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Regulation of Therapeutic Research is Compromising the Interests of Patients[1]

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Abstract

In this paper, I consider the impact of research regulation on the duty of doctors to help to resolve uncertainties about the effects of treatments; in particular, treatments already in use within 'normal' or 'usual' clinical practice. After providing examples of ways in which current research regulation is obstructing this professional duty, I consider the influence of "a confused ethical analysis", the double-standard in informed consent to treatment within and outside of controlled trials, and the failure of research regulators to use their powers to reduce unnecessary research and promote full publication of necessary research. I suggest that these problems should be addressed by more thoughtful ethical analyses, more effective protection of the interests of patients by research regulators and empirical research to inform the future development of research regulation. Because ethicists and research regulators have paid insufficient attention to these issues, I conclude that they have contributed to the avoidable suffering and deaths of millions of people, the vast majority of whom have *not* been participants in clinical research.

A recent European survey of procedures for reviewing protocols for clinical research documented widespread, constantly changing, differences in the way ethical review is being conducted in different countries.[1] These international differences in practice may sometimes be justified by variations in national laws and regulations, but such variations cannot explain differences in research regulation within countries.[2] As an editorial in the *BMJ* concluded, "It is time that a more concerted effort be made to assess the likelihood of benefits, harms, and costs of different approaches to ethics review for different types of evaluation".[3] In England, ethics review is only one element of research regulation. The Research Governance Framework was introduced following a politically motivated government enquiry into alleged research misconduct in Stoke on Trent.[4] Although the enquiry failed to uncover any evidence of research misconduct,[5,6] it fuelled expansion of research regulation, and a member of the enquiry team was appointed to establish and direct a Central Office for Research Ethics Committees.

Research ethics review does not have a particularly long history. Its development was stimulated in particular by the publication of an article in the *New England Journal of Medicine* by Henry Beecher,[7] an American anaesthesiologist, and a book entitled *Human Guinea Pigs: Experimentation on Man* written by a British doctor, Maurice Pappworth.[8] Beecher and Pappworth exposed various examples of ethical misconduct by researchers, for example, studies exploring disease mechanisms involving injection of live cancer cells, physiological studies involving invasive and risky procedures, and studies of 'natural history' involving the withholding of effective treatment. A feature of many of these studies was that the people studied had not been properly informed, and many of them were vulnerable in other ways. Quite properly, Beecher's and Pappworth's revelations caused a scandal, and led to the institutionalisation of research regulation that followed.

Research regulation has undoubtedly helped to curb the kind of abuses that Beecher and Pappworth exposed. However, it has introduced new problems resulting from the very wide variety of

1 This paper is based on issues addressed in the Joseph Hoet Memorial Lecture, delivered at a meeting of the European Forum for Good Clinical Practice, Brussels, Belgium on 30 January 2007; an account of the Joseph Hoet Lecture, as delivered, has been published in the Newsletter of the European Forum for Good Clinical Practice, Spring/Summer 2007, pages 3–5.

types of research now deemed in need of scrutiny.[9] These extend far beyond the kind of research highlighted by Beecher and Pappworth. Indeed, in some countries, regulation has extended beyond research into audit and quality improvement.[10] As a recent headline in the *New York Times* put it, "As ethics panels expand grip, no field is off limits".[11] These developments, taken together with the effects of the European Clinical Trials Directive, have resulted in daunting layers of bureaucracy facing anyone wishing to pursue any activity that might be designated as research.

In this paper, I wish to focus very specifically on the impact of these developments on a particular class of research: clinical research designed to reduce uncertainties about the effects of treatments already in use within 'normal' or 'usual' clinical practice.

1. What Are the Duties of Professionals When Faced with Uncertainties About the Effects of Treatments?

The UK General Medical Council recently published a new edition of *Good Medical Practice* – its principal guidance for doctors.[12] Among the many duties of doctors listed in the booklet, one in particular is relevant to the theme of this paper:

"You must work with colleagues and patients to maintain and improve the quality of your work and promote patient safety. In particular, you must ... help to resolve uncertainties about the effects of treatments." (Paragraph 14 f.)

This is an important duty because medical professionals have unwittingly – and with the best of intentions – harmed, and sometimes killed, their patients because they have not addressed uncertainties about the effects of the treatments they have been using.

The class of uncertainty I am considering here is not uncertainty resulting from a doctor's failure to access the best research evidence available, or to solicit a patient's preferences. Nor is it the type of inevitable uncertainty that accompanies any medical advice: will this treatment have the predicted effects in this patient? Rather it is the uncertainty that remains after all the relevant research evidence has been reviewed systematically.[13]

Innumerable examples could be used to illustrate the importance of addressing this last kind of uncertainty, but one will suffice to make the point. Consider recent research on the effects of systemic corticosteroids given to people with acute traumatic brain injury – a treatment that has been used for over three decades. In 1997, a systematic review of existing evidence revealed uncertainty about whether this treatment did more good than harm.[14] This uncertainty was reflected in variations in the extent to which systemic corticosteroids were used in everyday clinical practice. Because this uncertainty related to a problem of global significance, a proposal for a large, multinational, randomised trial to address the issue was submitted to the UK Medical Research Council (MRC). Recruitment to the trial was discontinued when it became clear in an interim analysis that the treatment increased the likelihood of death.[15] We now know that tens of thousands of patients died unnecessarily because uncertainties about the effects of systemic corticosteroids for traumatic brain injury were not confronted at the time the treatment began to be used in practice.

2. Current Research Regulation is Obstructing the Professional Duty to Help Resolve Uncertainties about the Effects of Treatments

Many years have passed since an editorial in *The Lancet* pointed out that "The clinician who is convinced that a certain treatment works will almost never find an ethicist in his path, whereas his colleague who wonders and doubts and wants to learn will stumble over piles of them".[16] Since then, there have been repeated reports of the bureaucratic impediments facing researchers who wish to address uncertainties about the effects of treatments (see examples in Salman et al.,[17] Slowther et al.[18] and Warlow[19]).

An article in *The Lancet* in 2003 entitled *Consent is not Enough: Putting Incompetent Patients First in Clinical Trials*[20] illustrates the need to consider the possible consequences of unevaluated research regulation. The authors asserted that clinical trials carry "serious risks" and that although "research participants might benefit from their involvement in trials, ... this potential benefit is not the express purpose [because] clinical trials are designed to discover whether a particular medical intervention is effective for a population of patients and can *never* [my emphasis] be primarily in a patient's best interests".

In response, I suggested that such requirements have probably helped to perpetuate ignorance about how to protect incompetent patients from the unintended adverse effects of inadequately assessed treatments. For example, such requirements might well account for the fact that, since 1958, there have been no clinical trials to assess the effects of antipsychotic drugs in people who are both psychotic and have learning disabilities. I suggested that the writers needed to explain how they thought their proposals would help to serve the interests of these incapacitated and often incompetent patients.[21]

In the multicentre CRASH (Corticosteroid Randomisation After Significant Head Injury) trial,[22] which investigated the treatment of semiconscious or unconscious patients with acute traumatic brain injury, some local research ethics committees

waived the need for consent while others required consent to be sought from relatives to administer a treatment that had been used for years in usual clinical practice without requiring relatives' consent. These requirements slowed recruitment to the trial and, thus, delayed in discovery that this widely used treatment is lethal.

Another recent example concerns the use of caffeine in newborn babies. Neonatologists have been using this treatment intermittently for 30 years because they thought caffeine made breathing more regular. However, its use was patchy because the prevention of intermittent brief apnoea (a surrogate outcome) was not regarded as important, and there was some concern that it might be harmful. Because of these uncertainties, the Canadian MRC funded a multinational trial to assess the effects of caffeine on more substantive outcomes. The trial took a year longer than expected because recruitment from centres in Europe was poorer than had been pledged. Recruitment in the UK was particularly poor, and regulatory delays caused several UK units to pull out of the study. Recruitment was further damaged because the UK multicentre ethics committee insisted that parents had to be told that caffeine could cause fits, an effect that had only been seen after an inadvertent 10-fold overdose. As a result, many parents, on reading the four-page information leaflet decided, in some confusion, that they did not want to join the trial but did want their baby to have caffeine (Hey E, personal communication). The completed trial has now shown that, as well as reducing the need for ventilatory support and supplementary oxygen, caffeine reduces the incidence of cerebral palsy and developmental delay the survivors.[23] Research regulation delayed the discovery of this important benefit of a widely used treatment.

I am chair of the data monitoring committee for one of five internationally co-ordinated clinical trials addressing a question that has remained unanswered for 60 years: namely, how much oxygen should be given to prematurely born babies? If too much oxygen is given, infants may be blinded by retinopathy of prematurity; if too little is given, they may die, or survive with cerebral palsy. A bid for a single large international trial was submitted to the US National Institutes of Health in late 2003, but turned down in June 2004. A plan was then laid to launch five parallel trials – in Australia, Canada, New Zealand, the UK and US. Two months later, an outline bid was submitted to the UK MRC, which invited a full funding bid in late 2004. This was submitted in January 2005 (BOOST-II UK: ISRCTN008422661); the MRC gave provisional backing to the trial in June 2005; and funding was granted in November 2005 (after confirmation had been received that all the other parallel trials had been approved). In January 2006, 36 potential UK collaborating centres were asked to prepare to start recruiting, albeit with a warning that there was much regulatory paperwork to complete before this could happen.

MRC money became available in April 2006 and work began on preparing the 76-page submission to the Medical and Healthcare products Regulatory Agency (MHRA) and the 102-page electronic submission (with 10 attachments) to the Multicentre Research Ethics Committee (MREC). These were submitted in November 2006. MHRA approval was received 6 months later [EUDRACT No. 2005-006174-97], and MREC approval the following month. However, formal comparison of two widely used regimens for administering oxygen could not begin until the trial's official 'sponsor' (the University of Oxford) had entered into separate formal legal contracts with each of the 36 potential recruiting centres, and the research governance offices of each of the centres had agreed to support the trial. At the time writing (early October 2007) – 22 months after funding was agreed for the trial – the required legal agreement has been achieved for only one of the 36 potential collaborating centres. Two babies (twins) in that centre are now collaborating in the study (Hey E, personal communication). An additional 1198 babies are needed if the UK trial is to make its planned contribution to the international effort to address this important unanswered question about the care of prematurely born babies.

I believe these examples illustrate a serious problem. It is not clear how prevalent the problem is because, as far as I am aware, the decisions of research regulators are not audited to find out how often they have delayed the identification of important beneficial and harmful effects of treatments in common use. Who should take the blame for these avoidable delays?

3. The Influence of "a Confused Ethical Analysis" and the Double Standard in Informed Consent to Treatment

The situation illustrated in the previous section reflects the influence of "a confused ethical analysis". This was put succinctly three decades ago by British paediatrician Richard Smithells;[24] he noted that he needed permission to give a treatment to half of his patients (to find out whether it did more good than harm), but that he did not need permission if he decided to give the treatment to all of his patients (assuming, without good evidence, that it must be beneficial and safe). As the American bioethicist John Lantos has observed: "This confusing real world situation seems to reflect a confused ethical analysis".[25] This "confused ethical analysis" has led many bioethicists and lawyers to promote the erection of the formidable hurdles that now face health professionals, patients and researchers who wish to collaborate in confronting uncertainties about the effects of healthcare interventions.[13]

As William Silverman and I put it, "Illogically, and with no empirical evidence to support it, a mischievous view has been

promoted that the interest of the vast number of patients involved in the poorly controlled experiments of informal medical 'tinkering' are less in need of protection than are those of the relatively small number of patients who are involved in planned, properly controlled clinical experiments".[26]

In the UK, this "confused ethical analysis" and its application by research ethics committees seems likely to have reflected the influence of Maurice Pappworth, the author of *Human Guinea Pigs*.[8] In 1978, in an article in a widely read journal about the functions of research ethics committees,[27] he reiterated his concern about what he referred to as "medical experimentation". In response, the journal published a letter from me stating that, while sharing much of his concern about medical experimentation, I was not as sure as he seemed to be that the medical world could be neatly divided into clinical experimenters ('the bad guys') and altruistic clinicians ('the good guys'). I urged him to consider whether the doctors who had done controlled trials to assess whether diethylstilbestrol (DES) was a useful drug in pregnancy – and who had stopped prescribing it when they were unable to detect any benefit – were more or less ethical than the vast majority of other doctors who went on prescribing it for the next quarter century, only to find that the drug caused cancers in the daughters of the women they had treated. I suggested that it seemed very possible that there was a more urgent need to protect patients from the uncontrolled experimentation that characterised much accepted medical practice by altruistic, but uncritical, clinicians. I noted that the number of patients 'at risk' was much larger than those whose interests are protected, to a greater or lesser extent, by research ethics committees.[28]

Pappworth did not respond to my challenge then, nor 12 years later when, in response to an article by him reviewing the history of *Human Guinea Pigs* (an article called *"Human guinea pigs" – a history* published in the *BMJ*),[29] I invited him again to make his position clear.[30] I noted that the specific example of DES was unimportant, but the general issue that it illustrated was one that many medical ethicists seemed unwilling to confront straightforwardly. I suggested that influential commentators on medical ethics like him needed to explain the apparent double standard they were promulgating.

The "confused ethical analysis" is reflected in a double standard applied to informed consent to treatment and this continues to jeopardise efforts to find out how to improve treatments for patients (for example, Stobbart et al.[31]). William Silverman[32] had little doubt about the origins of the double standard in the US; he dated it very precisely to 8 February 1966, the day the Surgeon General first issued a directive about what had to be done to obtain 'fully informed consent' before undertaking 'clinical investigations using human subjects'. From that day on, the extent to which a patient had to be briefed about any planned treatment became much more rigorous if treatment was being offered in a properly organised evaluative study than if the patient was offered the same treatment simply because the doctor had a 'hunch' that it might be beneficial. The resulting problem has been characterised succinctly by another paediatrician, Edmund Hey (personal communication):

"If I can convince myself that some totally new treatment strategy 'must' be good I am allowed to take it into use without getting any prior ethics clearance, and without bothering to tell the patient that it is a new and untested treatment. If I am cautious enough to want to be able to compare the new strategy with the one previously used, then unsystematic clinical drift suddenly becomes 'research' and I become swamped by an unending deluge of bureaucracy. Sloppy medicine is considered ethical while careful, thoughtful, medicine is treated as potentially unethical."

The double standard in informed consent to treatment was highlighted in a satirical, but serious article published in the *BMJ* in 2001.[33] A cartoon illustrating the main point of the article showed a smiling patient receiving a prescription from a smiling doctor who is saying "Here's a prescription for ZAPIT Ms Jones. Let me know if you have any troubles". Janus-like, the same doctor, this time grim-faced and clutching a sheaf of paper, is addressing an obviously worried patient as follows: "ZAPIT is a drug that has been used for many decades Ms. Jones. We believe it might be useful for what ails you, but we are not certain. Therefore we are conducting a randomised trial. If you want to be a guinea pig in this trial, you will need to read this 126 page informed consent form that includes a list of 528 possible side effects. You will also need to sign a legal contract to protect me, the investigators, the manufacturers of ZAPIT, their stockholders, and our ethics committee from lawsuits should we unintentionally kill you along the way".

The text of the article drew attention to the way that it is only when doctors propose to select treatments within the context of research addressing acknowledged uncertainties that they are required to be explicit about the basis for their recommendations. When recommending treatments outside the context of research, doctors are not required to be explicit about the reasons for their advice. The reasons can include ignorance of the best evidence available, the recommendations of representatives of commercial companies, or personal or institutional financial vested interests in particular treatments (a recent cartoon in *The New Yorker* showing a doctor advising a patient carried the legend "Try this – I just bought a hundred shares").[34] Our article about informed consent ended with an illustration of the interactive, personalised approach to informed consent to treatment that we felt should be the basis of a single standard.[33]

In 2001, commenting on the chapter on double standards in informed consent to treatment in a *BMJ* book entitled *Informed Consent in Medical Research*,[35] the medical ethicist editor of the book acknowledged the need for a more balanced ethical analysis, and expressed his hope that the chapter on double standards "would have the significant impact on future debates that it deserves to".[36]

4. What Do I Want for Myself, as a Patient?

The views I have expressed in this article might be dismissed as special pleading by a former clinician and health services researcher. So one way of assessing them is to ask myself what I want as a patient. I tried to make my position clear in an article published more than a decade ago,[37] and my views have not changed substantially since then.[38] I admitted that I was hardly a typical patient: while working as a clinician, I had come to realise that I had sometimes harmed my patients unintentionally because my practice had been based more on the unquestioned authority of my teachers than on evidence from research. This experience has coloured my views as a patient.

When systematic reviews of evidence expose important uncertainties about the relative merits of my treatment options, I want to be invited to participate in properly controlled trials. This wish is not altruistic. It is motivated by well informed self-interest.

First, although there may be some inconvenience associated with receiving treatment as a participant in a controlled trial (additional investigations, for example), the best evidence suggests that participation poses no special risk compared with receiving treatment outside a trial: on average, routine care is just as dangerous/safe as care within trials.[39] Indeed, some people have maintained that the closer attention devoted to the treatment of participants in controlled trials may confer benefits.[40]

Second, as would be expected if (as they should) controlled trials are addressing genuine uncertainties about the effects of treatments, new treatments being assessed in randomised trials are as likely to be inferior as they are to be superior to existing treatments.[41,42] Randomisation, thus, provides an efficient hedging strategy in the face of these evenly balanced odds.

Third, my participation in randomised trials will help to generate reliable information on which to base future decisions about my healthcare, particularly for the prevention or treatment of recurrent or chronic health problems.

My wish to be invited to participate in controlled trials when there is uncertainty about the relative merits of the treatment options facing me should not be taken to imply that I have no conditions for accepting invitations to participate. I also made clear in my article that I want decisions about my healthcare to take account of systematic reviews of reliable research evidence. These are required to produce the kind of evidence that I am likely to believe, and that I would wish to be taken into account by those offering me care – whether within or outside a controlled trial.[43] There is now plenty of evidence of the human costs of failing to cumulate evidence in systematic reviews: failures have meant that advice on some life-saving therapies has been delayed for more than a decade, while other treatments have been recommended long after controlled research has shown them to be harmful.[44,45]

These requirements are reflected in advice offered in a recently published book, *Testing Treatments: Better Research for Better Healthcare*,[46] written particularly for patients and the public. The book advises: "Agree to participate in a clinical trial only on condition: (i) that the study protocol has been registered publicly; (ii) that the protocol refers to the systematic reviews of existing evidence that the trial is justified; and (iii) that you receive written assurance that the full study results will be published, and sent to all participants who indicate that they wish to receive them".

5. Reducing Unnecessary Research and Promoting Full Publication of Necessary Research

Research ethics committees have considerable power to approve, require modification or reject the proposals submitted to them. There is no question that this power is necessary for scrutinising proposals for research of the kinds that fall within the many categories that I have specifically excluded from consideration in this article, for example, invasive, nontherapeutic research. However, as illustrated by the examples given earlier in this paper, research ethics committees sometimes exercise their powers in ways that are manifestly not in the interests of patients receiving inadequately evaluated treatments. Regulations and the judgments of committees need to be tailored to reflect the likely risks of different kinds of research. Specifically, they should foster, not obstruct, the duty of doctors to help to resolve uncertainties about the effects of treatments.

In other ways, research regulators are too coy about exercising their powers. In 1996, a medical ethicist (Julian Savulescu), the chair of a large research ethics committee (Jennifer Blunt) and I published a paper in the *BMJ* asking the question *Are Research Ethics Committees Behaving Unethically?*[47] We suggested that there were two ways in which committees could protect the interests of patients more effectively. These are outlined in the following two sections.

5.1 Reducing Unnecessary Research

A good deal of clinical research is proposed for perverse reasons, reflecting the interests of industry and academia more

than those of patients.[48] This is an issue for the medical research community in general, but research ethics committees are part of that community, and it is reasonable to expect that they will use their powers to reduce unnecessary research – which, by definition, cannot be ethical.

Ten years ago, the Danish National Research Ethics Committee System[49] stated that "it is crucial that all relevant literature has been reviewed by the research group before submission", and that this is "a precondition when the evaluating committee is judging the originality of the project and, for example, the permissibility of using placebo and not an already known treatment in a control group". This principle was reiterated in 2001 in guidance issued by the English Department of Health: "It is essential that existing sources of evidence, especially systematic reviews, are considered carefully prior to undertaking research. Research that duplicates other work unnecessarily or that is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical".[50]

Quite properly, the Research Governance Framework assigns to the sponsor of the research the ethical duty to review systematically what is known already: research ethics committees cannot be expected to assume the task of doing the needed systematic reviews of existing evidence themselves. But because it is a matter of such fundamental ethical importance, neither should research ethics committees try to absolve themselves from any responsibilities in this regard. Just as they check research proposals for other aspects deemed ethically necessary, so should they also check that the researchers have made clear – by reference to systematic reviews of existing evidence – why the proposed new research is justified. In brief, to discharge its duty under the *Governance Arrangements for NHS Research Ethics Committees*,[50] what questions should a research ethics committee ask of the scientific review?

To illustrate the consequences for patients of failure of research ethics committees to insist on this, our 1996 article[47] published a graph showing how placebo-controlled trials of prophylactic antibacterials during surgery for colorectal cancer had continued to receive approval from research ethics committees long after systematic reviews of previous trials could have shown that antibacterials reduced the risk of death. In other words, by allocation to placebo, patients were being denied an effective treatment, with the approval of research ethics committees.

Over 50 placebo-controlled trials of prophylactic antiarrhythmic drugs in myocardial infarction were done between the 1970s and 1990s[51] – in spite of the fact that systematic reviews of the earliest trials had not detected any advantage of these drugs,[52] and that systematic reviews done in the late 1980s had demonstrated that they were lethal.[53,54] In this example, patients were being given a lethal treatment with the approval of research ethics committees because they had failed to realise that uncertainty had long since been sufficiently reduced by previous trials and systematic reviews.

A recent analysis of reports of trials assessing the effect of aprotinin on the use of perioperative blood transfusion provides a further example.[55,56] The first of 64 controlled trials of aprotinin reported between 1987 and 2002 showed a dramatically lower use of blood transfusions among patients who had received the drug than for control patients. This difference was confirmed in 14 trials over the 5 years from 1987, yet research ethics committees approved at least 49 further trials between 1992 and 2002.

The problem continues: the Committee on Publication Ethics (a group established by medical journal editors; their website can be found at www.publicationethics.org.uk) receives a steady stream of complaints about "research that did not need to be done".[57]

5.2 Promoting Full Publication of Necessary Research

The second of the two issues raised in our 1996 *BMJ* paper concerned acquiescence in biased under-reporting of research.[47] In the foreword to the second edition of their book *Fraud and Misconduct in Medical Research*, Stephen Lock and Frank Wells[58] wrote that "... under-reporting of research is another form of misconduct, given that this can lead to seriously misleading recommendations for clinical practice and for new research". Two years later, the ethics committee of the Faculty of Pharmaceutical Medicine (which was chaired by Frank Wells), stated that "Pharmaceutical physicians ... have a particular ethical responsibility to ensure that the evidence on which doctors should make their prescribing decisions is freely available ... the outcome of all clinical trials on a medicine should be reported".[59] Nor is the problem confined to the biased reporting of whole studies: there is now important evidence of biased reporting of elements within studies.[60]

Over recent years there has been increasing recognition of the human costs of biased under-reporting of research. A striking example concerns research on the prophylactic use of antiarrhythmic drugs in myocardial infarction. To their great credit, Cowley and his colleagues[61] reported in 1993 a trial of one of these drugs that had been done 13 years previously: "When we carried out our study in 1980 we thought that the increased death rate that occurred in the [antiarrhythmic drug] group was an effect of chance .... The development of [the drug] was abandoned for commercial reasons, and this study was therefore never published; it is now a good example of 'publication bias'. The results described here ... might have provided an early warning of trouble ahead".[61]

At the peak of their use in the late 1980s, it has been estimated that drugs in this class were causing between 20 000 and 70 000 premature deaths every year in the US alone;[62] a yearly total of deaths of the same order of magnitude as the *total* number of Americans who died in the Vietnam war.

Under-reporting clinical trials is unethical, unscientific and harmful to patients.[63,64] As has been suggested by Howard Mann,[65] research ethics committees should: find out at their initial review of research proposals how investigators propose to disseminate research results; scrutinise any sponsor-imposed contractual impediments to dissemination; and insist on public trial registration before allowing the trial to proceed. He goes on to suggest that committees should then follow up with continuing review until the primary outcome data have been reported, and consider failure to report results as possible research misconduct.[65]

It is disturbing that, in their often-cited paper *What Makes Clinical Research Ethical?*, the American ethicist Ezekiel Emanuel and his colleagues[66] make no specific mention either of the registration of clinical trials, or of systematic reviews as the most appropriate way to assess existing knowledge on a topic.

6. What Can Be Done to Address These Problems?

The problems identified in this article need to be addressed by more thoughtful ethical analyses, more effective use of research regulation to protect the interests of patients, and empirical research to inform the future development of research regulation.

6.1 More Thoughtful Ethical Analyses

More than a decade has passed since the American medical ethicist John Lantos[25] drew attention to the "flawed ethical analysis" underlying many of the problems to which I have alluded. In 2000, the British medical ethicist Richard Ashcroft, reflecting his recognition of these problems, wrote that, for ethical as well as scientific reasons, when there is uncertainty about the relative merits of alternative treatments, "the trial is the treatment".[67] Put in other words, random allocation is the best method of making decisions under conditions of uncertainty.

More recently, in his book introducing medical ethics to a lay readership, another British medical ethicist, Tony Hope, drew attention to the double standard on informed consent to treatment.[68] He contrasted the same treatments being offered within and outside the context of a clinical trial: "In the research case the guidelines and research ethics committees require Dr A to inform B about both drugs, and about the method of choosing which to prescribe. In the clinical case this standard of informing is not the norm. Is this difference justified? If it is, then the standards are simply different. If it is not then we are operating 'double standards' – i.e. standards that are different and where the difference is not justifiable. Double standards are an example of inconsistency. They tell us that at least one of the standards needs to be changed".

Because ethical commentaries such as the report of the US National Bioethics Advisory Committee have provided no clear guidance on how to distinguish – ethically – between treatment offered within and outwith formal evaluations,[69] a workshop was convened with support from the UK Economic and Social Science Research Council to ask whether there should be a difference between the governance of medical research and governance of medical practice. Ethicists, philosophers, social scientists, researchers, researcher funders, regulators and others agreed at the workshop that the double standard in informed consent had been ignored for too long and needed now to be seriously addressed.[70] A comment at the workshop by the American sociologist Charles Bosk encapsulated nicely the irrationality of the current situation: While "the right to enrolment in clinical trials" is being jeopardised, "you can do anything you want in a clinic as long as you promise not to learn from your experience".

Some ethicists and philosophers have been developing analyses that challenge the dominant theories. In 2005, the American bioethicist Rosamund Rhodes noted that "if you are a North American bioethicist, everything looks like a problem of informed consent". She went on to suggest that "the solution to every problem looks like another group that should be declared 'vulnerable'". She noted that the consequence of these attitudes has been that "current policies, reports, and guidelines presume that all of those who can be classified as 'vulnerable' should be paternalistically protected from researchers".[71]

Indeed, Rhodes[71] and others[72-74] have gone further and asked whether participation in research should be regarded as a moral duty and whether, when systematic reviews of existing evidence have revealed uncertainties about the effects of treatments, those treatments should only be offered within the context of evaluative research.[71,75,76]

These are encouraging signs of challenges to the ethical theories that have dominated thinking and practice over the past several decades.

6.2 More Effective Protection of the Interests of Patients by Research Regulators

Having served on a busy research ethics committee myself for 4 years, I am aware that the volunteer members of such committees do their best with limited training and resources. Furthermore, research ethics committees are not responsible for the laws and regulations that govern their activities and decisions. However, as

illustrated by the examples given earlier, these committees certainly have the power to delay and sometimes scupper efforts to address uncertainties about the effects of treatments.

It is disingenuous of those associated with research ethics committees to maintain – as some do – that they have no powers to reduce unnecessary research and to promote the conduct and full publication of necessary research. Sponsors and researchers often have vested interests in promoting research that holds no likelihood of benefits for patients, as well as in suppressing research results that do not support their interests. As a result of scandals exposed in the print and broadcast lay media about redundant research, biased choice of comparators, biased under-reporting of research and other forms of misconduct, public interest in and knowledge about competing interests has increased dramatically over recent years. These issues could hardly have been put more starkly than they were in the titles of books written by two former editors of the *New England Journal of Medicine* – *The Truth About The Drug Companies: How They Deceive Us, And What To Do About It*,[77] and *On The Take: How Medicine's Complicity With Big Business Can Endanger Your Health*.[78]

Research regulators need to acknowledge that they are part of the system that has allowed this situation to develop. Not only must they therefore bear some of the responsibility for it, they need to indicate more clearly how they intend to serve the interests of patients and the public more effectively. Patients and prospective participants in clinical trials assume that research regulation is protecting their interests, but it is clear that it sometimes fails badly to do so.

Research regulators should use their powers to: (i) insist on registration of clinical trials prior to approval; (ii) promote publication of protocols to make clear (by reference to relevant systematic reviews) why the new research is justified, and what the prespecified outcome measures are; and (iii) insist on written undertakings from researchers that they will make the full results of their studies publicly available within a reasonable time after primary data collection has been completed. One experienced research ethics committee chairman has suggested that better accountability of research ethics committees would be achieved by opening up the system to public scrutiny.[79]

6.3 Empirical Research to Inform the Future Development of Research Regulation

As the ethicist Daniel Sokol has suggested,[80] "armchair bioethics ... must make way for a more streetwise form of bioethics in which conceptual analysis is coupled with an awareness of clinical reality ... [and that] ... one way for ethicists to appreciate the realities of their chosen subject is by reading or conducting social science research." The research by Mary Dixon-Woods and her colleagues[81-86] on informed consent provide good examples of the kind of research needed. As Flory, Wendler and Emanuel[87] have observed, "nobody knows for certain what is and is not a satisfactory consent process".

Evidence from empirical research, albeit informed by more thoughtful ethical analysis, should count for more than it has done in shaping research regulation. There are nearly 100 references keyworded under 'evidence based ethics' available on the Ethics and Research Information Catalogue (http://www.eric-online.co.uk). This body of evidence needs to be reviewed systematically and priorities for additional empirical research identified.

Investigations to evaluate research regulation should include studies to estimate the opportunity costs of the review process. Just as clinical trials are done to assess whether the benefits of a treatment exceed the harms (costs), so also is there a need to estimate the benefits and costs of research regulation. In the CRASH trial, for example, one staff member was employed throughout the entire trial period to service ethics committees (Roberts I, personal communication); and in a survey of Research and Development departments at 50 UK National Health Service hospital trusts governing 57 hospital sites, a delay of more than 20 working days (unexplained in 56%) was incurred by 75% of the applications, at an estimated cost to funding agencies of £53 743.[17]

The British ethicist Richard Ashcroft[9] notes that one consequence of the risk-orientated approach to research regulation has been to emphasise safety and governance of the means used in medical research over moral evaluation of the ends of such research. "[I]n essence they act as risk assessment and control mechanisms to reduce, control or allocate the exposure of the population to the relative risks of research participation (and by the same token, the exposure to relative benefits)". Ashcroft invites his readers to regard research ethics committees as public health interventions, which should be assessed for their efficiency, effectiveness and relative cost-effectiveness.[9]

7. In Conclusion

Current arrangements for regulating research addressing uncertainties about the effects of treatments already in use in everyday clinical practice have operated against the best interests of patients. Three decades have passed since I first challenged Maurice Pappworth to acknowledge this problem, and over a decade has passed since I co-authored a paper challenging research ethics committees to consider whether they were behaving unethically by acquiescing in unnecessary research and biased under-reporting of research findings.[47] Because ethicists and research regulators

have failed to confront these issues, I believe that they have contributed to the avoidable suffering and deaths of millions of people,[88] the vast majority of whom have *not* been participants in clinical research.

Some of the people responsible for research regulation give the impression that they believe their interventions in the lives of other people must inevitably do more good than harm. In the same way that a combination of theory and worthy intentions is an inadequate basis for health professionals and clinical researchers to intervene in the lives of others, so too is it an inadequate basis for the prescriptions and prescriptions of ethicists and research regulators.[21]

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