical trial is not recommended, and a de-identification procedure, as in the double-coded category, would probably be the most applicable category for clinical trials subjected to regulatory review. Data from the anonymisation category would be for hypothesis generation and population studies, since the sample does not contain any individual identifying data. Furthermore,

collection of data that does not link a particular subject's genotype to his or her response to the drug being studied is rendered worthless:

'...knowledge of a DNA sequence is of no worth without knowledge of what happened to that patient when he or she took the medicines studied...'

(Nuffield Council 2003, p.34, 3.35)

In selecting the most appropriate methodology to serve pharmacogenetic research aims, it must be remembered that ethical integrity is essential; in other words, the methodology must also recognise the other principles inherent in Principlism. However, it seems that such integrity is based solely on the level of protection of privacy and confidentiality afforded to the subject. Furthermore, ethical integrity is based on whether a subject can make a truly informed choice to participate by assessing fully the risks and benefits (including the level of privacy and confidentiality) of utilising their data.

In summary, the definitions from these position papers are mainly descriptive, with predominately prescriptive sample category definitions. Both sets of procedural and terminology definitions set out to highlight the consequences of the protection of privacy (of research participants), without any reference to any ethical implications. Instead, conclusions demonstrate different degrees of permitted sample and data anonymity, which depend on the different types of pharmacogenetic research; i.e. population studies, or license applications. Without no ethical basis for such discourse, only statements of certain research aims are adequately served by the various methodologies, regardless of the implications of privacy and confidentiality to the research participant, or justice implications of the outcomes of the

research. One of the possible reasons for this could be the scientific and regulatory community's reluctance to discuss new ethical consequences regarding new medical technology prior to implementation, due to consequences being evident only once studied with empirical certainty.

5.4.2 Nuffield Council on Bioethics

The report *Pharmacogenetics: ethical issues*, published by the Nuffield Council on Bioethics (Nuffield Council on Bioethics, 2003), examines pharmacogenetics in terms of its scientific background in the context of research and development of new medicines. Moreover, it anticipates the regulatory and public policy implications, and ethical issues that could arise when (and if) pharmacogenetics emerges into everyday medical practice. The report aims to encourage discussion of the issues and make recommendations on the future policy and practice of pharmacogenetics. The ethical issues discussed are concerned largely with aspects of consent, privacy and confidentiality. However, the report does acknowledge justice concerns, considering the importance of equity in pharmacogenetic research governance:

> *'Pharmacogenetic information may affect decisions about which treatments to fund, by revealing information about the effectiveness of treatments. It is important that decisions should take into account considerations of fairness. The National Institute for Clinical Excellence (NICE) is responsible for assessing cost-effectiveness in England and Wales. We endorse NICE's approach of reviewing cases on an individual basis, considering equity as well as cost-effectiveness.'*
>
> (Nuffield Council on Bioethics 2003, paragraph summary 4.11-4.32).

Furthermore, the report notes that relying on cost-effectiveness criterion of medications should not be the only factor when introducing medicine:

> *'…it is not the total increase in health which is important, but the fair distribution of that benefit among the members of a population. Unless such considerations are set alongside those of cost effectiveness, those suffering from rare conditions may be overlooked in the allocation of resources because their numbers are not large enough to count against the more prevalent conditions…'*
>
> (Nuffield Council on Bioethics 2003, paragraph summary 4.11-4.32).

Interestingly, the report moves away from issues based on the principle of respect for autonomy, to those concerned with breaches of the principle of solidarity. Solidarity based on altruism and feelings of compassion and empathy, is interpreted as the principle of reciprocity; an awareness of interdependency, and interrelatedness that is the basis of a sense of obligation to do something in return (Hoedemaekers, Gordijn et al., 2007). In this case, the participation in research is for the common good and the sharing of research benefits (Sutrop, 2004). The genetic database is perceived as a common public good; therefore, participation is a duty, and a obligation to know and inform others (Sutrop 2004, p.7). Issues of consideration were concerned with inequalities in the provision of healthcare where it was noted that the benefits of pharmacogenetics would only be available or affordable to the wealthy.

The position paper, therefore still considers moral viability in terms of the principle of autonomy. Conversely, the report's acknowledgement of solidarity, and its strong commitment to the justice principle of realisation of shared interests and goals, indicates a move away from

this predominant position of individualism and autonomy in relation to pharmacogenetic ethical concerns. This is an example of how ethical thinking evolves in line with science; thereby illustrating how various ethical principles can be the focus at different times.

5.5 Protectionism as Dogma

Contemporary research ethical codes in human experimentation, such as GCP and the Declaration, are a result of the atrocities performed during Nazi medical research programmes in the Second World War. Such a legacy has focused policies narrowly on the protection of human research participants, rather than asserting a balance of the moral assessments of risk and efficacy. Indeed, compliance with GCP guidelines:

> *'...provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible…'*
>
> (EMEA, 1996)

Moreover, there is no mention of ensuring social justice and equality for research participants. Instead, 'protection' of the research participant is considered paramount and is enshrined in the concept of informed consent. This has become the:

> *'...centrepiece of regulatory attention…'*
>
> (Rhodes 2005, p.1)

The practice of informed consent is used as a tool for 'ensuring' this protection of the research participant; Rhodes' article defines informed consent as:

> *'...the cornerstone principle of research ethics…'*
>
> (Rhodes 2005, p.8)

This suggests that informed consent is a practical aspect of the principle of respect for persons or autonomy and is a principle in its own right. In other words, the exercising of informed consent is the only moral requirement to respect other people's autonomy[42] and is a view also accepted by others[43]. Furthermore, I argue that this has contributed to the predominance of the concept of autonomy (a psychological feature) in research.

In Rhodes's article, the concept of autonomy is described as a first and second-person model to present a true understanding of what informed consent should mean in research. As a first-person model, autonomy is described in Kantian terms, as:

> *'... [a] person reflecting on the issues involved in a situation, considering her options in terms of her values and moral commitments, and making a choice that reflects her priorities and the ethical standards she embraces…'*
>
> (Rhodes 2005, p.11)

[42] Noting that the principle of respect for autonomy can also be upheld by ensuring privacy and confidentiality are not breached.
[43] David Archard – who equates the taking of informed consent to a principle of respect for autonomy in his example of the taking of a mouth swab without consent (Archard, 2008).

As a second-person model, it aims are :

> *'...to reflect the appropriate moral attitude towards others who are capable of autonomous action…'*
>
> (Rhodes 2005, p.11)

However, Rhodes notes this as a call to respect the autonomy of persons, and further proposes that 'reasonable' individuals should serve periodically as research subjects in what one would term as a sort of 'national research service'. This suggests that our first-person sense of autonomy would be satisfied by being able to choose the research programme in which we would like to participate; while the second-person sense would be satisfied by the decision-making process in which we are allowed to engage. With this in mind, Rhodes states that informed consent would have the following four functions:

Asserting Trustworthiness of researcher and research project - perceived by participants as part of a trust-affirming exercise. The purpose is to make research more trustworthy, which this thesis agrees (as critique in section 3.5) is essential for participant or public acceptance, and engagement with research.

Minimizing subjective disclosure of research risks and benefits - if participants choose their own research projects, without being asked to volunteer, then it is noted that their own judgement on risks and benefits would not be influenced so much by others who have a stake in the study, such as the researchers. Researchers are concerned with the outcome of the

research project and regulatory bodies; their concern is with the moral integrity of the research project.[44.]

Transparency of research design – this relates to the biomedical community as well as the participant. Such an exercise is already underway with the website portal http://clinicaltrials.gov/, which provides patients, family members and the public with information about current on-going clinical research studies.

Respect for autonomy - defined by Rhodes as:

> *'...requires us to presume that others are acting from the values and principles that they embrace and to leave them alone and allow them to live by their own lights…'*
>
> (Rhodes 2005, p.11)

She continues to suggest that informed consent would:

> *'...allow individuals to fulfil their research obligations within a framework of recognition and respect for their other values, goals, and commitments…'*
>
> (Rhodes 2005, p.16)

[44] In the second function of informed consent, Rhodes notes 'full disclosure' of 'I presume' information of the risks and benefits of research, which suggests that this is not normally done – this is a misnomer. Full disclosure of a research project's risks and benefits are always provided as fully as possible to the participant, but cannot always be guaranteed to be the full information since, due to the nature of research, this information is still being sought.

This implies that those participants who have an input in choosing their research programme and in evaluating their own notions of risk and benefits, would not be considered part of the current protectionist regime.

These four functions of informed consent are noteworthy, but one would not agree that they are all a function of informed consent. For instance, the first function - *'Asserting Trustworthiness of researcher and research project'* - could be equated to the principle of non-maleficence, which is the moral requirement of avoiding the causation of harm. Furthermore, the second function – *'Minimizing subjective disclosure of research risks and benefits'* - could be considered to be the principle of beneficence, which is the moral requirement of providing benefits, and balancing these against risks and costs.

Conversely, informed consent, according to Beauchamp and Childress (Beauchamp, Childress 2009, p.120), is a temporal process that cannot be defined by a set model; rather, it can be addressed in relation to two different conceptions. First, informed consent is the autonomous authorisation by individuals of their involvement in research, and occurs only if the subject has substantial understanding in the absence of control by others. Second, informed consent is assessed in terms of the social rules of consent, in institutions that must obtain legally-valid consent from patients or subjects before proceeding with therapeutic procedures or research. However, the meaning of informed consent is analysed in terms of autonomous authorisation.

Therefore, informed consent is defined further by a series of 'elements', which are divided into information and consent components. The information component refers to disclosure of

information and comprehension of that information. The consent component refers to a voluntary decision and agreement to undergo the recommend procedure (Beauchamp, Childress 2009, p.145). These elements are divided into the following analytical components that capture the basic notions of informed consent, which, it seems, have not been discussed or considered in Rhodes' article:

IV. Threshold Elements (Preconditions)

8. Competence (to understand and decide)
9. Voluntariness (in deciding)

V. Information Elements

10. Disclosure (of material information)
11. Recommendation (of a plan)
12. Understanding (of 3. and 4).

VI. Consent Elements

13. Decision (in favour of a plan)
14. Authorisation (of the chosen plan).

Thus, in recognising only informed consent, I concur with others (Simmerling, Schwegler 2005) who state that this alone does not constitute sufficient proof that a research project is ethical. However, one could go so far as to state that by recognising informed consent according to the aforementioned proposed four functions, Rhodes is actually recognising a number of principles within Principlism. Indeed, if these 'consent' functions are

acknowledged, the research project would be ethical according to the Principlism ethical framework, but not because they are solely considerations of informed consent.

Therefore, Principlism in current research ethics has been interpreted by some as providing ethical guidance based on the assumption that research is inherently dangerous to research participants, who need to be protected. This interpretation of protectionism is a result of the backlash arising from the research atrocities unearthed following World War II. This led to further concerns and increased perceptions of unethical research in terms of research participant liabilities. I hope to have demonstrate that this is due, in part, to one aspect of Principlism; its focus on the principle of respect for autonomy, to being applied ardently to the extent that other normative principles, such as the principle of beneficence and the principle of non-maleficence, are interpreted as functions of informed consent (Gillon, 2003).

5.6 Conclusion

Codes and guidelines in research have emerged as a result of historical atrocities performed on research participants. The ethical merit of research involving human research participants became based on the application of principles, described initially in the US National Commission's *Belmont Report*, and later expanded upon by Beauchamp and Childress in their *Principles of Biomedical Ethics*. These principles are commonly referred to as Principlism.

The impact of pharmacogenetics in drug development on these, and subsequent, guidelines highlighted the shortcomings of Principlism's current interpretation; notably, its preoccupation with autonomy breaches. This is a concern that, I note, is possibly a resultant reaction to

research participant rights abuses in the past. Moreover, it could be due to the interpretation of the other normative principles in Principlism as aspects of informed consent. In the next chapter, this argument will be developed further, especially with regards to the principle of justice, by noting that this interpretation of the other principles is due to the non-specificity of their application.

GCP guidelines, which underpin the governance of current pharmacogenetic clinical trial conduct, are yet to propose guidance on the breaches of justice and equity evident in this technology. However, pharmacogenetic-specific guidelines are beginning to acknowledge these potential ethical issues, but have thus far not provided specific ethical guidance on how to resolve these issues. Therefore in the next chapter, I will develop the proposal that we need to make the principle of justice within Principlism more specific, in order to address the actual pharmacogenetic ethical concerns of the fair distribution of research outcomes. This can be achieved by appealing to respect for fairness, as noted in the principle of justice, which represents both deontological and utilitarian theories, and the basis of the social contract. On a practical note, for regulatory concerns and the moral viability of research policy, the process of 'overlapping consensus', as advocated by Rawls, will be discussed as a method for helping achieve the aim of respect for fairness.

6. Chapter Six: Rawls's 'Overlapping Consensus': a possible way forward?

6.1 Introduction

Issues of justice in healthcare research gave rise to controversies and incidents such as the Tuskegee experiment, mentioned previously in section 5.2. This experiment triggered public indignation not only because of failures of consent or unacceptable risk-benefit ratios, but also because of the distribution of the research outcomes. In 1997, the Clinton administration addressed and recognised this public indignation, and a formal apology to the victims and their families was given (see Appendix (iii)). This gesture was indicative of the rising importance of the principle of justice as a principle which conferred fair distribution of burdens and benefits in a social system, and shows that when considered over time, it is concerned with the comparative treatment of persons (Lebacqz, 1981).

In this chapter, I will argue how the principle of justice in Principlism could be made more apparent as a guiding norm for the actual pharmacogenetic research outcome concerns in particularly research prioritisation, as outlined in chapter four. This will lead on to my defence of the argument that ethical issues which arise from pharmacogenetic interventions in drug development are more concerned with the fair distribution of pharmacogenetic outcomes (such as drugs), and are therefore a matter of justice and not autonomy. My argument will develop into the claim that the principle of justice as fairness exercised in an overlapping consensus as introduced in *Theory of Justice* (Rawls, 1999) and fully developed in *Political liberalism* (Rawls, 2005) would provide the appropriate moral guidance system for pharmacogenetic ethical issues. Furthermore, the development of such a moral guidance

system into a procedural approach known as 'accountability for reasonableness' , i.e. a method of decision-making given unresolved moral disagreements as put forth by Daniels and Sabin (Daniels, Sabin 2002), will be defended. Discussions on these concepts will highlight the equal primacy of social justice (exercised within the principle of justice) in pharmacogenetic research ethics – interpreted as fair distribution of pharmacogenetic research outcomes – with that of the principle of respect for autonomy.

Chapter three illustrated how the language of emotions or intuition as theorised by Rawls's reflective equilibrium can be used to underpin moral guidelines to form the basis of a non-dogmatic normative belief system. The procedure to express this belief system or take into account stakeholder values to develop a moral position would be through the method of overlapping consensus (Rawls, 1993).

However, in order to establish whether such a system is really better suited to the justice concerns of pharmacogenetic outcomes, we need to establish whether the norm of the principle of justice within Principlism is currently sufficiently exercised. Previous chapters suggest that norms such as the principle of respect for autonomy and, to a lesser extent, the principle of beneficence and non-maleficence seem to come to the fore in pharmacogenetic ethics, as illustrated by the predominance of privacy, confidentiality and rights of access issues. Yet, it has been argued in chapter four that, rather than relying on the current interpretation of the protection of autonomy (in which all ethical problems are seen to result from breaches of autonomy), pharmacogenetic research governance guidelines need to provide specific guidance for the actual ethical issues which are concerned with justice. These ethical issues include the distribution of research benefits, research prioritisation discrimination manifested as an increase in social risk (such as racially-based genetic categorisation), and

increased liability of the researcher due to the deterministic interpretation of research outcomes.

Therefore, in section 6.2, I will first turn to how the moral norm of the principle of justice from Principlism is currently exercised, in order to investigate the deficiencies in application of this ethical norm in pharmacogenetic clinical trials. These discussions will lead onto section 6.3, where the basic requirements of an effective principle of justice model for pharmacogenetic research governance will be analysed. The type of principle of justice model I will uphold should promote the ethical requirement of achieving the 'common good' and that this requirement should be considered to be as equally important as the concept of protecting the individual research participant. In this instance the common good is concerned with societal value exercised as research that is based on a needs-driven logic as well as the reduction of the inequality of accessibility of pharmacogenetics research outcomes as already noted in chapter four. In my analysis I will appeal to Susan Cozzens[45] notable position on how the principles of distributive justice can support science and technology policy (Cozzens, 2007) .Cozzens's assessment of justice models provides key points on how the common good in research governance can be realised through the reduction of inequity and inequality. The key theory critiqued from Cozzens's work is identified as the egalitarian justice model of Rawls, which provides an illustration of how inequality in research outcomes can be minimised in research governance by removing unfairness observed as removing ideas that provide advantage to one culturally defined group over another. Cozzens further notes that Rawls' theory permits the growing gap between rich and poor and suggests that to

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counterbalance this effect a communitarian perspective is required which would ensure the upholding of the essential respect of human rights as well as the acceptance of social responsibility. Such communitarian considerations will be addressed with the critique of David Thomasma[46] 'global research ethics framework' (Thomasma, 1997). Thomasma puts forth the question, 'Could bioethics worldwide be based on some other principle than patient rights?' (Thomasma, 1997, p.295), thus supporting the stance of a more robust justice principle for research governance. The framework provides moral guidance within an international setting that subscribes to a minimal morality that is not necessarily culturally dependant, a criticism which has been levelled at Principlism.

Both Cozzens's work and Thomasma's rules address the actual ethical concerns of fair distribution of research outcomes and discrimination and, to a lesser extent, liability, providing ethical guidance for the community (with the help of Thomasma's framework) as well as the individual research participant. They provide additional key elements to the principle of justice required for pharmacogenetic research governance which I uphold to be that of the Rawlsian justice model. Furthermore in this section, discussions will turn to an example of how the issue of research prioritisation can be alleviated with consideration of promoting the common good by appealing to Thomas Pogge's Global Justice Fund. Pogge[47], a former student of Rawls, argues that the *Theory of Justice* does not take into account the power of external parties prevalent in supranational governance (Nili, 2010) who play a pivotal role in determining a nation's economic fate. These parties in turn have a bearing on the current

[46] Editor Emeritus Theoretical Medicine & Bioethics
[47] Director of the Global Justice Program and Leitner Professor of Philosophy and International Affairs at Yale University.

market-driven approach prevalent in drug-development. Therefore, this section will discuss how the principles that underlie Pogge's fund can add specification to the Rawlsian justice model. This would lead me to my last point, a proposal in section 6.4, of a possible application of the Rawlsian Justice model for pharmacogenetic research governance. I will propose to utilise the principle of justice as fairness and overlapping consensus from Rawls to provide a coherent systematic framework based on the 'accountability for reasonableness' proposed procedural–substantive model for regulatory policy decision making in pharmacogenetic research governance.

6.2 Justice in Principlism

Within the research context, Justice is interpreted in distributive terms as the principle of justice, concerned with the requirement of fair access to research participation and access to the results of research. In this section, I will analyse whether this aspect of justice is exercised through the application of Principlism in pharmacogenetic research governance.

Since the inception of Principlism, the ethical principles of most prominence have so far been the principle of respect for autonomy and the principle of beneficence. These are principles which are concerned with the protection of rights of the research participant, and harm being avoided by doing only research which subscribes to the concept of the balancing of harms and benefits. As noted in Chapter four, the actual ethical issues arising from pharmacogenetic research are concerned more with breaches of justice than autonomy. These ethical issues are due to the stratification of the research participant population into genetic groups, making it

apparent that pharmacogenetic technology creates issues of equitable distribution of research knowledge and research priorities rather than ethical issues which point to the inference of disease knowledge as implied by autonomy concerns of privacy, confidentiality and discrimination. Such inference is due to the mistaken role of pharmacogenetics in drug development as outlined in chapter three. This chapter clarified pharmacogenetics' role in obtaining risk assessment information for the effectiveness of a drug in a given patient population, and not of obtaining disease susceptibility information.

The current liberal, individualistic model of the self has become dominant in Principlism (Gillon, 2003), and is enshrined in the principle of respect for autonomy in Principlism. This dominance, seen with the principle of respect for autonomy, has led to the overshadowing of other principles in Principlism (in this case, the principle of justice) as discussed in chapter five. Such overemphasis on the principle of respect for autonomy has manifested itself as 'protectionism' of the research participant, where research ethics in research governance is considered mainly in terms of the protection of autonomy. This has resulted in much effort being invested in securing the informed consent of individual participants, while often ignoring the broader issues of justice in places where the research takes place. It has thus (perhaps inadvertently) reduced the value of Principlism to the principle of respect for persons, a principle which has further been narrowly understood as a respect for autonomy, as critiqued in chapter five. The use of the minimal risk standard in research governance, as discussed in chapter three, was referred to as a 'normative approach to risk-benefit assessment' for assessing the probability and psychosocial risks of harm, but mainly with regard to breaches of informed consent, confidentiality and threats to privacy. Furthermore, it has been argued that

the factual, value-laden content of the minimal risk standard is belief-dependant. This means that the beliefs are held by 'experts', such as regulatory body members, reiterating that risk assessment is more of a measurement of utility, than something concerned with informing what ought to be done in research, or whether the research (in this case, pharmacogenetic assessment) is acceptable and should be utilised in a clinical trial. As a result, research governance is seen to be concerned with the language of emotions when assessing risk, which is in turn based on the principles of uncertainty as discussed in chapter three. All of these are ultimately subjected to mental dispositions or attitudes which have led to various interpretations of the minimal risk standard, and inconsistent application of regulatory assessment and subsequent approval. Therefore, it is necessary to establish a moral assessment which critically takes into account these mental dispositions and aims for coherence between moral judgements of the experts, as well as considering principles, and background theories. Such moral assessment is the overlapping consensus approach by Rawls, which will be critiqued further in section 6.4.

Concluding from this, I argue that the minimal risk standard reduces all ethical problems to breaches of autonomy. To coin a phrase: if the only 'tool' you have is a hammer, then everything looks like a nail (London, 2005). The 'tool' in this context is, of course, the protection of autonomy through the central requirement for informed consent in research ethics, and the 'nail' is all ethical problems resulting from breaches of autonomy (Azétsop, Rennie 2010). This has led to autonomy-focused bioethics which is concerned with procedures that protect choice, with consent itself rather than what is consented to, being the main focus, rather than more substantive issues. Moreover, agency, benefit, participation, risk, and

vulnerability are all understood from the standpoint of individually-focused disease management, whether in the clinical setting or the research site. This highlights that Principlism, in its current form and exercised in pharmacogenetic governance, is therefore concerned with individual protections at the expense of providing ethical guidance for issues concerned more with the fair distribution of research outcomes, which are a matter of justice.

6.3 Common Good and Justice

The position I would like to advance is that normative ethical theory should also promote the pursuit of 'the common good' in research, rather than being concerned solely with providing modes of conduct to ensure non-exploitation of the research participant. The feature of the common good, I will uphold is as important as Principlism in the moral underpinning of pharmacogenetic research governance. The 'common good' in this context, refers to the requirement of pharmacogenetic-based clinical research to produce 'generalisable knowledge' regarding drug responses, with the aim of improving health by developing diagnostics for drug response and/or increasing understanding of human biology. To provide an illustration of the common good in research governance I will appeal to Susan Cozzens's assessment of the egalitarian distributive justice model of Rawls when utilised in science and technology policy (Cozzens, 2007) , which emphasises the aim of achieving 'the common good'. But first I will begin with substantiating why I have considered Rawls's justice model as appropriate, by discussing the basic requirements or elements that constitute a distributive justice model as put forth by Hervé Moulin, in *Fair Division and Collective Welfare* (Moulin, 2004). Elements

which I uphold provide the required specificity for a principle of justice in similar vein to elements which constitute the principle of autonomy as noted in chapter four.

6.3.1 Principles of a distributive justice model

All theories of justice have a minimal requirement attributed to Aristotle who noted (in his celebrated maxim) that equals must be treated equally, and unequals must be treated unequally;

'...things that are alike should be treated alike, while things that are unalike should be treated unalike in proportion to their unalikeness...'

Aristotle, The Nicomachean Ethics V.3, 1131a-b (Blunt, 1991).

Furthermore, in the classical Latin tag definition of justice - '*suum cuique tribuere*' (to allocate to each his own), it is suggested that justice has always been concerned with the idea of deserving and equality (Barry, Mattraver 2000, p.429). In the modern rendition of the Aristotelian maxim, however, it is the formal definition of distributive fairness, known as 'formal' since no criterion is attributed to the constitution of equality, or equality for more than two individuals, meaning the relevant factors for comparing individuals or groups has not been set. Equal treatment of equals is a clear-cut principle - if two persons have identical characteristics in all dimensions relevant to the allocation problem at hand, they should receive the same treatment; the same share of goods, of decision power, or whatever is being distributed. On the other hand, the phrase 'unequals must be treated unequally' is not as clear-cut, and is therefore open to interpretation (Moulin, 2004). However, an Aristotelian

interpretation (Smith, 1999) notes that the appropriate criterion for differentiating among various functions, and thereby justifying the unequal treatment of citizens in certain cases, is to be found in reference to one's contribution to the common good of society.

In essence, as some contribute more to a morally good life, so too should they receive proportionately more in return. This is a concept which is difficult to put into practice when comparing the contribution of vocations which have different remits, such as a good farmer compared to a good skilled craftsmen (Wiser, 1986).The notion that

'... [all should be treated] in proportion to their unalikeness...'

means that all ought to be treated in proportion to the relevant similarities and differences, in which 'relevance' refers to the following defined elements or principles of distributive justice : compensation, reward, exogenous rights, and fitness as put forth by Susan Cozzens (Cozzens, 2007). These four principles guide the definition of 'relevance' and are not exclusive of one another; all belong to the principle of fairness (Moulin, 2004).

Compensation

Some of us require more resources than others—and the compensation principle would justify this inequality in order to restore equality (or at least, diminish inequality) of the shares of the essential commodity in question. For example: those of us who cannot metabolise a key vitamin from their food deserve a free supply of pills; those who lose their home to a natural

disaster deserve assistance. The common feature in these instances of compensation is the justification of unequal shares of certain resources.

Reward

Merit by extraordinary achievement calls for reward: prizes to a creator, an athlete, a peacemaker, and other outstanding individuals. However, a central question is the fair reward of individual productive contributions: the familiar Lockean argument entitles

'one to the fruit of my own labor'

(Olivecrona, 1974)

but this hardly leads to a precise division rule, except when the production of output from the labour input unambiguously separates the contributions of the various workers. Separating the fruit of my labour from that of your labour is easy only when your labour creates no externality on mine, and vice versa. If we are fishing in the same lake, cutting wood from the same forest or sharing any other kind of exhaustible resources, this separation is no longer possible; hence, the fair reward of one's labour is not a straightforward concept. The same difficulty arises when sharing joint costs or the surplus generated by the cooperation of individuals or bodies with different input contributions: some bring capital, some bring technical skills. Furthermore, we reward an employee for their contribution to the profit of the firm, an athlete for their contribution to the success of the team, an investor for the risk they took in financing the project. In each case, a larger share of the pie is justified by a larger responsibility in making the pie (Uzgalis, 2014).

Exogenous rights

Equal treatment of equals is the archetypal example of an exogenous right. Consider the democratic principle 'one person, one vote', expressing the basic requirement that voting procedures must not be biased in favour of particular electors, and implemented by the simple device of anonymous ballots (I can't tell who casts which ballot; hence, I can't give more weight to the vote of a particular citizen). Certain principles guiding the allocation of resources are entirely exogenous to the consumption of these resources and to the responsibility of the consumers in their production.

One example of exogenous rights is the Fairness Principle of Equality in the allocation of certain rights, such as political rights, the freedom of speech and of religion, or access to education. Examples of unequal exogenous rights, beside private ownership, are the difference in status brought about by social standing or by seniority. Furthermore, when the beneficiaries of the distribution are institutions or represent groups of agents, inequality in their exogenous rights is commonplace: shareholders in a publicly traded firm, or political parties with different sizes of representation in the parliament, ought to have unequal shares of decision power.

Fitness

As noted by Moulin resources must go to whoever makes the best use of them (Moulin 2004, p.23). Thus, fitness justifies unequal allocation of the resources independently of needs, merit, or rights. Formally, fitness can be expressed in two conceptually different ways; sum-fitness (a utility measurement) and efficiency-fitness (concerned with efficiency) (Moulin 2004, p.24).

An example of the interplay of these principles is illustrated in the allocation of organs for transplant. Here, compensation gives priority to those who will survive the shortest time or whose life is most difficult without a new organ; reward gives priority according to seniority on the waiting list (first come, first served); exogenous rights enforces strict equality of chances (lottery) or priority according to social status, or wealth (if the donation of the wealthy patient does not increase the availability or organs); fitness maximises medical fitness, namely chances of success of transplant.

Therefore, each individual principle cannot alone address all the problems of justice, but collectively are acceptable minimal requirements of the formal principle of justice, specifying relevant characteristics for equal treatment by identifying substantive properties for distribution. Employing this process of deliberation to the principles as a formal requirement of the principle of justice would avert the limitation of access to therapeutic applications due to income, gender, and race. Systems of governance would instead need to be set up to ensure that society as a whole benefitted from the biotechnology (in this case, pharmacogenetics), and not just specific individuals or groups. Susan Cozzens's assessment of Rawls's egalitarian justice model considers these key elements and will be turned to next.

6.3.2 The Egalitarian Model

The egalitarian model has centrally the concept of equality of all persons and its aims are for individuals to be as much equal as each other (Wetmore 2007, p.345). Although egalitarian models of justice note that persons should receive an equal distribution of certain goods - in this case healthcare – no egalitarian theory advocates the sharing of all possible social

benefits. An egalitarian theory must therefore, allow at least some basic equalities amongst individuals and in effect permitting inequalities which still have some benefit to the least advantaged (Cozzens, 2007).

An example of the egalitarian justice model is described in the classic *A Theory of Justice* by John Rawls (Rawls, 1999). Rawls wanted to develop a theory that could account for the different moral background theories people hold, whilst maintaining that they could morally agree on certain issues (Doorn, 2010).

His approach does not take one of the extreme positions of giving authority to either moral theory or the empirical data; instead, both moral theory and empirical data are integrated to reach a normative conclusion for moral practice;

> *'...My aim is to present a conception of justice which generalizes and carries to a higher level of abstraction the familiar theory of the social contract as found , say, in Locke, Rousseau, and Kant..'*
>
> (Rawls 1971, p.11)

Within Rawls's later work *Political Liberalism,* he acknowledges that agreement on principles of justice, even among reasonable and rational citizens, is difficult to achieve and puts forth the idea of 'overlapping consensus'. This idea allows agreement on liberal justice amongst reasonable people on the basis of citizens' moral sense of justice grounded in their different reasonable comprehensive views (Rawls, 2005, p.144).

In the *A Theory of Justice*, two main goals are pursued: the first is a methodology for deriving principles, and the second is an account of what would be derived were we to follow that method;

> *'...The theory of justice may be divided into two main parts (1) an interpretation of the initial situation and a formulation of the various principles available for choice there, and (2) an argument establishing which of these principles would in fact be adopted…'*

(Rawls 1971, p.54)

Rawls describes the method for deriving principles as Contractarian; rational agents who choose principles for a hypothetical situation in which they are free and equal (Graham 2007, p.9). Cozzens's notes further that under such a contract theory 'a fair system of distribution is one that rational individuals would freely agree to after deliberation' (Cozzens, 2007, p.89).

Rawls noted that the negotiation of a contract is influenced by the starting point of an individual, e.g. if you are affluent, one set of rules will be more appealing than if you are poor. Consequently, he introduced into these hypothetical situations a moral system or social cooperation, in which the negotiating of the contract by individuals is done behind a 'veil of ignorance', known as 'the original position; where individuals would not know what their starting position was (Cozzens 2007, p.89). As noted by Rawls

'…the original position is the appropriate initial status quo which insures that the fundamental agreements reached in it are fair…'

(Rawls, 1999, p.17)

For healthcare, basic questions are thus not based on considerations of utility or the market respectively, but on the appeal to those principles of justice which would have been chosen in the original position.

The original position relies on the idea of the stability of a well-ordered society. One of the features of a well-ordered society is that its regulative principle of justice is publicly known and regularly appealed to as a basis for deciding and justifying laws. In effect, there is a criterion of justice that would be agreed upon by all under conditions that are fair to all, and not distorted by the particular features and circumstances of the existing basic structure of society.

Rawls states that the persons in the original position would adopt two principles, which would then govern the assignment of rights and duties, and regulate the distribution of social and economic advantages across society;

> *'…They are the principles that free and rational persons concerned to further their own interests would accept in an initial position of equality as defining the fundamental terms of their association. These principles are to regulate all further*

agreements: they specify the kinds of social cooperation that can be entered into and the forms of government that can be established. This way of regarding the principles of justice I shall call justice as fairness…'

(Rawls 1999, p.11)

The first principle, also known as 'the equality principle', is concerned with each person having an equal right to the most extensive basic liberties, compatible with the idea of a similar kind of liberty for all. The second principle (or the Difference Principle) notes that social and economic inequalities are to be arranged so that they are both (a) to the greatest benefit of the least advantaged and (b) attached to offices and positions open to all under conditions of equality of opportunity. This situation allows for the unequal distribution of some primary goods, as long as these inequalities benefit all members of society (especially the worst-off members). These principles are to be lexically ordered: the first must be satisfied before we can try to satisfy the second; trade-offs are prohibited.

Such a model is based on the assumption that members of a well ordered society have an effective sense of justice and are normal, cooperative members who would not normally violate just laws. It is further based on an ideal of a society of free and equal citizens who take responsibility for their ends and cooperate with one another based on reciprocity and mutual respect. In this context, 'reciprocity' means that each person engaged in cooperation should not simply benefit, but should benefit on terms that are fair. It is the moral requirement on citizens and officials that they should reasonably believe the terms of cooperation (policy, laws etc.) they propose to be reasonable accepted by others as free and equal citizens, and not

as manipulated, dominated citizens subject to social or political inferiority. Here, citizens are able to live together despite conflicting moral values and ideals as long as they share a moral commitment to society's basic structure. Citizens who are naturally handicapped are allowed to have partial compliance to these terms of cooperation, and for persons whose capacity is not impaired, 'strict compliance' is expected (Graham, 2007).

In the Rawlsian model benefits are conferred to all persons, more so than in a utilitarian model of justice where, despite the increase in total well-being, this would be at the expense of someone else's well-being. Rawls refers to his model of conferring benefits to all as 'justice as fairness' (Rawls, 1999, p.20). He proposed a distributory system from which the worst-off get at least some benefit in this case non-responders or the orphan population[48] (known as the 'social minimum'), even if some are permitted more benefit than others. This 'social minimum' is the basic social entitlement to enabling resources such as wealth and income, yet at the same time it permits inequalities in income and wealth in order to maximally promote the effective exercise of providing the social minimum to the worst-off. For example, growing state economies such as the US, produce tangible benefits for the least well-off, whilst producing more benefits for the most well-off (as observed in the improvement of wages in the bottom 20% of households between 1990 and 2000), but at the same time a growing inequality was observed in the income gap between the top 20% and bottom 20% (Larin, McNichol 1997). The 'social minimum' is enabled by the principle of equality of opportunity, which implies that the basis for obtaining this minimum should be based on factors within

[48] As noted in section 4.6.2; a patient group with a rare genetic profile where there is currently no pharmacogenetic-based drug available.

each person's control, such as motivation, character, and merit. Racial profiling for example, therefore thwarts fair equality of opportunity by making inclusion to a clinical trial dependent on one's parentage, a factor that is morally arbitrary (as previously critiqued in chapter four). Concluding that under 'justice as fairness' there is no tolerance for 'culture-based' patterns of unequal distribution.

Furthermore the 'justice as fairness' principle promotes a distribution system in which the least advantaged get at least some benefit, but this morally permits a growing gap between rich and poor. To which I agree with Cozzens's does not gives rise to a sustainable society

'...rising inequality is the most dangerous social trend of our time...A high degree of inequality causes the comfortable to disavow the needy. It increases the social and the psychological distance separating the haves from the have-nots...'

(Cozzens, 2007, p.91)

In order to reduce such inequalities Cozzens's therefore suggests appealing to Communitarianism which notes that an action is moral when it strengthens community life. Both individual freedoms and society –wide values are considered as equally important, since to maintain community it is essential to respect human rights, and I agree with Cozzens's who notes that to respect human rights one must also accept social responsibilities (Cozzens 2007, p91). The introduction of communitarian considerations would ensure that social responsibility would be taken as seriously as economic growth. This could be achieved by appealing to a minimal morality which would exercise the social minimum. In the context of

this discourse where key elements are being derived to specify and add to the principle of justice in Principlism for research governance, the key element of minimal morality would need to be exercised globally due to the international remit of clinical trial governance. David Thomasma's 'global research ethics framework' (Thomasma, 1997) could be considered since it features ethical rules for the consideration of the community. Rules which acknowledge features of existence and culture that unite human beings without overruling the real differences, that aim to keep within the principles of an egalitarian model of justice – where individuals have equal access to goods and services which is a required feature for research governance.

6.3.3 Thomasma's 'Global research ethics framework'

David Thomasma's analysis of human rights and bioethics gave rise to a proposed set of international rules for the governing of free social intercourse; (Thomasma 1997, p.303) acknowledge universal human experiences in a multicultural setting, such as illness, suffering and death. These rules are considered to be the basis for international multicultural bioethics a 'global research ethics framework', and note that the basis for morality lies in our capacity to understand these experiences and obligations to respond to them. However, Thomasma notes that if

'…this process proves too philosophically cumbersome…'

(Thomasma 1997, p.299),

then an ethical framework based on modern contractarian theory could be used. Contractarian theory is based on rational agents choosing principles in a hypothetical situation in which they are free and equal (Sugden, 1990), and includes such theories as those by John Rawls, which necessitate that no moral (or legal) norm can legitimately violate human rights. In other words, human rights are non-negotiable goods. Rights violations are illegitimate in all moral and political frameworks and their illegitimacy is not dependent on the norms of any moral or legal framework (Baker 1998, p.235).

Thomasma's rules for setting up a 'global research ethics framework' aims for research ethics to incorporate the pursuit of the 'common good', which is interpreted as the promotion of equal distribution of health needs to a diverse population, without unfairly placing the burden of research participation on those who are unable to benefit from the knowledge outcomes. These aims are in keeping with the principles of the egalitarian model of justice – a model such as Rawls.

The ethical framework is an example of Rawls's overlapping consensus since it has features that are interpreted as rules and are moral guidelines considered to be derived from coherence between moral judgements, principles and background theories that would create a non-dogmatic framework of normative beliefs.

Thomasma's rules are as follows:

1. The rule of peaceful dialogue; that is, appealing to the human capacity to be open to new experiences whilst maintaining one's own cultural and religious traditions (Thomasma 1997, p.300).
2. Rule against xenophobia; noting that *'...No individual is an island; no culture or community is the only true society. The truth lies in the mean…'*(Thomasma 1997, op cit 54). It is also noted that as a matter of survival, cultures should not be closed to one another or at least myopic. They should have the illusion of being open to other viewpoints.
3. Rule of respect for cultural pluralism: the type of tolerance observed in world trade and open markets is cited as an example, due to the element of self–interest observed together with knowledge (as a power), gained from the use of technology such as the internet. The presence of tolerance diffuses the notion of power, and a cited example is that of patients' use of the internet for direct information about their diseases and possibly treatments, thereby bypassing the traditional authority of their physicians (Thomasma 1997, p.301).

4. The rule of the common good: as an alternative to the predominance of the concept of autonomy as a basis for human rights. In this instance, autonomy works together with communitarian ethics where individual good and rights coincide with the community's good, noting that one cannot be without the other. As observed from ethical and religious sources of morality which stress the fact that reality is transactional; that it requires individuals to rub shoulders with one another and to be influenced by one another.

5. The rule of cultural apprehension; by appreciating another culture, one ought not to abandon one's own cultural beliefs by supplanting one's beliefs with that of another culture; instead one ought to suspend total abandonment and perceive this as appreciation.
6. The rule of respect for persons in context; in which Thomasma notes that international bioethics ought not to be concerned with just autonomy or community (Thomasma 2001, p.306), but also with persons and their cultural values. Thomasma considers the use of overlapping consensus as a method of balancing values without topping one with another *a priori* (Thomasma 1997, p.302). Therefore, this would mean the allowance of values and issues of individuals and communities, without the abandonment of their cultural traditions.
7. The rule of existential 'a prioris'; which considers the requirement for some *a priori* commitments that have arisen from cultural history and experience, as opposed to metaphysical enquiry. He suggests two such *a priori* commitments; the rule of respect for healing, and the rule of protecting the vulnerable[49] from harm[50], noted as *'...the goal of assisting individuals to enhance their autonomy in the context of their family, to enhance their moral personhood in healthcare decisions...*'(Thomasma 2001, p.307)

[49] Thomasma notes that people are subjected to vulnerability due to the clash of western and non-western values, in which the western values concern of objectification of 'persons and materials' to the extent of that these objects can be manipulated to supplant "the highest power or God in some cultures and religions".
[50] This a priori commitment rests on the notion of consent and the assumption that medicine's intention is to heal, and without patient consent, no other interventions can be contemplated. Furthermore, this is derived from historical experiences of biomedical research done without consent, where the goal of medicine (to heal) was distorted when consent was not present.

These rules highlight the appreciation and tolerance of the differences between cultures, and the recognition of individual human rights (Thomasma 2001, p.307). They would be an appropriate feature for international governance considerations of pharmacogenetic-based clinical trials since they allow the acknowledgment of the following conditions noted to be essential for effective international intercultural bioethical discourse (Marshall, 1994).

- Minimal agreement being reached on the cultural context of the meaning and value of ethical concepts and processes of moral reasoning.
- Commitment to the understanding of cultural context, which may require the acceptance of pluralism.
- Recognition of transcultural structures in human behaviour and existence, for example the theoretical acceptance of fundamental human rights around the world
- Priori commitments must be present in discourse about biomedical ethics; such commitments might be the goal of assisting individuals to enhance their autonomy in decisions to be made, or commitments that emerge from consensus of actions to be taken through ethics committee deliberations or governing policy committees.

Thus Thomasma's framework allows the values and issues of individuals and communities to be heard and acknowledged without the abandonment of their cultural traditions or beliefs. The theoretical underpinnings of this framework maybe communitarian in outlook but the essence of this framework is that of a collection of principles with considerations to transcend specific cultural and ethical beliefs. The aim of these principles is to promote a solid intercultural foundation for bioethics, one that is not just based on the ethical remit of

autonomy and self –determination, but on international human rights which can be expressed through Rawls's overlapping consensus. Thomasma notes that

'…the individual is identified as the locus of decisional capacity for informed consent, even though in many of these countries indigenous populations use a communal or family model of decision making…' (Thomasma 2001, p.298)

This highlights how our sense of personhood and the principle of autonomy in the West informs current medical decision making, including how consent and confidentiality is conducted in the patient –physician relationship. Furthermore, noting that decisional capacity may only be socially expressed in societies that stress the overriding importance of an individual's relationship with family and community thereby rendering the concept of informed consent as meaningless. Thomasma's rules would act as a supportive framework for the Rawlsian model of justice in pharmacogenetic research governance. The framework's focus on respecting human rights would ensure that the aspect of social responsibility noted to be lacking in Rawls's 'justice as fairness' would be upheld, providing in governance a focus on economic freedom and avoidance of discrimination. Research outcomes such as drugs would therefore be ethically reviewed by governance in light of how they contribute to social responsibility, with a focus on promoting health and economic rights in all countries through the recognition of global social justice freedom.

Rawls's overlapping consensus would be applied as the ethical framework for structuring discussion and debate with the aim of coming to a justified agreement. Overlapping consensus

would be in line with Thomasma's substantive rules on the respect for persons in context, the rule of cultural apprehension and the rule of the common good. All of these rules would allow the values and issues of individuals and communities to be heard and acknowledged without the abandonment of their cultural traditions or beliefs. The method could be used, for example, as a means of attaining a coherent basis for decision-making by regulatory bodies, and to gain support for particular decisions in the context of public policy. A Rawlsian model of justice exercised within Thomasma's global ethical framework would allow for stratification in healthcare provision, which would arise through pharmacogenetic drug profiling. This would be allowed as long as the resulting inequalities were (a) to everyone's advantage, and (b) do not undermine fair equality of opportunity or equality of liberty. Behind the veil of ignorance (exercised as an anonymous genetic sample with limited validity information), the rational individual would not be categorised by gender, race, tribal affiliation or nationality. Distributed services principles would not be based on characteristics which are outside individual control, since justice as fairness does not tolerate 'culture-based' patterns of unequal distribution (Cozzens 2007, p.90). The Rawls model of justice is therefore aptly applicable to the pharmacogenetic situation where it has been noted earlier that racially profiled prescribing is subject to significant scientific limitation, questioning whether ethnic or racial categories have any relevance to the understanding of drug response.

As a result a Rawlsian theory has the potential to answer questions on integrating the interests of multiple stakeholders, and - within Thomasma's global ethical framework- of performing justice in different cultural and moral traditions in international settings. All of the above is required for effective research governance for international clinical trials. The added aspect of

Thomasma's framework provides the key element of social responsibility to the Rawlsian procedural concept of overlapping consensus. A key element required to ensure that research is based on societal value rather than a market-driven logic which in turn would promote research committed to the common good. An example of how this key aspect of social responsibility would be applied I will examine in the following section, with reference to the actual pharmacogenetic drug development ethical issue of research priorities and to a lesser extent equitable distribution of research knowledge

6.3.4 Research Prioritisation and Thomas Pogge

As mentioned in section 3.2, governance in health is concerned with utilitarian initiatives, which increase population health gains and promote actions that maximise welfare. Informing this approach, the alleviation of health concerns has benefited corporate interests at the expense of innovative and affordable medicines. This impedes both health gains and economic development in developed and developing countries. The existing global patent system (discussed in section 4.6) will clearly not answer global population health needs, by diverting pharmaceutical research from the health needs of developing countries whose economies cannot secure sufficient financial returns to recoup industry investments in pharmaceutical research, since a market monopoly incentive is irrelevant when market prospects are absent (Trouiller, Olliaro et al. 2002).

Knowledge, a pharmacogenetic outcome as established in Section 2.4, is commonly regarded as a common good which can be described as a global public good (Smith, Thorsteinsdottir et al. 2004), and is defined as:

'...a good which it is rational, from the perspective of a group of nations collectively, to produce for universal consumption and for which it is irrational to exclude an individual nation from its consumption, irrespective of whether that nation contributes to its financing…'

(Smith, Thorsteinsdottir et al. 2004)

Patents alter the character of knowledge, by permitting the exclusion of knowledge from others, yet this is justified on the one hand, since the public receives benefits to compensate for this loss of access such as further knowledge creation, all of which are based on national economies and national public goods. On the other hand, the patent system is designed to provide incentives to develop genomics knowledge in those countries where there is a health economy. Being reliant on market forces, patents are therefore unable to work where there is a non-existent or weak market, and where it is unlikely that the cost of R&D of a drug is unlikely to be recouped. Such a system is therefore unable to encourage innovation in areas targeted at low-income countries. So in order for research to serve the common good interpreted as the promotion of generalised knowledge or providing specific guidance to justice concerns, this market driven logic in R&D needs to be shifted towards a needs-driven logic, based on societal value. This could be done by adding a neglected disease research obligation to pharmaceutical research, manifested as reinvestment of pharmaceutical sales into neglected disease R&D either directly or through public programmes such as a global fund as first introduced in section 4.6.

A global fund based on a proposal by Thomas Pogge (Oprea, Braunack-Mayer et al. 2009) rewards global pharmaceutical research based on community health gains measured in terms of decreased morbidity and mortality. It is an international financing organisation which is based on a human rights framework. Pogge notes that such a framework provides the main political tool to assess policy from an ethical perspective at the international level and where

'…the object of a human right is whatever this human right is a right to…'

(Pogge 2005, p194)

The 'right' in this case would be the right to research outcomes i.e. knowledge, and the violation of this right is seen as the denial of access. Pogge proposed that through ensuring improved access to medical treatments and thereby upholding the common good, this would greatly reduce severe poverty by enhancing the ability of the poor to work, and to organize themselves, for their own economic advancement. This in turn would provide medical innovators stable and reliable financial incentives to address the medical conditions of the poor (Pogge 2005, p190), support human rights in all countries and in turn promote social justice as well as the common good.

The Global Fund has been seen to be beneficent since its aim is to improve global health through rewarding the development of innovative, effective and affordable therapies in all countries (The Global Fund, 2015). However, the limitation of the Global Fund is that it is more suited to supporting large purchases of medicines. Thus more suited to the large –scale health concerns such as Malaria and Aids and less so with orphan or medical conditions which

affect smaller populations or sub-populations as derived from pharmacogenetic differentiation. Its set-up also does not aim to incentivise innovation. However, one might say that its purchases do have an incentive effect: innovators can now expect that, if they develop a high-impact medicine for AIDS, TB or malaria, they will earn money from mark-ups on sales supported by the Global Fund in behalf of poor patients.

Further to the initiative of the Global fund, Pogge has since developed the Health Impact Fund (HIF) which is similar in that it is financed mainly by governments. Its main difference turns out to be that HIF develops and distributes internationally, medicines for typically neglected diseases at low prices. By limiting prices of already registered medicines to the lowest feasible cost of production and distribution. It rewards a new medicine only for the improvement relative to the treatment that patients would otherwise have had. This incentivises innovators to concentrate their efforts to where they can realise the largest incremental health benefit. HIF works in collaboration with the Global fund where medicines produced by the HIF are available for purchase by the Global fund without the mark-up. However, the HIF has not been without its critics, such as Jorn Sonderholm who perceives the HIF as a 'free ride' given to developing countries by developed countries on the basis of Pogge's[51] controversial assumption that the developed world is significantly causally responsible for the public health problems in the developing world (Sonderholm 2010).

[51] Pogge actually notes that '…the question is not whether affluent countries should subsidise advanced medicines for the poor. Rather , the question is whether affluent countries may promote the enforcement of temporary monopolies that make advanced medicines to the majority of humankind (Pogge 2011, p2)

The HIF together with the Global Fund could promote social justice at a global level by shifting international relations away from an emphasis on national interests (which restrict international cooperation to humanitarian assistance of vulnerable groups whose needs are not met by the market economy) and toward shared economic and health values via increased solidarity between countries. Such shared values would improve global health through the promotion of rewarding industry for drugs based on the actual impact on health, resulting in the encouragement of developing more innovative, effective and affordable drugs that would re-orientate the market to focus on improving community health. The facts above would lead to the introduction of the concept of shared health and economic value as a common good. Combining market and community incentives, such focused interest on resource poor settings would prompt the industry to concentrate on affordable therapeutic solutions, such as pharmacogenetics, which promises to decrease R&D. Furthermore, this would focus the business interests of industry towards incorporating the health needs of low-income countries into global research agendas, whilst continuing to support the health needs of high-income countries. Research outcomes would therefore be reviewed by governance with a focus on social responsibility. This aspect has been partly achieved (McCoy, Kembhavi et al. 2009) by developing global fund programmes to reward worldwide pharmaceutical research based on community health gains, measured in terms of decreased morbidity and mortality. Such an approach offers the greatest benefits to the worst-off social groups within countries, and reduces global inequalities in health.

Therefore Pogge's HIF and the Global fund has the requirement of introducing the concept of shared health and economic value as a common good, in addition to the access of knowledge

as a common good. It has the potential to support research for neglected diseases as a research priority at a global level. Providing the introduction of a more integrated global approach to drug development, since the business interests of industry would incorporate the health needs of low-income countries into global research agendas, whilst still continuing to support the health needs of high-income countries. The key elements of the common good together with other key elements such as that of minimal morality and social responsibility noted from Cozzen's assessment of Rawls's justice model and Thomasma's global ethics framework would provide additional ethical guidance for pharmacogenetic research governance. This ethical guidance would support and uphold the Rawlsian procedural concept of overlapping consensus which has been shown to best deliver the required specifications of justice for pharmacogenetic research governance, and to which I will now discuss.

6.4 Rawls's 'Overlapping Consensus': a possible way forward?

How would the egalitarian Rawlsian model be applied in pharmacogenetic research governance? As I argue in this section, would be through Rawls's method of overlapping consensus. As noted in chapter three, mental dispositions such as intuition seem to play an important role in genetic governance discourse, and the aim of Rawls's overlapping consensus is the harnessing of the mental dispositions into a coherent systematic framework of normative beliefs. I will use Daniel and Sabin's (Daniels, Norman 2002) procedural approach to healthcare resource allocation to illustrate how overlapping consensus could be applied in the moral assessment of pharmacogenetic based research protocols by governance levels such as

regulatory and policy makers. Daniel and Sabine proposed 'accountability for reasonableness' framework for priority setting of decisions in healthcare in the face of widespread disagreement about values. Accountability for reasonableness is the idea that the reasons or rationales for important limit-setting decisions should be publicly available (Daniels, Norman 2002, p.44) and that such a framework is an attempt at providing rules or conditions for a procedure for ensuring that resulting decisions are fair, reasonable, and legitimate to the point where even those who would be adversely affected will have a reason to abide by them.

6.4.1 Overlapping consensus

The Rawlsian method of overlapping consensus seeks to find a balance between considered judgements and intuitions of particular cases, providing an approach which enables decision-making in a pluralist context with different stakeholders who often endorse different or possibly conflicting cultural and moral frameworks. The concept was introduced in his later work 'Political Liberalism' (Rawls, 2005) and arose due to Rawls's recognition of the plurality of incompatible and irreconcilable moral frameworks within a democratic society. In other words, people are able to live together despite conflicting moral values and ideals as long as there is a sharing of moral commitment to society's basic structure. The focus of overlapping consensus is that people with divergent comprehensive doctrines can overlap in their acceptance of a conception of justice. They do not have to agree on everything but they do have to agree on 'principles of fairness' which specify the fair terms of cooperation among citizens and the conditions under which a society's basic institutions are considered as just (Doorn, 2010). Therefore, overlapping consensus is the justificatory basis for principles of justice and in this context of providing specification to the principle of Justice in Principlism

for pharmacogenetic governance; overlapping consensus will be used in a procedural way as a framework for structuring discussion and debate with the aim of coming to a justified agreement.

Overlapping consensus is aimed at the convergence of three different levels of moral viewpoints namely (1) considered moral judgements about particular cases or situations, (2) moral principles, and (3) descriptive and normative background theories. Instrumental to the success of such a method of providing procedural justification and dealing with moral issues is the achievement of reflective learning, which is open and inclusive.

Central to the application of overlapping consensus to pharmacogenetic research governance is the review of the differences in risk perception by the various agents involved, such as society, science and industry. As highlighted in chapter three, in application, one must focus firstly on the descriptive or conceptual issues concerned with semantic or empirical disagreements. Focus thus shifts to one or more normative issues on what ought to be done in research, or what should be done to make the research acceptable and appropriate. Finally, collective cooperation is encouraged through the convergence of viewpoints or overlapping consensus.

Descriptive concerns

Descriptive concerns are considered judgements which are a response to moral issues at hand. As noted earlier in chapter three, they are value judgements based directly on emotions which can be unreliable, which are also considered to be the moral voices within a person (Barilan,

Brusa 2011). These 'voices' tend to come with supportive reasons and are not just confessions of mere feelings. For example, the statement 'I am sure we must not do this' is not a considered judgement, unlike the statement 'It seems to me that the proposal is too similar to deception', which is a considered judgement. However, the latter statement lends itself to further inquiry and reason exchange, which is a requisite for deliberation. The concept of uncertainty previously discussed in chapter three examines examples of such descriptive concerns, where the language of compassion and empathy become tools in standard policy generation, helping to link genomics and the public through the language of reflection. For regulatory agents using the concept of uncertainty for assessing risks, the precautionary principle would still be appealed to - that of society not waiting until it knows all of the answers before attempting to protect against significant harm. Focus will however also be on the benefits of this technology and normative outcomes, rather than just epistemic information (i.e. facts concerning what we should believe in as derived from the minimal risk standard). Emphasis of risk assessment could be based partly upon the principle of solidarity, as noted in chapter five, where, for example, the report *'Pharmacogenetics: ethical issues'* from the Nuffield Council on Bioethics notes issues concerned more with breaches of the principle of solidarity, and moves away from issues based on the principle of autonomy apparent from the minimal risk standard assessment. In this instance, solidarity is based on altruism and feelings of compassion and empathy, and is interpreted as the principle of reciprocity; an awareness of interdependency and interrelatedness that is the basis of a sense of obligation to do something in return as aforementioned, this is an important feature of Rawls's egalitarian justice model. The participation in research is assessed along the lines of the common good (generating knowledge) and the sharing of research benefits. Furthermore, the genetic database is

perceived as a common public good. The principle of reciprocity would therefore be a structural vehicle in the overlapping consensus model for bringing to the fore such considered judgements.

Normative concerns

Normative concerns are derived from the different normative background theories that the various agents subscribe to. In the case of current pharmacogenetic governance, normative concerns as expressed by regulatory bodies seem to be limited to the interpretation of risk through the minimal risk standard. This is a standard that assesses the potential benefits of research projects, in terms of knowledge gained in proportion to the potential physical and/or psychological harm it might cause to the research participant during drug interventions, associated tests and monitoring procedures encountered in a clinical trial. For industry, normative concerns are seen as breaches of GCP and risk perception is more of a scientific assessment of risk as probabilities of harm (as noted in chapter three). Industry focuses their normative concerns on the application of Principlism (notably the practical application of the principle of respect for autonomy that is informed consent) to ensure the protection of research participants' privacy, confidentiality and non-discrimination, as highlighted in chapters four and five. However, these normative concerns need to widen to breaches of justice and equity apparent for this technology. Equal access to the benefits of this technology and solidarity (as social responsibility through benefit sharing as discussed earlier in this section) should be considered in regulatory discourse, as well as considerations of consent, privacy and storage (confidentiality).

Convergence of viewpoints

For research governance Van de Poel and Zwart (van,de Poel, 2010) argue that learning about one's value systems is a prerequisite for arriving at an overlapping consensus, as only then do people become aware of the legitimacy of other people's opinions and normative background theories. In order to encourage these learning processes, the overlapping consensus approach firstly acknowledges the differences in meanings attached to the notion of risk for different agents, in order to constructively work toward a justified outcome. These differences are derived as noted from the different background theories from which the different notions of risk are derived. For example, regulatory bodies see risk as physical, moral and emotional harm related to drug interventions, associated tests and monitoring procedures encountered in a clinical trial as noted. The industry sees risk as probabilities of harm, while users of the outcome of this technology see risks in relation to its acceptability, whereby the elements of determinism and reductionism come to the fore (as discussed in chapter three).

Moral reflection occurs due to the examination of moral judgements in particular matters or layers when applying the concept of an overlapping consensus,. This is as follows: (1)descriptive and normative background theories as previously discussed with more general or (2) broader beliefs and principles on similar issues (obtained from considered moral judgements about particular cases or situations), and (3) moral principles. In order to come to a decision on how to respond to moral issues, agents move back and forth between these beliefs and considerations, reflect on them, revise them if necessary, and attempt to achieve an acceptable coherence between their moral judgements on particular matters, and more general

or broader beliefs and principles on similar issues. Overlapping consensus in effect becomes a process of facilitating the integration of scientific objectivity and the non-scientific view (or some aspects of the regulatory body view and the introduction of the user's view) by recognising the different rationalities of both approaches. This is achieved by noting that an agent's personal normative background theory (or 'ethics position') influences their judgements, actions, and emotions in morally laden situations, in which their judgements can be traced back to or are informed by their different ethical positions.

6.4.2 'Accountability for reasonableness' framework

Accountability for reasonableness is the concept that uses reasons or rationales for important limit-setting decisions, and that these reasons are ones that a person would use to seek cooperation with others through justification (Daniels 2002, p.44). Daniels and Sabine proposed 'accountability for reasonableness' framework as an acceptable fair process for priority setting decision making in healthcare when agents were faced with widespread disagreement about values. The framework is an attempt at rules or conditions of a procedure for ensuring resulting decisions are fair reasonable and legitimate to the point where even those who would be adversely affected will have a reason to abide by them. It sets limits through the application of meeting four conditions and these conditions makes decision makers 'accountable for the reasonableness' of their decisions (Daniels 2002, p.10). The proposed four conditions necessary for a legitimate decision-making process regarding health-care limits are:

1. Publicity Condition: limit-setting decisions must be public. Both the grounds for making direct and indirect limits to care as well as the decisions must be made publicly available.
2. Relevance Condition: the grounds for the decisions must be ones that fair-minded people can agree are relevant to meeting health care needs under restraint. The deliberation of these grounds are focused on a shared goal, in this case the common good, and these grounds provide reasonable explanation of how the organisation seeks to provide 'value for money' in meeting the health needs of a defined population under resource constraints. Such grounds or rationale are considered reasonable if they appeal to evidence, reasons and principles that are relevant to mutual justifiable terms of cooperation (Daniels 2002, p.12).
3. Revision and Appeals Condition: limit-setting decisions must be subject to revision and appeal and the process for this must meet the first two conditions. Furthermore, these decisions must be revised in time in light of new evidence.
4. Regulative Condition: some form of regulation must be put in place to ensure that conditions 1-3 are met. This could either be voluntary of public regulation.

This four conditioned approach connects health-plan decisions to a broader educative and deliberative democratic process (Daniels 2002, p.46). In summary transparency of reasons for a decision is through the Publicity Condition. The Relevancy Condition sets justification of the decision. The Revision Condition makes learning from experience and responding to disagreements central to the decision-making, and the Regulative Condition provides the backbone to the other conditions.

I will be critiquing the application of the conditions for pharmacogenetic governance at the governmental level, and will be appealing to the analysis by Michael Schlander of the real-life performance and robustness of NICE (National Institute for Health and Care Excellence) technological appraisal process using ADHD (Attention Deficit / Hyperactivity Disorder) as a case study (Schlander, 2007). I will also evaluate how NICE could have applied overlapping consensus for technological appraisal no. 295 of breast cancer drug, Everolimus (trade name, 'Afinitor', Novartis Pharmaceuticals UK), which has the pharmacogenetic biomarker HER2 negative for hormone-receptor-positive advanced breast cancer, and was rejected for such treatment in August 2013. The reason for such analysis is due to NICE's importance in pioneering technology assessment outside of the UK with other foreign governments as well as on behalf of the Department of Health for England and Wales, and how such an analysis could be used as an example of the application of overlapping consensus in a global research governance setting.

Schlander compared NICE's technology appraisal process with the 'accountability for reasonableness' framework. The technology appraisal is a recommendation for the use of new and existing medicines and treatments within the NHS in England and Wales, such as:

- medicines
- medical devices (for example, hearing aids or inhalers)
- diagnostic techniques (tests used to identify diseases)
- surgical procedures (for example, repairing hernias)

- health promotion activities (for example, ways of helping people with diabetes manage their condition).

(National Institute for Health and Care Excellence, 2014)

The process of the technological appraisal consists of four phases;

1. **Scoping**; experts and stakeholders are identified as 'consultees' and 'commentators', together with an independent academic group to assist in the appraisal. A draft remit is set –up and discussed at a scoping workshop which outlines the clinical problem, the patient population, the technology and its comparators (if applicable), treatment setting, health outcome measures and costs, timelines. A final remit is prepared by Ministers for formal appraisal by NICE.
2. **Assessment**; the main activity is the evaluation of the evidence (noted in an evaluation report) relating to the technology in question to produce an assessment report.
3. **Appraisal**; comprises of four elements which are carried out by a standing advisory committee (AC) who comprise of members drawn from the NHS, patient and care giver organisations, relevant academic disciplines and the pharmaceutical (and medical devices if applicable) industry. The elements are; (1) AC considers evidence in the assessment report to (2) develop an Appraisal Consultation Document (ACD) (3) distribution of the ACD to 'consultees' and 'commentators' (4) review of the ACD in light of comments received during the appraisal committee consultation and preparation of the Final Appraisal Determination (FAD) document which forms the guidance for NICE on the use of the appraised technology.

4. **Appeal**; FAD is distributed and published as NICE guidance unless consultees lodge an appeal within 15 working days from receipt of the FAD.

A summary of these phases as applied to the technological appraisal of Everolimus;

Scope

Draft scope issued for initial review in January 2012, the objective of the scope was to provide clinical and cost effectiveness data of Everolimus. Consultees (experts) were Novartis Pharmaceuticals UK (Everolimus); patient/carer groups - Breakthrough Breast Cancer and Breast Cancer Care. Professional groups such as Cancer Research UK, Royal College of Nursing, Royal College of Pathologists and Royal College of Physicians. The Department of Health and Welsh Government were also consulted. The following commentators who had no right to submit an appeal were British National Formulary, Commissioning Support Appraisals Service, Department of Health, Social Services and Public Safety for Northern Ireland and Healthcare Improvement Scotland. A number of scopes were issued and reviewed by the consultees until 31 October 2012, and all scopes were published on the NICE website (National Institute for Health and Care Excellence, 2014).

Assessment

The Assessment group provided the final evaluation report in 21 March 2013 which was published on the NICE website on 30 April 2013. The report provided evidence based data from the consultees on Everolimus, and gave rise to an assessment report which was produced on 3 July 2013.

Appraisal

Appraisal Committee meetings were held on 3 February 2013 and 23 April 2013, the first meeting published the Appraisal Consultation Document (ACD) which summarised the evidence and views of the consultees and resulted in setting out draft recommendations made by the Committee in the final appraisal determination (FAD) published on the NICE website on the 5 July 2013. The FAD was then used as the basis for NICE's guidance on using Everolimus in the NHS in England and Wales in which Everolimus was not recommended since it was found not to provide enough benefit to patients to justify its high cost.

Appeal

No appeal was lodged.

In comparing Everolimus technological appraisal NICE process with the 'Accountability for Reasonableness' conditions we find that the first condition; Publicity, was fully being met, and that there was a good level of transparency in the overall process. Key features of which were the publication of assessment reports, FAD, and ACD to the publically accessible NICE website, public appeal hearings and the publication of appraisal committee meeting minutes. The second condition; Relevance, it was noted for Everolimus assessment that the issues were mainly concerned with clinical and cost effectiveness data, which was considered (by Novartis) to not produce the required evidence for the treatment. Novartis noted that evidence was based on18 months trial data instead of the provided twenty-two months therefore there were limited data points for analysis such as disease free survival data. Furthermore, I note that if bioethical input was employed via inviting bioethicist to be a part of the 'consultees' and 'commentators' then considerations of effectiveness , equity , and patient choice would be apparent in the assessment. As noted by 'accountability for reasonableness' , these factors (

consideration of effectiveness, equity and patient choice) constitute a values framework which is implicit in resource limit deliberations This values framework further breaks down the consideration of effectiveness into four elements;

1. Effectiveness – 'does the treatment achieve a desired effect?
2. Value to the patient relative to the value of other treatments
3. Impact – value weighed for degree of effectiveness
4. Efficiency – impact per unit cost

(Daniels 2002, p.162)

All of which Daniel and Sabine had envisaged that NICE would adopt, but notes that there is a way to go with the decision –making process which is seen primarily as the task of experts.

The third condition – Appeal and revision, even though no appeal was lodged it was noted from Schlander's critique (Schlander, 2007) on ADHD that NICE's appeal process was more restrictive than what Daniel and Sabin's 'accountability for reasonableness' framework envisaged especially with regard to timelines, where there was only 15 business days to lodge an appeal against the FAD for example, not enough time to instigate a legal review deemed necessary. Moreover, 'accountability for reasonableness' recommends that a broad scope of stakeholders are engaged in the process of deliberation (Daniels 2002, p.58), a recommendation that cannot be upheld if limited timeframes are set-up. The fourth condition-Enforcement, Schlander notes that implementation of the NICE guideline may be enforcement itself. Also he noted that a quality assurance system should be included in which currently one

does not exist for the NICE technology assessments. Such a system would ensure the adoption of the three previous conditions (Publicity, Relevance and Revision) without legal recourse. Regulation under accountability for reasonableness could therefore be voluntary private enforcement or public regulation, in which either would be sufficient to ensure the facilitation of the review on matters of fairness without fear of legal reprisal (Daniels 2002, p.60).

The example of the NICE technology appraisal process setting shows how accountability for reasonableness can be employed as a means of ensuring that the principle of justice can be exercised. The appraisal process did adhere to A4R with regard to showing a high level of transparency fulfilling the publicity condition. However, the Relevancy condition was an issue with regard to the agreement on the type of data that was assessed as well as the imposition of cost constraints. Furthermore the Appeal and Enforcement condition were observed to need improvement such as further guidelines for quality review and explicit enforcement.

6.5 Conclusion

With the advent of international research collaborations, and the centralisation of regulations and laws associated with scientific and technological developments as noted in chapter three, participating countries in research programmes will not be able to decide which ethical issues will be of most concern for them when partaking in pharmacogenetic-based clinical trials. As a result, the debate on prominent ethical issues will become more of a centralised issue – a

constituent of the global research agenda. The supply of drugs is one example where regulation is on an international scale, but the demand and reimbursements are more regionally and locally organised; therefore, ethical issues arise in areas of supply and demand, concerned with the inequity of distribution. These differing tendencies in the development of new drugs also exacerbate research prioritisation issues as discussed in section 4.6, particularly between economically rich and poor countries. Developed countries, for example, are more concerned with drugs for subgroups, whilst developing countries which make up 85 per cent of the world's population (Oprea, Braunack-Mayer et al. 2009) are more concerned with generic and affordable drugs which are economically suitable for large populations. Hence, essential drug lists should take into account the genomic variations between populations in these countries, and there should be an emphasis on research that looks at whole populations, rather than subpopulations. This would be done in order to further understand and harness global genetic diversity, as well as to enable a move away from concentrating on protecting the individual, thus collectively ensuring the distribution of access to pharmaceutical outcomes.

As noted in the concluding remarks in chapter five, Principlism puts the individual in focus due to the principle of respect for autonomy, in which breaches of Principlism in the research setting are interpreted as autonomy violations. These bring the language of individual rights to the fore. However, this individualism is challenged in pharmacogenetic based research, due to genetic information not being solely for the individual. Pharmacogenetics as a risk assessment tool gives rise to ethical issues which in reality are more concerned with fair distribution of research outcomes (i.e. justice) than autonomy. Furthermore, the stratification of the research

participant population into genetic groups brings about issues relating to equitable distribution of research knowledge and research priorities, rather than the inference of disease knowledge.

These ethical issues arising from the use of genetic information in pharmacogenetic-based clinical trials are not just concerned with the individual, but with the community at large, especially when a genetic database is used. This emphasises that the risks and benefits of a pharmacogenetic project require assessment at different levels to cater for the varied participatory agencies, such as the research participants and their families, or particular groups and their communities. So, as well as ethical considerations being based on liberal individual rights, where individuals' rights and resources determine their access to goods and services, communitarian ethical considerations where individual rights need to be balanced with social responsibilities may also be useful. These communitarian considerations are noted to be concerned with participation in research for the common good, and the sharing of research benefits (known as solidarity) (Sutrop, 2004).

Therefore it is an ethical challenge for pharmacogenetic-based clinical trial programs to acknowledge liberal considerations such as an individual's rights to privacy, confidentiality, and right to know/not to know, together with communitarian considerations concerned with collective rights and solidarity (where the genetic database is perceived as a common public good, and it is seen as a duty to participate in research, to know, and to inform others) (Sutrop 2004, p.7). Similar questions arise when evaluating the use of population–based genetic databases or Biobanks.

When taking into account both liberal and communitarian sets of considerations, or the balancing of these considerations (and in turn reducing ethical conflict), it is vital to acknowledge the cultural setting of these rights, especially for a global research ethics.

From this discourse Rawls's justice model has therefore been found to be an appropriate liberal model for the specification of the principle of justice inherent in Principlism. This model addresses the issue of inequitable distribution of research knowledge outcomes, allowing for benefits for the disadvantaged as well as the advantaged due to the principle of justice as fairness which ensures that benefits are attributed to everyone regardless of their background moral or otherwise. Such a model is however not morally robust enough to operate within research governance on an international setting which is required due to the global nature of pharmacogenetic clinical trials. Rawls's theory minimises inequality in research outcomes by removing unfairness observed as removing ideas that provide advantage to one culturally defined group over another, however the theory would permit the growing gap between rich and poor i.e. developed and developing countries, thereby perpetuating 'morally' unsustainable societies. Therefore, the introduction of communitarian considerations as noted by Cozzens would ensure that social responsibility would be taken as seriously as economic growth. Thomasma's rules exercised within the global ethics framework would provide the additional key element of social responsibility lacking in Rawls's justice as fairness principle by appealing to a minimal morality which would ensure the maintenance of social cohesion by keeping socioeconomic inequality within bounds - which is a moral issue for many societies. But such reduction of inequalities would only be observed if inequality is seen in light of its effect on societal relationships. Issues of research prioritisation can also be

addressed by appealing to the societal value of research but within a socioeconomic context as exampled by Pogge's HIF and the Global Fund which promotes research committed to the common good. Lastly, the principle of justice as fairness as exercised in the Rawlsian method of overlapping consensus would be applied to reconcile pluralism of ethical views by allowing for moral decision making in a pluralist context with different stakeholders, without giving a priori priority to any of them. Emphasis is placed on analysis of the agents in this ethical assessment, their agendas, considered moral judgements, and belief and value systems, when applying this approach.

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7. Chapter Seven: Overall Summary and Conclusion

In this thesis, the main research question, Research governance in pharmacogenetic-based drug development: why the principlist approach?, was addressed by assessing critically whether the ethical framework of Principlism underpinning current research governance is too broad to address specific ethical justice issues for drug development involving pharmacogenetics. Arguments made throughout the research were based on the following claims:

1. There is an overriding deference to the principle of respect for autonomy, as witnessed in the current ethical interpretation of the management of risk.
2. The principle of justice needs to be specified when applied to genomic concerns. Its current non-specificity may be a reason for the over-compensatory application of the principle of respect for autonomy.
3. Current interpretations of Principlism represent moral values that are culturally dependent. Pharmacogenetic research outcomes have a global impact, ergo Principlism or another moral guidance framework ought to be representative of common moral values which are culturally neutral.

The arguments presented answered the main thesis question by highlighting that Principlism fulfils the remit of current research ethics by providing guides of conduct on a commensurable ethical scale, on the steps that need to be taken in the management of ethical research. In effect, Principlism simplifies bioethical decision-making; a feature that has popularised this ethical approach. Moreover, the constituent principle of respect for autonomy has proposed

(questionable) entrenched concerns and increased perceptions of unethical research in terms of research participant liabilities within the current ethical guidelines on pharmacogenetic governance. Such concerns emanate from the legacy of research participants being subjected to physical atrocities, and which, I argued, have highlighted the current predominance of the execution of the principle of respect for autonomy at the expense of the other principles; in particular, the principle of justice, within the pharmacogenetic governance setting. Furthermore, I have maintained that the expression of such concerns is made at the expense of the required research ethics remit of serving the common good (the facilitation of the production of knowledge concerned with improving health and/or increasing understanding of human biology).

Moreover, my critique highlighted that the multi-layered regulations inherent in research governance are based on assessing risks of harm in research projects. However, I argued that this assessment was precautionary in its approach and potentially prohibitive for the development of pharmacogenetics-based drug development. Research governance's aim of managing risk was noted to be perceived as calculable, but it was established to be value driven or influenced by belief states. Furthermore, this was argued as the reason for the rise of the variability of regulation interpretation. Moreover, it was contended that the presence of these value-laden risk perceptions presented considerations on whether these perceptions should be taken into account when establishing robust regulatory mechanisms; especially in the assessment of the genomic technologies, such as pharmacogenetic drug development regulation.

From the analysis of the minimal risk standard, it has been demonstrated that this methodology, as an example of current research governance risk assessment (albeit for paediatric research and research that involves vulnerable populations), proved inadequate for providing information on what ought to be done in research involving pharmacogenetic information. However, as a methodology based on 'measurement of utility', it does provide indicators of what we should believe in; i.e. an epistemic interpretation. Indeed, since it has been established that risks remain present but are inherently unknown in pharmacogenetic research outcomes, the view that uncertainty is a prevalent concept in this type of research was made apparent. This highlighted the need to test for the options or features selected for regulatory assessments which highlight the benefits of this technology in the governance of pharmacogenetic-based clinical trials, rather than focusing on detecting the hazards. Furthermore, I introduced the idea that a possible test option for consideration would be Rawls's 'overlapping consensus', since this approach takes into account the aspect of mental dispositions. This was established as a feature when genomics was introduced in research.

Throughout this thesis, I have argued that pharmacogenetic ethical issues are not concerned solely with autonomy. I further contended that pharmacogenetics - in terms of drug development - is used as a risk assessment tool, and that ethical issues that arise are more concerned with the outcomes of this research tool; namely, ethical issues concerned with equity, fair distribution and research prioritisation, resulting from the differentiation of patient categories according to genotype in these clinical trials. These ethical issues were noted as matters of injustice rather than autonomy, and arose due to an inappropriate use of patient differentiation or through failure to use such differences, especially when pharmacogenetic-

based clinical research is employed on a multicentre, global scale. Furthermore, I argued that the perception of pharmacogenetic-based clinical trials as being inherently exploitive to research participants was based on the concept of pharmacogenetics as a disease susceptibility tool; thereby raising ethical concerns relating to breaches of autonomy. These implied that ethical concerns for pharmacogenetics were demonstrated as illustrating how the current interpretation of Principlism has entrenched concerns and increased perceptions of unethical research in the field of pharmacogenetics, in terms of research participant liabilities.

This led to the conclusion that Principlism, with its current interpretation focused on autonomy concerns, is not a robust ethical framework for pharmacogenetic drug development research governance. Therefore, I proposed that further specification of the principles of Principlism, namely the principle of justice, is required and incorporated into the Principlist ethical framework for pharmacogenetic research governance. I argued that this 'improved' Principlism ethical framework must take into account international genetic governance considerations, since pharmacogenetic outcomes are globally operational. Moreover, such an ethical framework does not necessarily need to be culturally dependent, but should subscribe to a minimal morality; thereby counteracting criticisms levelled at Principlism for its tendencies towards American values.

I proposed the incorporation of Thomasma's established rules as worthy additional moral guidelines in the establishment of a 'global research ethics framework'. Rules which subscribe to a minimal morality to further ensure that social responsibility is incorporated in research

governance. These rules, which are not necessarily culturally dependent, take into consideration the pursuit of the common good as one of the aims of research ethics. These rules, together with the 'improved 'or 'enhanced' Principlism framework provide more insight into treatment options for conditions that seriously impair autonomous and social functioning, without placing the burden of research participation on those who are unable to benefit from these knowledge outcomes.

Furthermore, I contended that the current market-driven logic in research and development, based on the patent system (inherent in the current research governance structure), needs to make a shift towards a needs-driven logic, in accordance with societal value. It was established that research based on societal value would promote research committed to the common good, expressed as shared health and economic values, as well as generating information or knowledge for the improvement of clinical practice. The Global Fund and the Health Impact Fund, has the potential to support research for neglected diseases as a research priority at a global level, was proposed as an example of the common good and social responsibility, based on justice requirements (as in the commitment to improve health and/or increase understanding of human biology under the remit of achieving equality or reducing inequality).

Further to establishing that the variability of the interpretation of the minimal risk standard was due to value-laden risk perceptions, I argued that these perceptions ought to be considered when developing regulatory mechanisms for the assessment of genomic technologies, such as pharmacogenetic drug development regulation. Therefore, Rawls's 'overlapping consensus'

was identified as a means of integrating the aspect of intuitions and these value-laden risk perceptions into pharmacogenetic research governance. However, it was noted that, for research governance to integrate this approach, an active role would be required to provide connections between the introduction of new technologies such as pharmacogenetics, and the moral concerns of citizens. The role of research governance would, thus, be in the alleviation of the cultural and moral basis of societal unease concerning this biotechnology by integrating public, industry and regulatory body discourse into the governance process. The role of the bioethicists could be utilised to effect this integration through the procedural approach developed by Daniels and Sabine of the 'accountability for reasonableness' framework. This would undertake the role of employing the medium of 'overlapping consensus' into the research governance process. I hope to have highlighted that the presence of Rawlsian considerations in governance assessment promotes the assurance that research benefits would be attributed to everyone, regardless of their economic, racial, cultural or moral background. This is due primarily to the principle of justice as fairness, taken from Rawls's *A Theory of Justice*. Therefore, a Rawlsian justice model was analysed principally for its readiness for incorporation into current ethical guidelines on a global level, which were lacking in specificity of the principle of justice.

Therefore, moral guidelines for research governance of pharmacogenetic-based clinical trials would be derived from the non-dogmatic framework of normative beliefs, such as Rawls's 'overlapping consensus'. Coherence would be achieved between moral judgements, principles and background theories, as well as the principle of justice as fairness. This principle would provide specification for the principle of justice inherent in Principlism, which would ensure

that benefits are attributed to everyone, regardless of their background. I argued further that greater specification for the principle of justice would ensure that this principle could be exercised effectively in order to alleviate pharmacogenetics' actual ethical issues. These relate to the equitable distribution of research knowledge and research priorities, rather than inferences of disease knowledge (as implied by ethical concerns regarding informed consent, privacy and confidentiality).

Due to the requirement of establishing my arguments within the extensive knowledge arena of the subject matter, I was unable (but would have liked) to provide an analysis of how overlapping consensus would be disseminated specifically through the various research governance layers; in particular, following its inception at the clinical trial application stage, to the ethical committee level. Furthermore, more analysis could have been performed on the development of employing uncertainty as the concept of permissiveness in research governance, an alternative or option to overlapping consensus. This is where the introduction of test options in drug regulation would be assessed in a quantitative manner using a practical reasoning framework (i.e. a non-normative approach) and an underlying risk-benefit assessment, such as virtue ethics, that would ask the question 'what is good research?', rather than what we ought to do in light of the facts.

Finally, since informed consent is a prominent feature in current research ethics, the analysis of the consent model known as 'informed request', based on a contractarian ethical model, would have been beneficial in highlighting the current failings of informed consent for genomic research. Informed request places the research subject at the centre of responsibility

for decision making by redirecting responsibility away from the researcher and towards the individual in contract-based consent; thereby providing an ideal consent model for the global ethical framework based on egalitarian justice values. Thus, the issue of participation in a research project is decided by the subject, rather than the researcher. The decision to participate in a research project by the subject is based on the 'stewardship' concept of property; i.e. subjects possessing their bodies in a trust rather than as outright owners (Rao, 2007). This is a concept that was further developed by David Winickoff's Charitable Trust Model, which aimed to create partnerships between researchers and subjects in the context of genomic biobanks (Winickoff, 2007).

In conclusion, I have answered the thesis main research question and discussed the fact that Principlism's ease of use and appeal to rights-based concerns has made it the ethical framework of choice for current pharmacogenetic research governance. By evaluating critically whether Principlism could continue to be the dominant ethical framework for research governance in pharmacogenetics-based drug development, I have argued that there is room for further harmonisation and clarity of regulatory frameworks. I have proposed a solution based on the ethical evaluation of pharmacogenetic drug development, in terms of a Justification model within recognised ethical parameters. A solution that is not overtly concerned with ethical evaluation based on safety and efficacy or a matter of choice, but, rather of need.

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FIGURES

APPENDICES

Appendix (i) The Nuremberg Code.

Appendix (ii) The Declaration of Helsinki.

Appendix (iii) Remarks by the president in apology for study done in Tuskegee.

Appendix (i) The Nuremberg Code.

NUREMBERG CODE

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

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

(National Institutes of Health)

Appendix (ii) The Declaration of Helsinki.

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor

ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the

study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the

publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix (iii) Remarks by the president in apology for study done in Tuskegee.

THE WHITE HOUSE
Office of the Press Secretary

For Immediate Release May 16, 1997

REMARKS BY THE PRESIDENT
IN APOLOGY FOR STUDY DONE IN TUSKEGEE

The East Room

2:26 P.M. EDT

THE PRESIDENT: Ladies and gentlemen, on Sunday, Mr. Shaw will celebrate his 95th birthday. (Applause.) I would like to recognize the other survivors who are here today and their families: Mr. Charlie Pollard is here. (Applause.) Mr. Carter Howard. (Applause.) Mr. Fred Simmons. (Applause.) Mr. Simmons just took his first airplane ride, and he reckons he's about 110 years old, so I think it's time for him to take a chance or two. (Laughter.) I'm glad he did. And Mr. Frederick Moss, thank you, sir. (Applause.)

I would also like to ask three family representatives who are here -- Sam Doner is represented by his daughter, Gwendolyn Cox. Thank you, Gwendolyn. (Applause.) Ernest Hendon, who is watching in Tuskegee, is represented by his brother, North Hendon. Thank you, sir, for being here. (Applause.) And George Key is represented by his grandson, Christopher Monroe. Thank you, Chris. (Applause.)

I also acknowledge the families, community leaders, teachers and students watching today by satellite from Tuskegee. The White House is the people's house; we are glad to have all of you here today. I thank Dr. David Satcher for his role in this. I thank Congresswoman Waters and Congressman Hilliard, Congressman Stokes, the entire Congressional Black Caucus. Dr. Satcher, members of the Cabinet who are here, Secretary Herman, Secretary Slater, members of the Cabinet who are here, Secretary Herman, Secretary Slater. A great friend of freedom, Fred Gray, thank you for fighting this long battle all these long years.

The eight men who are survivors of the syphilis study at Tuskegee are a living link to a time not so very long ago that many Americans would prefer not to remember, but we dare not

forget. It was a time when our nation failed to live up to its ideals, when our nation broke the trust with our people that is the very foundation of our democracy. It is not only in remembering that shameful past that we can make amends and repair our nation, but it is in remembering that past that we can build a better present and a better future. And without remembering it, we cannot make amends and we cannot go forward.

So today America does remember the hundreds of men used in research without their knowledge and consent. We remember them and their family members. Men who were poor and African American, without resources and with few alternatives, they believed they had found hope when they were offered free medical care by the United States Public Health Service. They were betrayed.

Medical people are supposed to help when we need care, but even once a cure was discovered, they were denied help, and they were lied to by their government. Our government is supposed to protect the rights of its citizens; their rights were trampled upon. Forty years, hundreds of men betrayed, along with their wives and children, along with the community in Macon County, Alabama, the City

of Tuskegee, the fine university there, and the larger African American community.

The United States government did something that was wrong -- deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens.

To the survivors, to the wives and family members, the children and the grandchildren, I say what you know: No power on Earth can give you back the lives lost, the pain suffered, the years of internal torment and anguish. What was done cannot be undone. But we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say on behalf of the American people, what the United States government did was shameful, and I am sorry. (Applause.)

The American people are sorry -- for the loss, for the years of hurt. You did nothing wrong, but you were grievously wronged. I apologize and I am sorry that this apology has been so long in coming. (Applause.)

To Macon County, to Tuskegee, to the doctors who have been wrongly associated with the events there, you have our apology, as well. To our African American citizens, I am sorry that your federal government orchestrated a study so clearly racist. That can never be allowed to happen again. It is against everything our country stands for and what we must stand against is what it was.

So let us resolve to hold forever in our hearts and minds the memory of a time not long ago in Macon County, Alabama, so that we can always see how adrift we can become when the rights of any citizens are neglected, ignored and betrayed. And let us resolve here and now to move forward together.

The legacy of the study at Tuskegee has reached far and deep, in ways that hurt our progress and divide our nation. We cannot be one America when a whole segment of our nation has no trust in America. An apology is the first step, and we take it with a commitment to rebuild that broken trust. We can begin by making sure there is never again another episode like this one. We need to do more to ensure that medical research practices are sound and ethical, and that researchers work more closely with communities.

Today I would like to announce several steps to help us achieve these goals. First, we will help to build that lasting memorial at Tuskegee. (Applause.) The school founded by Booker T. Washington, distinguished by the renowned scientist George Washington Carver and so many others who advanced the health and well-being of African Americans and all Americans, is a fitting site. The Department of Health and Human Services will award a planning grant so the school can pursue establishing a center for bioethics in research and health care. The center will serve as a museum of the study and support efforts to address its legacy and strengthen bioethics training.

Second, we commit to increase our community involvement so that we may begin restoring lost trust. The study at Tuskegee served to sow distrust of our medical institutions, especially where research is involved. Since the study was halted, abuses have been checked by making informed consent and local review mandatory in federally-funded and mandated research.

Still, 25 years later, many medical studies have little African American participation and African American organ donors are few. This impedes efforts to conduct promising research and to provide the best health care to all our people, including African Americans. So today, I'm directing the Secretary of Health and Human Services, Donna Shalala, to issue a report in 180 days about how we

can best involve communities, especially minority communities, in research and health care. You must -- every American group must be involved in medical research in ways that are positive. We have put the curse behind us; now we must bring the benefits to all Americans. (Applause.)

Third, we commit to strengthen researchers' training in bioethics. We are constantly working on making breakthroughs in protecting the health of our people and in vanquishing diseases. But all our people must be assured that their rights and dignity will be respected as new drugs, treatments and therapies are tested and used. So I am directing Secretary Shalala to work in partnership with higher education to prepare training materials for medical researchers. They will be available in a year. They will help researchers build on core ethical principles of respect for individuals, justice and informed consent, and advise them on how to use these principles effectively in diverse populations.

Fourth, to increase and broaden our understanding of ethical issues and clinical research, we commit to providing postgraduate fellowships to train bioethicists especially among African Americans and other minority groups. HHS will offer these fellowships beginning in September of 1998 to promising students enrolled in bioethics graduate programs.

And, finally, by executive order I am also today extending the charter of the National Bioethics Advisory Commission to October of 1999. The need for this commission is clear. We must be able to call on the thoughtful, collective wisdom of experts and community representatives to find ways to further strengthen our protections for subjects in human research.

We face a challenge in our time. Science and technology are rapidly changing our lives with the promise of making us much healthier, much more productive and more prosperous. But with these changes we must work harder to see that as we advance we don't leave behind our conscience. No ground is gained and, indeed, much is lost if we lose our moral bearings in the name of progress.

The people who ran the study at Tuskegee diminished the stature of man by abandoning the most basic ethical precepts. They forgot their pledge to heal and repair. They had the power to heal the survivors and all the others and they did not. Today, all we can do is apologize. But you have the power, for only you -- Mr. Shaw, the others who are here, the family members who are with us in Tuskegee -- only you have the power to forgive. Your presence here shows us that you have chosen a better path than your government did so long ago. You have not withheld the power to forgive. I hope today and tomorrow every American will remember your lesson and live by it.

Thank you, and God bless you. (Applause.)

Clinton, W.J. 1997