

MODULE THREE: VULNERABLE/SPECIAL PARTICIPANT POPULATIONS

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ABSTRACT

This module is designed to sensitise you to the special needs of participants who belong to populations that are more vulnerable than other participant populations. These populations typically include incompetent persons women who may or may not be pregnant, children, prisoners and refugees, impoverished people, and ethnic minorities. These and similar groups deserve special consideration for a number of important ethical and historical reasons, specifically those that surround the potential for exploitation, problems with informed consent, and concerns about respect for participant autonomy. This module introduces modus operandi that are based on national and international research guidelines for dealing with vulnerable/special participant populations, offering contextually-dependent advice and relevant ethical considerations/arguments for and against their involvement in scientific research endeavours.

INTRODUCTION

Clinical trials and related scientific research necessarily rely on the successful recruitment of human participants in order to yield meaningful results. In this sense, human participants are instrumental in securing data useful to the researcher, which is often extrapolated to develop clinical techniques/drugs/methodologies applicable across a broader range of human populations. Quite simply, researchers in clinical trials are concerned

with generalisable results with predictive value, and particular human sub-populations are critically important in producing those results.

This interplay between results-driven research and the necessary involvement of human participants naturally creates tension between procuring scientific data and the proper ethical treatment of research participants. As public exposure of Nazi experimentation (conducted under the guise of 'scientific research') made painfully obvious during the Nuremberg Trials, the ethical standing of research participants is at constant risk of sacrifice by researchers intent on deriving scientific knowledge. Incidents of ethical transgressions – in which human research participants were exploited, unfairly treated, or in some other way harmed – on behalf of Nazi doctors and other scientists throughout the latter half of the twentieth century has prompted closer inspection of clinical research and the development of ethical guidelines for the protection of research participants.

Of concern are individuals who are already disadvantaged or vulnerable to harm independent of their involvement in clinical trials. Such participants, for whatever reasons, have been marginalised by society and are susceptible to exploitation. They typically stand in unequal power relationships with others and/or possess substandard mental faculties, rendering them incompetent. Pressing examples include the mentally disabled, abjectly impoverished persons, prisoners/refugees, women/pregnant women, children, and ethnic minorities, though this list is not exhaustive.

Vulnerable populations are attractive for research purposes precisely because of their vulnerability. Transgressions of ethical boundaries become easier as does the consequent procurement of scientific data. It is of no surprise, then, that the majority of sensationalised research ethics cases in the past sixty years have involved vulnerable persons – indeed, the entire field of research ethics has been built upon and refined according to examples of 'extreme' clinical research that have dotted modern history.

In order to appreciate the ethical considerations and arguments guiding contemporary clinical research it is first necessary to review a few exceptional breaches of research conduct. This is followed by considerations of vulnerabilities specific to the groups mentioned above. A final discussion of the ethical arguments for and against the potential use of vulnerable human participants in clinical research concludes the module.

HISTORY

Nazi experiments (1939–1945)

Modern research ethics only took form during the Nuremberg trials in 1947.¹ Facing mounting wartime casualties and the Führer's fatal intolerance of German failure (coupled with an persistent faith in 'Aryan superiority'), some Nazi doctors busied themselves with experimentation on concentration camp prisoners, with the intent of furthering the war effort (inflicting gunshot wounds on prisoners, deliberately infecting prisoners with typhus and other battlefield diseases, exposing prisoners to freezing temperatures for prolonged periods, etc.) or of buttressing Nazi ideology (eliminating homosexuality, sterilising Jews and other 'undesirables', exposing differences in anatomical structure across 'races', etc.)

Other common Nazi experiments on humans included forcing prisoners to drink sea water or breathe dirty air for extended periods of time, developing novel techniques of castration, and performing bone and limb transplantations.²

Though fifteen Nazi doctors were eventually tried and convicted in Nuremberg, Dr. Joseph Mengele, the most notorious physician escaped. Posner offers chilling testimony regarding Mengele's research into the differences in eye colour between Gypsy teenage twins, illustrating the extent of his cruelty:

In the work room next to the dissecting room, fourteen Gypsy twins were waiting and crying bitterly. Dr. Mengele didn't say a single word to us, and prepared a 10 cc and a 5 cc syringe. From a box he took Evipal and from another box he took chloroform, which was in 20 cc glass containers, and put these on the operating table. After that the first twin was brought in . . . a fourteen year old girl. Dr. Mengele ordered me to undress the child and put her head on the dissecting table. Then he injected the Evipal into her right arm intravenously. After the child had fallen asleep, he felt for the left ventricle of the heart and injected 10cc of chloroform . . . After one little twitch

¹ P. Boleyn-Fitzgerald. 2003. Experimentation on Human Subjects. In *A Companion to Applied Ethics*. R.G. Frey & C. Wellman, eds. New York. Blackwell Publishers: 410–423.

² R.N. Procter. 1992. Nazi Doctors, Racial Medicine, and Human Experimentation. In *The Nazi Doctors and the Nuremberg Code*. G.J Annas & M.A. Grodin, eds. New York. Oxford University Press: 17–31.

the child was dead . . . in this manner all fourteen twins were killed.

Mengele then removed the eyes from the dead twins and shipped them off to Berlin for further study.³

Revelations of Nazi experiments at Nuremberg sparked the beginning of ethical analyses and oversight of research protocols involving human participants, leading to the development of the Nuremberg Code, 'the first international normative framework regulating the standards of research clinical trials.'⁴ This and other research guidelines are discussed more fully below.

Jewish chronic disease hospital cancer experiments (1963–1966)

Questionable clinical trials conducted by Dr. Chester Southam in Brooklyn, New York, were first reported in a landmark ethics article published in the *New England Journal of Medicine* by Dr. Henry Beecher.⁵ Interested in the immunoreactivity response to cancer, Southam began routinely injecting twenty-two elderly Jewish patients with live cancerous liver cells and monitoring their response – entirely in the absence of informed consent by the patients (who were told they would be 'receiving some cells').⁶ No therapeutic value ever accrued to the patients (many were harmed and subsequently died from the injections), nor were the experiments conceived of to that end.⁷

Willowbrook state school hepatitis experiments (1955–1970)

Experiments conducted by Saul Krugman investigated the effects of hepatitis infection among mentally disabled children at the Willowbrook State School, located in Staten Island. To do so, Krugman did not treat the children already infected with hepatitis and deliberately infected others with the virus.⁸ Again, the

³ U. Schüklenk. Protecting the Vulnerable: Testing Times for Clinical Research Ethics. *Social Science and Medicine* 2000; 51: 969–977. Available at: <http://www.wits.ac.za/bioethics/res.htm> (Accessed 19 September, 2003).

⁴ Ibid.

⁵ H. Beecher. Ethics and Clinical Research. *New England Journal of Medicine* 1966; 274: 1354–1360.

⁶ Ibid. Boleyn-Fitzgerald, *op. cit.* note 1.

⁷ R. Finn. 1999. *Cancer Clinical Trials: Experimental Treatments & how they can Help You*. New York. O'Reilly and Associates. Available at: http://www.patientcenters.com/trials/news/ethics_of.html (accessed 19 September, 2003).

⁸ Boleyn-Fitzgerald, *op. cit.* note 1.

ethical foundation of this experiment was first questioned by Beecher, who noted that none of the students had been adequately informed of this experiment, nor could they have been given their mental status.⁹ The experiment was intended to track the development of the viral infection, and carried no direct therapeutic benefit to the children involved.¹⁰

Tuskegee syphilis study (1932–1972)

Following the Nazi concentration camp experiments, the Tuskegee syphilis study is perhaps the most well known example of unethical human experimentation. Sponsored by the US Central for Disease Control (CDC) and headed (initially) by Taliaferro Clark of the National Public Health Service, the ‘Tuskegee Study of Untreated Syphilis in the Negro Male’ examined the untreated effects of the disease in 600 blacks (399 who had the disease, 201 who did not) in rural Alabama.¹¹

Though the participants in the study had voluntarily agreed to receive treatment for their ‘bad blood’ (the local term for syphilis, as well as anaemia and fatigue), none had been informed about the true purpose of the study. Each had been misled into believing that he was receiving proper treatment. Worse, even when an effective syphilis treatment (penicillin) had been discovered midway through the study, none of the participants were informed of the treatment, were offered the treatment, or were given the chance to quit the study.¹²

The Tuskegee syphilis experiment ended following the publication of a front-page *New York Times* article by Jean Heller describing the study and its effects.¹³ It has been estimated that at least 28–100 participants died because of the experiment (for a comprehensive account of the Tuskegee study, see Jones¹⁴).

⁹ Finn, *op. cit.* note 7.

¹⁰ D. Berkich. 2003. *Medical Ethics Online: Human Experimentation Cases*. Available at: http://www-unix.oit.umass.edu/~phil100/units/unit-08/lecture-01/human_experimentation_cases.html (accessed 19 September, 2003).

¹¹ United States Center for Disease Control. 2003. *Tuskegee Timeline Website*. Available at: <http://www.cdc.gov/nchstp/od/tuskegee/time.htm> (accessed 19 September, 2003).

¹² *Ibid.* Boleyn-Fitzgerald, *op. cit.* note 1.

¹³ J. Heller. Syphilis Victims in U.S. Study Went Untreated for 40 Years. *New York Times* 26 July, 1972: A1.

¹⁴ J. Jones. 1992. *Bad Blood: The Tuskegee Syphilis Experiment*. New York. Free Press.

ZDV (AZT) drug trials in developing world countries (1997)

An HIV-related clinical trial that took place in South Africa and other developing countries came under heavy criticism by South African expatriate doctor Peter Lurie and his colleague Sydney Wolfe in a landmark *New England Journal of Medicine* article in 1997.¹⁵ The trial was designed to determine the efficacy of several new drug regimens in the prevention of vertical HIV transmission from mother-to-child, in hopes of finding a cheaper (yet equally effective) drug protocol. The standard zidovudine (ZDV, formerly AZT) treatment used regularly in developed world countries (in particular, the United States and Europe) cost at the time approximately US\$1000 and was far too costly for use in the poorer developing world. Researchers were searching for cheaper drug regimens that could be feasibly introduced in developing world countries.

While the intent of the research was admirable, the methodology raised significant ethical problems. Instead of comparing the new drug regimens against the best proven diagnostic and therapeutic method of care, as required at the time by the Declaration of Helsinki, these studies were comparing the new drug regimen against a placebo. The unfortunate consequence was that only half of the pregnant mothers in the study were benefiting from participation. No clinical equipoise existed between the trial arms, because zidovudine was already accepted as the gold standard of care at the time. Worse, it was unclear whether these mothers would receive any potential benefit in the *future*, either, since results from the study were being exported back to the United States, with little indication what (if any) benefits would accrue back to the placebo-treated study participants. Indeed, the South African government refused to implement the treatment regimen underpinning the trial.

As Lurie and Wolfe forcefully pointed out, such placebo-controlled studies could never have been conducted in developed world countries – all participants would have been guaranteed to receive at least the standard ZDV treatment protocol. Accordingly, the placebo-controlled studies were accused of being exploitative, capitalising on the poor of the developing world who had no alternative treatment to prevent HIV transmission under ‘local standards of care.’ (See the module on ‘Standards of Care’ for a

¹⁵ P. Lurie & S.M. Wolfe. Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries. *New England Journal of Medicine* 1997; 337: 853–856.

more detailed discussion of this matter.) The developed world researchers, they argued, knew that their work could only be 'acceptably' carried out among the poor of the developing world, who had little choice about treatment and who would be 'grateful' to receive any treatment at all – their vulnerability thus made them prime research targets. Indeed, the ZDV studies were justified by its proponents along these lines, who noted 'it is an unfortunate fact that the current standard of perinatal care for the HIV-infected pregnant women in the sites of the studies does not include any HIV-prophylactic intervention at all.'¹⁶

VULNERABILITY

These five paradigmatic cases in research ethics share a common theme of exploitation.

Nazi concentration camp prisoners were powerless against their captors, who had no other options (aside from immediate death) but to undergo horrific medical research. Dr. Southam's cancer research was only feasible insofar as his elderly Jewish patients lacked information about his true motives and were significantly disadvantaged because of their advanced age (i.e. they were likely to be more trusting of medical professionals, less willing or able to question their 'treatment', etc.), while Dr. Krugman capitalised on his participants' young age and mental incompetence to pursue his hepatitis studies. The Tuskegee syphilis study, on the other hand, exploited the socio-economically disadvantaged status of adult black males living within the racist, segregated society recently characteristic of the southern United States. Similarly, the ZDV (AZT) studies exploited poor, pregnant African women who could not afford 'standard' Western drugs to prevent vertical transmission of HIV and who were more likely to agree to participate in such studies because they sought care for their unborn children.

That exploitation has persisted, even under a growing body of national and international legislation/regulation addressing the structure and conduct of ethically acceptable clinical trials, shows that research involving the use of vulnerable populations remains a serious issue that cannot be ignored by the clinical researcher.

¹⁶ United States Department of Health. 1997. *The Conduct of Clinical Trials of Maternal-Infant Transmission of HIV*. Washington, DC. Government Printing Office.

As mentioned previously, all vulnerable populations stand in unequal power relationships with others that typically do not characterise 'normal' (or most) members of society. Such relationships may instantiate themselves in numerous ways to create differing vulnerabilities across groups. The clinical researcher must be aware of the concerns specific to each vulnerable population and adjust his research protocols to compensate. What may be considered ethically acceptable research involving prisoners, may be entirely unacceptable when applied to mentally incompetent adults, pregnant women, or children.

Each vulnerable population deserves individual treatment according to their specific circumstances.

Prisoners

Prisoners have been deprived of freedoms normally enjoyed by other members of society. Their actions are directly controlled by others (locally, prison guards and more generally, the state), whom they rely upon for food, shelter, clothing, and other basic necessities of life. In other words, they find themselves in a strictly hierarchically ordered form of life with detrimental consequences for their capacity to live autonomously. For whatever punitive or rehabilitative reasons supporting their confinement, imprisoned persons are intentionally made vulnerable.

Coercive conditions necessarily impose constraints on the degree of free decision-making exercised by prisoners. Specifically, prisoners may be unable to make informed judgements regarding their participation in clinical trials, for a number of reasons.¹⁷

Pleasing authorities

First, prisoners may fear retribution from prison guards or other authority figures if they do not appear co-operative. Constantly seeking to please those in charge of them, if only to make daily prison life easier, prisoners may readily agree to engage in clinical research if they think it will send a positive signal to authorities and possibly confer future benefits, or at least prevent the harm that comes with not acting like a 'good' prisoner should.

¹⁷ L.D. De Castro. Human Organs from Prisoners: Kidneys for Life. *Journal of Medical Ethics* 2003; 29: 171–175. Available at: <http://jme.bmjournals.com/cgi/content/full/29/3/171> (accessed 19 September, 2003).

Annas et al. have reported a series of studies in which prisoners ‘voluntarily’ agreed to be subjected to cholera, typhoid, and other diseases.¹⁸ During the 1940s in the United States, for example, prisoners consented to participate in clinical trials (led by Dr. Andrew Ivy under the supervision of the US military) in which they were directly exposed to malaria. Dr. Ivy’s defence of his work consisted in appealing to earlier studies conducted by US Colonel R. P. Strong, ‘who injected attenuated plague organisms into 900 condemned prisoners in Manila in the 1900s.’¹⁹

Clearly these experiments (and others like them) call into question the voluntariness of the prisoners’ actions. Few, if any, normal, non-incarcerated adults would have given informed consent to participate in this research, casting doubt upon the ethical acceptability of using prisoners in these trials, who were likely only trying to curry favour from those who had power over them.

Prospects of Rewards

Prisoners may be unduly influenced by potential gains offered by research participation, such as reduced prison time or ‘extra’ perks (more/better food, increased access to entertainment or exercise facilities, increased ‘free’ time, etc.) These rewards may cloud prisoners’ judgements and prevent them from adequately assessing the potential risks involved in the proposed research. This same concern applies to research involving non-vulnerable human populations – the prospect of immense gains can arguably outweigh any risks, no matter how devastating or probable.

With prisoners, however, the prospects of rewards through research participation should be taken even more seriously, if only because of their coercive environment. The possibility of rewards becomes all the sweeter – and coercive – when punishment is the standard offering.

Lack of Other Options

Prisoners may consent to participate in clinical trials simply because they have very few other options to pursue. Prison life is highly regimented with little variability in day-to-day activities. The

¹⁸ G. Annas, L. Glantz & B. Katz. 1997. *Informed Consent to Human Experimentation: The Subject’s Dilemma*: 1–36. Available at: <http://www.bumc.bu.edu/www/sph/lw/pvl/book/Ch4.pdf> (accessed 19 September, 2003)

¹⁹ *Ibid.*

sheer novelty of research participation, along with the opportunity to distinguish oneself from other inmates, may unduly influence the prisoner's decision. Kahn has noted that clinical research conducted in prisons has always been successful and 'very popular' among the prison population, to an extent that does not typically characterise research in non-prison settings.²⁰ The mere option of participation may be an overriding influence barring informed consent in the same way the prospects of rewards or pleasing authorities distorts prisoners' judgements.

The prison population is attractive to clinical researchers because of the controlled conditions characteristic of prisons themselves. Researchers have less trouble keeping track of their research participants, environmental conditions remain relatively constant, and follow-up studies are easy to pursue – the prisoners, after all, are not going anywhere and the prisons themselves are unlikely to change significantly over time. Moreover, researchers may be more willing to conduct risky or 'sloppy' research in prisoners precisely because they are perceived (consciously or unconsciously) to be less valuable than other (non-incarcerated) members of society.

Because potential harm to prisoners 'doesn't mean as much' as harm to non-prisoners, researchers may also be more lax in adherence to research protocols, thereby exposing prisoner research participants to riskier experimentation than that which the prisoners and researcher initially agreed upon. These reasons, combined with the aforementioned motivations of prisoners to participate, merits prison populations special consideration during the development and implementation of clinical trials.

Refugees

The plight of refugees is very similar to that of prisoners. Refugees are persons that have been displaced from their permanent homes or residences and who now live elsewhere – within foreign boundaries – as non-citizens. As Leaning has noted, refugees are vulnerable for several reasons.²¹

²⁰ J. Kahn. 6 September, 1999. Prison Research: Does Locked up Mean Locked Out? *CNN Health: Ethics Matters Website*. Available at: <http://www.cnn.com/HEALTH/bioethics/9909/prison.research/> (accessed 19 September, 2003).

²¹ J. Leaning. Ethics of Research in Refugee Populations. *Lancet* 2001; 357: 1432–33.

Indefinite Legal Status/Lack of Rights/Dependency on Host Country Governments

Because of their non-citizen status, refugees inherently possess fewer legal rights than the citizens of the host country in which they are residing and 'stand outside the regulatory protection of domestic legislation and are vulnerable to arbitrary action on part of the host country.' The United Nations and other international regulatory bodies have only issued provisional recommendations regarding the status of refugees, leaving almost total discretion to the host country for their treatment under domestic law. Lacking impetus from the international community, host countries to refugees have consequently pursued few reforms or legislation aimed specifically at refugee populations, placing refugee groups in an ill-defined relationship with the host country's government and citizens.

Endemic Hostility Toward Refugees

Refugees are typically created in the midst of severe societal upheaval and destruction, 'where human rights abuses are rampant and where refugees are considered hostile targets by those who force them to flee.' Additionally, citizens of the host countries to which refugees eventually migrate are also frequently unwelcoming. A direct consequence of this hostility is that there may be little oversight or protection afforded to refugee groups who are considered for clinical research projects. Possibly caring little about the lives of refugees to begin with, authorities from both the countries from which they were expelled as well as the countries where they temporarily reside may do little to ensure proper ethical standards are satisfied during clinical research trials involving refugees.

Lack of Guidance from International Regulations and Ethics Recommendations

The international regulations that provide guidance on clinical research have not addressed research involving refugee populations. Neither the Declaration of Helsinki nor the Council for International Organizations of Medical Sciences (CIOMS) research guidelines specifically mention refugee populations, for example. The Belmont report and the Nuremberg Code are also silent on this issue. Lacking credible ethical guidance to structure research involving refugees, they are exposed to breaches of ethically acceptable research protocols.

Barriers to Informed Consent Arising from Social, Cultural, Economic, Linguistic and Other Factors

Refugees are usually economically destitute and can be easily influenced to participate in research at the prospect of minimal financial gain. Procuring genuine voluntary informed consent amidst such poverty may prove an insurmountable challenge to the researcher. Additionally, language barriers, unspoken cultural norms, the desire to appear compliant within a foreign country, and other refugee-centric factors may cause additional problems.

Psychological and Emotional Stress

The World Health Organization has noted that clinical research involving refugees must consider their 'recent drastic physical and psychological losses' contributing to extreme psychological and emotional stress.²² Obtaining informed consent from refugees experiencing disarrayed mental states can be difficult. Participation in clinical trials may further contribute to and exaggerate this psychological stress.

Like prisoners, refugees are attractive to researchers because of external constraints on movement and location as well as the composition of refugee populations. Follow-up studies are also easier to implement within well-defined, geographically isolated refugee camps. The camps are also quite conducive to standard research methodologies. As Leaning notes, 'the physical layout of these camps provides some accessibility and population density most amenable to rapid systematic sampling and data collection.' These reasons, coupled with 'a humanitarian justification based on urgent human need' contributes 'to the mounting momentum for carrying out research in these settings.'²³

Mentally incompetent persons

Research involving mentally incompetent persons poses somewhat different problems from those encountered with prisoners or refugees faculties. By virtue of lacking certain mental facilities, the mentally incompetent are *innately* vulnerable to exploitation by others.

²² J. Leaning. 1997. *Annex – World Health Organization Ethics Template Website*. Available at: <http://www.who.int/disasters/resource/pubs/160499p.htm> (accessed 19 September, 2003).

²³ *Ibid.*

Informed Consent

Whereas obtaining informed consent is at least *possible* with prisoners or refugees (though likely hindered by the factors discussed above), it is, by definition, impossible to obtain informed consent from the mentally incompetent. Informed consent necessarily demands the capacity for rational, informed decision-making, characteristics the mentally incompetent do not possess.²⁴

Informed consent, however, has often been touted as a necessary requirement for participant entry into clinical trials. For example, the Nuremberg Code, the first body of formalised guidelines concerning research involving human participants, states that, 'voluntary consent of the human subject is absolutely essential' for proper ethical research.²⁵ As Schüklenk has observed, however, this 'absolutely essential' criterion 'would render a whole range of research clinical trials involving incompetent mentally ill patients impossible . . . Evidently if we wish to improve the situation of those who suffer from diseases that impair their capacity to provide informed consent, it is necessary to conduct research involving such people.'²⁶ This same consideration led the World Medical Association, during its initial formulation of the Declaration of Helsinki (1964), to adopt proxy consent as an acceptable alternative for those research participants who are unable to directly give informed consent.²⁷

But proxy consent can be problematic as well. Perhaps the most important question to ask is proxy consent *by whom?* Most ethics committees and national/international bioethics committees recognise proxy consent conferred by legally authorised authorities.

Another important question is proxy consent *for what?* That is, what sort of clinical research is acceptable under the conditions of proxy consent? At issue here is the difference between therapeutic and non-therapeutic research. The former confers direct benefits to research participants, while the latter does not. By

²⁴ M. Cuenod & J. Gasser. Research on the Mentally Incompetent. *Journal of Medical Ethics* 2003; 29: 19–21. Available at: <http://jme.bmjournals.com/cgi/content/full/29/1/19> (accessed 19 September, 2003).

²⁵ *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law. No. 10: Nuremberg, Oct. 1946–1949.* 2 Volumes. Washington, DC. Government Printing Office.

²⁶ Schuklenk, *op. cit.* note 3.

²⁷ Boleyn-Fitzgerald, *op. cit.* note 1.

extending the potential pool of research participants to include the mentally incompetent, the Declaration of Helsinki permits therapeutic research on these subjects, i.e. research that would be beneficial, *in particular*, to mentally incompetent persons. This research might include testing of new psychiatric drugs, behavioural therapies, or surgical interventions.

Non-therapeutic research, however, *does not* help mentally incompetent persons *qua* their status as mentally incompetent. Non-therapeutic research can usually be carried out using normal adults and does not demand the involvement of vulnerable populations. With respect to mentally incompetent persons, non-therapeutic research might include testing the efficacy of a new vaccine against HIV or assessing the risks of side effects of a new drug. Non-therapeutic research may also include research that gathers relevant data specific for a given population but which does not benefit the population in question. For example, researchers may be interested in learning about the incidence of erectile dysfunction among mentally incompetent persons. Clearly the involvement of mentally incompetent persons is necessary for such a study, but no direct benefit will accrue to the research participants.

Following this distinction, and the underlying idea that therapeutic research carries less risk and more benefits for vulnerable research participants, advisory groups like the US National Bioethics Commission have argued that non-therapeutic clinical research requires more extensive review at the federal level than therapeutic clinical research of minimal risk.²⁸

This reasoning reflects a more widely shared sentiment that proxy consent may not sufficiently protect mentally incompetent persons from exploitative research agendas that lack positive benefits to participants and which are primarily directed at the mentally incompetent because of their vulnerability. The removal of first person informed consent may more readily serve the interests of researchers than it does the interests of research participants – after all, the importance of informed consent may often be weakened when placed in the hands of an imperfect decision making proxy. The mere presence of proxy consent thus cannot always substitute for first person informed consent, and special precaution should therefore be taken with research involving mentally incompetent individuals.

²⁸ Schuklenk, *op. cit.* note 3.

Other Considerations

Even if informed consent is met via proxies for mentally incompetent persons, other considerations make their use in clinical trials particularly difficult. For example, it is probably more difficult for mentally incompetent persons and their proxies to signal ongoing consent for participation in clinical trials. Mentally incompetent patients may be subject to prolongation of participation against their will, if only because of difficulties in communication with proxies or the inability of proxies to recognise a change of mind in their dependants.

Additionally, given that many researchers and proxies may be narrowly concerned with meeting standards of informed consent in the beginning of a trial, they may subsequently be less perceptive to attitudinal shifts among mentally incompetent research participants and could therefore be prone to ignoring participant complaints or signs of discontent with research involvement. Unlike research with normal adults, in which procuring informed consent is a once-off occurrence, research with mentally incompetent persons requires constant monitoring and intimate, continual communication between the participants and proxy to insure that the former are always informed and consenting.

Mentally incompetent persons may also be more susceptible to outside influences, particularly by people close to them, such as family members or caregivers, who may coerce their judgement or inclinations regarding participation in a clinical trial. For example, such external influences might easily convince a mentally incompetent person to participate in research, who in turn informs his proxy that he wishes to participate. Worse, such external influences could easily emanate from the proxy herself, placing increased responsibility on the clinical researcher to ensure that informed consent is free from such manipulations.²⁹

Impoverished people

Impoverished people encompass a broad range of individuals, possibly including members of other vulnerable groups discussed above. Research involving impoverished persons is a global concern of research ethics (poor people can be found everywhere), but it is a particular problem for developing world countries, especially when confronted with a barrage of developed

²⁹ Cuenod & Gasser, *op. cit.* note 24.

world researchers seeking to conduct trials amongst the developing world's poor. As Dickens and Cook aptly note:

Resource-poor settings are often found in economically developing and disadvantaged countries, but they also exist in developed countries, such as among inner-city ghettos and barrios, and aboriginal, immigrant, and refugee settlements. Concerns have arisen with special regard to developing countries, however, that commercially-inspired sponsors of studies from developed countries may take advantage of them as host sites to test products intended for sale in affluent markets. These countries may allow studies that recruit suitable participants who are more willing to participate, perhaps for inexpensive inducements, less understanding of study risks, and, for instance, less likely and able to pursue grievances and litigation in the event of injury, than developed-country residents.³⁰

Incentives

Impoverished people are, above everything else, highly susceptible to prospects of financial gain. Even small financial rewards can act as a coercive force, compelling the poor to do what the rich would be reluctant to consider. Like prisoners, refugees, and mentally incompetent persons, the impoverished may be unable to give informed consent when confronted with compensation for research participation. The poor of the developing world are often severely destitute and desperate for survival, literally living day to day perpetually in the face of death.

Non-financial rewards that could potentially improve the standard of living of impoverished individuals may also be overly coercive. These rewards might include food, shelter, clothing, medical treatment, etc. Again, the depressed level of economic subsistence characterising the developing world can transform these simple rewards/basic entitlements into forceful incentives for the poor. Researchers conducting trials among the poor of the developing world must not assume that the incentive structure characterising the poor of their home (developed) countries applies equally.

The problem of coercive incentive structures in research protocols becomes compounded when one considers that the

³⁰ B.M. Dickens & R.J. Cook. Challenges of Ethical Research in Resource-Poor Settings. *International Journal of Gynecology and Obstetrics* 2003; 80: 79–86.

impoverished of many developing world countries belong to cultures where reciprocity is the norm. That is, researchers are expected to offer something in return for subject participation.³¹ In principle, this is not problematic, since there is nothing innately unethical about offering compensation in exchange for participation. The problem arises for the researcher, however, in trying to meet such conditions of reciprocity without offering compensation that is coercive. Nonetheless, for many impoverished communities reciprocity is an important criterion to satisfy that should not be ignored:

In cultures founded less on market principles than on reciprocity, however, it is offensive to seek an advantage without affording a reciprocal advantage in return. Powerful oppressors may indeed demand, take, or steal from the poor, but where mutual respect and esteem prevail, an advantage requested must be reciprocated by an advantage given. What is sought and given need not be of equal value since this assimilates the exchange to marketplace bargaining. The purpose is the offering not of goods or services, but of respect, esteem, and recognition of dignity.³²

As this passage suggests, incentives may be structured to meet cultural demands of reciprocity – which, incidentally, satisfy developed countries' precaution against commodification – without pre-empting informed consent. The impoverished, like any other vulnerable group, should not be discriminated against and removed from research *because* they are vulnerable. Rather, vulnerability and susceptibility of the poor to incentives merits them special protection and oversight in clinical trials – not total exclusion.

Standards of Care and Exploitation

Researchers must also refrain from using the disadvantaged status of impoverished people as an excuse to engage in sub-standard clinical research procedures, as exemplified in the ZDV (AZT) clinical trials discussed previously. Because the poor (particularly the poor of the developing world) are unable to afford standard treatment protocols that might be quite common in the other

³¹ Cuenod & Gasser, *op. cit.* note 24.

³² *Ibid.*

richer, developed countries does not exclude their provision in clinical trials.

The arguments put forth justifying the placebo arm of the ZDV trials (and all other clinical research in which some participants receive non-standard treatment that would be deemed unacceptable in developed countries) usually invoke 'local standards of care', that is, the participants in the study are left to be no worse receiving sub-standard treatment (like placebos) since this is what they would have received anyway (being poor they would be unable to afford the standard treatment protocols, so it is ethically acceptable to deny them this treatment during clinical trials – so the argument goes). Unfortunately this reasoning misses a crucial point – that the local standards of care in question are a direct result of profit-oriented, developed world drug pricing, which has no particular moral status and which could set drug prices for standard treatment protocols at much more cost-friendly rates for the developing world. It is thus ethically unjustifiable to argue as though impoverished people must make do with what they have (i.e. doing without) simply because they are poor, since their diminished purchasing power is the result of morally arbitrary pricing schemes of the developed world. Clinical research involving impoverished people must therefore guarantee participants the best *absolute* standards of care available and should ignore the wealth of the participants themselves.

Pregnant women

Concern about potential harm to the foetus and harm to the mother underlies much of the reluctance of investigators to recruit and enroll pregnant women.³³ Guideline 17 of the 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects notes that pregnant women are eligible for participation in such trials, given that they 'are adequately informed about the risks and benefits to themselves, their pregnancies, the foetus, and their subsequent offspring, and to their fertility.' The CIOMS guidelines further recommend that

³³ A. Kornblum. Trial and Error: Should Pregnant Women Be Research Participants. *Environmental Health Perspectives* 1994; 102: 1–5. Available at: <http://ehpnet1.niehs.nih.gov/docs/1994/102-9/spheres.html> (accessed 19 September, 2003).

research should be therapeutic and restricted to issues regarding women/maternal/foetal health, with evaluation and emphasis placed on assessing risks for teratogenicity.³⁴

Concerns and Debate

The CIOMS guidelines highlight the relevant concerns of using pregnant women in clinical research. Again, the basic objection is that informed consent becomes hindered because of lack of scientific knowledge on research with pregnant women (and women in general, for that matter). Because pregnant women have been systemically excluded from scientific research, the effects of drugs on the mother and foetus pose greater risks (due to increased uncertainty of their effects) than do equivalent studies carried out with male participants. (For a comprehensive look at this topic, see Mastroianni et al.³⁵)

Unfortunately, strict protectionist policies prohibiting or discouraging pregnant women from participating in clinical research only perpetuate this vicious cycle, for if the justification for not allowing pregnant women to participate is that little scientific evidence exists to assess the risks of their participation, then how will pregnant women ever become acceptable research participants?

Similarly, advocates of including pregnant women point out another important dilemma. Because of protectionist attitudes preventing pregnant women from participating in clinical trials, subsequent drug design and development rely heavily on data collected from adult men. However, when these drugs are introduced into the market, they are meant to be consumed by everyone – including pregnant women. The exclusion of pregnant women from clinical trials, during which these drugs are tested, means that the effects of these drugs are unknown within the pregnant women population. In this manner, the benefits of barring pregnant women from participating in research may, in the end, harm expecting mothers and their foetuses more than their inclusion in clinical trials.

³⁴ Council for International Organizations of Medical Sciences. 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva. Available at: http://www.fhi.org/training/fr/Retc/pdf_files/cioms.pdf (accessed 19 September, 2003).

³⁵ A. Mastroianni, R. Faden & D. Federman, eds. 1994. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*. Washington, DC. National Academy Press.

Critics like Ruth Macklin, for instance, believe exclusion amounts to nothing less than paternalism on behalf of the wider medical community, who have implicitly discounted the personal knowledge, cognisance, and intimate decision-making ability a pregnant mother has over herself and her unborn child: 'If not paternalistic, then what is exclusion? . . . Why should some distant scientist whose relationship lasts a brief time make the ultimate determination rather than a woman who presumably cares more about her unborn child?'³⁶

Ultimately, the issue of whether pregnant women should be involved in clinical research remains divisive, entangled with different risks and benefits. Therapeutic research of direct, relevant importance to the health of pregnant women *per se* is less contentious than non-therapeutic research that may as easily be carried out with other, less vulnerable populations, and yet the integration of pregnant women into the latter is important to achieve higher efficacy in drug design and development across *all* populations. The decision to include or exclude pregnant women from clinical trials decisively hinges on obtaining informed consent. Whether this can occur in the absence of pertinent knowledge regarding the risks, benefits, and harms surrounding clinical research with pregnant women is questionable.

Women and Children

The same arguments to include/exclude pregnant women also apply to research involving (non-pregnant) women and children. Again, whether informed consent can be obtained or not is the critical issue, given that women and children have likewise been generally excluded from clinical research because of risk and uncertainty. This marginalisation has left them, like pregnant women (and foetuses) at a significant disadvantage in terms of prescription drug efficacy, since comparatively little is known about the dosages and effects of prescription drugs in these groups.

CONCLUSION

The discussion above highlights the difficulties of clinical research involving a number of vulnerable populations. The first

³⁶ Ruth Macklin cited in: A. Kornblum, *op. cit.* note 33.

step in addressing these vulnerabilities is, importantly, recognising that such vulnerabilities do indeed exist.

Beyond this, however, there are no 'hard and fast' rules. The ethical acceptability of including or excluding members from any vulnerable populations cannot easily be derived from a set of guidelines or normative ethical theory. However, there are some constraints that *any* clinical research involving vulnerable populations should satisfy:

Informed consent must *always* be secured from potential research participants, either directly or indirectly from a legally designated proxy.

The research must never seek to inflict *actual* harm on participants.

The research should maximise *possible* benefits and minimise *possible* harm.

The last two constraints are laid out in the influential Belmont Report produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavior Research in 1978.³⁷ Though these same constraints apply to non-vulnerable populations, their relevance for vulnerable populations is greater since they are more likely to fall victim to one or more forms of exploitation. Notice that these constraints are not novel to the discussion presented here – the pitfalls associated with research involving vulnerable populations have occurred when these constraints have not been satisfied. The concerns and recommendations specific to each of the groups discussed above revolve around these constraints, which have only been made more explicit here for the purposes of erudition.

As this module has indicated, clinical research involving vulnerable populations must proceed with extreme caution. Adhering to these principle constraints is an important first step in this process. Proper clinical research must never ignore the potential for exploitation of vulnerable populations. Research involving these groups is not innately unethical but can certainly become

³⁷ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1978. *Ethical Principles and Guidelines for the Protection of Human Subjects. The Belmont Report*. Washington, DC. Government Printing Office.

so in the absence of proper oversight and the continual recognition of population vulnerability.

CASE STUDY I

Suppose, for example, that a team of clinical researchers wants to conduct a study examining the potential side effects of a new, non-invasive medical diagnostic device that pulses high intensity radiation through human tissues to produce an X-ray type image. The researchers have decided they wish to conduct this study on a prisoner population and have made arrangements with the prison officials so that any prisoner who participates receives special prison allowances (more family visitation time, less prison duties, more frequent access to the prison gym and other entertainment facilities, etc.) You have the final decision about whether or not the research should proceed.

Questions for further thought

Is this research ethically acceptable? What specific concerns should be addressed when dealing with prisoners in this example? Do these same concerns apply equally to normal, non-incarcerated adults? Why might have the researchers chosen to work with prisoners instead of normal, non-incarcerated adults? If the prisoners insist that they can indeed give informed consent – even in the presence of incentives – should they be allowed to do so? Is the heightened precaution and increased oversight of clinical research endeavours dealing with prisoners really just a form of (unjustifiable) discrimination?

CASE STUDY II

Suppose a team of clinical researchers begins testing a new vaccine for the West Nile virus amongst a group of Sudanese refugees currently residing in Algeria. Suppose further that there were no local internal review boards or other regulatory bodies that oversees clinical research endeavours involving these refugees, and thus the vaccine team simply enters the Sudanese

refugee camps, explains to the Sudanese the methods and purpose of the research, and begins testing the new vaccine against a placebo (there is currently no vaccine against the West Nile virus). As a result of their efforts, the vaccine team discovers the new vaccine was far more clinically effective and drastically reduces the number of new West Nile cases within the refugee camps.

Questions for further thought

Should the researchers have continued to pursue clinical trials when obtaining local ethics approval was impossible? What factors may have prevented the refugees from giving informed consent, even after the nature and purpose of the research was explained to them? Did the fact that the refugees experienced an overall benefit from participating in the clinical research make it more ethically acceptable? Would other clinical research that offered no therapeutic benefit to the refugees pose more ethical problems, and if so, what are they? Why might conducting research on the Sudanese refugees be more pragmatically appealing than research on native (resident) Algerians?

CASE STUDY III

Consider again the Willowbrook State School hepatitis experiments, in which Dr. Southam deliberately infected mentally incompetent schoolchildren with hepatitis to study the progression of the disease.

Questions for further thought

Suppose it is unclear whether proxy consent was obtained in this study. Would any form of proxy consent be ethical in this situation? Is clinical research that leaves participants clearly worse off than they were before ethically acceptable, and is this study an example of such research? Would the same research be ethically acceptable if mentally competent children were chosen instead for the study? Does the fact that the actual participants were mentally incompetent matter when determining whether the study was ethical or not?

CASE STUDY IV

Suppose a group of poor black South Africans are being specifically recruited from local townships for a clinical research study examining the efficacy and potential side effects of a new drug to combat high blood pressure. The team of physicians conducting the study is from a local research hospital and is intimately familiar with the customs, culture, attitudes, and beliefs of their research participants. The team has chosen to test the new drug in the townships because poor blacks living there frequently suffer from high blood pressure.

Questions for further thought

What are the relevant considerations of working with impoverished persons that may hinder this research? How does the fact that the research has therapeutic value affect your decision? How does the fact that the researchers are very familiar with their subject population affect their ability to procure informed consent? Does the fact that most of the potential clinical trial participants will be unable to buy the new blood pressure medication (if indeed it is proven effective) affect your decision to allow or disallow the research? If you decide the trial is not ethically acceptable, is this discrimination against impoverished people?

CASE STUDY V

Consider again the ZDV (AZT) study involving pregnant, HIV-infected mothers described above, but now suppose that instead of conducting a placebo arm of the study, the mothers in the control group now received the standard HIV treatment protocol.

Questions for further thought

How does the absence of a placebo arm affect the ethical acceptability of the clinical trials? Suppose later it was discovered that the new ZDV (AZT) regimen being tested increases the risk of birth defects in newborns. Should the trials proceed in light of this new information? How does this new source of potential harm

affect the ability of HIV-infected mothers to give informed consent?

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