



# Pharmacogenetics: the bioethical problem of DNA investment banking

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## Abstract

Concern about the ethics of clinical drug trials research on patients and healthy volunteers has been the subject of significant ethical analysis and policy development—protocols are reviewed by Research Ethics Committees and subjects are protected by informed consent procedures. More recently attention has begun to be focused on DNA banking for clinical and pharmacogenetics research. It is, however, surprising how little attention has been paid to the commercial nature of such research, or the unique issues that present when subjects are asked to consent to the storage of biological samples. Our contention is that in the context of pharmacogenetic add-on studies to clinical drug trials, the doctrine of informed consent fails to cover the broader range of social and ethical issues. Applying a sociological perspective, we foreground issues of patient/subject participation or ‘work’, the ambiguity of research subject altruism, and the divided loyalties facing many physicians conducting clinical research. By demonstrating the complexity of patient and physician involvement in clinical drug trials, we argue for more comprehensive ethical review and oversight that moves beyond reliance on informed consent to incorporate understandings of the social, political and cultural elements that underpin the diversity of ethical issues arising in the research context. © 2006 Elsevier Ltd. All rights reserved.

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## 1. Introduction

The systematic collection and storage of DNA and health related information from individuals participating in large-scale population studies for the purpose of medical research is fast becoming a site of social and ethical tension and controversy. The conventional governance mechanisms for safeguarding the welfare of research subjects, such as national and international ethical codes and systems of ‘independent’ ethics review, are based on the ethical requirement to obtain the informed consent of research subjects and to weigh the risks and benefits of participation in research. But these mechanisms (and the field of bioethics more generally) face severe challenges insofar as a traditional reliance on the principles of informed consent, privacy and confidentiality appear inadequate in face of the complexities and opacity of DNA banking. Despite much current bioethical deliberation on these issues, as Henry Greely notes: ‘In the ethics of human population genetics, at this point hard questions are much more common than clear answers’ (Greely, 2001, p. 786). In particular, the increasing dependence during the past thirty years on securing an individual’s informed consent as a way of providing justification for biomedical research is, as Onora O’Neill rightly claims, particularly problematic ‘because the merger of genetic and information technologies make it possible to assemble massive quantities of complex information that defeat individuals’ best efforts to grasp what is at stake, or to give or withhold informed consent’ (O’Neill, 2001, p. 689). Risk-benefit calculations also pose problems for regulatory bodies such as Research Ethics Committees, as research proposals increasingly seek the storage and use of ‘banked’ samples for purposes undefined at the time samples were obtained. Furthermore, and perhaps most importantly, as many of the existing DNA banks are at least partially funded or reliant on commercial support, conflict can arise over control, ownership and profit sharing (Marks & Steinberg, 2002).

Issues of intellectual property rights and the granting of patents in particular have confronted policy makers with severe challenges. The now much discussed 1990 U.S. Supreme Court case of *John Moore v. Regents of University of California* (793 P.2d 479 (Cal. 1990)),<sup>1</sup> has highlighted tensions surrounding the issues of property rights and profits in relation to tissue sample collections (Boyle, 1992; Landecker, 1999). More recent cases have brought to the fore the potential conflicts endemic in the development of tissue databases. For example, in the case of the widely criticised Icelandic Health Sector Database (cf. Merz & Sankar, 1998), deCODE Genetics (the company with exclusive rights to use of the database) only belatedly agreed to give the Icelandic health authorities a share of its profits. Moreover, the company has been charged with failing to deliver on the promised benefits to Icelandic society (Specter, 1999), and for worsening the country’s already weak economy following the collapse of deCODE’s share values and the subsequent ripple effect through the ‘grey stock market’ (Meek, 2002). In the United States, a disease advocacy

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<sup>1</sup> John Moore’s spleen, removed as treatment for his leukaemia, was used by his physician without Moore’s knowledge or consent as the source of the *Mo* cell-line, which was later patented and sold to the drug company Sandoz for US\$15 million. Moore claimed rights to a share of the profits from the cell line, but the court found against Moore’s claim because while he contributed the source tissue, he had not contributed to its development and transformation into a socially useful product. Nevertheless, the court did agree that Moore’s physician had violated the fiduciary patient-physician relationship by not seeking Moore’s consent to the use of tissue for research and commercial purposes (Gilmour, 1993; Nelkin & Andrews, 1998).

organization, the Canavan Foundation, sued the Miami Children's Hospital (the owner of the patent on the gene linked to the disease) for restricting research and access to genetic testing. As the gene becomes an important commodity, so notions of health and wealth become inexorably inter-related (Merz, 2002). These cases challenge bioethics to broaden its terrain; 'the bioethical debate will have to become more political, and to take fuller cognisance of the realities of the contemporary world, its technologies and institutional possibilities' (O'Neill, 2001, p. 702).

So why has the field of bioethics (not to mention public policy and health law) experienced such severe challenges in the face of genetic population studies? To be sure, such research raises complex issues and the commercial stakes are high with the boundaries between commercial and non-commercial research becoming increasingly blurred. Nevertheless, complexities exist elsewhere and there is a long history (though much ignored) of commercial research in biomedicine. In this paper, we will demonstrate that while the collection and storage of bodily tissue and health related data present some unique challenges, there is also a great deal of continuity insofar as many of the issues currently up for debate are present, though not analysed, in existing forms of research. We suggest that the problems currently being faced by bioethics stem from its historical inattention to 'biopolitics'. In particular, by examining pharmaceutical company sponsored clinical drug trials as a case study, we find an area that on the surface seems to operate with well-established bioethical frameworks, but where in fact unwarranted assumptions are made while others issues are simply never addressed. Our contention is that the lens through which conventional bioethics tends to look is limited insofar as its dominant tool—analytic moral philosophy—has a very individualistic perspective that ignores key social, cultural and political dynamics. A sociological perspective can provide a more socially and politically informed approach that examines issues relating to the commercial and institutional aspects of pharmaceutical research, as well as a more contextualised perspective on the issue of consent to these studies. In this article, we bring to bear a sociological lens on the issues that arise with the collection of DNA samples and health-related data for pharmacogenetics research, in the context of clinical drug trials. In so doing, we are not trying to usurp the bioethical endeavour but rather hope to demonstrate what an understanding of the social, political and cultural levels might contribute to bioethical and policy debates (Haimes, 2002).

## **2. Pharmaceutical industry research: in whose interest?**

While there has been a great deal of attention to and debate surrounding the collection of DNA samples for use in public genetic databases (cf. Martin & Kaye, 2000; Lavori, Krause-Steinrauf, Brophy et al., 2002; Knoppers, Caulfield, & Kinsella, 1996), there has been virtually no discussion of the formation of such databases by the pharmaceutical industry. This is somewhat surprising given that much of the debate surrounding public databases concerns their potential commercial exploitation (Marks & Steinberg, 2002). The collection of blood samples for pharmaceutical research has been facilitated by pre-existing ethical regulatory mechanisms that govern the conduct of conventional clinical drug trials. Rather than accept, uncritically (as bioethics so often does) the notion of societal benefit, it is important to establish who stands to benefit and in what ways?

The necessity for ethical guidance in biomedical research stems from the potential conflict that can arise when the needs of society oppose the best interests of the individual

patient. This tension is articulated in the introduction of the *Declaration of Helsinki*, the international ethical treatise governing biomedical research. ‘The health of my patient will be my first consideration’, physician-researchers are counselled, yet ‘Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects’ (World Medical Association, 2000). In other words, the underlying conflict of interest in research is that it is conducted to gain knowledge that is not necessarily designed to benefit the individual patient taking part in the research; rather the research is necessary to further ‘medical progress’ and to benefit society as a whole. Research ethics then requires a balance to be struck between the welfare and freedom of the individual subject, and those benefits pertaining to society as a whole. To what extent can we assume that the aims of the pharmaceutical industry coincide with ‘medical progress’ and the benefit of society? If we simply assume that all such research is conducted for the sake of ‘medical progress’, we fail to recognise that clinical drug trials are also a commercial endeavour and that the drive for profit to increase share-holder value is a crucial part of the equation (Evans, 1999).

Nevertheless, most bioethical guidelines have emerged in almost complete absence of any debate about the particular ethical issues that arise with pharmaceutical or other commercially sponsored clinical trials. Despite a number of recent articles published in the medical and bioethics literatures highlighting the potential conflicts of interests of pharmaceutical sponsored research (Glass & Lemmens, 1999; Steffox, Chua, O’Rourke et al., 1998; Lewis, Baird, Evans et al., 2001), with the exception of guidance recommending that payment to healthy research subjects and physicians conducting research be not so high as to unduly influence participation, there is at present little formal guidance regarding such research and discussions do not go much beyond the notion of ‘conflict of interest’.<sup>2</sup>

In recent years, commentators within the industry have noted that traditional approaches to drug discovery and development are reaching the limit of their ability to yield innovative new drugs; the traditional ‘trial and error’ approach to drug development and the huge financial risk involved has led to an innovation deficit. This is evident from the large number of ‘me too’ drugs that have reached the market in recent years. Industry reports for the year 2000 reveal that only thirty-two new molecular entities were launched worldwide, compared to fifty-two in 1991 and averages of eighty to hundred per year in the 1960s (van den Haak, 2001; Horrobin, 2000). Drug development is also an extremely time consuming and costly operation, taking ten to fifteen years and costing US\$300–\$600 million with a success rate of about 1 in 10, only a fraction of which will be ‘blockbusters’. With new blockbuster drugs becoming increasingly difficult to find (Horrobin, 2000), it should not then be surprising that many in the pharmaceutical industry are turning to advances resulting from the Human Genome Project for help.

‘Pharmacogenomics’—the name given to a broad-based pharmaceutical industry led initiative—aims to capitalize on this knowledge base to discover new therapeutic targets and interventions and to elucidate the constellation of genes that determine the efficacy and toxicity of specific medications. ‘Pharmacogenetics’ is a more specific term used to define the narrower spectrum of inherited differences in drug metabolism and disposition linked to individual genetic variations. Many large pharmaceutical companies are now

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<sup>2</sup> The amount made payable to the volunteer is not permitted to be ‘such as to persuade people to volunteer against their better judgement, nor induce them to volunteer more frequently than is advisable for their own good’ (Royal College of Physicians, 1986).

engaged in genomic-based research and making substantial financial investment in this area. This research, although not without contention (Williams-Jones & Corrigan, 2003; Ozdemir & Lerer, 2005; Webster, Martin, Lewis, & Smart 2004), promises to lead to revolutionary forms of drug development with potentially substantial financial gains for the industry:

Industry analysts predict that, by improving medical outcomes by the use of pharmacogenomics-enhanced drugs and diagnostics, pharmaceutical companies could benefit to the order of US\$200 million to US\$500 million in extra revenue for each drug. . . . For these reasons, pharmaceutical companies have begun to integrate pharmacogenomics into drug development programs. (Bogdanovic & Langlands, 1999, p. 182)

The financial motivations cannot be overemphasised. New drugs developed by pharmaceutical companies are required to go through lengthy testing procedures before being granted a licence and made available for the general patient population. Industry sponsored clinical drug trials take place on a global scale, with perhaps several thousand patients world-wide simultaneously taking part in any single clinical trial. Following a period of lab testing including standard animal and *in vitro* tests, the new drug is tested on human subjects during several phases of clinical trials. During Phase I trials, the drug is tested on human subjects for the first time, with most of these studies conducted on healthy volunteer subjects in specially designated clinical trial suites (much like a private hospital ward). Phase I studies are conducted either directly by the sponsoring pharmaceutical company in corporate premises, or the trials are sub-contracted to specially designated Clinical Research Organisations (CROs). During subsequent phases physicians are recruited by the sponsoring pharmaceutical company to act as ‘trial investigators’ and oversee the study and the administration of the drug according to pre-determined trial protocols. A major hope for pharmacogenetics is that increased knowledge about how drugs are absorbed and distributed will eventually speed up clinical trials, reduce trial sizes, and thereby capitalize on potential profits made during the valuable patented life of the product. Currently DNA samples and health related data are being collected from patients and healthy volunteers during otherwise conventional pharmaceutical sponsored clinical drug trials for the purpose of pharmacogenetics related research.

### 3. Biovalue and labour value

Blood samples and data that are donated for genetic testing purposes during the pharmacogenetic part of a clinical trial are considered valuable commodities in the production of genetic-based drug development. This transformation of biological materials into value is part of a wider trend in medicine, what Catherine Waldby calls ‘biovalue’ (a surplus value of vitality and instrumental knowledge) (Waldby, 2000). That said, human subjects have been value-creating experimental vessels for the production of drugs and subsequent commercial profit for well over half a century. In pharmacogenetic clinical trials then, it is not simply DNA tissue that is at stake, but also human bodies and their labour. Karl Marx (Marx, 1867/1999) argued that the value of any commodity is determined by the socially necessary labour time that goes into its production. Marx used the term ‘socially necessary labour time’ because the labour time required to create a commodity depends on the society’s levels of technology and craft. In Marx’s theory, commodities should in

principle be exchanged in the market place for prices that exactly correspond to the necessary labour time embodied in them. When a commodity is exchanged or sold for more than its labour value, a surplus value is realised.<sup>3</sup>

Not only does the collection of DNA samples provide the ‘raw material for industry’ (Lewis, 2004), but trial subjects are also worked upon and transformed into data that are essential drug product components. ‘Healthy volunteers’ taking part in clinical drug trials are financially rewarded to compensate for their time and discomfort (not to forget the adverse drug reactions or allergic responses such subjects often experience). The basis by which payment is determined relates to the work undertaken, i.e., the time spent by the subject in the clinic, number of tests and procedures carried out, and length of the study. Subjects are paid more for invasive procedures as this demands more bodily toil, but payment is not in any way related to the perceived risk involved in trial participation. This inattention or unwillingness to pay for risk, however, would be considered unacceptable in many other fields of work. There are many occupations in which individuals are given ‘risk bonuses’ or ‘danger pay’ for undertaking tasks that are more than ‘normally’ risky, e.g., construction work at heights, maintenance of high voltage electricity pylons, or engineering projects in remote regions.

Current drug development relies on being able to test the drug for toxicity on healthy research subjects during Phase I trials before establishing the basic safety features of the drug and progressing (or not) to Phases II and III. As most healthy volunteers participate primarily (if not exclusively) for financial reward (Corrigan, 2003), these studies are only made possible by financial incentive. However, ethical guidelines reflect a concern that payments should not be so large, ‘as to induce prospective subjects to consent to participate in the research against their better judgement (‘undue inducement’)’ (Council for International Organizations of Medical Sciences, 1993, Guideline 4). Again, these guidelines fail to draw a distinction between commercial and non-commercial research, but rather are based on differences between therapeutic and non-therapeutic research. A number of ethicists have challenged this international ethical orthodoxy, arguing instead that the payment of research subjects (healthy or ill patients) is indeed an ethical and reasonable recompense.

Many people would not work if they were not paid; in that sense wages are inducements. Few people think that, as a result, it is wrong to offer wages. Those who do have concerns about the existing wage system usually object that wages are too low, not that they are too high, or not offered at all. (Wilkinson & Moore, 1997)

Though not limiting research subjects to ‘healthy volunteers’ or abandoning the therapeutic/non-therapeutic distinction, Wilkinson and Moore fail to acknowledge the differences between trials sponsored by for-profit and not-for-profit organisations.

In the case of clinical drug trials (commercial and not-for-profit) involving patients, subjects are not paid for their involvement although most studies offer travel expenses to and from the clinic. Drug trials involving patients take the guise of a therapeutic encounter, where patients (potentially) obtain therapeutic as opposed to financial benefit. Although some trials last only a short period and are not particularly onerous, many trials last for months and even years, requiring those taking part to attend the clinic at regular

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<sup>3</sup> This theory of value provides the foundation of Marx’s claim that labour is exploited in a capitalist society. Workers are paid less than the market value of the commodities produced and the surplus value is captured by capital and largely re-invested to augment the means of production.

intervals for blood and other tests, and many trials even require patients to fill in detailed health-related diaries. Most patients taking part in clinical drug trials believe that the new drug being tested is likely to be an improvement on existing therapy whereas in reality most trials will not lead to an improved drug.<sup>4</sup> Only 20 per cent of drugs that begin clinical trials reach the marketplace, and most are withdrawn from trials due to safety problems and lack of efficacy (FDA, 1995).<sup>5</sup> This is not to say that patients receive no therapeutic benefit as a result of participating in a drug trial; patients normally receive some form of therapy during the trial, and even when the drug is being tested against an inactive treatment, patients can still benefit from ‘placebo effect’. In fact, many drug studies fail because the drug shows less benefit than the placebo, which can sometimes account for as much as 30 per cent benefit in some patients (cf. Khan, Detke, Khan et al., 2003; Burneo, Montorib, & Faught, 2002).

For the most part, in western countries where health care is provided as part of national public health insurance plans, patients would receive therapeutic treatment regardless of trial participation.<sup>6</sup> One could of course suggest that participation be based on altruism, and indeed such assumptions frequently take place in the bioethics literature. But this is much more difficult to justify when seen in the light of pharmaceutical companies who can sometimes make enormous profits, or the physicians who are financially rewarded (often sums are paid per patient enrolled) by the sponsoring pharmaceutical company for their involvement in the drug trials.<sup>7</sup> Indeed, physicians play a crucial role insofar as the drug company usually has no direct contact with patients. Rather, recruitment of patients, administration of drugs and conduct of tests are carried out on behalf of the pharmaceutical company by clinical investigators and their research nurses.

In considering the labour involved on the part of clinicians in running a company’s trial, it seems appropriate that such work be compensated. Yet to not then also compensate patients as research subjects (workers through the use of their bodies), is at the minimum inconsistent if not unjust. A hesitancy on the part of commercial or not-for-profit organizations to compensate patients as research subjects is likely based on a number of different factors. First, patients may not be viewed as actively *working* in their participation (unlike clinicians), but instead are seen as the passive recipients of care—this is similar to one of the main arguments made in the *Moore* case, i.e., that individuals do not have property rights in products derived from their own tissues (Andrews & Nelkin, 2002). Secondly, if patients are paid to participate, this may undermine altruism and social conscience, which many public health systems are at pains to sustain, e.g., in the case of blood or organ donation. Finally, the financial impact of having to pay patients for research participation would significantly increase costs for companies, and potentially

<sup>4</sup> Social science research demonstrates that so called ‘therapeutic misconception’ is common among patients participating in clinical trials (Corrigan, 2003; Bamberg & Budwig, 1992; Dresser, 2001).

<sup>5</sup> According to the US Food and Drug Administration (FDA, 1995), 65 per cent of drugs being tested fail to progress beyond Phase II trials, with a further third or more failing to go beyond Phase III, the final pre-marketing stage of drug testing. While initial Phases I and II carry the most risk, these tend to involve smaller numbers of patients (up to several hundred). In contrast, up to several thousand patients will take part in Phase III studies.

<sup>6</sup> In stating this, we recognise that for some patients, such as in the documented cases of AIDS sufferers (Epstein, 1996), trial participation may be highly sought after as a means of obtaining potential therapy where none otherwise exists.

<sup>7</sup> Not all clinical drug trials are commercially sponsored, but all pre-marketing trials are.

lead to expectations that not-for-profit research also compensate patients. Nevertheless, as things currently stand commercial research relies on an undisputed notion of patient altruism (and non-existence of work) that is not also expected from healthy volunteers. A sociological view brings this issue to the fore by showing the true complexity of the situation, thereby challenging the accepted norm in the context of clinical research trials, much in the way that appropriate notions of property and work are being challenged in discussions of organ and tissue donation or sale (Laurie, 2002).

Similarly, a more detailed investigation of the roles of physicians in clinical trials demonstrates that in many ways physicians can be mere instruments (not fully independent participants), insofar as they have little or no say in the design of the study, and have limited access to and control over the data being accrued. As physician Michele Brill-Edwards argues:

In general, academic clinical researchers do not design and implement drug trials in an environment free of influence by the manufacturer of the product being studied. Data collection, interpretation, analysis and publication are generally in the hands of the company, and the physician investigators are very often just along for the ride because they are the people with access to patients. (Brill-Edwards, 1999, p. 45)

Ethnographic research conducted by Mary Mueller (1997) on the clinical and institutional aspects of drugs trials involving AIDS patients reveals how clinical practice is set up in such a way to ensure the successful discharge of physicians' contractual obligations to their sponsors, as well as to facilitate the advancement of physicians' careers. She describes the activities of the research centre's senior clinical investigators as:

limited to the 'backstage', or non-clinical, aspects of clinical trial work, like writing grants, designing trial protocols, analysing protocol data, writing papers for publication, and maintaining relations with local physicians. (Mueller, 1997, p. 62)

Sociologist Renee Fox (Fox, 1996) notes that in forty-five years as a participant observer of clinical research, she has witnessed a move away from 'patient oriented' research where the physician-researchers once had more freedom with regard to experimental design, and where scientific research goals and standards were sometimes compromised for the sake of clinical care. More common now is an environment of standardised research, characterised by an intellectual demise of patient oriented clinical research and a prioritising of research objectives over patient safety or priorities. Of course, physicians are not forced to conduct research trials and can still exercise their professional integrity through decisions about the kinds of drug trials they choose to undertake. As an interview with a senior breast cancer consultant reveals:

We support all the multinational trials because they have good pedigree and are reputable and you feel they are going to get worthwhile results. Therefore you put your patients into a study that will be meaningful . . . there are other studies that we have joined and then we've let lapse because we felt that the questions have been answered as the study started to develop . . . and I have found it more difficult to recruit a patient into a study.<sup>8</sup>

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<sup>8</sup> This extract is taken from an interview transcript collected for research undertaken as part of Corrigan's Ph.D. (Corrigan, 2000).



This same physician, however, also disclosed details of a study that she had been involved in as a junior doctor at a prestigious London teaching hospital, where she was told by the clinical investigator (senior physician in charge of the trial) to recruit patients into a trial where ‘the side effects appeared to be truly horrendous . . . and some had died and it was difficult to know if it was from the disease or the drug and it was awful and that was very difficult.’ Another physician, when asked about what motivated him to conduct clinical drug trials, said that the money he was paid from being involved in trials enabled him to employ his wife as a senior research assistant. Physicians, then, are subject to a variety of influences and pressures (financial, professional, administrative) that may put them in conflicts of interest, and while this is an issue gaining some prominence in the bioethics literature, one needs also to consider the social, political and cultural contexts that underlie these pressures. An awareness of these issues (and the not insubstantial power differential between patients and physicians in the research context) highlights the fundamental weakness of informed consent as a mechanism for protecting patients as research subjects.

#### **4. Issues of consent**

In pharmacogenetics related trials, subjects are asked to consent to three separate aspects of research: the main clinical drug trial; an ‘add-on’ pharmacogenetic study in which subjects consent to an ‘identified’ genetic test for research related to drug effect; and a ‘non-identified’ test for unspecified future research. These three aspects are progressive insofar as giving consent to the second and third aspects is dependent on prior consent to the first and second. Patients asked to take part in clinical drug trials are often given no prior notice about the potential research, rather the possibility of participating in research is introduced by their physician during a clinical consultation. This initial aspect of informed consent involves considerations relevant to participation in the drug trial itself. Subjects are given written and verbal information relating to the known risks of the drugs as well as details about procedures such as the length of the study, number of hospital visits required, and blood tests or X-rays associated with the study. In consenting to this first stage, patients agree to take part in a therapeutic drug trial and it is expected, as part of the consent process, that they will consider issues relating to the potential benefits and risks of the trial, including harms such as adverse drug reactions. Social science research examining the experiences of patients who have given their consent to take part in such trials demonstrates that despite the ethical rhetoric of informed consent based on adequate understanding of the information given to prospective subjects, in practice the reality is often very different. Despite the fact that patients are given information under headings such as ‘possible risks’ (usually relating to drug induced side-effects), patients are often unable to subsequently recall the mention of any side-effects (Bergler, Pennington, Metcalf et al., 1980; Cassileth, Zupkiss, Sutton-Smith et al., 1980; Estey, Wilkin, & Dossetor, 1994; Hassar & Weintraub, 1976).

Clinical drug trials are generally randomised so that neither the patient nor the medical team knows whether a particular trial subject is taking the study drug, an alternative drug, or in some cases a placebo. Studies show that trial subjects have poor understanding of the process of randomisation in clinical drug trials (Snowdon, Garcia, & Elbourne, 1997; Jan & DeMets, 1981; Cassileth, Zupkiss, Sutton-Smith et al., 1980), and as a consequence are sometimes under the misapprehension that they will be receiving an active treatment (Corrigan, 2003). Furthermore, given the clinical context of these studies, from the perspective

of the patient the boundaries between research and treatment are often unclear. In such circumstances, a request to consent is often interpreted as *guidance* to consent, insofar as patients have pre-existing expectations and norms regarding the role of the physician as a professional offering advice to patients about their best interests. Research in this area demonstrates that this so called ‘therapeutic misconception’ is common (Bamberg & Budwig, 1992; Dresser, 2001). There is also evidence that some patients who consent to take part in clinical drug trials experience such decisions as ‘burdensome’ (Taylor, 1988). Research indicates this is more likely to be the case for patients who have an acute condition or who are in pain or suffering great anxiety (Corrigan, 2003).

Nevertheless, while research ethics guidelines recognise that for some patients giving ‘adequate’ consent might be difficult and such subjects should be considered ‘vulnerable’, these guidelines apply mainly to ‘incompetent’ subjects such as those who have some form of cognitive impairment (World Medical Association, 2000; Council for International Organizations of Medical Sciences, 1993). Such guidelines do not therefore address the varying needs of ill but otherwise competent patients. Although there is a growing awareness of problems relating to the practice of informed consent in clinical trials, solutions to such problems focus on improving written information given to patients, making sure that such information is comprehensive, and detailing trial procedures and risks likely to be encountered by subjects (ICH, 1998). In relation to consent to the collection of DNA tissue samples, here too problems frequently centre on adequacy and comprehensiveness of information, while the solutions are proposed in terms of comprehensively designed ‘model’ consent forms (Knoppers, 1998; Merz & Sankar, 1998). There is scant regard in either conventional bioethics guidelines or more socially nuanced policy perspectives of the need to appreciate fully the social context in which consent is acquired. In the case of pharmacogenetics add-on studies to clinical drug trials, not only are patients being asked to consider complex issues related to the treatment of their condition and the potential risks and benefits of participating in the trial, but they are further required to consider issues relating to the pharmacogenetics aspect of the trial.

In consenting to this second part of the study, patients give the sponsoring pharmaceutical company permission to carry out genetic research on their blood sample, including linkage to personal medical information such as details of medical conditions and family history. The sample at this stage is ‘identified’, meaning that the patient’s name, medical history, and DNA sample data all remain linked. According to an information leaflet produced by a pharmaceutical company to inform patients about such research: “we will use the Identified Sample to look at genes that might be involved in the condition you have, and how those genes might affect the study medication you are receiving” (Patient Information Leaflet, 1998).<sup>9</sup> Subjects are informed that samples will remain ‘identified’ for approximately six months after completion of the main drug trial study, and that such trials may take several years to complete. Indeed, patients may be informed that their identified sample could be kept for up to a maximum of ten years.

The third part of the consent process involves a request to store the sample after completion of the trial for an unlimited period in order to carry out future, as yet unspecified, research. Subjects are informed that at this stage the sample will be ‘non-identified’. By

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<sup>9</sup> The patient information leaflet is a document produced by a large pharmaceutical company given to patients as part of the informed consent process prior to patient participation in a pharmacogenetics clinical trial. This is a private document held by Oonagh Corrigan.

non-identified the pharmaceutical companies mean that the DNA sample, data derived from it and medical data concerning the subject will be stored, but that it will not be possible to link this information to the name of the subject and as such anonymity will be secured. If subjects agree to consent to the third stage then identification markers linking the patient to the sample will be destroyed and the sample will be stored anonymously:

[The pharmaceutical company], or people working with [the company] will store your blood sample (or genetic sample prepared from your blood). They will also store information about your medical history. After [the company] takes your identification off, they will store the sample, all medical information, and any genetics results for an unlimited amount of time. (Patient Consent Form, 1998)

The information given to patients and healthy volunteers is expected to be sufficient for making informed choices. However, unlike conventional clinical drug trials where information regarding potential risks relates mostly to the risk of bodily harm, apart from the slight possibility of bruising when a small blood sample is extracted from the subject, no other direct physical risks are involved in the pharmacogenetics aspect of the trial. Sponsoring pharmaceutical companies indicate that the risk of harm from participation in the genetic study is ‘small’ (Patient Information Leaflet, 1998). Risks are identified rather as relating to potential problems concerning confidentiality and anonymity. A patient information leaflet given to subjects gives assurances that sufficient measures are put in place to ensure the confidentiality and anonymity of this data. But subjects are also informed that the pharmaceutical company ‘cannot be certain that your genetic test results could never be linked to you’ (Patient information leaflet, 1998). Although the risk of such harm is described as ‘small’, genetic information arising from such studies is potentially dangerous insofar as it may lead to discrimination in the workplace (cf. MacDonald & Williams-Jones, 2002) or difficulty in obtaining insurance (cf. Lemmens & Bahamin, 1998) if individuals are thought to have greater than average risk of ill-health. Indeed, an information video produced by the pharmaceutical company GlaxoSmithKline (GSK) aimed at informing clinical investigators about pharmacogenetic trials emphasises the need for doctors to ensure that the patient’s privacy is protected. GSK representatives state that access to the data is to be restricted and such data must not be given to patients or insurers.

Insofar as consideration of potential benefits are concerned, unlike the main drug trial where patients may directly benefit as part of their involvement in the study, there is no likely direct benefit to the patient in taking part in the collection of samples for pharmacogenetics purposes. Whether or not patients in a clinical drug trial achieve the ‘ideal’ of autonomous decision-making, or they find the experience of consent empowering, there remains at least a potential therapeutic benefit to the patient in trial participation. Indeed, the hope of therapeutic effect is a reason often cited by patients for consenting to drug trials (Corrigan, 2003). When clinical drug trials are non-therapeutic, as in the case of Phase I trials conducted on healthy volunteers, subjects are financially rewarded for their participation.<sup>10</sup> There is no expectation (either from subjects or trial operators) that the drug will be individually beneficial – the trial is designed only to test toxicity and safety for a move

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<sup>10</sup> Other forms of non-therapeutic trials sometimes take place in the clinical setting, as for example in epidemiology or observational studies, but to our knowledge these are not sponsored directly by pharmaceutical companies or other commercial organisations.

into Phase II. As discussed above, patients participating in Phase II and III trials at least have the possibility of receiving a therapeutic benefit. Yet the case of pharmacogenomics research is very different. Patients participating in such research are not informed of the results of their genetic test even when such information may reveal that the patient is potentially a poor metabolizer for the study drug (or indeed for other drugs that rely on the same metabolizing enzyme), and thus are potentially at greater risk of experiencing adverse drug reactions. Instead, patients are informed that they are unlikely to benefit directly and an appeal is made to altruistic reasons for donation:

[The pharmaceutical company] expects no immediate benefit to you although your participation in this research may eventually help people with migraine. . . . We may also learn which patients may suffer side-effects from certain medicines. (Patient Information Leaflet, 1998)

The risks to patients to be considered for this aspect of the trial are small, but so too are the benefits! Furthermore, patients at this stage are consenting to as yet unspecified commercial research and have no future control over the kinds of research to which their samples may be used. Should individuals not wish to consent to this third part of the study, they are informed that their sample will be removed and destroyed. However, as Graham Lewis indicates (Lewis, 2004), given the complex arrangements concerning storage of these samples by third party companies (many of which are currently undergoing mergers), this endeavour may prove difficult and without effective oversight it may be hard to ascertain whether companies are adhering to these promises.

## 5. Conclusion

Increasing demands from pharmaceutical companies on Research Ethics Committees to approve quickly greater numbers of clinical drug trials are putting pressure on the already overworked and overloaded volunteer members of these committees. This, along with a climate in which informed consent has become something of an ethical panacea (Corrigan, 2003), results in an all too frequent narrowing of attention to evaluations of informed consent forms in lieu of more comprehensive ethical review.<sup>11</sup> The danger—highlighted by the complex set of issues faced by research subjects and physicians participating in pharmacogenetics add-on studies to clinical drug trials—is that other important considerations besides informed consent will be ignored. Even for informed consent, the information, issues and concerns faced by prospective healthy or patient research subjects (e.g., social, cultural, psychological and financial implications of potentially indefinite DNA banking) extend well beyond those faced in more standard drug trials (e.g., patient awareness of drug safety and risk). Informed consent is a necessary but insufficient mechanism for protecting patients or healthy subjects involved in pharmacogenomics research.

In challenging the utility or sufficiency of informed consent in clinical trials, we are in line with a growing critique of this principle (Doyal & Tobias, 2001; O'Neill, 2001) and the

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<sup>11</sup> A survey of fifty-eight members belonging to six Local Research Ethics Committees in the UK reveals that members rated their duty 'to ensure prospective subjects understand the implication of taking part in the study as the most important aspect of their work' (Kent, 1997, pp. 186-190). This was given priority over and above the duty to protect subjects from harm. In the US, IRBs have also been shown to prioritise informed consent over risk benefit analysis (Weijer, 2000).

overall architecture of the governance of research ethics (McDonald, 2000; Williams-Jones & Holm, 2005). Moreover, we suggest that the case study here presented, i.e., the addition to standard pharmaceutical drug trials of blood sample collection for pharmacogenetics research, is illustrative of the need for in-depth empirical and ethnographic research to support more sophisticated and robust ethical analysis and governance of research. By bringing to bear a sociological gaze, foundational assumptions or convictions are shown to be unwarranted or insufficiently justified. For example, the assumption that the patient participates as a research subject primarily for altruistic purposes is, if not overturned, at least placed in a more complex setting. Further, sociological analysis raises an *ethical* question of whether patients and healthy volunteers participating in research are being treated justly. Why should patients engage in pharmacogenetics research—research in which they are not afforded the possibility of a therapeutic or financial benefit—while their healthy volunteer counterparts in clinical trials are unproblematically paid, if not for their work then at least for their time and expenses? By considering issues of labour and value one can see how the current relationship between sponsoring pharmaceutical companies and patients could be considered exploitative. The reasons for patient participation (and that of healthy volunteers) are multifaceted and complex, and an assumption of altruism in the one case is both inadequate and potentially unjust.

An ethical review that integrated these more complex aspects of subject involvement in pharmacogenomics research would still be found wanting if it did not consider other, equally relevant aspects of the case. Physicians, as overseers and operators of clinical research trials, are important participants who are also exposed to a range of ethical concerns. Embedded as physicians are in complex social and political environments, they are sometimes the master but at other times may be the servant to other powerful actors. This may lead to situations in which physicians are placed in conflicts of interest that both negatively affect the physicians' professional independence and the possibility of informed consent on the part of patient-subjects (Schafer, 2004; Nathan & Weatherall, 2002). Even less direct influences, such as financial incentives or pressure from hospital administrators or peers may, while not leading to explicit conflicts of interest, nonetheless have an effect on the way physicians discharge their responsibilities towards their patient-subjects (Schafer, 2004; Nathan & Weatherall, 2002). These broader ethical or *social* considerations, however, are infrequently considered through the lens of traditional bioethics, not to mention those harried members of Research Ethics Committees.

The collection and storage of DNA and health related information from participating individuals in large-scale population studies present a significant challenge for bioethics scholars and policy-makers. Not least as the relationships between the various actors involved—pharmaceutical companies, physicians, research nurses, patients and healthy volunteer subjects—have been insufficiently interrogated. Although in recent years the growing significance awarded to informed consent in clinical trials has alluded to a more active and emancipated form of subjecthood, this paper suggests that the rights of patients in clinical trials extend well beyond those of informed consent—a more nuanced relationship based on reciprocity is required.

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