Chapter 8
Realizing Benefit Sharing: Is there a Role for Ethics Review?

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Abstract The donors of human genetic resources deserve benefits in return for their contribution to scientific research. In the context of developing countries this claim holds as a matter of justice. But how can this demand be realised and implemented? This chapter looks at the role of ethics review as a possible benefit sharing mechanism. In particular the promising role of research ethics committees in monitoring the Declaration of Helsinki's post-study obligations is considered. However, a range of obstacles are identified, which would have to be overcome before ethics review could reliably achieve justice for the donors of human genetic resources in developing countries. These issues are addressed in specific recommendations. The

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chapter concludes that the provision of health care, however extensive, in return for the donation of human genetic resources does not represent undue inducement, but rather fair benefit sharing.

Keywords Benefit sharing • Research ethics • Developing countries • Post-study access • Declaration of Helsinki

8.1 Introduction

'The arc of the universe is long, but it bends towards justice.' This is how Martin Luther King Jr. expressed his hopes for the future. Of course, justice does not arrive of its own accord. Four years after receiving the Nobel Peace Prize in 1964 for his non-violent work to advance civil rights King was assassinated. Today, there is a black President of the United States, giving an indication that some of King's dreams of justice have been realized. However, when we turn to international justice, we note that the US is one of a handful of countries[1] that are not parties to the international Convention on Biological Diversity (CBD). In the previous chapter, an expansion of the CBD was suggested in order to achieve justice for donors of human genetic resources.[2] This chapter will explore the potential for utilizing the existing, well-established system of ethical review to advance benefit sharing.

How does one protect human research participants from harm and exploitation? Four basic markers for the occurrence of harm in the research context can be distinguished (see Chap. 2).

1. Unfavourable risk-benefit ratio
2. Breach of confidentiality or privacy
3. Invalid consent
4. Lack of access to the benefits of research.

Exploitation is mainly relevant to the fourth marker and equates to 'a failure to benefit others as some norm of fairness requires' (Mayer 2007: 142) (see Chap. 2). Ethics committees have increasingly taken on the responsibility of preventing such exploitation. They appear in two main varieties: clinical ethics committees have been in existence since the early 1960s, mostly to support staff, patients and families in making end-of-life decisions, while research ethics committees have been in existence since the late 1960s (see below) to govern research involving human participants (Aulisio 2003: 841).[3]

[1] Two exceptions at the time of writing are Andorra and South Sudan.

[2] By human biological resources, we mean human biological samples collected for genetic studies and related data.

[3] For more on clinical ethics committees see McGee et al. (2001), Kuczewski (2004), Slowther (2007) and ASBH (1998).

Research ethics committees are most relevant to this chapter. Their primary role is to decide whether a particular research project is ethical or not by reviewing its study protocol. Such committees usually comprise scientists, professionals and lay people supported by an administrator. Standard questions for such a committee would be:

- Are the research participants appropriately informed?
- Is the balance of risks and benefits posed by the research fair and reasonable?
- Are the research participants likely to be worse off for participating in research? If so, does their consent represent a sufficient protection of their interests (or are they being exploited)?
- Is the research likely to be useful and informative? (Ashcroft 2007: 684)

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Ethical review generally follows a particular pattern. Study protocols are received from researchers, and are then reviewed by a single member, a small consultation team or the full ethics committee. Applications may be approved at that point; if not, they are returned to the applicant with queries before being reconsidered and finally approved or rejected. The legitimacy of ethics committees derives from the fact that they are lawfully established and adhere to a process of deliberation as a diverse group of experts (including lay people) who reach consensus after discussion (Garrard and Dawson 2005: 423). While review requirements differ between (and sometimes within) countries, Fig. 8.1 shows the most basic steps.

In assessing whether a protocol is ethically acceptable, research ethics committees refer to international guidelines (e.g. the Declaration of Helsinki), national guidelines (e.g. UK Medical Research Council guidelines) and national law (e.g. National Health Council of Brazil resolutions). A research ethics committee therefore seeks to protect the interests of research subjects by ensuring compliance with ethical guidelines. Many countries (e.g. the US and the UK) have made it a criminal offence to start medical research without ethical approval from the relevant research ethics committee. This, de facto, gives ethics committees the role of a regulatory authority, a position with 'immense power over the research that is carried out' (McGuinness 2008: 695).

The Nuremberg Code (1949)[4] and the World Medical Association's Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (1964) placed responsibility for safeguarding research participants on the investigator. In 1975, however, the Tokyo revision of the Declaration of Helsinki introduced ethics committee review of research as its second basic principle (Levine 1995: 2312):

> The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance (WMA 1975).

[4] The Nuremberg Code of 1949 is a set of principles and rules to be observed when undertaking research with human participants. It was developed after the Nuremberg trials in 1946 and 1947 of Nazi doctors who had committed atrocities against concentration camp internees as part of medical research. It was superseded by the Declaration of Helsinki in 1964 (see Chap. 3).

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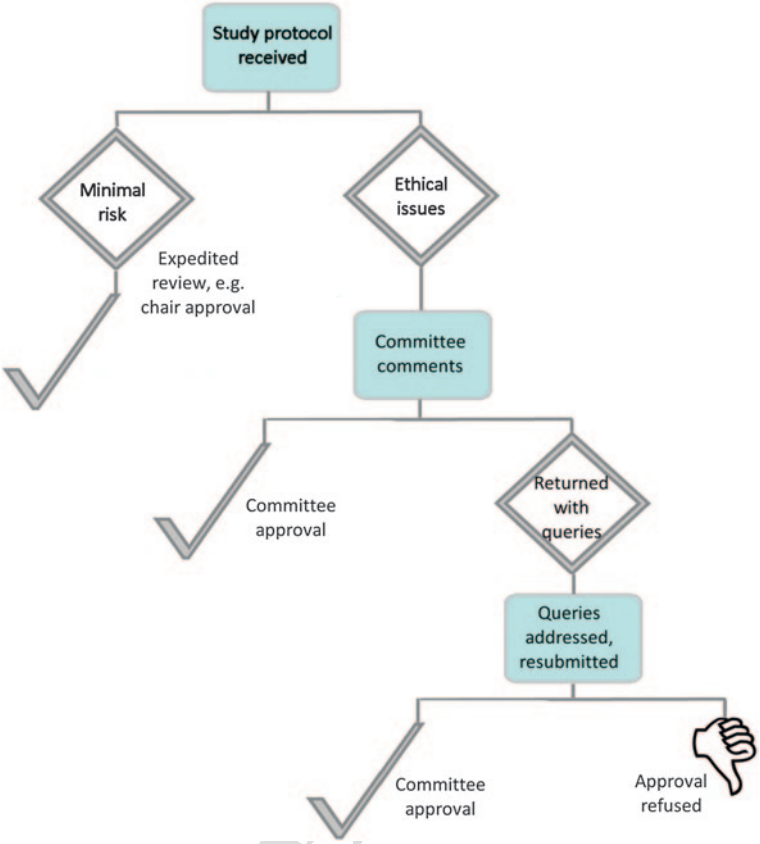

Fig. 8.1 Simplified Ethical Review Process

Since 1975, repeated revisions of the Declaration of Helsinki have specified in increasing detail what is implied by ethics committee review. Principle 15 of the current (2008) declaration reads:

> The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee (WMA 2008).

Until the end of the twentieth century, ethics committee review concentrated on pre-start approval, but nowadays it is increasingly seen as a process that does not stop until the research has been completed. For instance, funding bodies such

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as the Economic and Social Research Council in Britain see monitoring as a minimum ethics requirement. The council's Framework for Research Ethics includes the following:

> Procedures for institutional monitoring should be in place. Universities and other research organisations should establish appropriate procedures to monitor the conduct of research which has received ethics approval until it is completed, and to ensure appropriate continuing review where the research design anticipates possible changes over time that may need to be addressed (ESRC n.d.: 5).

It would therefore be feasible for ethics review of a research project to continue up to the point at which it may be possible to determine whether vulnerable research participants, especially in developing countries, have benefited from taking part in research. To complement the Chap. 7, which recommended expanding the provisions of the CBD to include access and benefit-sharing arrangements for human biological resources, we will ask:

> Could research ethics committees ensure compliance with post-study obligations (a form of benefit sharing), in order to avoid burdening medical research with further governance structures?

Before answering this question, it is worth revisiting and strengthening a claim made earlier (see Chap. 2), namely that the developing world should be treated differently from the developed world when it comes to the governance of human biological resources. The alleged altruism shown by European DNA donors, for instance, cannot be expected of donors from developing countries without perpetuating exploitative relationships.

8.2 Benefit Sharing Versus the Altruism or Solidarity Model

For decades human tissue has been provided voluntarily by individuals for research purposes, in most cases without any expectation of benefit. The case of blood donation in the United Kingdom for blood transfusions and research purposes is a case in point (Keown 1997). This altruism is also apparent among research participants in developing countries. In interviews undertaken with sex worker participants enrolled in long-term HIV/AIDS research in Majengo, Nairobi (see Chap. 5), one respondent said:

> On my faith … they can get a cure from my blood and it can help the whole world. So that is why I gave myself. Even if I am infected…I am ready because I agreed to collaborate in the research.[5]

This respondent donated her blood to help the whole world. However, international ethics guidelines (see Chap. 3) now *require* benefit sharing with research

[5] Interview with Majengo participant in GenBenefit project, April 2007.

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participants. To recap, paragraph 14 of the Declaration of Helsinki (WMA 2008) requires as follows:

> The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

Hence, every research project which is presented for ethics approval must outline in its protocol how it will deal with post-study obligations. This is particularly important in the case of vulnerable populations, which is why the Declaration of Helsinki (WMA 2008) adds in paragraph 17:

> Medical research involving a disadvantaged or vulnerable population or community is only justified if … there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

The question arises: why should humans not be able to simply donate their tissue for the good of the world, without requiring burdensome and bureaucratic arrangements for post-study access to benefits? It seems that most people who provide blood or samples for research in the developed world are content to do so purely on the assurance that the tissue supplied will be utilized for the betterment of humankind. Why then should individuals from the developing world expect any more from the same transaction? No work is involved in producing DNA, nor do donors incur significant risks in donating samples. One could say that we need to draw upon the altruism of humankind to ensure the provision of resources that are so important for health research (Berg and Chadwick 2001: 320).

Altruism, which in its broadest sense means promoting the interests of another (Scott and Seglow 2007: 1), is an interesting concept. Under scrutiny it reveals complex questions about morality. For example, to donate one's blood or organs with the proviso that they can *only* be given to those of one's own race would be altruistic, but morally questionable. A UK government investigation found it 'abhorrent' that a hospital had accepted an organ donation on condition that it benefited a white patient (BBC 2000). Hence, acts of altruism might not always be as morally pure as they appear at first sight.

The eighteenth-century political economist Adam Smith maintained that egoism or self-interest would lead to general welfare, stating that it was not 'from the benevolence of the butcher, the brewer or the baker that we expect our dinner, but from their regard to their own interest' (Smith 1976: 26f). On the other hand, French philosopher Auguste Comte, who coined the term 'altruism' in the early nineteenth century, believed that promoting other people's interests meant that morality triumphed over egoism (Scott and Seglow 2007: 15). Immanuel Kant provided useful guidance on the motives behind altruism. He distinguished beneficence (*Wohltun*), which is understood as doing good, from benevolence (*Wohlwollen*), which is understood as wishing well. Beneficence is then benevolence in action; acting in accordance with a 'maxim of making others' happiness one's end' (Kant 1996: 452). While this might appear noble in essence, the motive Kant provided for beneficence is actually close to self-interest. He claimed that one would not want to live in a world where those in need were not supported or

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assisted, simply because one might require similar assistance from others in the future.

This scenario of individuals mutually acknowledging their human needs and subsequent duties has been called the duty of mutual aid (Herman 1993). In this context, reciprocity and expectations are important. Such reciprocity protects the altruist, even though it might provide a less than perfectly noble motive for her good deeds. Reciprocal altruism is performed in the hope of obtaining a future reward, for instance in the form of assistance, and is therefore something of a hybrid between altruism and self-interest.

Reciprocity was examined by Marcel Mauss in his classic 1950 anthropological study *The Gift* (2002). Mauss examined gift-giving in ancient times and in more recent Roman, Jewish, Germanic and other Indo-European societies. The seemingly ubiquitous practice of gift-giving existed separately from commercial transactions in all these societies. He defined a gift as 'a voluntary, unrequited surrender of resources' (Mauss 2002: 3). The apparent generosity of the gifting practices seemed to indicate very high levels of solidarity, charity and trust. However, Mauss famously concluded that in all such societies there were no free gifts. The giving of gifts engaged the giver and the receiver alike in finely woven, if implicit, obligations and commitments that reflected and resonated with the institutions of the day. Morality did not seem to enter the transaction, and the society's (unwritten) norms and expectations framed what was required in certain circumstances. Mauss established that the entire notion of a free gift was based upon a misunderstanding of the nature of such a transaction, and concluded that a gift that expected no return, that did nothing to enhance solidarity, was a contradiction in terms (Mauss 2002: xii). His work encourages us to consider that material items, whether sold or given, always retain something of the identity of the giver, and often require reciprocation in some form.

The work of Richard Titmuss added significantly to the understanding of altruism. In his book *The Gift Relationship* (1997) he attempted to counter policies that promoted the commodification of human blood. His primary aim was to advocate voluntary blood donation, which allowed people the moral choice to give blood as a 'symbolic gift of life to an unnamed stranger' (Titmuss 1997: 140). What might be regarded as particularly altruistic was that the gift of blood was to unknown individuals. Hence, it was not given to those in close relationships to whom, in Mauss's societies, one might turn in times of need. The only reward for the donors was the knowledge that they had contributed to the public good.

One of Titmuss's most powerful arguments was that the opportunity to behave altruistically was an essential human right. He believed that specific instruments of public policy were able to harness and encourage that crucial element of altruism in opposition to the 'possessive egoism of the marketplace' (Titmuss 1997: 59). His plea was that people should be enabled to choose to give to unnamed strangers, and not be 'constrained by the market' (Titmuss 1997: 310). However, whether the donation of blood is a true gift that expects no return, or instead creative altruism that fosters a sense of belonging to a community of assistance, is difficult to establish (Scott and Seglow 2007: 111).

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Titmuss's plea has been echoed in more recent appeals for altruistic donation (or solidarity) in the context of genetic research. Kåre Berg and Ruth Chadwick talk about a 'duty to facilitate research progress and to provide knowledge that could be crucial to the health of others' (Berg and Chadwick 2001: 320). Solidarity and equity are suggested as frameworks or paradigms in which the emphasis is on the duty of individuals and communities to participate in health research for the benefit of others. This approach might, however, contradict the post-study obligations outlined in paragraphs 14 and 17 of the Declaration of Helsinki (WMA 2008), as quoted above, given that these require benefit sharing.

Berg and Chadwick give two main reasons for preferring a solidarity framework over benefit sharing. First as noted above, no work is required to produce DNA or blood:

> The populations, families and individuals, whose samples have formed the basis for new products and revenue, have not themselves done anything to make their samples 'valuable'… If anything, their samples have become valuable because of work conducted by scientists (Berg and Chadwick 2001: 320).

Second, 'the emphasis on distribution of benefits might be seen not as an exercise in … justice, but as an attempt to buy people off' (Berg and Chadwick 2001: 321). The implication of 'buying people off' is that providing specific benefits to donors would entail the risk of unduly influencing individuals to participate in research. Such undue inducement is prohibited by almost all ethics guidelines, as is the commodification of the body (i.e. the possibility of obtaining money in return for body parts or bodily tissue).

It is difficult to see how the first point could be justified morally. At first it appears as if it might be based on John Locke's widely accepted labour-desert theory. He argued in the seventeenth century that ownership can be achieved if one mixes one's labour with otherwise unowned objects. In the *Second Treatise on Civil Government* he writes: 'As much land as a man tills, plants, improves, cultivates, and can use the product of, so much is his property' (Locke 1690: Chapter V, 'Of Property', section 32). For instance, if one looked after raspberry bushes on unowned land, one might be able to declare ownership of the bushes after a period of time. But the basis for Locke's theory is his belief that we all own our individual bodies. Hence, the labour of geneticists is not mixed with *unowned* objects. Besides, if the samples were not valuable in themselves, there would be no interest in obtaining them. Assuming that value is only added later is reminiscent of debates prior to the adoption of the CBD. Vandana Shiva (2005: 15) wrote in this context:

> [It is assumed] that prior to prospecting, the resources of desire were unknown, unused and without value. Using terminology derived from earlier 'prospecting' for minerals and fossil fuels, 'bioprospecting' obscures the fact that living resources are not non-renewable and are not without value prior to exploitation by global commercial interests for global markets.

Hence, to assume that value is only created through doing something with a resource, as scientists might, risks falling back into pre-CBD exploitative practices in relation to accessing the resources of developing countries. With the adoption of

the CBD, it has been legally accepted that natural resources in developing countries are not unowned, only to become valuable with added (Western) labour. The fact that nobody has 'made' their own DNA is not therefore in itself an objection to benefit sharing.

The objection to benefit sharing which arises from prohibitions against undue inducement and commodification of the body is more serious. At the same time, it must be understood that benefit sharing does not mean handing over cash for DNA samples, which could be regarded as straightforward commodification. The CBD's Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (see Chap. 2) lists considerably fewer monetary than non-monetary benefits. The latter include collaboration in scientific research, collaboration in education and training, institutional capacity-building, access to scientific information, contributions to the local economy, research directed towards priority needs, such as health and food security, livelihood security benefits and social recognition.

This brings us to an important point that helps us explain why research participants in the developing world should be treated differently from those in developed countries in relation to the governance of human biological resources. DNA donors from Northern countries generally benefit automatically from education and livelihood security benefits. Those contributing to medical research in the North can usually rest assured of (see Chap. 2):

- Access to ever-increasing numbers of medical interventions to achieve and maintain health, which are tailored to local health needs and (in principle) accessible to all
- Increased knowledge about human health, which is made available to citizens through general education or health campaigns.

Hence, the 'altruistic' donor in the North could be regarded as part of a community which offers a fair exchange model to such donors. People experience a tangible form of reciprocity for their participation in the complex social and economic network encompassed by the health care system, reminiscent of a Maussian society, ensuring the fairness of the entire exchange. Assured of far more than the mere cup of tea and biscuit traditionally received by blood donors since Titmuss's time, individuals from affluent countries might appear to be acting out of solidarity with their group, but their ostensible altruism is strongly bolstered by the fact that their contribution is virtually risk-free, and reciprocation is provided through the assurance of fair compensation via the health care system.

It is still the case that others may free-ride (type 1 exploitation, see Chap. 2) on the willingness of research participants to donate their time or even take risks. In this regard, Berg and Chadwick (2001) are right to appeal for more solidarity within communities. But it would be highly exploitative to demand such solidarity from donors who are outside the fair exchange model and who contribute their DNA without receiving *any* benefit in return. Participants from an impoverished developing country are assured of none of the above benefits, and the use of their donated genetic material for the benefit of affluent, distant strangers deserves

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critical attention, which returns us to the question: could research ethics committees ensure compliance with post-study obligations (a form of benefit sharing), in order to avoid burdening medical research with further governance structures?

As African bioethicist Godfrey Tangwa notes:

> In medical research the principle of justice demands fairness in the treatment of individuals and communities and the equitable distribution of the burdens and benefits of research. This has important implications for such issues as … post-study benefits, and long term access or distribution of the benefits of the study. These are the issues, which preoccupy every research ethics committee sitting to review a health research protocol in Africa today (Tangwa 2009: S5).

When assessing the question of how justice might be secured within current regulatory frameworks, it is essential to distinguish between two types of benefit-sharing arrangements which have different compliance challenges associated with them. First, we shall consider obstacles to enforcing post-study obligations which aim to provide a successfully tested health care intervention to research participants after the study has been concluded. We term this duty 'post-study access'. Second, we shall analyse obstacles to enforcing the provision of benefits not directly linked to the study, such as access to health care, support for the local health infrastructure or health information campaigns. These will be referred to as 'other benefits'. We shall discuss first the challenges that apply to both benefit-sharing types, and then those that apply exclusively to either type.

8.3 Post-study Access and Other Benefits

The following challenges to implementing a benefit-sharing framework of post-study obligations apply both to giving research participants access to successfully tested interventions and to the provision of 'other benefits'.

8.3.1 Whose Duty?

The Declaration of Helsinki does not specify whose obligation it is to discharge post-study obligations. Is it the duty of individual researchers? After all, they are the interface between sample donors on the one hand and research studies on the other. They are also the ones with the most to gain, aside from research participants. Unlike physicians, whose prime duty is the promotion and safeguarding of patient health, researchers have potentially competing obligations to their sponsors, as well as aspirations to achieve scientific progress.

While the Declaration of Helsinki clearly stipulates that '[i]n medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests' (WMA 2008: paragraph 6), such 'other interests' cannot be ignored altogether. What is, however, identical in the two relationships – that

between doctor and patient and that between researcher and research participant – is that trust plays a major role and the relationship is often highly personal.

The breaking off of a relationship between researcher and research participant can be very difficult, even traumatic. If, as is frequently the case in the developing world, participation in a research study is the only way to access health care, then the end of a study implies the end of health care. In particular, researchers working with AIDS patients often find it difficult to withdraw in the knowledge that those patients are likely to die from a treatable disease (Shapiro and Benatar 2005: 45). Needless to say, the sense of abandonment for the research participant is even stronger, especially when the study provided the only access to health care. In the worst cases, the end of the research results in death.

It is in this context that post-study obligations to research participants are advocated. Focus group research conducted among patients, clinical researchers and research administrators in Kenya showed that all stakeholders believed strongly that researchers had a long-term obligation to participants. 'The rationale behind this belief – whether fear of death, inability to continue therapy, or an ethical obligation – warrants attention' (Shaffer et al. 2006: 55). Focusing on the ethical obligations, one would argue that research participants, having contributed to the advancement of knowledge, deserve some benefit in return. This aligns with the argument for non-exploitation as advocated throughout this book.

Importantly, though, a number of participants in the focus groups noted specifically that the loss of access to health care would result in a general loss of trust between research participants and researchers, potentially making the community unwilling to participate in research at all (NBAC 2001: 59). Both sides consider it unacceptable to abandon, at the end of a study, research participants who are in dire need of medical attention.

In terms of who has how much invested in the relationship, it might therefore make sense to allocate post-study obligations to researchers. However, these could also be among the duties of research funders and sponsors, who, one would assume, are best placed to find the resources to discharge such obligations.

One of the few countries with binding national law on post-study obligations is Brazil (see Chap. 3). In 1997, a resolution by that country's National Health Council set the following stipulation:

> Access to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter, if there is no sponsor, in the event its superiority to the conventional treatment is proven (National Health Council 1997: article IV.1(m)).

The Declaration of Helsinki lacks a similarly clear assignment of duties to a specified group. One might argue that this allows the flexibility needed in guidelines that must apply all over the world. In practice, however, this flexibility is partly responsible for the ineffectiveness of the guideline and the concomitant lack of good practice examples for post-study obligations. If the commitment to benefit sharing re-emphasized in the 2008 Declaration of Helsinki is to be effective, then research ethics committees need to know whose duty it is to provide access to successfully tested interventions or 'other benefits' in order to ensure compliance.

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8.3.2 Insufficient Capacity for Review

Concerns about workload and personnel resources are factors that detract from the effectiveness of research ethics committees even in affluent settings (Schuppli and Fraser 2007). It is therefore not surprising that ethics committees in developing countries often lack the resources to give adequate attention to ethical review. A study published in 2009 that examined the effectiveness and training needs of African research ethics committees concluded that the 'major constraints identified are shortage of resources and inadequate training of the ERC [ethical review committee] members' (Nyika et al. 2009: 193). The study also summarized the constraints hindering the adequate review of study protocols in African settings. Table 8.1 lists the constraints in order of perceived gravity: that is, the first constraint is the one noted by the highest number of respondents.

Other studies have also shown that 'the capacity to conduct ethical review in developing countries needs to be developed or enhanced' (Hyder et al. 2004). Evidently, insufficient resources, lack of expertise and so on can render the protection of human research participants unreliable or even non-existent. Under these circumstances, it is unlikely that research ethics committees in developing countries would be in a position to enforce the requirement of benefit sharing. In order to carry out this task, they would need investment in both infrastructure and training. As the next subsection will show, this issue is particularly problematic when research ethics committees in the country of the research funder or sponsor are likely to ignore the obligation. Encouragingly, though, a funding stream from the European and Developing Countries Clinical Trials Partnership is successfully funding the establishment of new ethics committees in Africa and capacity-building for existing committees.[6]

8.3.3 US Withdrawal from Post-study Obligations

The previous chapter suggested that an expansion of the provisions of the CBD to include human biological resources would close an important gap in the international legal framework. It would establish an *inclusive* approach to biodiversity, both human and non-human, bring legal clarity to a contentious area and, most importantly, provide a way forward when a spectrum of genetic resources are used by various industries (e.g. when a product is developed using plant and human genetic resources).

As noted in the beginning of this chapter, the US is virtually the only country that is not a party to the CBD. At the same time, the US is the leading innovation economy in the world. For instance, the *2011 World Intellectual Property Indicators* showed that 24% of all patents world-wide were granted by the US Patent and Trademark Office (WIPO 2011). In 2008, however, the US government effectively

[6] See the partnership's website at http://www.edctp.org.

Table 8.1 Constraints on African Research Ethics Committees

Insufficient resources
Expertise on ethical review lacking
Pressure from researchers
Lack of active or consistent participation by members
Lack of recognition of importance of committee functions
Lack of support from institute concerned
Insufficient independence
Pressure from sponsors
Unequal treatment of applicants in review

Source Nyika et al. (2009) (modified)

opted out of the Declaration of Helsinki when the US Food and Drug Administration discontinued its reliance on the declaration and issued independent Guidelines for Good Clinical Practice. The new guidelines omit the two standard benefit-sharing principles of the Declaration of Helsinki, namely post-study access to successfully tested interventions and the requirement that research, particularly in developing countries, must benefit local communities and be responsive to local health needs (Kimmelman et al. 2009). This means that US government requirements for the treatment of research participants are now in direct conflict with the prescriptions of the Declaration of Helsinki (aside from the fact that the US is not a party to the CBD).

This development could mean that US research ethics committees (or institutional review boards) will in general put less pressure on researchers to describe compliance with post-study obligations in study protocols than their international counterparts that fully subscribe to the Declaration of Helsinki. While this is a serious concern, resource provider states are not entirely powerless in relation to compliance where they rely on ethics review. US researchers, like any others, require local ethics review in order to access human genetic resources. Such local ethics review (for instance in Kenya, Thailand or Bolivia) can, if well informed and decisive enough, provide approval only on condition that benefits to research participants and local communities are explicitly articulated. This strategy presents a distinct advantage over CBD expansion. In fact, strong ethics committees or national legislation in developing countries (see for instance Brazil's benefit-sharing legislation as outlined in Chap. 3) can enforce benefit-sharing compliance *now*, without additional legal frameworks.

8.3.4 Timeliness of Research

A related advantage of utilizing ethics review to achieve benefit-sharing compliance is that the procedure needs to be undertaken by researchers in any case. For instance, informed consent documentation and risk-benefit ratios will always be checked by an ethics review committee whether or not benefit sharing is *also* regulated through independent mechanisms. Adding benefit-sharing information to that

already required in the protocol in terms of the Declaration of Helsinki puts only a limited extra burden on the existing approval process.

Assuming that benefit-sharing requirements for human research participants were to be regulated through the CBD framework, another approval process would have to be added. According to Laird and Wynberg (2008), '[t]he negotiation of consent and benefit sharing agreements between those who access and those who provide non-human genetic resources takes on average 1–2 years and sometimes longer' This would be a significant additional burden with considerable impact on the timeliness of research. Especially in health research, such delays can be highly detrimental to global public health and individual patients.

8.4 Post-study Access

The constraints we have listed so far concern enforcing the provision of post-study access to successfully tested interventions and 'other benefits'. However, some challenges are limited to ensuring post-study access.

8.4.1 Unrealistic Timeframe for Post-study Access

By the time a post-study obligation becomes relevant, some of the researchers involved are likely to have left the study site and even the country. In 'helicopter research' (flying in and out of locations, for instance in a current epidemic), researchers leave as soon as the data is obtained. Many research units have long-standing collaborations with host countries, but some do not, leaving research ethics committees with no recourse to researchers after the completion of their study. In any case, it takes on average a decade to bring a drug to market (Trade and Industry Select Committee 2002). To be required to return to participants a decade after the study to see whether they are in need of the developed intervention is rather unrealistic and cumbersome to say the least. More importantly, for the purposes of this chapter, it would be highly unrealistic to expect research ethics committees to ensure compliance ten years after a project's completion.

8.4.2 Inbuilt Unfairness in Post-study Access: The Research Participant

Research ethics committees aim to protect *all* human research participants from exploitation, not just some.

Failure rates in drug development are extremely high. Of those developments that make it into clinical trials, 38% fail Phase I (safety), 60% of the remainder fail

Phase II (basic efficacy), 40% of the rest fail Phase III (comprehensive efficacy) and 23% of those still in the running will not be approved by the relevant health agency (Lowe 2004). As a result, the chances for any individual participant that the particular research she or he was involved in will actually lead to a marketable product are very slim, particularly for donors of biological materials in the early phases of research, and participants in Phase I and II drug trials.

Even if post-study access could be assured a decade after a study's completion, it would only benefit those research participants lucky enough to have been part of bench-to-bed research which overcame all hurdles smoothly. But since those whose participation shows that a product is unsafe or not efficacious contribute as much to medical research as their luckier counterparts, one cannot argue that only the latter are entitled to benefit sharing – and there is no way to predict which participants will fall into which category. By the time a research ethics committee can establish which participants will not have an option of post-study access, it is likely to be too late to ensure any other benefits either. The committees are therefore restricted in their ability to provide equitable protection for *all* research participants.

A related problem is that of involvement in basic research, which is not likely to lead directly to any new medical interventions. In this case, however, research ethics committees could opt for the choice of 'other benefits' from the start.

8.4.3 Inbuilt Unfairness in Post-study Access and Possible Side Effects

It has been argued that imposing post-study obligations on researchers or their sponsors could mean that developing country research focused on local health needs would not be undertaken due to prohibitive costs (Brody 2002: 2857; McMillan and Conlon 2004: 206). One could respond with Solomon Benatar that '[r]equiring greater sensitivity to the plight of the poor and some degree of solidarity with them is not an excessive moral requirement' (Shapiro and Benatar 2005: 42).

However, this could mean that attempts to achieve compliance with the benefit-sharing regulations of the Declaration of Helsinki in order to achieve justice for resource providers in line with the CBD might be self-defeating. Currently, the demand to provide post-study access to successfully tested interventions applies equally to researchers who are using charitable funds to develop drugs for neglected diseases that only exist in, say, South East Asia, and pharmaceutical companies running clinical trials in developing countries for diseases that are prevalent and widespread in the North. However, the former is arguably not a case of exploitation, whereas the latter could be. Benefit sharing is intended to be an instrument to mitigate such exploitation. Yet if the mechanism is so coarse that it makes valuable (and arguably non-exploitative) research prohibitively costly, then enforcing benefit sharing through ethics review could undermine global efforts to realise access to locally tailored health care. In this case, the global injustice in

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terms of access to health care could deepen rather than lessen, and concentrating on smaller details could cause the bigger picture to be overlooked.

Based on the three challenges to post-study access discussed above, one could venture that 'other benefits' may be a more promising and consistent benefit-sharing tool for research ethics committees to require.

8.5 Other Benefits

In practice, when benefit sharing is addressed through ethics review, 'other benefits' are generally thought to be a more realistic arrangement than post-study access. The most common example of this type of benefit sharing is access to health care during a study, as was and is the case for the Majengo sex workers (see Chap. 5). However, there are two problems here.

First, the latest (2008) Declaration of Helsinki may inadvertently have restricted the use of 'other benefits' as a benefit-sharing mechanism. The 2004 declaration required study protocols to include information on post-trial access or 'other benefits', and imposed no restrictions on what might constitute 'other benefits'. It did not exclude, for example, health care during or after a study. By contrast, paragraph 33 of the 2008 declaration states:

> *At the conclusion of the study*, patients … are entitled … to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits' (WMA 2008: paragraph 33) (our emphasis).

This formulation aligns with the general usage of terms, as one usually speaks of *post*-study obligations. However, it means that comprehensive health care delivered *during* a study, even a longitudinal study, is no longer included under 'other benefits' as a benefit-sharing mechanism.[7] Yet many of the Nairobi sex workers interviewed in the course of our research indicated that access to health care was an important benefit they received in return for donating samples (see Box 8.1).

Box 8.1 Comments from sex workers in Majengo on the provision of free health care[8]

- I don't pay for the medicine, I don't do anything with respect to them, but they give me medicine. When I get some little ailment, they help me.
- I came and joined the clinic and I have been helped a lot. I used to have

[7] Of course, one could argue that comprehensive health care during a study offers too little in terms of benefit sharing. However, where comprehensive health care is offered to study participants and their families, sometimes for decades, as is the case with some Nairobi sex workers, the fair exchange model available to donors from affluent countries is being approximated.

[8] Interviews with Majengo research participants, GenBenefit, April 2007.

bad headaches, you know when your immunity goes down you get other ailments and they are worse than normal … but once you know your status you can come and be treated quickly before it gets worse… So I'm grateful to this clinic, it has done us a lot of good.

- Yes, treatment. I get it for free; if they want to carry out some research and they need blood they give us bus fare because the appointed day may come to take your blood or urine sample and you may not be able because you don't have bus fare.
- I expected treatment, free of charge. Every time I fall sick I come for treatment and it's free.
- They just passed by telling people on the streets, and I learned there is a clinic for helping people to detect diseases and in return they use your blood for research. We agreed that it is OK.
- You see, they usually check us down there to see how we are getting on; you could be developing something. So you get to know about it early enough and save yourself. That for me is a benefit.
- No, I did not expect money or such things, just treatment.
- They give us free medicine because of the nature of our work. If you have a problem they help you.
- Because that is what I need. That is what is important, they give me what I would otherwise not be able to get [treatment].
- I was told I would get benefits of [testing for and treatment of] communicable diseases. If I am found with them, I would be treated, there is a doctor here, and there is medicine…
- Yes, I am satisfied because when I come here I get a cheerful doctor who I can confide in without fear and tell her about my pains, and when I have problems there is a counsellor I can go and talk to and [s]he counsels me until I am satisfied… I like this clinic because since we realized the benefits of the clinic, we try to bring many people so that they too can benefit. And the benefits I get from this clinic have also helped me in doing my work. I can protect myself against infections according to how we are advised at the clinic and I also teach others so that they can protect themselves too.
- We have a very nice doctor, sisters, they all welcome us in the clinic.
- For me I see that the benefits I would expect is treatment because whatever kind of sickness I get I am treated. So this clinic has a lot of benefits.
- I don't think there should be any other kind of benefits … we are given free medicine, free treatment.
- I think it's forever, because there are some women I have heard saying they have been here since 1986. So it can go on forever, that is so long as you are going to sponsor it [Interviewer: So you will be getting these free services forever?] Yes, hopefully! God willing. [Laughter].
- I don't know what I will do if they close down.

If the emphasis in the Declaration of Helsinki is on *post*-sharing of benefits, some of the challenges of securing post-study access (for example, the unrealistic timeframe) would now also apply to 'other benefits'. In other words, if only those benefits delivered *after* a study is completed count towards benefit sharing, seeking compliance through an ethics review committee could become difficult, as the committee usually ceases its monitoring work once the research is complete.

Second, offering access to health care as a benefit to participants could violate undue inducement prohibitions, a topic we have considered before (see Chaps. 2 and 5). When undertaking research on economically disadvantaged or otherwise vulnerable populations possibly suffering from hunger or malnutrition, and lacking access even to elementary health care, any prospect of health care (for example, a general check-up as part of being enlisted in a study) can be regarded as an undue inducement. It is no surprise that UNESCO's Universal Declaration on Bioethics and Human Rights includes two requirements of benefit sharing: first, that '[b]enefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries', but, secondly, that those '[b]enefits should not constitute improper inducements to participate in research' (UNESCO 2005: article 15).

Some international guidelines, such as the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Science (CIOMS), accept that research participants may receive free medical services. However, CIOMS also notes that these services should not be 'so extensive as to induce prospective subjects to consent to participate in the research against their better judgment' (CIOMS 2002: guideline 7). And research has shown – unsurprisingly – that the need to access medical services can amount to pressure to join research studies in developing countries. One cannot reliably determine how many participants actually take part 'against their better judgement', but it is clear that many feel they effectively have no choice. As one of the Majengo research participants said, 'I don't know what I will do if they close down.'

When 347 Ugandan parents with children enrolled in a malaria study were asked whether they had felt coerced to join, more than half said they had 'felt pressure to enrol their children because of the child's sickness' (Pace and Emanuel 2005). As Annas and Grodin (1998) have formulated it,

> in the absence of health care, virtually any offer of medical assistance (even in the guise of research) will be accepted as 'better than nothing' and research will almost inevitably be confused with treatment.

Ironically, strict prohibitions against undue inducement lead to a rather paradoxical result. The poorer a community is, the smaller the benefits that can be offered without potentially exercising undue influence on the decision to participate. The conflict here occurs because participants are meant to be protected against undue inducement on the one hand and exploitation on the other. Yet limiting benefit-sharing possibilities gives research sponsors who outsource research to developing countries a convenient 'ethical' argument for limiting the benefits to

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study participants (Ballantyne 2008: 190). As long as this paradox remains unresolved, ethics committees will not be in a position to decide definitively whether the 'other benefits' in a given case constitute benefit sharing or an undue inducement. This makes it extremely difficult for committees to play their governance role successfully.

The authors of this chapter are continuing their research on the potential tension between benefit sharing for human genetic resources and undue inducement. They are already satisfied, however, that it is possible to provide benefit sharing while avoiding undue inducement. The commodification of the body can indeed open up further opportunities for exploitation, especially in developing countries. An example would be paid surrogate pregnancy, when Indian mothers, for instance, carry babies for affluent mothers in the North (Taneja 2008). But such commodification can be avoided by prohibiting one-to-one financial gain from a research transaction. If individual donors for DNA were given no cash except for legitimate expenses, the risk of undue inducement would be much reduced.

What, then, might legitimate benefit sharing that avoids undue inducement look like? Here it is important to look at two of the main reasons for legislating against undue inducement (see Chap. 2): namely, that research participants might accept a risk (usually to their health) that would not otherwise be acceptable, and that they would then participate in research against their better judgement.

It has already been noted that the donation of human genetic resources carries minimal risk and imposes a minimal burden.[9] Hence, the foundation of the undue inducement principle does not apply to access to genetic resources in the same way as it applies to enrolling in Phase I clinical trials. If risk reduction can only be achieved by restricting benefits to research participants (as, for instance, in burdensome, risky trials involving healthy volunteers), minimal risk studies can concentrate more on benefit sharing than misplaced concerns about undue inducement. Access to health care for research participants and their local communities is therefore the ideal benefit to be shared with the donors of human biological resources. Through such benefit sharing, they would come one step closer to the fair exchange model that exists between medical researchers in the North and their research participants. Global research without borders would then contribute to global justice without borders when it comes to access to health care. At least *some* additional access to health care, *some* new health care facilities and *some* health care training and education could be achieved this way.

At the same time, it is essential to note that benefit sharing cannot resolve deep-seated issues of distributive injustice or human rights issues that render national governments unable to respect, protect, and fulfil the human right to access to health care. For this reason, we shall present in Chap. 9 an example of a reform plan that provides a way forward for increasing the availability of life-saving medicines for the poor, with the potential to close the health care gap between developing and developed countries.

[9] Some exceptions, as outlined in Chap. 2 xx, would have to be dealt with separately, for instance where blood might have sacred meaning.

8.6 Conclusion

Can compliance with benefit-sharing obligations as outlined in the Declaration of Helsinki be achieved through ethical review? As we have seen, the obstacles are manifold. In particular, post-study access does not seem to be a promising scenario, given the unrealistic timeframes and the potential for injustice. 'Other benefits' are a more realistic option, in particular the provision of comprehensive health care during long-term studies. In order to strengthen the capacity of ethics review to ensure benefit sharing, we submit the following recommendations:

- Research ethics committees and other parties need to know whose duty it is to discharge post-study obligations. This could be specified in the Declaration of Helsinki, Specification in national law (as in Brazil) is another possibility. Solutions should be integrated with local health systems in developing countries so that research sponsors and local authorities understand their specific roles in providing health care to populations.
- Effective research ethics committees require adequate resources, training and time to fulfil their important roles. As studies have shown, this cannot be taken for granted in developing countries. There is already a pressing need to facilitate

> innovative ways of offering training and education in research ethics. As well as supporting and enhancing current training programmes it will be essential to build up a cadre of trainers located in developing scountries, as well as establishing a process of mentoring for local ethics committees (Bhutta 2004).

- In addition, further ways of providing financial support to ethics committees in developing countries need to be found.
- Applying post-study obligations to all types of research without further refinement would be unlikely to achieve broad acceptance of the duties entailed and may even lead to new injustices, in particular if valuable publicly funded research tailored to Type III diseases[10] were abandoned in developing countries. Such research could attract exemptions or waivers from post-study obligations, as they already comply with fairness requirements.
- The tension between benefit sharing and undue inducement needs to be resolved for developing countries. The ideal solution would be the global success of the fair exchange model between the health care industry, human research participants and national governments: human research participants show solidarity with others (Knoppers 2000; Berg and Chadwick 2001) by taking part in medical research and are rewarded, like their fellow citizens, with the fruits of medical progress, generated through industry and partly funded through national governments. In such circumstances, concerns about undue inducements would be restricted to substantial monetary rewards and other excessive remunerations.
- However, as long as this ideal solution remains no more than an aspiration, ways must be found to avoid the exploitation of research participants in

[10] Type III diseases are those that occur exclusively or overwhelmingly in poor countries.

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developing countries. One such way is to promote access to health care, as well as health care training and education, as a standard and legitimate means of sharing benefits for research involving minimal risk. To substantiate this recommendation, one could argue that CIOMS supports it indirectly.

> When research interventions or procedures that do not hold out the prospect of direct benefit present more than minimal risk, all parties involved in the research – sponsors, investigators and ethical review committees – in both funding and host countries should be careful to avoid undue material inducement (CIOMS 2002: guideline 7, commentary).

- In other words, concerns about undue inducement – which essentially aim to avoid a situation where participants take risks with their health, against their better judgement, in order to qualify for a benefit – are much less problematic when a research intervention poses only minimal risk (for example, sample donation). In such cases, the provision of health care (however extensive and for however long) should not count as an undue inducement. On the contrary, it should count as desirable benefit sharing.
- Overall, it is important not to lose sight of the bigger picture when discussing benefit sharing. Research sponsors and funders are, after all, not the main duty bearers for providing health care to those who cannot afford it. It is essential to support and strengthen the capacity of national governments to discharge their duties with regard to the right to health. Such support efforts should go far beyond the monitoring of post-study obligations through research ethics committees and concentrate on other factors, for instance the fact that – with reference to the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and free trade agreements (FTAs) – 'TRIPS and FTAs have had an adverse impact on prices and availability of medicines, making it difficult for countries to comply with their obligations to respect, protect, and fulfil the right to health' (Grover 2009: paragraph 94). The next chapter will introduce a reform plan which aims to contribute a part-solution to this problem.
- Last, but not least, Martin Luther King's country of birth, the United States, should be put under pressure for opting out of the benefit-sharing frameworks of the CBD and the Declaration of Helsinki.

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