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### IS "THERAPEUTIC RESEARCH" A MISNOMER?

Peter Lucas

#### 1. Introduction

The distinction between therapeutic and non-therapeutic research is a familiar one in research ethics. This chapter argues that the term "therapeutic research" is a misnomer. I consider two broad types of ostensibly therapeutic research: controlled trials, and innovative/experimental treatments. I argue that in the former case the term therapeutic research is a misnomer because no reasonable researcher can expect patients/subjects to derive any therapeutic advantage from being entered into an ethically conducted controlled trial. In the latter case, while accepting that there may well be a reasonable expectation of therapeutic benefit from innovative treatments, I argue that the decision whether it is in the interests of a given patient to receive a given treatment is properly made on purely clinical grounds. There is no special feature of the research situation, in either of these types of case, which serves to ensure that participation, *qua* research subject, is in a patient's interests.

#### 2. "Therapeutic" and "Non-Therapeutic" Research

The distinction between "therapeutic" and "non-therapeutic" research is a notable feature of versions of the Helsinki Declaration of the World Medical Association, which sets out an ethical framework for the regulation of medical research involving human subjects, from the original 1964 version of the declaration, up to and including the 1989 revision. The 1989 version of the declaration refers to a "fundamental" distinction between

medical research, in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.<sup>1</sup>

Some searching questions could be asked about the therapeutic–non-therapeutic distinction drawn here. We might for example question the

assumptions apparently embodied in this statement concerning the relationship between diagnostic procedures and research. Are we to consider all diagnostic procedures to be forms of research (despite the fact that, standardly, diagnosis applies, but does not yield, generalizable knowledge)? No doubt the case for such a view could be argued. But if it were ever to become a generally accepted view, the implications for clinical practice would be radical—since clinical diagnostic procedures would then fall under the particularly stringent ethical frameworks developed for research.

We could also question the particularist emphasis in the above quotation, suggested by the phrase “diagnostic or therapeutic *for a patient*” (my emphasis). Are we to take it that therapeutic research necessarily, or even typically, has as its essential aim the production of direct therapeutic benefit for particular patients? And if so, how is this to be squared with the more familiar view that the essential aim of research is the generation of *generalizable* knowledge?

Notwithstanding the above worries, the distinction between therapeutic and non-therapeutic research has attained considerable currency. Most introductory medical ethics textbooks, if they deal with research ethics at all, will at least mention the distinction, which is typically explicated with reference to the intentions of the researcher.<sup>2</sup> This approach is given canonical form in Ian Kennedy and Andrew Grubb’s *Principles of Medical Law*, where therapeutic research is said to be characterized by a “dual intention” on the part of the researcher.<sup>3</sup> In therapeutic research there is an intention on the part of the researcher “both to seek to benefit the patient who is the research subject, and to gather data of a generalizable nature.” In non-therapeutic research, by contrast, there is “only a single intention: to gather data.”<sup>4</sup>

This reference to the researcher’s intentions does not seem an altogether happy one, in that it seems to involve an implicit appeal to what we might call a “reasonable researcher” standard, which would be much better made explicit. In order to rule out examples of irresponsible experimentation, based on unreasonable expectations of therapeutic benefit, from qualifying as therapeutic research, the Kennedy and Grubb characterization of therapeutic research would be better reformulated as “research intended to produce generalizable data, and to benefit the patient/subject of the research, *where the relevant research procedure could reasonably be expected to deliver such a result.*”

Reformulated in this way, however, the Kennedy and Grubb interpretation suggests that there exists a distinctive form of medical research in which the twin goals of delivering therapeutic benefits to patients/subjects, and of generating generalizable data, are intrinsically linked. In this chapter, my central focus will be the concept of therapeutic research, understood in this way. I will argue that, when it is so understood, the term “therapeutic research” is a misnomer. No ethically conducted program of medical research can construct the sort of essential link between the therapeutic goal and the

scientific goal, which the above characterization implies. After considering and dismissing two different broad types of research which might (erroneously, in my view) be termed "therapeutic," I will close with some thoughts on why the point is an important one, and on what would be a more appropriate label for so-called therapeutic research.

### 3. Controlled Trials

To begin however, let us consider some salient features of the general ethical context within which biomedical research is pursued. The principle that a doctor is obliged to treat her patients according to the best proven diagnostic or therapeutic method is a well-established principle of biomedical ethics.<sup>5</sup> This principle is for example enshrined in successive versions of the Helsinki Declaration.<sup>6</sup> And yet there is an evident tension between adherence to *this* principle, and the involvement of *patients* in any form of medical research.

Unless the research in which the patient is involved bears no relation to her condition at all (in which case, for all but the most trivial complaints, their involvement as research subjects is questionable in itself), the patient/subject will be likely to be the recipient of an unproven treatment. Where this treatment is given as an alternative to the established best standard treatment for the condition the patient clearly does not receive the best *proven* treatment for his/her condition, for the simple reason that both the efficacy of the treatment in question, and the severity of any associated risks, are not yet proven. In a case in which the treatment given is in addition to the established standard treatment the patient/subject may well receive the benefits of both treatments. But she will also be exposed to the risks associated with both. These may well be compounded, and in the case of the non-standard treatment will be, again, unproven.

This tension between the principle that patients are entitled to the best proven treatment for their condition, and the involvement of patients in research, is implicitly acknowledged in the 2000 version of the Helsinki Declaration, which requires that when research is combined with clinical care, patients/subjects should be assured of the best proven treatment at the *conclusion* of the study.<sup>7</sup> Of course, the requirement that patients are given access to the best proven treatment at the conclusion of a study does not necessarily preclude their having access to that same treatment at an earlier stage. But in many research contexts, and most clearly in controlled clinical trials, some patients at least will not receive the best *proven* treatment during the course of the study (namely, those receiving the experimental treatment); nor will all patients necessarily receive the best proven treatment at the conclusion of the study—for example if their treatment regime remains

unchanged, and the new "best proven" treatment is the former experimental treatment.

In order to evade some of the ethical difficulties associated with administering unproven treatments to patients in research contexts, it is standard, in research, to apply a negative version of the principle that patients should receive the best proven treatment: no patient should receive a known inferior treatment.<sup>8</sup> So in a controlled clinical trial, whether randomized or not, and whether placebo-controlled or not, the researcher proceeds ethically if and only if she remains in a state of *equipoise* between the different arms of the trial.<sup>9</sup> From the point at which it becomes clear that one of the arms of the trial is receiving markedly inferior treatment it is unethical to continue with the trial.<sup>10</sup>

It is an interesting question whether this entails that it is unethical to demand very rigorous standards of proof in controlled trials. It may well be clear to the researcher that one or other arm of the trial has a therapeutic advantage some time before fully statistically significant results have emerged. But at the point at which the researcher can reasonably be said to "know" that one arm of the trial is subject to a therapeutic disadvantage it seems unethical, by the above principle, to continue with the trial, regardless of whether fully conclusive results have yet been obtained.<sup>11</sup> For our purposes however, the more relevant implication of the principle of *equipoise* is that there can be no reasonable expectation of therapeutic advantage to a patient from being entered into an ethically conducted controlled trial. In an ethically conducted placebo-controlled trial there can be no good reason to think that the active treatment is superior to the placebo. If there is good reason to think the active treatment is superior then the trial is unethical, since *equipoise* is lacking; and if there is no good reason to think that the active treatment is therapeutically superior (or inferior) to the placebo, there is no good reason to think that there will be any therapeutic advantage whatever to the patient from being entered into the trial. Whatever the researcher's intentions may or may not be then, ethically conducted placebo-controlled trials cannot reasonably be characterized as "therapeutic" research, since no reasonable researcher could expect any therapeutic advantage to accrue to the patient from being entered into the trial.

Suppose however that the trial is not placebo-controlled, and the control is the established standard treatment. In this case adhering to the principle of *equipoise* requires that there should be no good reason to think, either prior to or during the trial, that the standard treatment is either superior to or inferior to the treatment(s) under test. From the point at which it is established that either the new treatment or the control is markedly superior it becomes unethical to continue the trial. Again then, in an ethically conducted trial, there can be no reasonable expectation of therapeutic advantage to the patient from being entered into the trial—assuming that the alternative for the patient is that of receiving the standard treatment.

So much then for the idea that controlled clinical trials represent a form of essentially therapeutic research. There can be no reasonable expectation of therapeutic advantage from being entered into such a trial; and no reasonable researcher, advising a potential research subject on whether to participate in an ethically conducted controlled trial, is in a position to claim that therapeutic considerations have any bearing on the patient/subject's decision. From the point of view of the patient/subject the only relevant question is whether she wishes to contribute to the furtherance of the scientific goal, with the inconvenience and risks this may entail.

#### 4. Innovative Treatments

I want now to consider those forms of research which can reasonably be termed "innovative" or "experimental" treatments, that is, forms of biomedical research involving patient/subjects which either involve no comparison with a formal control, but only informal comparison with existing treatments, or no "comparison" at all, where there is no established treatment for the patient's condition. It turns out that these types of case also fail to merit the "therapeutic research" label, though for different reasons.

I have said that so-called therapeutic research is standardly characterized with reference to the dual therapeutic and research goals of the researcher. In turning to consider innovative treatments, it is reasonable to ask about the relationship between these two goals; and in particular whether they are ever essentially linked, such that the therapeutic goal is fulfilled by a process that simultaneously and necessarily involves the fulfilment of the research goal. (To clarify: if it were to be decided, as mentioned earlier, that diagnosis constitutes a form of research, this would qualify as a case in which the research goal and the therapeutic goal were essentially linked.) Raanan Gillon suggests that research and therapy are never linked in such a way when he remarks:

so-called therapeutic research always has two components: a component of pure research intended to produce generalizable medical knowledge, and a component of therapy, where the intention is to benefit the particular patient.<sup>12</sup>

This way of putting the point suggests that the "therapeutic research" label might be seriously misleading: there is in fact no distinct type of research which is inherently therapeutic, as the "therapeutic research" label suggests. Rather, therapeutic and research goals can sometimes be achieved through what is, essentially, one and the same process—though it is a contingent matter that this ever happens in practice. To appreciate the full significance of this

point, we need to step outside the narrow perspective of the researcher, which has, up to this point, been our preferred mode of access to "therapeutic" research, and consider the decision whether to participate in research paying close attention to the interests of the potential research participant.

Suppose we are dealing with an innovative/experimental treatment, in a case in which there is no established treatment for a patient's condition. The new treatment will have been subject to extensive laboratory-based testing prior to being available for use in a clinical context, and from this testing a reasonably clear picture of the likely risks and benefits of the treatment will have emerged. The decision to utilize this new treatment in a given case will, from the researcher's standpoint, have two motives: the motive of producing therapeutic benefit, and the motive of procuring generalizable knowledge. However, a consideration of the interests of the individual patient suggests that it is only the aim of producing therapeutic benefit that is relevant when deciding whether to consent to the new treatment. If, on balance, and bearing in mind the relative paucity of evidence, there seems to be a reasonable likelihood of therapeutic benefit to a given patient, then we may judge that the experimental treatment is clinically indicated in her case.

What kind of net benefit we need look for, and how much likelihood of producing it is required, will depend upon a host of other factors, not least amongst which are the severity of the patient's condition, and the severity of anticipated side effects. The associated question of how much risk-taking on the part of the doctor and the patient respectively is permissible, or required, is also relevant here. One area in which the label "therapeutic research" might be thought to have important application is in relation to experimental treatments for AIDS and related conditions. Controversy in these sorts of cases has tended to cluster around the issue of access to experimental treatments, and the rights of sufferers, particularly terminally ill sufferers, to expose themselves to potentially very high risks. In particular, the issue has been medical paternalism, and whether the medical profession has the right to prevent patients who wish to take risks from doing so. Nothing I say here should be taken to imply that patients should not be allowed to expose themselves to risks as research subjects. Rather, my concern is whether there is a branch of research with respect to which participation *qua* research subject can reasonably be expected to confer therapeutic benefit.

A patient considering an experimental treatment, where there is no established standard treatment, will certainly be hoping for therapeutic benefit. But the patient's motives are not the most important thing here. Even in the more common case of a placebo-controlled trial the patient will no doubt be hoping to have been included in the active arm of the trial, and will be hoping that the active treatment is therapeutically effective. Nevertheless, from the research ethics standpoint, the important question in such a case is whether we have something approaching proof that the treatment under test is likely to be

therapeutically beneficial. If we have, then the trial is unethical—since the placebo arm will then be receiving a known inferior treatment. If there is no good reason to expect therapeutic benefit from the treatment under test the trial is ethical, but the patient's hope is (so far as we know) a mere hope. Similarly, in the innovative treatment case, it is not the patient's hopes but the researcher's reasonable expectations which are of prime importance.

However, because in the case of innovative/experimental treatment we are not dealing with a formal trial, in which one or other arm of the trial stands to be therapeutically disadvantaged, the decision to administer the treatment comes down to this: is this particular innovative treatment clinically indicated? The answer to this question will either be "Yes" or "No"; and only if there is reasonable expectation of therapeutic benefit to the patient will the answer be "Yes." In this latter case then, unlike those of non-therapeutic research, and controlled trials, there may be a reasonable expectation of therapeutic advantage to the patient. Indeed the ethical acceptability of the treatment regime *qua* treatment regime will hinge on this. But despite the fact that, in this type of case, the patient in question may be said to have an interest in receiving the innovative treatment, and despite the hope shared by all concerned that the innovative treatment will turn out to be effective against her condition, she cannot be said to have an interest in serving as a research subject that is in any way parallel to that in which she has an interest in receiving the innovative treatment. It may well be that it is in our patient's interests that the research be carried out. But it does not follow that she has an interest in serving as a research subject, exposing herself to the associated inconveniences, and risks. We can certainly talk of patients benefiting from research through an improved understanding of their condition, and potential treatments. But from the fact that we can say with confidence that an improved understanding of my condition will result from my participation as a research subject, *it does not follow that this benefit to me accrues to me conditionally upon my participation in the research.* Any benefit to me that accrues from a given study accrues on the condition that the study is carried out, not on the condition that I participate in it. (And my participation in the study is not, except possibly in highly unusual circumstances, a condition for the study to be carried out.) From the fact that I will benefit from the study then, it does *not*, in general, follow that it is in my interests to participate—for the benefit to me will accrue whether I participate or not.

This is not to suggest that the patient cannot share the researcher's dual goal of the production of therapeutic benefit and the furtherance of biomedical knowledge. The point is simply that only one of these intentions is relevant when considering a given patient's receipt of an innovative treatment, under the heading of "therapeutic research." That the innovative treatment is clinically indicated is both a necessary and a sufficient ethical precondition for administering it in a given case. That administering the innovative treatment



will also contribute to the acquisition of generalizable knowledge is neither a necessary nor a sufficient ethical precondition for administering it in a given case. (Not necessary because a patient should not be denied access to a clinically indicated treatment just because administering the treatment in this case would be valueless in research terms; not sufficient because while knowledge might be gained even where the treatment is not clinically indicated, it would be wrong to administer the treatment where there was no expectation of therapeutic benefit—bear in mind that we are dealing here with patients, not with healthy volunteers).

So although the innovative/experimental treatment case does look to be one in which it is possible to proceed ethically while fulfilling the dual goal which we have seen is characteristic of so-called therapeutic research, closer inspection reveals that the question whether the innovative treatment is clinically indicated is the only one that really matters in a given case. So, as Jonathan Montgomery points out, the decision whether to proceed with an innovative treatment is best viewed as a matter of clinical ethics, rather than of research ethics.<sup>13</sup> There is no essential link between fulfilling the research intention and acting in the interests of a particular patient.

To return to Gillon's characterization of therapeutic research then, everything, I have suggested, hinges on quite how the two components he distinguishes are taken to be related. If they are understood to be essentially linked, such that, so far as we know, subjects could not receive such and such a therapeutic benefit without participating in a study designed to produce generalizable knowledge, then the established idea of therapeutic research would retain some validity. However, none of the forms of research we have considered manage to forge an essential link between participation as a research subject and anticipated therapeutic benefit. In the case of an ethically conducted controlled trial, considerations of therapeutic advantage do not enter in. In the case of innovative/experimental treatment, with no formal control, the therapeutic intention is the only relevant intention when we are considering whether it is in the interests of a given patient to participate. In both types of case it looks as if the two components, of therapy, and of the generation of generalizable knowledge, are only accidentally related.

The final type of case I want to consider is that in which participation in research is a precondition for receiving treatment—patients are effectively denied treatment unless they participate. Here, it seems to me, the patient's situation is in certain respects similar to that of the subjects of an innovative treatment. The decision whether to participate, where made with the patient's interests at heart, must rest exclusively on the potential therapeutic benefit—any anticipated research payoff is not to enter into the calculation, since this cannot be legitimately cited as a reason why *this* patient should participate in *this* study. Where the two cases do differ markedly, of course, is in the element of effective coercion. While we have no reason to think that innova-

tive/experimental treatments are, in general, ethically suspect, the effective coercion of research subjects *is* ethically unacceptable. It follows that this sort of case cannot be cited as an example of the existence of a form of ethically acceptable research properly characterized as "therapeutic." On the basis of the above examples then, we may conclude that the idea that there is a specific form of research in which the pursuit of the research goal and that of the therapeutic goal go hand in hand is an illusion.

### 5. Some Implications of the Above, and a Suggestion

The above considerations suggest that the "therapeutic research" label is a misleading misnomer. Why, particularly, does this matter? The upshot of the points I have been considering is that participation *qua research subject* is always fundamentally an altruistic act. This is of particular relevance to research with vulnerable groups. When considering non-therapeutic research with competent non-vulnerable adults we accept that, because participation as a subject is a significantly altruistic act, their consent is essential. Participants are inconvenienced, and may be exposed to significant risks, for no benefit to themselves. For these reasons we are normally hesitant about asking members of vulnerable groups to participate in non-therapeutic research. The potential for exploitation when working with such groups is increased, not least because it may be difficult or even impossible to obtain informed consent from them. In the case of therapeutic research on the other hand, it may be tempting to follow the route which is standard in clinical ethics and, where informed consent is unobtainable, allow ourselves to be guided by the patient's best interests, rather than by their choices. As long as we hold to the worryingly widespread myth that participation in "therapeutic" research is beneficial to the subjects of that research then, we may think we see a way open to relaxing consent requirements for so-called therapeutic research with vulnerable groups. Indeed, this is precisely what we find in current guidance on research with children. Non-therapeutic research on children is currently discouraged, unless the research in question would be virtually risk-free. The Medical Research Council, for example, suggests that only negligible-risk, non-therapeutic studies involving children are acceptable.<sup>14</sup> The reason for this, as Jonathan Montgomery reminds us, is that "in non-therapeutic studies there is no obvious benefit to be gained and it can be suggested that children are being put at risk for no possible gain."<sup>15</sup>

When we turn to the guidance concerning "therapeutic" research however, we find that here "higher risks may be acceptable," since in this case "it is hoped the child will benefit."<sup>16</sup> (Indeed it seems that legally it may be permissible to proceed with "therapeutic" research against the express wishes of the child concerned, provided the parents' consent has been obtained.<sup>17</sup>) On

this basis it is held that where valid parental consent is indeed forthcoming, "it is easy to justify [children's] involvement in therapeutic studies".<sup>18</sup> As I have argued at length above however, participation in so-called therapeutic research cannot reasonably be held to carry any benefits for research participants. If I am right, we should not be prepared to relax consent requirements for therapeutic research involving children in any such way. Proceeding with more than minimal-risk research with children, will, even given parental consent, be no more acceptable in the "therapeutic" case than in the "non-therapeutic" case. Moreover, since participants in so-called therapeutic research will necessarily be patients, and since patients as such can reasonably be said to represent a vulnerable group, there may well be grounds for imposing more stringent consent requirements for *all* such research.

If research involving patients is not to be termed "therapeutic," what should we call it? My suggestion would be: "Medical research combined with medical care." This is the formula employed in the 2000 version of the Helsinki Declaration, and it has the merit of explicitly directing our attention to the fact that the subjects of such research are simultaneously subjects of medical care. Instead of being a case in which it is appropriate to relax the stringent ethical safeguards governing medical research, and fall back on the standard clinical framework, which permits a good deal of risk-taking, based on an estimation of the patient's interests, this formula suggests that, *prima facie* at least, the "therapeutic" research context is one in which the requirements of *both* clinical and research ethics frameworks apply. The declaration does not speak of a relaxing of consent requirements when medical research is combined with medical care, but on the contrary counsels: "when medical research is combined with medical care, *additional standards* apply to protect the patients who are research subjects [my emphasis]."<sup>19</sup>

#### NOTES

1. WMA Declaration of Helsinki (1989), quoted in British Medical Association, *Medical Ethics Today: Its Theory and Practice* (London: BMA publishing, 1993), p. 198.

2. Alastair Campbell, Grant Gillett, and Gareth Jones, *Medical Ethics* (Oxford: Oxford University Press, 1997), pp. 171–172.

3. Ian Kennedy and Andrew Grubb, *Principles of Medical Law* (Oxford: Oxford University Press, 1998), p. 716.

4. *Ibid.*

5. Sophie Botros, "Equipoise, Consent, and the Ethics of Randomised Clinical Trials," *Ethics and Law in Health Care and Research*, ed. Peter Byrne (London: John Wiley and Sons, 1990), p. 9.

6. World Medical Association, Declaration of Helsinki (1989), para. II.3, <http://www.augsburg.edu/irb/helsinki.html>; World Medical Association, Declaration of Helsinki (2000), para. 30, <http://www.wma.net/e/policy/b3.htm>.

7. *Ibid.*
8. Botros, "Equipoise, Consent, and the Ethics of Randomised Clinical Trials," p. 18.
9. Baruch A. Brody, *The Ethics of Biomedical Research: An International Perspective* (Oxford: Oxford University Press, 1998), ch. 7.
10. See Ian Kennedy, "The Law and Ethics of Informed Consent and Randomized Controlled Trials," Ian Kennedy, *Treat Me Right* (Oxford: Clarendon, 1991).
11. *Ibid.*, p. 219.
12. Raanan Gillon, "'Fully' Informed Consent, Clinical Trials, and the Boundaries of Therapeutic Discretion," *Informed Consent in Medical Research*, eds. Len Doyal and Geoffrey Tobias (London: BMJ Books, 2001), p. 263.
13. Jonathan Montgomery, "Informed Consent and Clinical Research with Children," *Informed Consent in Medical Research*, eds. Doyal and Tobias, p. 174.
14. Medical Research Council, *Issues in Research with Children* (London: MRC, 1991).
15. Jonathan Montgomery, "Informed Consent and Clinical Research with Children," p. 179.
16. *Ibid.*, p. 173.
17. *Ibid.*, p. 177.
18. *Ibid.*, p. 179.
19. Declaration of Helsinki, para. 28.