Meaningful knowledge? Law and ethics in post-genomic gene therapy research*

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OPSOMMING

Betekenisvolle kennis? Die reg en etiek in postgenomiese geen-terapie navorsing

Nuwe metodes om menslike gene te "redigeer", soos CRISPR-Cas9, sal wetenskaplikes in die toekoms in staat stel om presiese veranderinge aan te bring aan die menslike genoom – 'n feitlik ondenkbare prestasie in die vorige eeu. Die toekoms van genetiese manipulasie is dus vol belofte – en voorspel 'n einde aan sommige van die mees uitdelgende menslike siektetoestande.

Dit is nou hoog tyd om die lesse wat ons geleer het uit die geskiedenis van kliniese navorsing te herroep: lesse van wetenskaplike, filosofiese en etiese belang. Hierdie lesse omvat ook die lesse wat ons geleer het uit die dood van Jesse Gelsinger in 1999 vanweë komplikasies as gevolg van die toediening van 'n proef-produk in 'n lewer geen-terapie kliniese proef.

Die artikel steun op die geskiedenis van kliniese navorsing ten einde voor te stel dat Suid-Afrikaanse navorsingsetiekkomitees die konsepte tradisioneel gebruik in die evaluering van kliniese navorsing, soos "toestemming", "risiko" en "geregtigheid", herevalueer sodat navorsing gedoen word wat betekenisvolle kennis sal oplewer. Die vraag word gevra na wat betekenisvolle kennis daarstel in postgenomiese geen-terapie navorsing, asook die omstandighede waarin sulke kennis betekenisvol sal wees vir wetenskaplikes, die deelnemers aan navorsing of hulle gemeenskappe.

1 INTRODUCTION

JACK*:* Yes, but you said yourself that a severe chill was not hereditary.
ALGERNON*:* It usen't to be, I know – but I daresay it is now. Science is always making wonderful improvements on things.
Oscar Wilde *The importance of being earnest*

Science has been making "wonderful improvements on things" for centuries. Of the most remarkable scientific discoveries in the history of humankind, many have been in the field of medical science.[1] Since the dawn of history, medical scientists have studied the human body, its diseases, and proposed means to treat

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1 The term "science" derives from the Latin *scientia* or "knowledge". What we term "science" was known as "natural philosophy" in earlier centuries. Eg, the full title of Isaac Newton's famous work published in 1687 was *Philosophiae naturalis principia mathematica* (*The mathematical principles of natural philosophy*): see Capra and Luisi *The systems view of life. A unifying vision* (2014) 2.

and combat those diseases. Together with industrialisation and agriculture, the advent and improvement of medical science have been major contributors in the general advancement of the human species.[2]

Over past centuries scientists developed cures, treatments, procedures and preventive vaccines for previously devastating diseases such as smallpox, poliomyelitis, organ failure, HIV and AIDS, many cancers, and so on. These treatments and cures were largely the result of clinical research[3] and the application of scientific method[4] known as the clinical trial.[5] Clinical research is a necessary demand on resources and the effects of neglecting such research would be disastrous. The World Medical Association's Declaration of Helsinki[6] recognises the value of clinical research for medical progress and the inevitability of that research including human participants: "Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects."

Below, a brief history of the clinical trial is followed by an outline of the history of abuse that has led to a regulatory framework for human participant protection in clinical research. Next, the peculiarities of gene therapy clinical trials are explored, highlighting the problems inherent in this specific type of clinical trial. These problems are practical, scientific and ethical in nature. The lessons learnt from the history of clinical research may be a guide in designing gene therapy clinical trials, so the focus is on how ethics committees should evaluate the appropriateness of trials for novel gene therapy agents so that we gain meaningful knowledge and benefit from our ability to "read" the human genome and to use gene editing technologies such as CRISPR. In this context, we need to reassess the meaning of concepts such as "consent", "risk" and "justice" in relation to clinical research.

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2 Koyfman "History's most important medical breakthroughs" (2015), available at https://bit.ly/2KM6Vtr (accessed on 31 March 2018).

3 The term "clinical research" refers to research "involving human subjects that is designed either to enhance the professional capabilities of individual physicians or to contribute to the fund of knowledge in those sciences that are traditionally considered basic" (Levine *Ethics and regulation of clinical research* (1986) 3, ("Levine"). Clinical research, thus, is research carried out on humans.

4 Some writers posit that modern scientific thought did not emerge with Galileo, as is usually stated by historians of science, but with Leonardo da Vinci (1452–1519) (see Capra *The science of Leonardo* (2007)). Da Vinci single-handedly developed a new empirical approach, involving the systematic observation of nature, reasoning, and mathematics, in other words the chief characteristics of the scientific method. It was a science of organic forms, of qualities, of processes of transformation (see Capra and Luisi 9).

5 According to the International Conference on Harmonization (ICHJ), clinical trials are: "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product, and/or to identify any adverse reactions to an investigational product, and/or to study absorption, distribution, metabolism, and excretion of an investigational product with the object of ascertaining its safety and/or efficiency" – Rick *Drugs From discovery to approval* (2004) 140. Such experimental research methods include randomised controlled clinical trials and non-randomised controlled trials.

6 Adopted by the 18th World Medical Association assembly, Helsinki, Finland, in 1964, and revised subsequently, most recently at the 64th WMA General Assembly, Fortaleza, Brazil, in October 2013, available at https://bit.ly/2rJdF3M (accessed on 15 March 2018).

2 THE CLINICAL TRIAL: A BRIEF HISTORY

Today we take for granted the evolution of an entire science that has produced effective medicines and treatment for disease, oblivious to the underlying history that describes the way in which medical scientists have been able to develop efficacious medicines and treatments. An outline of a few of the most important developments in medical experimentation follows, specifically developments that pertain to the clinical trial.

The world's first reported scientific experiment that has the beginnings of a clinical trial is recorded in the Book of Daniel in *The Bible* around 562 BC.[7] This experiment was conducted not by a medical scientist but by King Nebuchadnezzar, the ruler at the time of Babylon.[8] Nebuchadnezzar ordered his people to eat only meat and drink only wine, a diet he believed would keep them in sound physical condition. Several young men of royal blood, who preferred to eat vegetables, however, objected to this diet. In response the king allowed them to follow a diet of legumes and water for 10 days while the other men followed his preferred diet, eating meat and drinking wine.[9] When the ten days ended, the young vegetarians appeared better nourished – more "fleshy" – than the young carnivores. In response, King Nebuchadnezzar permitted the legume lovers to continue their diet.[10] Today this experiment would be described as an "open uncontrolled human experiment"[11] and may be viewed as the origin of the field of study today known as public health.

The first clinical trial in human history is mentioned by the Persian philosopher and physician Avicenna (Ibn Sina) (980–1037 AD) in *The canon of medicine* (1025 AD)[12] in which he outlined the experimental use of medicines and how to conduct scientific experiments to test their efficacy.[13] Avicenna's compendium subsequently was translated into Latin and became a standard in European universities, its use continuing into the 18th century.[14] Avicenna was said to be able to recite the Koran by heart at ten and at twelve he argued with adults concerning law and logic, "[s]o that he found medicine was an easy subject, not hard and thorny like mathematics and metaphysics".[15] In *The canon of medicine* Avicenna prescribes aspects of medical experimentation such as that the "drug must be free from any extraneous accidental quality";[16] that "the drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones".[17] Also, the "quality of the drug must correspond to the strength of the disease. For

7 Collier "Legumes, lemons and streptomycin: A short history of the clinical trial" 2009 *CMAJ* 23–24 ("Collier").
8 *Idem* 23.
9 *Ibid.*
10 *Ibid.*
11 *Ibid.*
12 Covering topics from contagious diseases and quarantine procedures to descriptions of roughly 800 different simple medicines and various compounded medicines as well; see Collier 23.
13 Machin and Fayers *Randomized clinical trials: History, practice and reporting* (2010) 16.
14 See Date "Sir William Osler's Arab and other Middle Eastern contacts" 1991 *The Ulster Medical J* 120–128.
15 *Idem* 124.
16 Rule 1.
17 Rule 3.

example, there are some drugs whose heat is less than the coldness of certain diseases, so that they would have no effect on them".[18] Furthermore, "the time of action must be observed, so that essence and accident are not confused"; the "effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect"[19] and "the experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man".[20] These rules of Avicenna suggest an almost modern approach to conducting clinical trials – remarkable if one considers that they were drafted nearly a thousand years ago.

In 1537 the first clinical trial of a new therapy was conducted more or less accidentally by the famous surgeon Ambroise Pare.[21] While on service under the Mareschal de Motegni, Ambroise Pare was responsible for the treatment of soldiers wounded in battle. But he ran out of the conventional treatment of the time – a concoction made up of oil.[22] In his words:[23]

> "[A]t length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at any ease, fearing that by lack of cauterization I would find the wounded upon which I had not used the said oil dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses."

However, it would take another 200 years before medical scientists arrived at what might be considered a planned controlled clinical trial. Dr James Lind (1716–1794) was the first to introduce the use of a control group and is widely considered the father of the modern clinical trial.[24] In 1747, while working as a ship's surgeon, Lind planned a comparative trial of the most promising cures for scurvy, at the time a major cause of death and disease among sailors.[25] His trial found eating citrus fruit to be most effective. He describes the trial:[26]

> "On the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants,

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18 Rule 4.
19 Rule 5.
20 Rule 6.
21 Bhatt "Evolution of clinical research: A history before and beyond James Lind" 2010 *Perspectives in Clinical Research* 6 7 ("Bhatt").
22 *Ibid.*
23 As quoted by Bhatt 7.
24 *Idem* 8; Collier 23; Twyman "A brief history of clinical trials. The human genome" (2004), available at https://bit.ly/2IoZMk9 (accessed on 30 March 2018); Dodgson "The evolution of clinical trials" 2006 *The J of the European Medical Writers Association* 20–21 (hereafter "Dodgson").
25 *Ibid.*
26 Chalmers *et al* "The James Lind library: Explaining and illustrating the evolution of fair tests of medical treatments" 2008 *J of the Royal College of Physicians Edinburgh* 259–264.

> sago and wine or the like. Two were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir vitriol three times a day . . . Two others took two spoonfuls of vinegar three times a day . . . Two of the worst patients were put on a course of sea-water . . . Two others had each two oranges and one lemon given them every day . . . The two remaining patients, took . . . an electary recommended by a hospital surgeon . . . The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty . . . The other was the best recovered of any in his condition; and . . . was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects."

The practice of a placebo-controlled trial was first introduced in 1863 by a physician in the United States, Austin Flint.[27] He planned the first clinical study comparing a placebo (or dummy remedy) to an active treatment. Flint treated thirteen patients suffering from rheumatic fever[28] with an herbal extract which was advised instead of an established remedy.[29] In twelve of the thirteen patients no difference was observed between the effect of the placebo and the active therapy, but in the 13th the possibility was that the active treatment might have been effective in preventing the complications that had emerged (pericarditis, endocarditis and pneumonia).[30] Prior to this investigation, outcomes from a particular intervention had been weighed against the natural history of untreated disease.[31]

The introduction of randomisation in a clinical trial arouses much debate. Some argue the first use of randomisation in a medical trial was in 1926 when J Burns Amberson tested a drug for tuberculosis on patients of the Detroit Municipal Tuberculosis Sanatorium.[32] In this study, 24 patients were divided into two approximately equivalent groups of 12 based on clinical, X-ray and laboratory findings; a flip of the coin decided which group would receive the active treatment and which would be the control group.[33]

Others say the first use of randomisation was by the British Medical Research Council in 1948 to evaluate the effects of streptomycin in tuberculosis.[34] In this study, patients were assigned to groups (streptomycin and bed rest or rest alone) by means of random sampling numbers and sealed envelopes.[35] In addition, blinded assessment was employed and neither the researchers nor the patients knew to which treatment group the patients belonged at the time of the study.[36]

Despite the trend towards greater scientific rigour that emerges through the history of clinical trials and the lessons that were learned along the way regarding the use of a control group, randomisation and a placebo, little attention was paid to the welfare and protection of the participants in these trials. The human participants in these early clinical trials were considered mere passive recipients of the treatments meted out to them – they were considered research

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27 Bhatt 9; Dodgson 21.
28 Some sources have the illness as rheumatism.
29 Bhatt 9; Dodgson 21.
30 *Ibid.*
31 *Ibid.*
32 Dodgson 21.
33 *Ibid.*
34 Bhatt 14.
35 *Ibid.*
36 *Ibid.*

subjects in every sense of the word. Protection of clinical research participants was unheard of despite the doctors who conducted these trials adhering to the Hippocratic Oath.[37]

The next section examines the emergence of a regulatory framework for the protection of research participants in response to the abuse that occurred during the Second World War.

3 HISTORY'S "ENIGMATIC LESSON(S)":[38] TRIAL PARTICIPANT ABUSE

Although the history of clinical research is traced back over many centuries, early on little attention was paid to what later became known as bioethics and its subfield research ethics, as well as the law in relation to clinical research. Even the early part of the 20th century saw modest attention in the literature to bioethics. This oversight may be due to several reasons: partly because doctors and scientists did not clearly distinguish between "research" and "treatment" and partly because doctors enjoyed a considerable amount of public trust. They were rarely criticised by their patients or by research "participants".[39]

This situation changed after World War II as a consequence of the Nuremberg Trials and the revelations of experiments conducted by National Socialist doctors on prisoners in the death camps.[40] The Doctors' Trial[41] is considered by many the "birth-moment" or transforming event in the history of clinical research ethics.[42] The Doctors' Trial involved 23 defendants, twenty of whom were physicians accused of murder and torture in the conduct of medical experiments.[43] The world's horror at and condemnation of these murderous and

37 Bhatt 18.

38 Huxley *The devils of Loudun* (1952) 155: "The charm of history and its enigmatic lesson consist in the fact that, from age to age, nothing changes and yet everything is completely different."

39 Much has been written on the concept of "paternalism" in research – see, eg, Resnik "Paternalism and utilitarianism in research with human participants" 2015 *Health Care Analysis* 19–31 and Miller and Wertheimer "Facing up to paternalism in research ethics" 2007 *The Hastings Center Report* 24–34.

40 Shuster "Fifty years later: The significance of the Nuremberg Code" 1997 *New England J Med* 1436 1437 ("Shuster"). The main trial at Nuremberg after World War II was conducted by the International Military Tribunal; see US Government Printing Office *Trials of war criminals before the Nuremberg military tribunals under control council law* (1949) 10(2).

41 The trial began on 9 December 1946 and ended on 19 July 1947. The case was heard by three judges and one alternate. Thirty-two prosecution witnesses and 53 defence witnesses, including the 23 defendants, testified. A total of 1 471 documents were introduced into the record. Sixteen of the 23 defendants were found guilty; 7 of them were sentenced to death by hanging, 5 to life imprisonment, 2 to imprisonment for 25 years, 1 to imprisonment for 15 years, and 1 to imprisonment for 10 years. Seven were acquitted. The sentences were confirmed by the military governor, and, after the US Supreme Court declined to review the case, the executions were carried out at the Landsberg prison (see Shuster 1436 1439).

42 These trials and their aftermath, of course, also were the birth-moment of the re-emergence of the concept of human rights.

43 Schuster 1437; see generally Grodin and Annas "Legacies of Nuremberg: Medical ethics and human rights" 1996 *JAMA* 1682–1683 and Annas and Grodin (eds) *The Nazi doctors and the Nuremberg Code: Human rights in human experimentation* (1992).

barbaric experiments saw the adoption of the Nuremberg Code,[44] the first modern document comprehensively detailing ethical principles of research and establishing the primacy of the welfare and interests of the research participant. For the first time the emphasis was on informed consent after disclosure by the investigator to the participants of the risks of research.[45]

The Nuremberg Code was followed by the adoption of the World Medical Association's (WMA)[46] Declaration of Helsinki. The Declaration of Helsinki is an international code of ethics overseeing biomedical research involving human participants that is framed to govern the status and behaviour of physicians. The Declaration was adopted by the WMA's 18th Assembly held in Helsinki, Finland, in 1964, and has been revised several times.[47] The Declaration of Helsinki represents the efforts of the WMA to develop an international consensus on the ethics of medical research involving humans, and is a guide to physicians involved in research on humans. Henceforth, reputable organisations and journals require that researchers include statements affirming that the principles of the Declaration of Helsinki are followed during research and, specifically, that informed consent has been obtained from participants.

However, transgressions of ethical guidelines and abuse of research participants have continued, evidence that mere reliance on informed consent does not protect research participants against exploitation; but a few examples suffice.

An experiment at Willowbrook State School in the 1950s in which researchers injected the Hepatitis B virus into mentally-challenged children in order to study the natural progression of the disease aroused public concern.[48] Participants were fed extracts from the stools of infected children. Participants who were "enrolled" in the trial at an earlier point in time, and who were already ill, received injections of "purified" virus.[49] The parents of children were able to have their children admitted to hospital only upon their agreeing to the children being part of the research.[50]

In the 1960s, details of an experiment at the Jewish Chronic Disease Hospital in Brooklyn, New York, came to light.[51] In this instance, researchers injected cancer cells into research participants without informing those participants of the risks or obtaining their informed consent.[52] The researchers defended their

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44 The Code deals with non-therapeutic research only (ie, research that does not investigate an illness or condition under which the participants suffer).

45 US Government Printing Office *Trials of war criminals before the Nuremberg military tribunals under control council law* (1949) 10(2) 181–182. The Nuremberg Code contains ten principles; the first of which is an acknowledgement that the voluntary consent of human participants is absolutely essential.

46 The WMA was created in September of 1947. Its founding was inspired by the events at the Nuremberg trials and took place when a large group of private physicians gathered to establish an international association, the World Medical Association; see *WMA Policy* available at http://www.wma.net/e/about.html (accessed on 31 March 2018).

47 See fn 6 *supra*; ("the Declaration").

48 Levine 70.

49 *Ibid*; Grady *The search for an AIDS vaccine* (1995) 40 ("Grady").

50 Levine 70; Grady 40.

51 Levine 70.

52 *Idem* 71; Grady 40. Later it was asserted by researchers that informed consent was negotiated orally but not documented.

actions arguing that they could not tell patients that they were going to receive cancer cells as that would have frightened them unnecessarily.[53] These researchers wanted to gain information on the nature of the human transplant rejection process.[54]

In 1966 Henry Beecher published an exposé in the *New England Journal of Medicine*, which identified 55 cases[55] during the preceding ten years in which there were instances of "unethical and questionably ethical procedures" which put research participants at risk.[56] A staggering 22 cases had their findings incorporated in articles that were published in the *New England Journal of Medicine*.

Beecher argues that two factors determine whether research is ethical – the informed consent of the participant and an "intelligent, informed, conscientious, compassionate, responsible investigator".[57] Beecher points out that the "gain anticipated from the experiment must be commensurate with the risk involved".[58] Most of the instances Beecher describes involve economically and educationally disadvantaged research participants. Subsequent publications have detailed even more severe abuses, such as those Pappworth[59] and Katz[60] describe.

The 1970s saw the disclosure of one the most serious abuses of research subjects to date: the Tuskegee Syphilis Study. The study began in 1932, lasted for 40 years, and is probably the most publicised of the abuses during this period.[61] The study recruited 400 black men of a low socio-economic background from Alabama in the USA with the promise of free medical care for a study into the natural progression of the disease.[62] Two hundred of these men were suffering from syphilis; the remaining 200 were healthy and served as controls.[63] The standard treatment for syphilis at the time was an injection of arsenic and bismuth.[64]

None of the men gave his informed consent to the treatment; in fact, they were told that some of the experiments, such as spinal taps, were not part of the research at all but "special free treatment".[65] Although, in the 1940s, penicillin was discovered to be an effective therapy for syphilis, and the fact that syphilis sufferers' life-spans were reduced by 20 per cent when the disease was left untreated by antibiotics, the men taking part in the study were not told and were left untreated.[66]

Also in the 1970s, the aim of the San Antonio Contraceptive study was to discover which side-effects of oral contraceptive use were due to the drug itself

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53 Levine 71; Grady 40.
54 Levine 71.
55 The results of which were published in international journals.
56 Beecher "Ethics and clinical research" 1966 *New England J of Med* 1354.
57 *Ibid.*
58 *Ibid.*
59 Pappworth *Human guinea pigs* (1967).
60 Katz *Experimentation with human beings* (1972).
61 Levine 69.
62 *Ibid*; Grady 40.
63 *Ibid.*
64 *Ibid.*
65 *Ibid.*
66 *Idem* 70.

and which were due to the "symptoms of everyday life".[67] Mexican-American women (poor and who had no other access to contraceptives and who have had multiple pregnancies), who attended a clinic seeking contraceptive advice, were enrolled in the study.[68] None of the women was advised that she was part of a research study and, in some instances, would receive placebos instead of contraceptives.[69] Eleven of the 76 research participants became pregnant during the study because of receiving a placebo instead of an active contraceptive.[70]

In the 1990s, the Kennedy Kriegler Institute at Johns Hopkins University conducted a research study on lead paint exposure.[71] In order to test their interventions the presence of small children was required, and researchers from the University encouraged landlords of lead-contaminated housing to rent to families (with otherwise healthy young children) who were told the homes had been abated of lead paint.[72] Those families subsequently were recruited to participate in a (fictitious) research study in which blood testing of the children would be done. However, the families were not informed that testing for the presence of lead was to be part of the study.[73] Families with children living in study houses were encouraged to continue living in the houses. The levels of lead that accumulated in the children's blood determined the success of the various methods of lead abatement.[74]

Exposure to lead has a detrimental effect on the health and cognitive development of young children.[75] When the true nature of the research study came to light, the mothers of two of the children filed court cases in which they complained that they were not fully informed of the risks and hazards involved in the study and were not warned promptly of the high levels of lead in their homes and in their children's blood – information that would have influenced their willingness to continue their participation in the study.[76] The judge in the case likened the lead paint study to the infamous Tuskegee experiments.[77]

Africa, too, has not been spared research participant abuse. An egregious example is Pfizer's Trovan experiments in Nigeria. In February 1996, an epidemic outbreak of cerebrospinal meningitis occurred in Kano, Nigeria. The World Health Organization's web-site indicated that by March 17,668 cases had been reported and that more than 2,500 people had died from the disease.[78] The epidemic left over 18,000 victims suffering from the disease.[79]

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67 *Idem* 71.
68 *Ibid.*
69 *Idem* 72.
70 *Ibid.*
71 See Spriggs "Canaries in the mines: Children, risk and non-therapeutic research, and justice" 2004 *J of Med Ethics* 176.
72 *Ibid.*
73 *Ibid.*
74 *Idem* 177.
75 *Ibid.*
76 *Ibid.*
77 See above.
78 "Disease outbreak news", available at https://bit.ly/2wxbK6u (accessed on 15 December 2018); Carr "Pfizer's epidemic: A need for international regulation of human experimentation in developing countries" 2003 *Case Western Reserve J Int L* 15 ("Carr").
79 The damage done by the virus has long-term after-effects, such as the loss of sight and hearing and paralysis.

Pfizer, an international pharmaceutical company, acted quickly to alleviate the epidemic. It delivered desperately-needed medical supplies as well as medical staff to Nigeria.[80] It also started trials of an experimental drug called Trovan for the treatment of viral meningitis.[81] At the time Trovan was not approved for human experimentation by the Food and Drug Administration in the United States.[82] Trovan is one of few drugs to have been withdrawn in the last five years from the US market due to known serious side effects.[83] Further, it is not approved for experimentation using children.[84]

Pfizer set up research headquarters in Kano next to the facility of Doctors Without Borders (DWB). It used DWB bed space and a section of DWB's treatment centre.[85] The doctors brought in by Pfizer were unaccustomed to offering medical care in a city of more than two million people ravaged by pollution, disease and death.[86] During the two weeks they spent in Kano, Pfizer's researchers treated over 200 children for spinal meningitis: 100 children used an oral or intravenous form of Trovan;[87] the remaining children were treated with the antibiotic Ceftriaxone, a drug already approved for use on children in the United States.[88]

At first the Pfizer researchers selected the most suitable children for treatment, but as the epidemic raged on they began treating any child presenting with the illness.[89] The ages of the children ranged from a few months to eleven years and varied in levels of infection from the early stages of the disease to partial paralysis and to near death.[90]

Due to the large number of patients treated in such a short time and the high illiteracy rate in Kano, many of the patients did not sign consent forms.[91] Many of the patients consented verbally, relying on an interpretation provided by a nurse, but frequently the nurses did not translate all the details on the consent form to the families.[92] It is alleged that the treatment with Trovan resulted in the deaths of eleven of the 100 children, while several more were allegedly left blind or deaf.[93]

When the media began an investigation into claims regarding unethical and illegal research practices by Pfizer, they uncovered a variety of violations of international research ethics. Research documents had been forged;[94] there were

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80 Carr 15.
81 Trovan had never before been tested on children.
82 Trovan is one of few drugs in the last five years withdrawn from the US market due to known serious side-effects; see Carr 16.
83 *Ibid.*
84 *Idem* 16.
85 *Idem* 18.
86 *Ibid.*
87 *Ibid.*
88 *Ibid.*
89 *Ibid.*
90 *Ibid.*
91 *Ibid.*
92 *Ibid.*
93 *Idem* 19.
94 Forged documents included individual consent forms, governmental permission forms and oversight approval forms (*idem* 16 fn 8). See Bosely "New drug 'illegally tested on children': Pfizer accused of irregularities during clinical trial in Nigeria" *The Guardian* 17 January 2001 19. Parents of the children participating complained that they did not know that the drug that was being given to their children was experimental.

no oversight and approval of research procedures during the trials[95] and the researchers failed to administer effective treatment to desperate participants.[96]

In 2001, the families of the children that had participated in Pfizer's Trovan research in Kano brought a case against Pfizer in a US court claiming that Pfizer had violated international and national laws in carrying out experimental research on humans. The case against Pfizer in the US represents the first in history in which individuals are suing a private corporation, in a foreign court, for wrongful experimentation in violation of US and international law.[97]

The examples outlined above[98] demonstrate that in spite of the existence of international ethical guidelines to protect participants in clinical research and the emphasis in these guidelines on informed consent, as well as after increased media awareness and scrutiny of clinical trials, abuse of research participants continues.

It is clear, despite the existence of the Nuremberg Code and the Declaration of Helsinki as well as other international and national codes, that the safeguards are insufficient in protecting research participants' rights. Researchers either outright ignored the ethical rules laid down in these documents or thought that their non-ethical actions were justified in the interests of science. The Trovan trial, specifically, shows the consequence of ignorance, overreach and arrogance among scientists.

The public outcry which followed the disclosure of the abuse of trial participants outlined above has led to several countries adopting legislation and regulations which require independent review of all research by a research ethics committee (also known as an institutional review board in some countries) before medical research on human participants may be undertaken. In the United States, for example, Senate passed the National Research Act in 1974.[99] The Act establishes the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. In 1979, the National Commission published the Belmont Report[100] synthesising the ethical guidelines basic to human subject research. In South Africa, the National Health Act requires that all

95 *Ibid.*

96 *Ibid.*

97 *Ibid.*

98 I have focused on the example of Pfizer's Trovan trials. Other abuses have been perpetrated in Africa: the Placebo-controlled trials of Zidovudine to prevent MTCT of HIV in Uganda; the Tenofovir trials in Cameroon and Nigeria; and the male circumcision HIV-transmission trials, Orange Farm, South Africa. See Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* 2007 (LLD-thesis UP 2007).

99 The Act is a domestic piece of legislation; therefore, it governs research carried out in the United States or funded by an agency in the United States and carried out elsewhere.

100 The American National Commission was established in 1974 by the National Research Act (Levine 15). The Act established the National Commission as advisory to the US Department of Health, Education and Welfare and stipulated that it was to be replaced by a long-term National Advisory Council (see Grady 41). Between 1975 and 1979 the National Commission published numerous reports, one of which was the Belmont Report (Grady 41); FR Doc 79-12065 (filed 17 March 1979), available at https://bit.ly/2FYSlv0 (accessed on 4 March 2018).

health research must be reviewed and approved by a health research ethics committee.[101]

The Belmont Report and the work of bodies such as the National Commission (in the US) illustrate a pre-occupation with the need to protect the research participant against the effects of irresponsible research.[102] This protectionist attitude is still evident, and is clearly seen in the South African National Health Act, in which children are (over)protected against potentially unscrupulous research practices in sections 71(2) and 71(3).[103]

An examination of gene therapy clinical trials and the problems they pose for clinical research law and ethics follows below.

4 GENE THERAPY RESEARCH: A BRIEF INTRODUCTION

4 1 Introduction: The science of genes

> "[Decoding the human genome sequence] is the most significant undertaking that we have mounted so far in an organized way in all of science. I believe that reading our blueprints, cataloguing our own instruction book, will be judged by history as more significant than even splitting the atom or going to the moon."[104]

Genes are the basic units of hereditary information found in the cells of all organisms, including humans,[105] containing the information needed to build, maintain and repair organisms.[106] Genes interact with other genes, the environment, other triggers and random chance to produce an organism.[107]

The sequencing of the human genome represents a momentous event in the history of biomedical science.[108] Since that achievement the reduced cost of sequencing and rapid advances in the computational power of the machines doing the sequencing have revolutionised our understanding of health and disease.[109] What has emerged from the sequencing of the human genome is the realisation that any two humans are typically 99.5% DNA identical – therefore, individual variation, including a susceptibility to disease and environmental

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101 Ss 73(1) and 73(2) National Health Act 61 of 2003.

102 The HIV and AIDS epidemics saw a change in this protectionist attitude in countries such as the USA: see Nienaber LLD-thesis (2007) ch 3–6.

103 In this regard, see Nienaber "The statutory regulation of children's participation in HIV-related clinical research: More questions than answers" 2008 *THRHR* 671; Strode *et al* "Child consent in South African law: Implications for researchers, service providers and policy-makers" 2010 *SA Med J* 247; Strode *et al* "Ethical and legal challenges in enrolling adolescents in medical research in South Africa: Implications for clinical trials" 2005 *SA J Science* 224; Nienaber "The regulation of informed consent to participation in clinical research by mentally ill persons in South Africa: An overview" 2010 *SA J of Psychiatry* 42; and Strode "How well does South Africa's National Health Act regulate research involving children?" 2005 *SA Med J* 265.

104 Collins' interview with PBS (23 May 1998), "Cracking the code to life", available at https://to.pbs.org/2KNeMqv (accessed on 30 April 2018). He is an American geneticist who mapped the genes associated with a number of diseases and led the Human Genome Project. He is director of the National Institutes of Health in Bethesda, Maryland, US.

105 Mukhergee *The gene* (2016) 480 ("Mukhergee").

106 *Ibid.*

107 *Ibid.*

108 Kumar *et al Robbins Basic pathology* (2018) 1.

109 *Ibid.*

impact, is encoded on only 0.5% of human DNA, which still represents about 15 million base pairs.[110]

The human genome has 3 088 286 401 letters of DNA.[111] It contains only four letters – AGCTTGCAGGGG – repeated in different sequence.[112] The human genome is divided into 23 pairs of chromosomes in most cells.[113] It encodes 20 687 genes in total, only 1 796 more than worms and 12 000 fewer than rice or wheat.[114] Genes are only part of the genome; there are long stretches of DNA that contain no genes and apparently encode no protein.[115] Some human genes appear to have resulted from horizontal transfer from bacteria and viruses at some point in our evolution.[116]

There is much that is not yet known about the human genome:

> "Although we fully understand the genetic code – ie, how the information in a single gene is used to build a protein – we comprehend nothing of the genomic code – ie, how multiple genes spread across the human genome coordinate gene expression in space and time to build, maintain, and repair a human organism."[117]

Many human diseases are powerfully influenced by genes,[118] most are polygenic – influenced by multiple genes.[119] Instances of monogenic diseases are rarer, but more than 10 000 monogenic diseases have been defined so far.[120] According to Mukhergee, genetic illnesses are a form of a mismatch between the organism's genome and its environment.[121]

Potentially, I am a carrier of Spinal Muscular Atrophy (SMA), which is caused by mutations in the SMN1 gene on chromosome 5q11.[122] This mutation has affected some of my siblings. The SMN gene is necessary for the creation of small nuclear ribonucleins which are involved in the process of the creation of mRNA – a protein that is important for the survival of motor neurons (SMN protein). In SMA, insufficient levels of the SMN protein lead to degeneration of the lower motor neurons, producing weakness and wasting of the skeletal

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110 *Idem* 2.
111 Mukhergee 322.
112 *Ibid.*
113 *Idem* 323.
114 *Ibid.*
115 *Idem* 461.
116 *Ibid*; International Human Genome Sequencing Consortium "Initial sequencing and analysis of the human genome" 2001 *Nature* 860.
117 Mukhergee 325. Reich *Who we are and how we got here. Ancient DNA and the new science of the human past* (2018) 9 writes as follows in this regard: "We are like kindergartners in our ability to read the genome. While we have learned to decode the individual words – as we know how the sequence of DNA letters gets turned into proteins – we still can't parse the sentence."
118 *Idem* 481.
119 *Ibid.*
120 *Idem* 482.
121 *Ibid.*
122 Cindro and Cindro "Motor neuron disease and neuropathy" 2015 *Collegium Antropologicum* 261–265. SMN1 gene determines the status of SMA carriers as well as SMA patients. In 95% of the cases of SMA the patients are homozygotes for the lack of axon 7 on SMN1 gene, while the 3.6% are complex heterozygotes with a point mutation on the second allele.

muscles.[123] A small clinical trial of SMN gene replacement therapy is now underway in individuals with SMA.[124] SMA is the second most frequent autosomal recessive disease with the frequency of 1 in 10 000 live new-borns; the carrier frequency is 1/35–1/603, depending on the population group.[125]

The aim of gene therapy is to replace a defective gene with a properly functioning version through a technique that has become known as "gene editing".[126] "Gene editing" is a process to alter an organism's genes, in some instances facilitating changes in the characteristics of the cell or organism.[127] Previously, gene editing technologies were inefficient, expensive and carried considerable risk for the recipient (not least because they added an extra gene sequence from a different organism into the genome).[128] However, with the advent of CRISPR-Cas9,[129] which eliminates the need to incorporate foreign DNA into the human genome, gene editing has become far more accurate and is considerably cheaper than previous technologies.[130]

Gene therapy is a revolutionary way to treat genetic diseases or to prevent the development of disease in unborn children.[131] Healthy genes are introduced into the body by a vector, usually a virus.[132] Inherited single gene diseases such as haemophilia (factors VIII and IX), cystic fibrosis (CFTR), Duchenne muscular

123 *Ibid*; National Institute of Neurological Disease and Stroke "Motor-neuron diseases fact-sheet" available at https://bit.ly/2K6OZsl (accessed on 30 March 2018).

124 *Ibid.*

125 Cindro and Cindro 2015 *Collegium Antropologicum* 262.

126 Hengst and Yun "Control and regulation of gene expression" in *xPharm: The comprehensive pharmacology reference* (2008) 2 ("Hengst and Yun").

127 Baum *et al* "Chance or necessity? Insertional mutagenesis in gene therapy and its consequences" 2004 *Molecular Therapy* 5–13; Chandavarkar *et al* "A framework for governing gene editing" in Takshashila Institution discussion document 3 April 2017, available at https://bit.ly/2rvQTLf. Gene editing sometimes occurs by itself in nature when a cell divides.

128 *Ibid.*

129 Short for Clustered Regularly Interspaced Short Palindromic Repeats; see Ehrke-Schulz *et al* "CRISPR/Cas9 delivery with one single adenoviral vector devoid of all viral genes" 2017 *Nature Scientific Reports*, available at https://go.nature.com/2AIXgSQ (accessed on 30 April 2018); and DiCarlo *et al* "Viral vectors, engineered cells and the CRISPR revolution" in Tsang (ed) *Precision medicine, crispr, and genome engineering. Advances in experimental medicine and biology* (2017) 3–27. CRISPR/Cas9 consists of the "Cas9 endonuclease that acts in cooperation with a chimeric guide RNA (gRNA) mediating the sequence-specific binding to its complementary target protospacer sequence preceding a protospacer adjunct motif (PAM)1. Due to its simple gRNA design and easy cloning procedure for customization, the CRISPR/Cas9 system is easier to handle than transcription activator-like effector nucleases (TALENs) and artificial zinc finger nucleases (ZFN)2" (Ehrke-Schulz *et al* 2017).

130 Baum *et al* 2004 *Molecular Therapy* 5–13; Chandavarkar *et al* 3.

131 Hengst and Yun 1; the US FDA defines gene therapy as products "that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient".

132 Techniques such as CRISPR have eliminated the need for a viral vector.

dystrophy (dystrophin), and SMA are candidates for gene therapy.[133] However, even though considerable advances have been made gene therapy faces several technical hurdles that must be overcome before it becomes a commonly employed therapeutic technique.[134]

Gene therapy consists of two distinct kinds: somatic and germline gene therapy.[135] Gene therapy performed directly in body cells, such as blood or muscle cells, is somatic gene therapy,[136] whereas gene therapy using egg or sperm cells is germline gene therapy.[137] With germline gene therapy the change is passed on to future generations and, in effect, becomes self-propagating[138] in that change transmits from one generation to the next.[139] Germline editing has been conducted successfully in animals, but major technical challenges remain in developing the technology for safe and predictable use in humans.[140] Currently, somatic cell gene therapy is being researched and trialled, but germline gene therapy is not. Partly, it is because of the ethical questions surrounding permanently altering the genome of unborn future generations.[141]

Currently, cancer is by far the most common disease treated by gene therapy. It composes over 60% of all on-going clinical gene therapy trials worldwide, followed by monogenetic and cardiovascular diseases.[142] In 2003, China became the first country to approve a gene therapy-based product for clinical use.[143] Gendicine™, developed by SiBionoGene TechCo, is an adenoviral vector, wherein the E1 gene is replaced with a human p53 cDNA. Gendicine is a non-replicative virus and received approval for the treatment of head and neck squamous cell carcinoma.[144] China's State Food and Drug Administration (SFDA) reportedly approved Gendicine without data from a standard phase III clinical trial.[145] Consequently, soon after the approval of Gendicine the efficacy of the treatment was debated.[146]

In July 2012, the European Medicines Agency (EMA) approved the first gene therapy product (Glybera).[147] Glybera, originally developed by Amsterdam Molecular Therapeutics and now marketed by UniQure, is an adeno-associated viral vector engineered to express lipoprotein lipase in muscle tissue for the treatment of severe lipoprotein lipase deficiency.[148]

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133 Leiden "Human gene therapy. The good, the bad, and the ugly" 2000 (86) *Circulation Research* 923.
134 Hengst and Yun 1.
135 Mukhergee 464.
136 It affects the function of the cell, but only for that human and that generation.
137 Hengst and Yun 1; Mukhergee 464.
138 Mukhergee 464; Hengst and Yun 2.
139 Mukhergee 464; Hynes *et al* "Toward responsible human genome editing" 2017 *JAMA* E1.
140 *Idem JAMA* E1–E2.
141 Hengst and Yun 1.
142 Wirth *et al* "History of gene therapy" 2013 *Gene* 165 ("Wirth *et al*").
143 *Ibid.*
144 *Ibid.*
145 *Ibid.*
146 Xin "Chinese gene therapy. Gendicine's efficacy: Hard to translate" 2006 *Science* 1233.
147 Wirth *et al* 166.
148 *Ibid.*

4 2 A short history of gene therapy clinical trials gone wrong

4 2 1 Jesse Gelsinger

Jesse Gelsinger was the first person to die as a direct consequence of participation in a gene therapy clinical trial.[149] Gelsinger had ornithine transcarbamoylase (OTC) deficiency (a liver enzyme that is required for the removal of excessive nitrogen from amino acids and proteins), a metabolic disorder that affects 1 in 40 000 new-borns by impeding the elimination of ammonia.[150] Babies born with the disease usually do not live beyond the age of 5.[151] Gelsinger had a different outcome because he had only partial OTC deficiency which he controlled by means of a low-protein diet and medication.[152] He was considered an ideal candidate for a gene therapy trial headed by Dr James Wilson, director of the Institute for Human Gene Therapy at the University of Pennsylvania.[153] On 13 September 1999, Gelsinger was given an infusion of corrective OTC gene encased in a dose of attenuated cold virus, a recombinant adenoviral vector, injected into his hepatic artery.[154]

Gelsinger experienced a severe immune reaction to the vector – the gene's delivery vehicle – and died four days after receiving the injection.[155] No one realised that the vector itself might pose a risk.[156] The US FDA immediately suspended the trial, citing a failure to train staff adequately, develop basic operating procedures and to obtain informed consent.[157] In January 2000, the FDA halted the remainder of the University of Pennsylvania's human trials involving gene therapy and began investigating other gene therapy trials under-way in the US.[158] Eventually, 28 trials were reviewed, with 13 requiring remedial action. Paul Gelsinger, Jesse's father, in October 2000 instituted court action against the researchers and others that was settled out of court for an undisclosed sum and the university's promise to move forward with "aggressive efforts to improve its oversight and monitoring of human subject research".[159]

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149 This certainly was not the first gene therapy trial in humans. For an overview of the history of gene therapy research, see Wirth *et al* 162–169. For a first-hand account of the trial, see Wilson "Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency" 2009 *Molecular Genetics and Metabolism* 151–157.

150 Sibbald "Death but one unintended consequence of gene-therapy trial" 2001 *JAMC* 1612. Most of these babies become comatose within 72 hours of birth and experience severe brain damage. Half die within a month of birth, and half of the survivors die by age 5.

151 *Ibid.*

152 *Ibid.*

153 *Ibid.*

154 *Ibid.*

155 See Stolberg "The biotech death of Jesse Gelsinger" 1999 *NY Times Mag* 136–140 149–150. Gelsinger became the first patient in whom death could be directly linked to the viral vector used for the treatment.

156 Verma "A tumultuous year for gene therapy" 2000 *Molecular Therapy* 415–416.

157 Sibbald 2001 *JAMC* 1612.

158 *Ibid.*

159 *Ibid.*

4 2 2 Jolee Mohr

Another death that has been ascribed to participation in a gene therapy clinical trial is that of Jolee Mohr.[160] Mohr, aged 36, was receiving systemic immunosuppressive therapy for rheumatoid arthritis and was enrolled in a gene therapy trial.[161] The trial aimed to evaluate the intra-articular delivery of a tumour necrosis factor α (TNF-α) antagonist, through an adeno-associated virus (AAV) type 2 delivery system, for inflammatory arthritis.[162] The expressed protein inhibits TNF-α, a key mediator of inflammation.[163] Ms Mohr died during the trial of a massive fungal infection complicated by major internal bleeding.[164]

The US Recombinant DNA Advisory Committee of the National Institute of Health reviewed the circumstances of Mohr's participation in the gene-therapy trial and the cause of her death.[165] They concluded that Mohr's concurrent receipt of the anti-TNF-α therapy and other immunosuppressive therapy while she was living in an area where histoplasmosis was endemic to be the most likely explanation for the massive infection that caused her death.[166] Nevertheless, although the fatal infection was unlikely to have been related to exposure to the agent administered in the gene therapy trial, the gene therapy agent could have been a contributing factor.[167]

Gelsinger's and Mohr's are not the only deaths to date that are suspected of being the consequence of participation in gene therapy clinical trials.[168] At this point, an important question needs be raised: what lessons have we learnt from these deaths and the abuses in clinical research outlined in the historical section of the article?[169] The next section outlines the implications for the evaluation by research ethics committees of gene therapy clinical trials in the light of what it is hoped has been learned.

5 IMPLICATIONS FOR THE EVALUATION OF GENE THERAPY CLINICAL RESEARCH BY RESEARCH ETHICS COMMITTEES

5 1 Introduction

The history of clinical research and the history of gene therapy research provided many lessons: lessons of scientific, philosophical and ethical import. History

160 Frank *et al* "Investigation of the cause of death in a gene-therapy trial" 2009 *New England J Med* 161–169; Johnson and Tanner "Woman's death calls gene therapy into question" available at https://nbcnews.to/2FYWBKY (accessed on 9 April 2018).

161 *Ibid.*

162 Frank *et al* 2009 New *England J Med* 161.

163 *Ibid.*

164 Wadman "Gene therapy trial to restart" *Nature* 27 November 2007, available at https://go.nature.com/2rxDC4Z (accessed on 30 April 2018).

165 Caplan "If it's broken, shouldn't it be fixed? Informed consent and initial clinical trials of gene therapy" 2008 *Human Gene Therapy* 5 ("Caplan").

166 Wadman *Nature* 27 November 2007.

167 Caplan 5–6.

168 According to Ziopharm, the third patient died 15 days after starting on a 30 mg dose of the gene therapy. The death has yet to be reported to the FDA: "We are collecting and analyzing information in order to properly and timely report it to the FDA." The other two patient deaths occurred 6.7 months following a 20 mg dose, and 3.9 months after treatment with a 40 mg dose, the company added, insisting that the deaths were unrelated to the study drug. See "Ziopharm confirms three patient deaths in gene therapy trial" available at https://bit.ly/2jLCwiD (accessed on 9 April 2018).

169 Para 2 *supra.*

may not repeat itself, but those who do not learn its lessons are fated to repeat its mistakes. The human genome is repeated in each generation, the history of clinical research also could be a repetition. The impulses, desires and weaknesses that drive human history and scientific discovery, too, are encoded in the human genome.

The genome itself is weighted with history – containing peculiar fragments of DNA inserted millennia ago – fragments which are neither human nor animal, but remnants of viruses long lost in the history of evolution.[170] The history of clinical research, similarly, has in its DNA lessons of past failure, the consequence of ignorance, overreach and arrogance.[171] These lessons should have been well-learned – but have they been?

5 2 Lessons well-learnt?

5 2 1 Lesson 1: Informed consent is not a cure-all, or the importance of thorough ethics review

In order to evaluate clinical research for approval research ethics committees (RECs) adhere to legal and ethical norms. Legal norms are embodied in various pieces of legislation and human rights instruments; ethical norms are embodied in documents of research ethics (such as the Nuremberg Code and the Declaration of Helsinki) as outlined above.[172] Three ethical principles are commonly used in the judgment of the ethical acceptability of clinical research, namely, respect for persons (or respect for autonomy), beneficence (which includes non-maleficence) and justice.[173] These ethical principles correspond to the three ethical concerns or questions in research, namely, the form of research which qualifies as both scientifically valid and necessary, that which is in the best interests of the participants and concerns about the autonomy of the research participant.

Because of abuses to be found in the history of clinical research,[174] and because of the emphasis in liberal democracies on the human rights of dignity, physical integrity and freedom of the person, the principle of personal autonomy, as embodied in research participant informed consent, has come to be regarded as an ethical panacea.[175] It presents as a common belief that as long as the participant consents to participation and accepts the risks of the proposed research, all will be well.[176]

It is submitted that informed consent has become over-emphasised in the ethics review process, beyond the problems experienced in South Africa and other developing countries in obtaining consent that is both informed and freely given.[177] It is an important lesson for RECs that informed consent should not be

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170 Mukhergee 483.
171 Based on an idea by Mukhergee 483.
172 See paras 2 and 3 *supra*.
173 See, generally, Beauchamp and Childress *Principles of biomedical ethics* (2012) ch 1–3 ("Beauchamp and Childress").
174 See para 2 *supra*.
175 Corrigan "Empty ethics: The problem with informed consent" 2003 *Sociology of Health & Illness* 768.
176 *Ibid.*
177 See paras 5.2.3–5.3.5 *infra*.

over-hyped at the cost of meaningful, serious and thoughtful attention being paid to the potential risks inherent in the proposed research. It is of particular importance in Phase I (or first-in-human studies) where there is a greater risk of harm and a lesser prospect of direct clinical benefit to research participants. As well, in these studies the risks as yet may not be known.

In instances where the potential research participants are extremely ill or have serious disease, the REC should nevertheless carefully weigh up the potential harm to participants against the expected benefits of research. This situation is of even greater significance in the case of the potential research participants being children or neonates.[178] In gene-therapy research the risks of the proposed research often are not evident, thus it is wise that RECs err on the side of caution. Jesse Gelsinger's death should have taught this: the REC evaluating the research study for approval either "misunderstood the nature of the expected harm and/or ethics committees' responsibilities in evaluating it, or (more likely) gave greater weight to consent than to expected harm".[179]

Therefore, responsible research ethics review not only ensures that informed consent is obtained from participants, but also provides an objective and meaningful evaluation of the prospect of harm arising from the research.

5 2 2 Lesson 2: The importance of pre-clinical[180] studies and reporting their results

RECs, in weighing up the risks of testing novel gene therapies in humans against the potential benefit of such a study, rely on information about the gene product and its behaviour obtained in pre-clinical studies. The research team is to provide the REC with all pre-clinical data in order for it to assess the potential utility of the technology and the types of toxicity that may be seen in humans.[181] The gene therapy deaths narrated above "raised questions about . . . the adequacy and interpretation of prior research involving animals and laboratory studies".[182] In the same vein Jesse Gelsinger's father had complained that the informed consent process did not disclose the deaths of two animals in the pre-clinical studies.[183]

Often, it is not until therapeutic agents, including gene therapy agents, are tested in humans that risks materialise. It is the task of the REC to anticipate and interpret the risk of harm based on reliable pre-clinical trial results. In the absence of pre-clinical studies, it is difficult to justify ethically and legally testing a gene therapy product in humans.

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178 It is likely that much gene therapy research, indeed, will be on children as many inherited progressive diseases manifest in childhood. In instances where children take part in gene therapy research researchers must adhere to the constitutional imperative that all decisions relating to a child must be in the best interests of that child (s 28(2) Constitution of the Republic of South Africa, 1996); and the legislative imperative in s 71(2)(a) of the National Health Act.

179 Savulescu "Harm, ethics committees and the gene therapy death" 2001 *J of Med Ethics* 148 149.

180 *In vitro* laboratory studies and animal studies.

181 Department of Health *South African good clinical practice guidelines* (2006) Guideline 2.2.

182 Caplan 5.

183 Smith "Gene therapy in the post-Gelsinger Era" 2002 *JONA'S Healthcare Law, Ethics, and Regulation* 107 ("Smith"); Wilson 2009 *Molecular genetics and metabolism* 154.

Any type of doubt as to risk involved in using a product in humans must be reflected clearly in the consent process.[184] It has been alleged that in the Gelsinger gene therapy trial the researchers removed a paragraph from the IRB-approved informed consent documentation that discussed two primate deaths during an earlier version of the protocol.[185]

5 2 3 Lesson 3: Voluntariness and meaningful choice: A contradiction with reference to gene therapy clinical trials?

The requirement that researchers obtain "the *voluntary* consent of the human subject" is listed first in respect of the ethical principles in the Nuremberg Code. This principle derives from the historical knowledge gained as a consequence of the abuses perpetrated by the National Socialists in their "experiments" on Jewish victims and others designated "asocial" persons. For these practices, the doctors at Nuremberg were found guilty of crimes against humanity and war crimes.[186]

"Voluntariness" is a description of an action that is free of controlling or coercive influences, chiefly referring to the influence of others.[187] As well, certain conditions, such as mental illness and drug addiction, may reduce or eliminate the element of voluntariness.[188] Therefore, it is informed consent that is voluntary that has become an ethical and legal imperative. This is true in terms of South African legal rules and ethical guidelines as well.[189]

I pointed out my potential carrier status of SMA – an incurable, virtually untreatable genetic illness that had devastating effects on my family. Sufferers living with the distress of this disease or those, like my parents, who are witnesses to their children's illness, will do anything in an attempt to alleviate their own or their children's pain. Many view gene therapy research as the only hope of finding a cure for a devastating illness. In this situation, it is doubtful whether one can speak of meaningful choice in participating in gene therapy trials. In the context of such desperation, what is the value of talk about "voluntary" participation? In this context, Berg *et al* remark that[190]

> "being ill brings with it a multitude of pressures, and a patient suffering from a life-threatening disease may feel as though she has little choice regarding treatment. Physicians should be aware of how vulnerable patients may be to the coercive influence of unrealistic hope, especially those suffering from chronic, life-threatening disorders".

184 Wilson 2009 *Molecular Genetics and Metabolism* 156.

185 Marshall "Gene therapy on trial" 2000 *Science* 951–957; Smith 107.

186 See para 3 *supra.*

187 McLean in Doyal and Thobias (eds) *Informed consent in medical research* (2001) 166–167; Burchell "Experimentation on human subjects: Protecting dignity and advancing medical science" 1988 *Acta Juridica* 217 218; Beauchamp and Childress 93. This view of voluntariness is narrower and is intended to differentiate it from a broader concept that would make it synonymous with autonomy.

188 Burchell 1988 *Acta Juridica* 216–218; Beauchamp and Childress 94.

189 S 12(2)(c) Constitution of the Republic of South Africa; s 71(1)–71(3) National Health Act; cl 2(d) Reg 135 "Regulations relating to research on human subjects" *GG* 29637 of 23 February 2007.

190 Berg *et al Informed consent: Legal theory and clinical practice* (2001) 145.

It is not to suggest that critically or terminally ill people are unable to make a voluntary decision to participate in clinical research, but merely that in such situations the voluntariness of choice is compromised.

Beauchamp and Childress outline three categories of influence which reduce or eliminate voluntariness: coercion, persuasion and manipulation.[191] In this context, manipulation is of particular importance. "Manipulation" refers to a "generic term for several forms of influence that are neither persuasive nor coercive".[192] The most common form of manipulation in research is the use of informational manipulation,[193] referring to the manner in which a researcher presents information (tone of voice, a forceful gesture, and so on) so as to change the participant's understanding of a particular situation and to influence her to act in a certain manner.[194] A straightforward example of informational manipulation is the use of a positive statement "we have a 35 per cent success rate" rather than the negative "we have a 65 per cent failure rate".[195] However, Beauchamp and Childress argue that the effect of manipulation in research should not be overstressed as research participants often make decisions in a context of rival influences, such as "personal desires, familial constraints, legal obligations, and institutional pressures".[196] Such influences do not necessarily exclude the probability of autonomy. Nevertheless, to ensure that research participants make autonomous choices it is important to establish the point at which autonomous choice is put at risk. Furthermore, in many situations it is difficult to distinguish between controlling and non-controlling influences.[197]

A gene therapy clinical trial in South Africa must assure that autonomous choice is not at risk and that trial participants do not feel compelled to participate. Extra effort must be taken to lessen the potential of others – including parents – making the decision to take part in a trial because they are desperate for a cure to be found. This point is dealt with in greater detail below.

In a related context, it is important for researchers to be responsible in reporting their findings as prior research results may easily be over-stated or misinterpreted, especially in the press, and so give false hope.

5 2 4 Lesson 4: Meaningful information? The complexity of information presented about gene therapy trials during the consent process

It has been pointed out that the value of informed consent should not override careful evaluation by RECs of the risks and benefits of the gene therapy research. Nevertheless, the informed consent of research participants must be obtained and must be based on information that will facilitate their *meaningful* knowledge and *meaningful* comprehension.

Both the Gelsinger and Mohr families subsequently complained that neither had given full informed consent to participation in the trial. Mohr's husband alleged that Mohr did not understand why she was in the study, despite having

191 Beauchamp and Childress 94.
192 *Idem* 95.
193 *Ibid.*
194 *Ibid.*
195 *Ibid.*
196 *Ibid.*
197 *Ibid.*

signed "a fifteen-page informed consent form".[198] Jesse Gelsinger's father, similarly, alleged that Jesse may not have understood the possible risks of the study. He, too, read and signed an elaborate, REC-approved informed consent document.[199]

In this context, is there any assurance that it is reasonably conceivable that lay persons have the necessary *meaningful* knowledge and comprehension about the workings of gene therapy agents to make *meaningful* choices about participation in gene therapy research when the science is so complex? This question is relevant in light of the fact that in evaluating potential gene therapy trials most RECs call on the opinions of experts in genetic research to help them decipher the potential risks of these trials – RECs, after all, are staffed mostly by medical professionals. It is highly doubtful that participants in gene therapy trials gain meaningful knowledge about the aims and objectives of the trial and the possible risks from the informed consent documents presented to them, and thus arrive at a *meaningful* decision.

Information about a gene therapy clinical trial needs to be presented in a manner that is understandable to the prospective participant. Merz, with others, calls for the development of written material which does not use medical jargon and technical language.[200] He recommends that where the use of scientific information is unavoidable (as no doubt it will be in gene therapy trials) definitions be given in a lay person's terms.[201] Proponents of this view insist on a user-friendly format being utilised in which information is set out in a logical manner, which is easy to read because of its use of headings and emphasis on specific information.[202]

Research has been conducted on the comprehensibility of informed consent documents. For example, Campbell *et al* comment that, despite efforts being made to ensure a comprehensive informed consent process, research participants still make poorly-informed decisions.[203] In general, the quality of informed consent documents is poor: Burman *et al* remark that the majority of informed consent forms are poorly written and cannot ensure effective informed consent.[204] They call for outside organisations to monitor the informed consent process so as to ensure that informed consent forms are of a sufficient quality.[205] In the case of gene therapy trials, the use of pictures and other graphic representations to explain concepts such as genes, DNA and CRISPR have been recommended.

If it is to reach a decision to approve a clinical trial protocol for research in humans, the REC should focus on whether in light of the information provided to participants it is likely that meaningful informed consent by the participants will be achieved. In part, this decision is executed after a careful examination of the

198 Caplan 5.
199 Beauchamp and Childress 95.
200 Merz "The ethics of research on informed consent" 2002 *Controlled Clinical Trials* 172–173.
201 *Idem* 173.
202 *Ibid.*
203 Campbell *et al* "Evaluating meta-ethnography: a synthesis of qualitative research on lay experiences of diabetes and diabetes care" 2003 *Social Science and Med* 671–684.
204 Burman *et al* "The effects of local informed consent documents from a multicentre clinical trials consortium" 2003 *Controlled Clinical Trials* 245.
205 *Idem* 247.

protocol and informed consent documents to determine if they meet the ethical and legal prerequisites. The REC must review the way in which the participant is to be informed about the proposed research and the precise way in which consent is sought.[206]

5 2 5 Lesson 5: Meaningful comprehension?

In many articles critics have commented on research participants' inadequate comprehension of the information given to them during the consent process.[207] Clearly, in order to achieve consent that is informed research participants need to understand the information that has been provided. Moreover, they have to understand the meaning and impact of that information on all aspects of their lives, such as on their physical, emotional and social well-being. In the context of gene therapy clinical trials in South Africa, participants must at least understand the methodology of a gene therapy trial, the nature of the risks posed by the trial and the possible benefits of trial participation so that they may make an informed decision. As researchers are responsible for the obtaining of consent and ensuring that it is informed consent, they are responsible for ascertaining that the research participant understands the information provided.

A research participant's ability to comprehend or understand information is a function of her intelligence, maturity and linguistic abilities. As pointed out above, information of a scientific or technical nature is difficult to understand for lay people no matter the level of education. In the developing world, where poverty, low levels of education and illiteracy are the order of the day, the meaningful comprehension of scientific and technical information poses a significant challenge. In the public healthcare sector in South Africa, due to their socio-economic background gene therapy trial participants are likely to have low educational[208] and literacy levels, have little medical or nil scientific knowledge and be second-language speakers of English. It is likely there will be cultural differences between the researcher and the research participants.[209] Bayer comments

206 Medical Research Council *Guidelines on ethics for medical research* (2004) Guideline 9.8.1.

207 See, eg, Coletti *et al* "Randomized, controlled evaluation of a prototype informed consent process for HIV efficacy trials" 2003 *J Acquired Immune Deficiency Syndromes* 161; Lynöe *et al* "Informed consent: Study of the quality of information given to participants in a clinical trial" 1991 *British Med J* 610; Schultz *et al* "Are research subjects really informed" 1975 *West J Med* 76; and Moodley *et al* "Informed consent and participant perceptions of influenza vaccine trials in South Africa" (2005) 31 *J Med Ethics* 727. Moodley *et al* 731 conclude that participants' recall of informed consent in randomised controlled trials in South Africa and other developing countries may "often be inadequate".

208 The education levels of South Africans aged 15 and over are alarmingly low (according to StatsSA's Community Survey, 2016): upper secondary school completion rate (aged 15 and older): 55,1%; secondary school completion rate (aged 25 and older): 30,7%; post-secondary completion rate (aged 25 and older): 11,4%: Statistics South Africa *Community Survey, 2016*, available at https://bit.ly/2I26Wvz (accessed on 30 April 2018).

209 Bayer "Ethical challenges of HIV vaccine trials in less developed nations: Conflict and consensus in the international arena" 2000 *AIDS* 1051–1057. Also see Ives *et al* "Does an HIV clinical trial information booklet improve patient knowledge and understanding of HIV clinical trials?" 2001 *HIV Medicine* 241.

on the difficulties these disparities create and that explaining concepts such as placebo and randomisation to participants, is very difficult.[210]

Gita Ramjee *et al* evaluated the comprehension of participants in a vaginal microbicide study conducted in KwaZulu-Natal.[211] According to the results of her study, almost 70 per cent of participants failed to understand vital scientific information regarding the study as well as factual aspects related to the drug, such as the fact that the microbicide was experimental, that it could not protect against HIV and other sexually transmitted diseases and that a placebo microbicide was used on some of the participants.[212]

In most cases in South Africa interpreters translate the scientific and other trial related information contained in the informed consent document from English into a local language. In a paper entitled "Informed consent in a cross-cultural context", Molyneux observes that although studies indicate that interpreters who are culturally and linguistically matched to study participants generally improve participants' understanding and the transfer of content information, there are still discrepancies in understanding of research procedures identified among South African research participants.[213] In the case of a gene therapy trial undertaken in South Africa, extra effort will be needed to ensure that translation into local languages is accurate and that the translation does not impede comprehension. Differences in knowledge systems will have to be borne in mind when a translation is made.

5 2 6 Lesson 6: Gene therapy research – should "therapy" be dropped from that concept?

In the opinion of ethicists two possible misconceptions predominate in clinical research: a therapeutic misconception which is a misplaced belief that the purpose of the research is to the *personal health benefit* of the participant and a curative misconception which is the misplaced belief that the research trial will provide a *cure for research participants*.[214] Both types of misconceptions will likely be present in gene therapy research.

Beauchamp and Childress's account of "voluntariness" described above[215] lacks an understanding of the form of manipulation that is likely to be most prevalent in a South African research setting, especially in relation to gene therapy trials. Their account occludes the complexities of power relations in a South African setting. A participant's autonomous choice is influenced by the context of the research, which in South Africa is likely to be public sector healthcare.[216]

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210 *Ibid.*

211 Ramjee *et al* "Challenges in the conduct of vaginal microbicide effectiveness trails in the developing world" 2000 *AIDS* 2553–2557.

212 *Ibid.*

213 Molyneux "Informed consent in a cross-cultural context", paper delivered at the First Annual IRENSA Conference, Cape Town (2003).

214 Horn and Grady "Misunderstanding in clinical research: Distinguishing therapeutic misconception, therapeutic misestimation, & therapeutic optimism" 2003 *IRB: Ethics & Human Researc*h 11–16. See also Miller "Phase I cancer trials: A collusion of misunderstanding" 2000 *Hastings Center Report* 34.

215 See para 5.2.3 above.

216 According to Barsdorf and Wassenaar "Racial differences in public perceptions of voluntariness of medical research participants in South Africa" 2005 *Social Science & Med* 1087–1098 there is a definite racial difference visible in the perception of voluntariness

continued on next page

Participants in gene therapy trials will probably have an economically disadvantaged background, and will believe that "doctor knows best" or at least that the trial presents their only opportunity to receive gene therapy which they perceive as an only chance of a cure.

Some research participants may be unable to distinguish research from care – especially in light of the term "gene *therapy*".[217] In this context McNeill remarks that it "it is the socially powerless that are most likely to be subjected to unethical research".[218] This lesson should have been learned from the Tuskegee Syphilis Study which exemplifies this type of research participant abuse and is evident as well in the experimentation that led to the Nuremberg Trials.

Various studies on informed consent in a South African setting confirm a lack in the ability to distinguish between research and care. For example, Molyneux *et al*[219] found that "many community members had great difficulty in distinguishing between the clinical and research aims of the work".[220] If the research subject is unable to understand that she is taking part in research and that the medication or therapy being tested is merely experimental and has no proven clinical value, it is self-evident that informed consent has not been obtained.

Abdool Karim *et al* report on a study that evaluated informed consent to HIV testing and research at King Edward VII Hospital, a major referral state hospital largely serving black patients around Durban.[221] Specifically, the study evaluates the informed consent obtained from women participating in an antenatal transmission study undertaken by the hospital.[222]

Women who attended the antenatal clinic for the first time were randomly selected to answer questions before and after HIV testing and counselling on the research project.[223] The women were divided into two groups, an evaluation study group who completed questionnaires before and after the HIV counselling and the information session regarding the research study (the antenatal-transmission study); and a sensitisation control group who completed only a post-counselling questionnaire.[224] Karim *et al* conclude in their article in relation to the study's findings, first, that the women's knowledge of HIV transmission and prevention

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in clinical research. The researchers show that Black respondents scored significantly lower on scores of perceived voluntariness than both Indian and White respondents.

217 The potential problems inherent in the use of "therapy" are extensively described in a different context (stem cell therapy) by Prinsen – see *An analysis of consent with specific regard to stem cell therapy and research* (LLD thesis UP 2007). Prinsen argues that, due to the uncertain scope and untested efficacy of stem cell therapy, treatment applications are tantamount to research involving human subjects.

218 McNeill "The ethics and politics of human experimentation", quoted in Barsdorf and Wassenaar 2005 *Social Science & Med* 1087.

219 Molyneux *et al* "Even if they ask you to stand by a tree all day, you will have to do it (laughter) …!': Community voices on the notion and practice of informed consent for biomedical research in developing countries" 2005 *Social Science & Med* 433.

220 *Idem* 451.

221 Abdool Karim *et al* "Informed consent for HIV testing in a South African hospital: Is it truly informed and truly voluntary?" 1998 *American J of Public Health* 637–640.

222 *Ibid.*

223 *Ibid.*

224 *Ibid.*

was little improved by the pre-test counselling that they underwent (most women's knowledge at the outset was relatively high regarding the modes of transmission and prevention of HIV) and, secondly, that despite assurances that the HIV test was voluntary 84 per cent of the women in the evaluation group and 93 per cent in the sensitisation group believed that it was compulsory to take the HIV test.[225] Moreover, 93 per cent of the women in the evaluation group and all of the women in the sensitisation group felt that the hospital would not allow them to quit the antenatal research study.[226] Almost a third of the evaluation group and a quarter of the women in the sensitisation group felt that that the "care they received at the hospital would change if they did not participate in the [antenatal] study".[227] More significantly, 28 per cent of the women believed that the research was integral to service at the hospital and agreed to take the HIV test because they thought that refusal would compromise their care.[228] The authors of the article comment:[229]

> "This subtle coercive element may stem from the social context of a hospital where the health professionals are held in high regard. This perception of potentially compromised quality of care is reinforced by the perception that the hospital would not allow them to quit the study even though they knew they had the freedom to do so."

Not only is the "social context of a hospital" one in which "health professionals are held in high regard", one should remember also that the hospital concerned is the only tertiary or state hospital to which these participants have access – their only chance to receive free medical care in circumstances in which they are unlikely to be able to pay for private medical care. Thus, they share a conviction that they have no choice but to be subject to whatever demands the staff at the hospital make of them – they *cannot* refuse to participate or quit the study. The authors of the article conclude that in the South African medical care setting, even though informed consent can be said to be relatively informed, it cannot be truly voluntary.[230]

These admittedly limited data provide empirical evidence that subtle and unexpected elements of coercion reside in the perception (real or imagined) held by patients recruited into a research project in a medical care setting and affecting their judgement. In light of that reality, informed consent cannot be achieved; it is possible only if research participants are so situated that they are able to choose freely between the different alternatives offered.[231] A gene therapy safety and efficacy trial in South Africa must take into account these misconceptions referred to above and ensure that trial participants do not, in any way feel, compelled to participate. It may be appropriate that clinicians not involved in the care of the participants obtain informed consent.

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225 *Idem* 638.
226 *Ibid.*
227 *Idem* 639.
228 *Idem* 640.
229 *Ibid.*
230 *Ibid.*
231 The Hastings Center 1988 *The Hastings Center Report* 35.

5 2 7 Lesson 7: Who reaps the benefit: A question of meaningful knowledge or exploitation?

The ethical principle of "justice," which is closely linked to the legal term, refers to the obligation to treat everyone justly in accordance with what is that person's due and with what is reasonable and fair.[232] There have been various philosophical proposals as to the manner in which social goods, such as access to health care, should be distributed. Utilitarianism, for example, aims to maximise public utility.[233] In these proposals, the term "distributive justice" is often used and a distinction is made between formal and material principles of justice.[234]

Justice often requires decisions about the allocation of scarce medical resources.[235] In a research setting, the principle of justice takes into account fair access to participation in trials (which is regarded as a benefit), as well as the access of the research population to the benefits of research.[236] Potentially, both areas are problematic in gene therapy clinical trials in South Africa, of course with the exception of gene therapy trials for a HIV cure which, if achieved, will have benefit for the lives of many South Africans.[237] At this point it is the problems inherent in the principle of just access by a research population to the benefits of research that are fore-grounded.

In order to be able to answer a question as to whether meaningful knowledge will be produced by a gene therapy clinical trial in South Africa, RECs must consider whether that trial has the potential to generate knowledge that is meaningful in the sense that it is of significance and of use to *South Africans*. For example, will they be able to reap the benefits if an efficacious gene therapy is developed, considering that even with the use of CRISPR these technologies remain highly complex technically and hence expensive? If the response is negative, then the trial is merely exploitative, as was the case with the Trovan trials in Nigeria and the Tuskegee experiments in the USA described above.[238]

The need for researchers to declare all financial as well as non-financial conflicts of interest relates to this point.[239] It is possible that the eagerness for a reward on the part of a researcher who has a financial stake in the outcome of the research may lead to a misinterpretation of data; also it may distort objectively reporting research results and hamper independent and objective peer-review. It should be noted that an accusation levelled against a researcher in Jesse Gelsinger's

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232 Smith *Human rights and biomedicine* (2000) 7; Gillon *Philosophical medical ethics* (1994) 86–89 ("Gillon"); Beauchamp and Childress 226.

233 Beauchamp and Childress 230.

234 See *idem* 226–229 and Gillon 86–91. This term is akin to the concepts of formal and substantive equality in law.

235 For a comprehensive discussion, see Gillon 93–98.

236 Smith *Human rights and biomedicine* 7.

237 See, eg, Peterson and Kiem "Cell and gene therapy for HIV Cure" 2017 *Current topics in Microbiology and Immunology* 71; and Peterson *et al* "Combinatorial anti-HIV gene therapy: using a multipronged approach to reach beyond HAART" 2013 *Gene Therapy* 695–702.

238 See paras 2 and 3 *supra*.

239 Accusations were levelled at the principal investigator in Jesse Gellsinger's gene therapy trial that he had a financial interest in the outcome of the trial; see Marshall 2000 *Science* 951–957; and Smith 107.

clinical trial was that he had a patent application pending which related to the gene therapy being tested.[240]

5 2 8 Lesson 8: "Meaningful" knowledge?

Lastly, and most pressingly: have we gained and will we gain meaningful knowledge regarding gene therapy from clinical trials now or in the near future? The question is raised in light of the following interview in the German newspaper *Der Spiegel* with Craig Venter, leader of the private effort to map the human genome:[241]

> "SPIEGEL: The decoding of your personal genome has so far revealed little more than the fact that your ear wax tends to be moist.
>
> VENTER: That's what you say. And what else have I learned from my genome? Very little. We couldn't even be certain from my genome what my eye color was. Isn't that sad? Everyone was looking for miracle 'yes/no' answers in the genome. 'Yes, you'll have cancer.' Or 'No, you won't have cancer.' But that's just not the way it is.
>
> SPIEGEL: So the Human Genome Project has had very little medical benefits so far?
>
> VENTER: Close to zero to put it precisely . . . Because we have, in truth, learned nothing from the genome other than probabilities. How does a 1 or 3 percent increased risk for something translate into the clinic? It is useless information."

Venter's hesitation and lack of optimism (though perhaps misplaced) prompts the question: Do we presently have enough – *meaningful* – knowledge to benefit from gene therapy clinical trials in South Africa? Can we meaningfully interpret the results that we gain from these trials? Are we able to meaningfully translate the results of these trials into effective gene therapies in a local hospital or clinic? Moreover, if in South Africa we cannot guarantee many people access to basic health care, such as access to a clinic in their community or adequate and professional obstetric care, can we honestly claim that we will implement the results of gene therapy clinical research and the knowledge we gain so that trial participants or their communities ultimately benefit?[242]

This section concludes by offering three quotations that throw light on these lessons. The first is by a gene scientist, Gina Smith: "Probably no DNA science is at once as hopeful, controversial, hyped, and even as potentially dangerous as the discipline known as gene therapy."[243] A second by the playwright, Tom Stoppard: "It's only we humans who want to own the future, too".[244] Finally, by the science writer, Georgina Ferry and scientist, John Sulston: "Our ability to read out this sequence of our own genome has the makings of a philosophical paradox. Can an intelligent being comprehend the instructions to make itself?"[245]

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240 *Ibid.*

241 Spiegel Online "SPIEGEL Interview with Craig Venter 'We have learned nothing from the genome'" available at https://bit.ly/2rvUAAB (accessed on 9 April 2018).

242 A similar point is cogently argued by Reardon in the context of African-American and other poorer communities in the USA: *The postgenomic condition* (2017) ch 6.

243 Smith *The genomics age: How DNA technology is transforming the way we live and who we are* (2004) 39.

244 Stoppard *The coast of Utopia* (2002) 100–101.

245 Ferry and Sulston *The common thread* (2010) 294.

6 CONCLUSION

The situation described above recalls the opening line of Charles Dickens' novel *A tale of two cities*:[246] once again it is the best of times and the worst of times. Towards the end of the second decade of the twenty-first century scientists are at the point of delivering on the promise of our ability to "map" the human genome and see it put to use. The future for genetic manipulation and of gene therapy research is full of promise – foreseeing an end to some of the most devastating of human diseases.

But at the same time the world – South Africa especially – faces multiple challenges: there is enormous disparity in wealth between countries and within countries; financial crises cause many to lose their jobs and their livelihood; devastating wars cause thousands to lose their homes and many more their towns, cities and even their country; and political cataclysms leave many questioning whether democracy results in the majority exercising rational choice. To quote from Goetzmann:[247]

> "It seems almost as if the ancient part of the brain, the part that thinks in myths and stories, has harboured a long grudge against the rational mind and, jealous of its increasing control over human behaviour, it has seized on the failures of reason."

Certainly, sometimes it appears as if the ancient part of the human brain is in control of the world around us.

It is in this uncertain setting that gene therapy clinical trials will take place in South Africa and the rest of the world. This will happen in the face of many unanswered questions: does our achievement in mapping the human genome – writing the book of ourselves – enable us to derive meaningful knowledge and guide us to make correct – meaningful – choices? Perhaps, also, an even more imponderable question: will it always be in our best interest, as a species, to alter our genome, even if the purpose is to eliminate devastating disease? Foreseeing a world in which disease has vanished, Mukhergee foretells the future of us:[248]

> "Illness might progressively vanish, but so might identity. Grief might be diminished, but so might tenderness. Traumas might be erased but so might history. Mutants might be eliminated but so would human variation. Infirmities might disappear, but so might vulnerability. Chance would become mitigated, but so, inevitably, would choice."

The future human species has a lot to lose if we do not take care now, in the present.

In these unsettling times, the legal norms and ethical standards we use to evaluate potential clinical gene therapy research must display the same rigour and be as innovative as the science that underlies gene therapy techniques.

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246 "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us."

247 *Money changes everything: How finance made civilization possible* (2016) 379.

248 Mukergee 492.