Controlled Medical Research or Routine Medical Procedure?

The Ethics and Politics of Drawing a Line

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1. Introduction

The aim of this paper is to formulate, illustrate and briefly discuss ethical issues actualised by the move of new medical technologies from the context of controlled medical research to the routine clinical use on patients. This area of the role of medical science and technology in society has not been given much attention in research ethics or ordinary medical ethics.(1) The main reason for this seems to be that ethical issues in this area fall somewhere between the traditional ethics of medical research and ethical issues actuali sed in the daily practice of clinical medicine. Another reason is that, until rather recently, no deep controversies has arisen regarding this issue. On the contrary, most medical scientists, physicians and political decision makers have been rather content with the way in which the step from medical research to clinical medicine is usually taken.

I will start by briefly describing the context in which this issue arises, and formulate two ethical queries: one regarding basic medical ethics and one concerning what policies to use in order to handle the basic ethical issue in society. For reasons to be explained, I will mainly concentrate on the latter query. After having described the standard solution to the policy issue, I will give an example of the introduction of a new medical technology in my own country, Sweden, which illustrates several serious flaws in the standard solution. From this background, I will then discuss three alternative models for how society should deal with the move of medical technologies from the area of research to routine health care. Of these, I will argue that what I will call the Bureaucratic Model is to be preferred. Finally, I will make some closing remarks of what I take to be important ingredients in a plausible answer to the more basic ethical issue.

2. Three Received Opinions in Medicine

The area for ethical inquiry to be examined in this paper is best explained from the basis of three views which seem to be more or less received opinions in the medical community (in which I include physicians, nurses and other assisting personnel, as well as medical scientists and laboratory workers and societal policy makers concerned with health care issues). These opinions are the following:

Beneficence, Safety and Reliability is Required in Routine Health Care

Medical procedures should not be used in routine health care unless it has been established (by scientific testing or long clinical experience) that their benefits (for the patients) sufficiently balance their risks in a reliable way. An exception to this general rule is cases of extreme and desperate emergency, where the patients life is severely endangered unless successfully treated within a short period of time and all standard ways of treat ment have already been tried and failed.

Clinical Medical Research is Acceptable

New medical procedures which do not (yet) meet the requirement of beneficence, safety and reliability may be tested on patients in order to find out whether or not they meet this requirement. Such testing must, of course, conform to standard scientific methodological requirements.

Extra Caution is Required in Clinical Medical Research

Any clinical medical research project must meet the following requirements:

1) The project has been scrutinised and approved of by an ethics com mit tee for medical research.
2) The project has sufficient chances of leading up to the introduction of a new medical procedure in routine health care.
3) Only patients who have significant chances of benefiting from the procedure to be tested are admitted into the project.
4) Patients are admitted into the project only after they have gone through procedures which to a sufficient degree guarantee their well-informed consent to participate.

Of course, also the daily doings in routine health care have their ethical standards to conform to. However, apart from the fact that research may apply procedures not fit for routine clinical use, these standards are usually not as strict as the ones required in clinical medical research. The latter are more restricting on which patients that are

admitted, and tougher regarding the need for obtaining informed consent. Moreover, the ethical monitoring is done beforehand, while, in routine health care, examination of ethical liabilities is possible only in retrospect (should someone file a complaint). The requirement of extra caution in clinical medical research, of course, is motivated by the fact that it is not known with sufficient certainty whether procedures tested in such research will in fact do any good for patients.

3. Two Ethical Issues ? One Standard Solution

So, although both clinical medical research and clinical routine health care have their respective ethical standards to conform to, these standards are more cautious in the former area. This actualises the question of how the move of new medical procedures from the area of medical research to routine health care should be handled. This question may be separated into two distinct issues:

The Basic Ethical Issue

What determines whether or not a medical procedure meets the requirement of beneficence, safety and reliability? Or, formulated in a slightly dif ferent way: What determines whether or not extra caution is required in the clinical application of a medical procedure?

The Political Issue

How should it be decided whether or not a medical procedure meets the requirement of beneficence, safety and reliability? Or, formulated in a slightly different way: How should it be decided whether or not extra caution is required in the clinical application of a medical procedure?

To be true, any complete answer to the political issue must be informed by some answer to the basic ethical issue. This will concern the question of what considerations that should be taken into account, and how these should be taken into account, when making societal decisions regarding the move of medical procedures from research to routine health care. Besides that, however, there is also a question of how such societal decision making should be administrated and organised (in contrast to the proper content of such decision making, regardless of how it is administrated and organised). In the following, I will mainly address this issue of administration and organisation, and restrict myself to some brief comment on the more basic ethical issue in the closing of this paper.

Most countries have adopted more or less the same solution to the problem of organisation and administration of the kind of decisions under consideration ?

namely, a system of approval through expert review. This standard solution (as I will call it) says that medical procedures are ap pro ved of as appropriate for use in routine health care when (and only when) the national experts on the procedure in question think so.

The standard solution has been applied for a long time and seems to work fairly well in many cases. Moreover, this solution has the political gain of saving policy makers from having to consider the basic ethical issue formulated above. Instead, the move of medical procedures from the area of research and into routine health care is handled in a purely procedural way where all decisional authority is left to those medical specialists that are appointed national experts. Of course, a presupposition of this system is that the national experts are expected to make their judgement from a purely medical and scientific point of view and according to acceptable standards of safety.

However, the standard solution has several serious drawbacks. I will illustrate these by a real case of introducing a new medical procedure from my own country, Sweden.

4. The Swedish Introduction of Preimplantation Genetic Diagnosis

Preimplantation Genetic Diagnosis (PGD) is the latest among methods for prenatal diagnosis that facilitates the selection of human offspring on genetic grounds. PGD is performed on early embryos that have been produced by in vitro fertilisation (”test-tube embryos”) before some of these are transferred into a woman’s uterus in order to achieve a pregnancy. PGD hence facilitates the preselection on genetic grounds of which of several available embryos that shall be given the chance of developing into a fetus and, eventually, a child. Unlike conventional prenatal diagnosis, PGD hence facilitates the preselection of future children on genetic grounds without any need for considering the possibility of an abortion.(2)

PGD was developed during the second half of the 1980’s, and was first clinically applied in 1989-90 by British specialists at the Hammersmith Hospital in London.(3) A few years later, Swedish specialists at the Sahlgrenska University Hospital in Göteborg were keen on applying PGD on certain patients.

Parallel to this development, the Swedish authorities had noted the emergence of PGD, and passed the question of whether or not to approve of this procedure on to various medical ethics bodies, in particular the National Council for Medical Ethics ("Statens medicinsk-etiska råd" in Swedish). In the period of 1989-92, the various

medical ethics bodies all gave the same recommendation: PGD should be approved of only as a case of clinical medical research. Thus, if the Swedish specialists wanted to use PGD on patients they would have to organise a research project that would have to meet the requirement of extra caution.(4)

At the same time, the authorities and the specialists also noted that it was unclear whether such use of PGD would actually be legal. According to the Swedish Embryo Research Act (adopted in 1991), it is absolutely prohibited to transfer into a woman's uterus embryos that have been subjected to "research or experimentation".(5) Apparently, if PGD was to be clinically applied in a research setting, this would mean that experiments were performed on embryos followed by a transfer of some of these embryos into a woman's uterus.

This tricky situation was resolved in 1992, when the Swedish specialists, after review of internationally published data, proclaimed PGD to have been established as clinical routine abroad. All they wanted to do was to "import" this routine procedure, which they had learnt to master through extensive education and training. Since these specialists were at the same time the only available national experts on PGD, this meant that, in line with the standard solution, PGD thereby also was appropriate for use in routine health care, no matter what was claimed by various medical ethics bodies. Thus, PGD could be applied to patients without having to meet the requirement of extra caution. Moreover, the ban on transferring into a woman's uterus embryos that have been subjected to "research or experiments" was not applicable, since the use of routine procedures is not a case of research, nor experimental in any other ordinary sense of the word.

This "real-life" case of the introduction of a new medical procedure illuminate several serious flaws of the standard solution.

First, it points to the risk of biased expert opinions. Regarding many new and advanced medical procedures, the risk is obvious that the available national experts will be identical to the specialists who want to use the new procedure. This, of course, opens for conflicts of interests.

It is a fact that in 1992, when the Swedish experts declared PGD to have been internationally established as a routine procedure, the international expertise in this field agreed that PGD is a case of clinical research where extra caution is appropriate. In fact, the international expertise still held this view as late as 1995!(6) Of course, as appointed national experts, the Swedish specialists were free to make their own judgement from international data regarding PGD. However, it is hard not

to find it rather odd that this judgement was not at all influenced by a compact international consensus that PGD is not a routine procedure.

This actualises the suspicion that the judgement of the Swedish experts was in fact influenced by considerations that may conflict with society's interest in unbiased expert assessments. It is, of course, quite possible that they themselves were not aware of any such influence. However, it is clear that the Swedish specialists had a strong interest in getting permission to use PGD on patients. First and foremost, they believed that PGD could be of great benefit to some patients. Secondly, being first in Sweden (and in Scandinavia) to clinically apply PGD would involve a certain status in the Swedish (and Scandinavian) medical community. Third, being first in this way would also mean a head start on other clinics to become the main national centre for PGD and other forthcoming procedures in this field.

A second flaw of the standard solution illuminated by the case of Swedish PGD is that it threatens to undermine legislations, such as the Swedish Embryo Research Act, thought to safeguard against the legal application of germ-line genetic modifications of human beings. The introduction of PGD could be used as a precedential case by specialists wanting to implement procedures for germ-line gene therapy. Such specialists may proclaim such procedures to have been established as clinical routine abroad and claim that if this prevented PGD from falling under the Embryo Research Act, the same should hold for other procedures as well. This aspect is relevant also in an international perspective, since the legislation thought to rule out legally performed germ-line gene therapy in many countries is constructed as a ban on certain kind of embryo experimentation or research, not clinical application of established routine procedures.(7)

This leads to the third flaw, which concern society's general interest in controlling the introduction of new biotechnological procedures in health care. Obviously, the possibility of such control is undermined if decisional authority is handed over to a handful of specialists who often have strong personal interests in using new procedures.

5. Three Alternative Models

The flaws of the standard solution leads to the query whether there are any better models available for society's regulation of the move of medical procedures from research to clinical routine. In this section, I will briefly review three alternative proposals, all of which are examples of a "no, unless-approach",(8) i.e. the idea that new and risky medical procedures in certain well-specified fields are not allowed for

use in routine health care, unless a special permission has been issued.

The Political Model

According to this proposal, decisions regarding the move of medical procedures from research to clinical routine should be explicitly politicised. The simplest variant of this model is that such decisions are taken by the national government or parliament.

The main gain of this model is that society is in control. Also, it reduces the need for vague, rigid and in other ways problematic legal bans, such as the Swedish Embryo Research Act. At the same time, however, the model has several drawbacks.

First, the political process is often very slow. To be true, one interest of society is to slow down the pace of new medical procedures being introduced for routine use. However, it is also important that it is not slowed down too much, since that may seriously harm patients who could benefit very much from the use of a new procedure.

Secondly, the political process is also rather unpredictable. If decisions are taken, for example, by the parliament, it will be hard for medical specialists, potential patients and even for the policy makers themselves to know how a certain proposal regarding some medical procedure will be handled and what the outcome may be. This is bad for several reasons. One is that no real policy will result and decisions may appear arbitrary. Another is that medical specialists and potential patients will get no real guidance regarding how to plan their activities and lives. Specialists need to know what kind of information is needed in order to have a chance of getting an approval, and potential patients need to know whether or not there is any point in expecting a possible approval for some new procedure.

Third, and perhaps most important, the outcome of a political process may to a large extent be determined by factors that do not seem relevant for the question of whether or not some medical procedure should be approved of for routine use. In politics, tactical considerations of various kinds often play an important role for the proceedings of some process of decision. Imagine, for example, that the question of whether or not to approve of some new medical procedure was to be entangled with the question of which political party is most suited to be in power (before an upcoming election), or become one of many issues open for "trading" in negotiations aimed at the formation of a government (after an election). It is a rather disturbing thought that decisions as serious as the ones under consideration should be that vulnerable to political tactics and power-play.

The Quasi-legal Model

Instead of leaving decisions regarding the move of medical procedures from research to clinical routine to the politicians, this proposal instead advocates that such issues be decided by an ethics committee of some form. The decision making of such a committee will not work in the same way as that of a government or a parliament, since it will not be involved in political tactics. Of course, the government or parliament will have to lay down guidelines for such a committee, for example, regarding the appointment of members and what it should take into account when making decisions. However, such a committee will still function more like a court of law (hence my choice of name for this model), making its rulings according to predetermined standards after careful considerations, than a political assembly. It seems, then, that this model could avoid many of the flaws of the political model, while retaining the gains of having society in control and making questionable legal bans unnecessary.

However, this model still has some important undesirable features.

First, it is by no means certain that the decision making of an ethics committee will not be vulnerable to political tactics. The form of the ethics committee is best suited for seminar-like discussions, not aimed at reaching political decisions, but rather to explore issues by open minded discussion as a means for deeper understanding and communication of ideas. When transformed into a decisional authority the committee will not easily be able to uphold this function, since it will be subjected to public scrutiny and different forms of political pressures.(9)

Secondly, as exemplified by the case of PGD in Sweden, ethics committees are very open to manipulation, since they have to rely completely on outside expertise. The whole idea of an ethics committee is to have a small group of people representing different perspectives, interests and specialities, who perform their duties in the committee beside their regular activities. The members in such a group have very little chances of real critical scrutiny of the information provided by outside experts, and thus few opportunities to safeguarding against being manipulated by these experts. This problem is not very likely to arise as long as the ethics committee is confided to its traditional task of conducting open minded discussion. However, when such committees are transformed into policy making bodies, the problem will most probably emerge and be very hard to safeguard against. In short, the quasi-legal model is to weak to be an efficient guard of society's interests in controlling the move of medical procedures from research to clinical routine.

The Bureaucratic Model

The flaws of the quasi-legal model naturally leads to the suggestion that decision making regarding the move of medical procedures from research to routine should be handled by an administrative body that is strong enough to able to sufficiently resist politicisation and manipulation due to biased expert-opinions. These objectives can be achieved in the form of a bureaucratic unit with its own case-officers, capable of critical assessment of the information provided by experts, and a well defined "Code of practice" regarding what information is needed in order for a procedure to be considered for approval, as well as the considerations that should be taken into account when deciding whether or not to issue such an approval. The role model for this type of organisation is agencies for licensing of new drugs, such as the FDA in the United States or Läkemedelsverket in Sweden. In fact, one country has already implemented this model regarding the field of human embryology and assisted procreation, namely the United Kingdom, by its Human Fertilisation and Embryology Authority.

Of course, such a unit will still be politicised to some extent, since its "Code of practice" and the considerations relevant for its decision making will have to be laid down by the government or parliament. However, in its daily work, it will be free of direct political influence.(10) Moreover, a well-defined "Code of practice" will ensure that everyone will know whether or not there is any point in asking for approval of a given medical procedure, and what processes are needed to be gone through in order to reach the point where an application for approval is meaningful. Of course, the final decision will still be indeterminate. However, specialists and potential patients are still in a much better situation regarding the chances to predict the outcome, and to calculate the time it may take before a decision is made.

Furthermore, the bureaucratic model retains the gains of the previously discussed models. It leaves society in control of the move of medical procedures from research to clinical routine. It slows down the pace of this process without making it unacceptably slow. It removes the need for rigid and vague legislations, which can be exchanged for the simple ruling that new medical procedures in certain specified fields (for example, the fields of genetics and assisted procreation) may not be used in routine health care unless permission has been issued by the licensing authority. Concerns about certain forms of extremely risky procedures (such as germ-line gene therapy) may be met by writing into the statues of the agency that considerations regarding long-term risks should be accorded a large weight in its decision making.

I do not claim that the bureaucratic model will not have any problems. On the contrary, it will most certainly be affected by many of the problems known to arise in bureaucratic organisations. However, in my view, this model is far superior to all the

other models that have been suggested so far. Furthermore, the use of this model also has the further gain of making the introduction of new and risky health care procedures more coherent. For the fact is that this kind of model has already been in use in many countries for many years regarding the introduction of medical procedures involving new drugs in routine health care, and with good results at that. It is hard to see any good reason why other kinds of medical procedures should not be handled in a similar way.

6. Relevant Considerations for A Licensing Authority

I will now close this brief presentation by making some remarks on the basic ethical issue formulated in section 3 above. Against the background of my suggestion that the bureaucratic model is the best solution to the political issue of how society should organise and administrate the move of medical procedures from the area of research into routine health care, the basic ethical issue can also be formulated as the issue of which considerations that are relevant (and to what degree) in the decision making of a licensing authority for new and risky medical procedures. I will not go deeply into this complex issue, but merely make some pointers to three types of considerations that would presumably have to play an important role in this context.(11)

Beneficence for Patients

A first and almost self-evident consideration has to do with the degree to which a given medical procedure would be beneficial for potential patients. To what extent does the procedure cure, relieve or ease inconveniences for these patients, and how serious are these inconveniences? The more beneficial effects for patients that may be achieved through the use of the procedure, and the more likely such beneficial results are, the more reasons to approve of it for use in routine health care.

Safety for Patients

Another, equally self-evident, consideration regards the probability that the procedure will harm the patients rather than benefit them. How great is this probability, and how serious are the harms that could result? The more harmful effects for patients that may be effected through the use of the procedure, and the more likely such harmful effects are, the more reasons to reject it for use in routine health care

Both these considerations has to do with balancing of possible benefits and risks. But, how should these be balanced? This is the hard part of the discussion of the basic ethical issue. Without putting forward any argument, I claim that this balancing should be made from the point of view of those very people that would be directly affected by the decision to use or not to use the procedure ? i.e., the potential patients

themselves. From the point of view of the decision makers in the licensing authority, this seems to suggest two important restrictions:

> 1) Medical procedures should not be offered to patients unless it may be rational for these patients (in the light of their own aims and values) to accept this offer after having been fully and successfully informed about risks and possible benefits.
>
> 2) Medical procedures should not be offered to patients unless there is enough information available regarding benefits and risks of the procedure in question in order to guide a rational decision of a patient regarding whether or not to accept such an offer.(12)

Safety for Other Affected Parties

This consideration becomes relevant in light of the common reason for why germ-line gene therapy should be resisted. The argument in favour of this usually refers to the grave uncertainties and risks for future generations involved in irreversible and inheritable genetic changes of human beings. In order not to be an expression of mere conservatism, this consideration must, of course, also involve the aspect that *not* making such inheritable genetic changes may also severely harm future individuals, and that research on germ-line gene therapy may produce valuable knowledge regarding germ-line genetic changes not caused by such therapy (but by such things as exposure to radiation or toxic substances). However, how these aspects should be balanced is much too big an issue to be discussed in the present context.(13)

Notes

1) One notable exception is Jonsson, Lena, "Hur avgöra när ny metod kan godtas i kliniken? Ett forskningsetiskt och politiskt dilemma" (How should it be decided when a new method should be clinically applied? A research ethical and political dilemma), *Läkartidningen*, vol. 91, no. 19, 1994, pp. 1953-1956. Internationally the issue has been mentioned in Pergament, Eugene & Bonnicksen, Andrea 1994, "Preimplantation Genetics: A Case for Prospective Action", *American Journal of Medical Genetics*, vol. 52, 1994, pp. 151-157. However, the issue is not actually discussed in this paper, although it is identified as very important. [BACK]

2) For an accessible presentation of PGD and some of the ethical issues that are actualised by this procedure, see Handyside, Alan, "Preimplantation Diagnosis", in "Genetic Testing and Screening", *Encyclopedia of Bioethics*, revised edition, vol. 2, London 1995: Simon & Schuster and Prentice Hall International, pp. 985-986. For an accessible overview of the current state of PGD and further

references, see Handyside, Alan, "Preimplantation Genetic Diagnosis Today", *Human Reproduction*, vol. 11, supplement 1, 1996, pp. 139-151. [BACK]

3) Handyside, Kontagianni, Hardy & Winston, "Pregnancies from Biopsied Human Preimplantation Embryos Sexed by Y-Specific DNA Amplification", *Nature*, vol. 344, no. 6268, 1990, pp. 768-770; and Handyside, Pattinson, Penketh, Delhanty, Winston & Tuddenham, "Biopsy of Human Preimplantation Embryos and Sexing by DNA Amplification", *Lancet*, vol. 1, 1989, pp. 347-349. [BACK]

4) *Den gravida kvinnan och fostret - två individer* (White paper from a government committee regarding prenatal diagnosis and abortion), SOU 1989:51, Stockholm 1989: Allmänna förlaget. Läkaresällskapets etikdelegation, "Prenatal diagnostik - etiska aspekter" (Ethical guidelines on prenatal diagnosis by the Delegation for Ethical Issues of the Swedish Medical Society), *Läkartidningen*, vol. 90, 1993, no. 23, ss. 2232-2236. Medicinska forskningsrådet, *Ang. utnyttjande av preimplantatorisk diagnostik* (Report regarding PGD from the Swedish Council for Medical Research), skrivelse till Socialdepartementet, september 9, 1991, Socialdepartementet, Dnr. 492/91. *PM angående preimplantatorisk diagnostik* (Final report on PGD by the National Council for Medical Ethics), Statens medicinsk-etiska råd, October 10, 1992. [BACK]

5) *Lag om åtgärder i forsknings- eller behandlingssyfte med befruktade ägg från människa* (te Swedish Embryo Research Act), SFS 1991:115. [BACK]

6) See, for example, International Federation of Fertility Societies, *Consensus Statement on Assisted Procreation*, 1995. (available from the International Federation of Fertility Societies); Verlinsky, Yuri, "Preimplantation Genetic Diagnosis", *Journal of Assisted Reproduction and Genetics*, vol. 13, 1996, no. 2, pp. 87-89; and Verlinsky, Handyside, Grifo, Munnè, Cohen, Liebers, Levinson, Arnheim, Hughes, Delhanty, Harper, Mathews, Kuliev, Simpson, Monk, Strom, Findlay, Gore-Langton, Lansendorf, Braude, Muggleton-Harris, Lissens, Ginsberg, Jackson, Giltin, Fisher, Readhead, Wilton, De Sutter, Selva, Ray, Thornhill, Kontogianni & Johnson, "Preimplantation Diagnosis of Genetic and Chromosomal Disorders", *Journal of Assisted Reproduction and Genetics*, vol. 11, no. 5, 1994, pp. 236-243. [BACK]

7) Countries with such legislations include, for example, Belgium, Denmark, France, Ireland, Norway and the United Kingdom. See MacKellar, C (ed.), *Reproductive Medicine and Embryological Research. A European Handbook of Bioethical Legislation*, Edinburgh 1997: European Bioethical Research. [BACK]

8) I have borrowed this expression from Henk Verhoog. [BACK]

9) A nice example of this has been given by Henk Verhoog, "Ethical Committees between Science and Society", paper presented at the conference "Are there Ethical Limits to Scientific Research?", Neuchâtel, Switzerland, 9-11 October, 1997. [BACK]

10) In some countries, this need not be true. For example, in France, ministers of the national government may interfere directly in the routine work of government agencies. However, as far as

I can see, the statues for an agency of the kind I am describing may very well be written so that such possibilities are ruled out. [BACK]

11) In my forthcoming book, *Pure Selection. The Ethics of Preimplantation Genetic Diagnosis and Choosing Children Without Abortion*, this issue is penetrated rather thoroughly. [BACK]

12) Of course, what may be rational for patients to decide and what information is needed in order to guide such a rational decision must be set in relation to the specific needs of each particular patient. For example, for a person dying in AIDS, much higher risks may be rationally accepted in order to get an uncertain chance of being cured than in the case of, for example, a person who wants to undergo a new type of plastic surgery merely to satisfy his or her vanity. [BACK]

13) This paper has been written as part of the research project "Prenatal Diagnosis and Genetic Counselling: Survey and Analysis of Ethical Aspects", run by the Centre for Research Ethics in Göteborg in co-operation with the Department for Clinical Genetics at the Sahlgrenska University Hospital/East in Göteborg, and financed by the Swedish Research Council for the Humanities and Social Sciences. I would like to thank the organisers of the colloquium "Are there Ethical Limits to Scientific Research?", Neuchâtel, Switzerland, 9-11 October, 1997, for giving me the opportunity to present and discuss the ideas appearing in this paper, and the participants of this colloquium for much stimulating discussion. In particular, I would like to thank Agnieszka Lekka-Kowalik for making me aware of important differences between the quasi-legal and the bureaucratic model and Stellan Welin for helpful comments and suggestions on an earlier draft. [BACK]

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