

PROFESSIONALISM, INTEGRITY AND TRUST ON TRIAL IN CLINICAL RESEARCH

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*In this article the author discusses
the professional and moral issues
surrounding clinical research in
human subjects*

Integrity is one of the key traits that health professionals are required to display in order to retain their patient's trust and their moral authority. The principle of holding one's patients' best interests at heart is embedded into the ethical codes of health care professions. This article will examine the professional tensions existing in clinical research, focusing predominantly on drug research in non-vulnerable patient groups (ie, excluding children, the mentally disabled and the elderly). The key issues addressed are power, integrity and trust. It will be argued that the pressure on investigators to undertake research is so overwhelming that it may compromise their professionalism and there is insufficient protection and information provided for the patient, who becomes the research subject.

The conflicting tensions are explored in many aspects of the research process. The issue of whether human research is a reasonable goal is examined, followed by a discussion of ethical principles and the aspects of moral character that may be challenged by conducting research. The consequence of the media's reporting of high profile cases of medical misconduct is explored. The key influencing drivers of research are identified and discussed. The concept of informed consent will be examined in detail. Issues such as futile research, research fraud, negative results and misleading statistical treatment of results are reviewed. The tensions present in the research hierarchy are also explored, including ownership of research and authorship.

DUAL ROLE OF INVESTIGATOR AND CLINICIAN

An individual doctor's dual role as clinician and investigator pull in opposite directions, producing conflicting obligations and interests. The researcher aims to generate scientific knowledge in the future. The clinician is responsible for the care of patients in the present, acting in their best interest. Clinicians and investigators are both concerned with helping the sick but the clinician cares for the current patient while the researcher's role is directed at unknown, future patients. Therefore where these roles are combined, as they often are in research, care for current patients may conflict with responsibility to future generations.

IS RESEARCH JUSTIFIABLE?

Medical and scientific knowledge are crucial societal goals but often research makes a dubious contribution to understanding. The medical community and society as a whole have an obligation to future generations to allow, support and encourage studies that can produce knowledge, but not to the point that it violates the rights and interests of current patients.

Research on humans is necessary but morally perilous because it exposes subjects to risk solely for the advancement of science. Several conditions must be satisfied for ethically justified research in humans including:¹

- 1 An expectation that the research will produce the knowledge that is sought
- 1 The need for human participants
- 1 A favourable expectation of the risk/benefit balance
- 1 A representative selection of subjects

"Equipose", which describes the idea of uncertainty, is an important concept in research. A patient should only be enrolled in a trial, if uncertainty about which of the trial treatments would benefit the patient most is so substantial that they are in equipose or "indifferent" to treatment options.² One of the key elements for justifiable clinical investigations is that true equipose exists among medical experts. (It

is recognised that expertise is contestable, but a full discussion of this is outside the scope of this article.) If equipose does not exist then the superior treatment must be given. In trial designs with several arms, each arm must exhibit equipose. If data emerge that disturb equipose then the rationale for involving patients is destroyed, because a treatment preference has developed.

Clinical research is ethically justifiable but it requires constant scrutiny, bearing in mind the demands of trust, integrity and the other moral and professional commitments that may be challenged in the process.

MEDICAL ETHICAL PRINCIPLES AND ASPECTS OF MORAL CHARACTER

The principle of nonmaleficence is closely associated with the maxim *primum non nocere*: above all (or first) do no harm. Another central principle of medical ethics is that of beneficence which describes an obligation to help others to further their important and legitimate interest. Applied to the research context these principles suggest that participants should not be subjected to a treatment that is less effective than the expected standard and they should not be coerced into enrolment in a study.

The justification of a study should always be that there is sufficient equipose to suggest that the new treatment may be at least as good as, if not superior to, the established one. There are examples in the literature where the trial treatment did not perform as well as expected in terms of lack of efficacy or unacceptable adverse effects. For example, a study of tumour necrosis factor in septic shock reported a mortality of 30 per cent in the placebo group and 53 per

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cent in one treatment arm.³ This study contributed to the understanding of sepsis, but this will be of little comfort to those subjects and their families who paid the ultimate price for that knowledge.

The principles of nonmaleficence and beneficence must be built into the trial process so that interim analyses are performed and the trial suspended if treatment harm or lack of relative benefit is seen. Early suspension of a study often yields less satisfactory results because the exact extent and impact of the harm is not determined but this knowledge must be sacrificed to protect the subjects. Nonmaleficence and beneficence should also be applied to ensure that there is sufficient insurance provision to compensate patients that do experience harm arising from trials. This is a particular issue with non-commercially sponsored trials.

Integrity is a prime professional virtue in research. Integrity represents two aspects of someone's character. First, a coherent integration of aspects of self-aspirations, emotions, knowledge, etc, so that a balance is formed that does not frustrate the others. Secondly, integrity describes the character trait of being faithful to the moral norms and defending them when necessary.¹

Trustworthiness is another key virtue required by investigators. Trust is an assured expectation and reliance upon the moral character and capability of someone else. In the research context, the participant and the person reading the resultant paper will need to trust the investigator. This entails a confidence that he or she will act with the right motives and in accordance with the appropriate moral norms.

Respecting the autonomous choices that patients make is fundamental to the recruiting process in human research. The concept of patient autonomy is central when attempting to examine an individual's decision, especially informed consent and refusal. Embodied in this is the concept that the subject may withdraw at any time from a study without penalty or loss of benefits. And there are many factors and circumstances that can adversely affect the trust and integrity that stand as the cornerstones of the patient-professional relationship.

"DOCTORS IN THE DOCK"

A professional's standing is reliant upon the relationship with the client, which itself depends on the client trusting that the professional will act in his or her best interests.⁴ However, this relationship may be undermined by public perception. The public's confidence in the medical profession has been dented by a series of high profile cases. The media presents the public with daily reminders that health care workers might be damaging their health, in

contrast to the former portrayal of trustworthy professionals who relieved suffering. The expression "trust me, I'm a doctor" has become almost ironic, suggesting that the public's faith in the medical profession has been tarnished. The public regard the medical self-regulatory bodies as overly protective of their own membership rather than the public.⁵ Cases that have damaged public faith include the gynaecologist Rodney Ledward, who incompetently operated for 16 years and the two heart surgeons at the centre of the

Bristol babies scandal who continued to operate even though they should have known their death rates were worse than other hospitals. Further scandals, such as the general practitioner Harold Shipman, who murdered many of his patients, and the revelations of the retention of children's organs after death have increased this negative perception. Newspa-

per headlines such as "Doctors plunge into new crisis"⁶ are now commonplace. The impact on research of these negative professional associations in the public's mind, may serve to prompt valid questioning of the motives of researchers.

MEDICAL REGULATION

The General Medical Council (GMC) is the regulatory body that attempts to maintain the standards that the public should expect of doctors. The GMC website⁷ entreats doctors to "make the care of your patient your first concern . . . and . . . serve the patients' best interests". But the GMC is perceived by the public to be self-serving rather than altruistic.

Focusing on research, the GMC acknowledges that the benefits of research are not always certain and may not be experienced by the participants and so the researcher must be satisfied that the research is not contrary to the participants' best interests. The GMC makes a bold statement regarding conflicts of interest:

"You must ensure that your judgement about the research is not influenced, or seen by others to be influenced, by financial, personal, academic, political or other external interests at any stage of the process. You should declare any conflicts that may arise . . . to the participants."

This laudable aim is clearly impossible to meet since innumerable tensions exist. (These will be discussed later in this article.) Furthermore, the GMC states that participants must be given information on how research is funded, including payments made to researchers and departments. It also says the researcher must publish all results, including adverse findings and must ensure the claims of authorship are justified.

In response to enormous criticism and pressure, the GMC has asked doctors to conform to difficult and high-minded standards. If followed, some of the tensions present will be revealed to potential trial participants.

INFORMED CONSENT

Informed consent, as a prerequisite before entering a trial, is a measure introduced to protect the patient from coercion to enrol, ie, to protect the patient from the overzealous researcher. Many patients feel under pressure to take part in clinical trials, although enrolment is voluntary.⁸ They may believe that if they decline to participate this will impair their relationship with the doctor, which could lead to poorer care. Sick patients might be heavily dependent on their doctor and may believe that any recommendation made by the doctor will be beneficial. The World Medical Association Declaration of Helsinki⁹ states that if the patient is in a dependent relationship with the doctor then the informed consent should be obtained by a well informed physician who is not engaged with the study and who is independent of the relationship. This important measure does not feature in the GMC guidelines. I support the merits of having a patient advocate, who would discuss with the patient the issues surrounding participation before consent is given.

Patients may believe they are participates in order to further scientific discovery and help subsequent sufferers. However the motive behind the trial may merely be an attempt by a pharmaceutical company to develop a profitable commercial product which offers no real advance on the treatments available. Patients will be unaware of this. The potential participant is without the means to assess how useful the research may be.

Use of coercion to recruit a patient is an abuse of professional power and knowledge but is not a new development. For example in Newgate Prison in 1772, several prisoners were offered their freedom as an alternative to hanging if they agreed to participate in a trial of smallpox inoculation.¹⁰ This approach of "participate or you will be hanged" may be considered somewhat harsh by today's standards but the prisoners considered this offer fortuitous as the condemned men all survived and were subsequently released. This coercion-manipulation interaction offered some hope to desperately needy people who without the offer would certainly have died.

There may be a parallel here with clinical research conducted in developing nations where the offer may be to "enrol in the trial or get no treatment". Critics of research conducted specifically in developing countries point to the treatment of subjects as laboratory animals and the lack of professional responsibility and beneficence shown for those who do not wish to enrol. Other concerns are that participants are not asked to give consent because "if we ask the subjects they might say no".

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PROBLEMS WITH INFORMED CONSENT

Obtaining consent is an essential process before a patient is enrolled in a clinical trial or any medical or surgical treatment. Patients clearly have a right to information about potential benefit, risks and options open to them, before they embark upon a path that could have serious implications for their health, employment, and social or personal life. For consent to be valid it should incorporate the following aspects:

- 1 The patient must understand the information given and the resultant consequences
- 1 The act of consent must be intended
- 1 The act of consent must be autonomous
- 1 The patient must give authorisation

Although these general principles are widely accepted, the issues around informed consent in clinical trials are hotly debated and in practice may not be achievable. Consent is a relatively recent term that was developed as a response to the Nuremberg trials, where appalling degrees of compulsion were exposed that infringed individual liberty and freedom of choice.¹¹ Consent represents a relatively new code of practice in medicine motivated by societal changes. The 'New Oxford Dictionary' defines consent as "permission for something to happen or agreement to do something".¹² It does not require some knowledge or understanding although this may be implied. Informed consent was developed to avoid this difficulty. It is taken to mean "permission granted in the knowledge of the possible consequences". In contrast, the 'Oxford English Dictionary', compact edition defines consent as "voluntary agreement to, or acquiescence in, what another proposes or desires, compliance concurrence, permission".¹³ This interpretation does not imply the absence of persuasive pressures to submit to another's will.

Notwithstanding the problems with consent discussed above, it is usually regarded as a voluntary, uncoerced decision, made by a competent, autonomous person to accept, or in this case, to enrol in a trial. The question of how this ideal conforms to the doctor-patient relationship will now be examined.

Emanuel and Emanuel put forward a model of patient-doctor relationship based on the conflict between the patient's autonomy and health, or between values held by the patient and doctor.¹⁴ They describe four forms of relationship: paternalistic, informative, interpretative and deliberative. In the paternalistic form the doctor acts as the patient's guardian, articulating and implementing what is best for him. The patient assents to the doctor's decision either at the time, or later. The informative model describes the doctor merely as a supplier of factual information. The patient digests this and formulates his or her own wishes. The doctor in the interpretative role elucidates and interprets the patient's values, provides information and implements the selection that the patient elects. In the deliberative role the doctor articulates and persuades the patients of the most admirable values and

then informs the patient and implements the patient's selected interventions.

The act of enrolling a subject into a study and the requirement for consent implies that the investigator is someone who "does something to the patient". The consent can be achieved with inadequate explanation in the paternalistic model or after endeavouring to "persuade the patient of the most admirable values" in the deliberative model. Consent is superfluous in the informative model because the patient has requested the intervention. Habiba argues that the idea of consent necessitates a dominant-subordinate relationship that is at odds with the ideals of liberty and autonomy that underpin the concept of consent.¹⁵ Coercion reduces the ability of the patient to refuse to consent and the use of coercion precludes voluntary consent. Consent allows the doctor to maintain the commanding position in the relationship by indicating the choices that they support. Thus consent does not appear conceptually relevant in a relationship that respects autonomy and liberty because only the patient who withdraws and withholds consent is free.

In practice, informed consent in the true sense is virtually impossible and aspires to a notion that is unrealistic. It suggests that decisions made by patients in health care should be based on a sound grasp of all the key issues, in contrast to important decisions made in everyday life that are based upon incomplete understanding, like buying a house or making an investment.

Some ethicists argue to replace the expectation of "fully informed consent" with the more realistic terms "adequately informed consent" and "extensively informed consent". This embraces the concept that "full" consent is unachievable because it suggests that the information provided is complete and no more can be added.

FUTILE RESEARCH

There is now a proliferation of medical and non-medical professionals who are required to conduct research as part of their MD, PhD, MSc, BSc or DPharm. Grimley Evans bemoans the fact that many of these studies will not lead to useful results and are unlikely to be published.¹⁶ Ethics committees do not necessarily include members who can judge the scientific quality of research proposals. Validation of proposals is not required by any peer review process other than the student's supervisor. It may be desirable for a larger number of health care professionals to learn about research but it may be misleading to the participants if their contribution is solely for the training of the investigator. Futile research may even be harmful. Evans recalls a mailed questionnaire about friendship networks. The questionnaire made one subject realise that he had lost all his friends and was unlikely ever to acquire new ones, this awakened reflections that were not helpful. Grimley Evans argues that research applications should be formally categorised by scientific review into those with scientific utility and those which are training exercises and then let the participant make the "informed" choice of whether to enrol.

Recruiting patients unknowingly into futile trials is an abuse of professional power and knowledge and undermines the goodwill shown by patients that underpins all human research. The National Health Service is beginning to address this issue by standardising the ethics committee application forms for investigators. Researchers are requested to state the scientific justification for the trial and are asked how the scientific quality of the research has been assessed.

"IN HOUSE" STUDIES

Drug research that is not commercially sponsored or directed, will soon have to ensure practices conform with Good Clinical Practice (GCP), an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. The Medicines Control Agency may investigate any study to determine if it is carried out to the standards of GCP.¹⁷ However, the standards are so high that individual investigators may find it extremely hard to comply. The pharmaceutical industry and institutional research bodies are the only groups that are likely to have the necessary resources and expertise to be able to comply with these stringent rules. These global bodies will thus continue to drive much of the research agenda. In-house studies will struggle to comply with GCP. The ethics committees currently lack the managerial resources to monitor compliance with these standards.

This will result in an erosion of power of non-commercially backed professionals to conduct research autonomously, so lessening their professional contribution to the generation of non-commercially oriented knowledge and understanding.

COMMERCIAL MULTINATIONALS DICTATING THE RESEARCH AGENDA

There are various drivers for research; those that are commercially motivated often bear little relationship to society's need. Multinational drug companies have a responsibility to their shareholders to develop profitable commercial products. Health institutions also have the role of co-ordinating research activities, eg, the Medical Research Council.

New drugs can be marketed, and profits made, on the back of well-conducted clinical trials, published in respected, peer-reviewed journals. The NHS is being urged to overcome its fear of innovation and enter into a partnership with the pharmaceutical industry to encourage research in the United Kingdom.¹⁸ This results in a profitable outcome for the sponsor of the research. Until recently independent academic groups, whose members played a key part in all aspects of the trial process, drove the research agenda. The cost of developing a new drug and bringing it to the market has been estimated to be over £300m in the United States.¹⁹ In order to control costs, the pharmaceutical industry is increasingly turning to contract research organisations to conduct its research, rather than academic units. The corporate sponsor can then dictate the terms of the trial, which

may not be in the best interests of the participants or the advancement of scientific discovery. The investigators have little input into trial design and data interpretation and no access to raw data.²⁰ The contract trialists are less well respected, have little autonomy and thus undergo a relative “deprofessionalisation” compared to their academic counterparts. The erosion of the trialist’s autonomy is further explored in this article in the section entitled “authorship”.

Many new drugs do not represent true medical advances but rather “me-too” agents that are introduced in order for the manufacturer to gain a slice of a profitable market. For example, there are currently eleven angiotensin converting enzyme inhibitors marketed in the UK. Most hospitals are content to use three or four of these agents; the rest are superfluous. Were the thousands of subjects who enrolled in the trials that enabled the registration of these additional drugs (or commercial products) aware that the development of these drugs did not, and was not expected to, contribute any additional benefit to health or society? It has been suggested that monetary payment would represent fairness to the participants when the expected outcome of the study is to pave the way for the development of a profitable commercial product.²¹ The GMC maintains that no payment can be made which could induce research volunteers to take risks that they would usually not take.⁷ Although payment is made to healthy volunteers in Phase I studies, most research subjects disagreed with the concept of paying volunteers in a recent trial by Russell *et al*²² but they did think that there should be greater recognition of the time and effort that they contribute to the study.

In certain clinical areas health institutions have an influential role in steering research agenda. Drug manufacturers recognise this and successfully attempt to provide financial and organisational support dependent on their drug being included in the trial protocol. The result is that effective but non-profitable drugs are not investigated as thoroughly as new “blockbusters”. In response to this problem in cancer, the newly formed National Cancer Research Institute has been set up to co-ordinate research and to encourage charity donors such as Marie Curie Cancer Care to fund trials involving non-profitable drugs in low profile areas, for example, in palliative care.

NEGATIVE RESULTS

The nature of equipoise is such that some trials will yield negative results. The question of how these results have been used raises issues of professional autonomy and intellectual ownership. If the research relates to a commercial product, then it would be in the interest of the manufacturer to suppress negative results. Van Heteren reported that a Dutch radio broadcast alleged that the “pill” manufacturer Wyeth had suppressed a study that indicated that third generation contraceptive pills increased the risk of deep vein thrombosis. The results remain unpublished. Wyeth maintain that they have not suppressed publication.²³

Previously, the tendency of the major journals was not to publish negative results, because the results were perceived to be less interesting. This attitude has been challenged by the greater emphasis now placed upon evidenced-based practice, which relies on both positive and negative results. Trials with non-significant results are less likely to be submitted for publication.²⁴ The trend has now changed and the GMC advises doctors to publish results, even adverse findings, wherever possible in peer-reviewed journals.⁷ The Helsinki Declaration⁹ states that negative results should be published or made publicly available. The advent of the internet enables researchers to make public their results, even if they cannot get them published. The major medical journals advise researchers not to enter into agreements with sponsors that interfere with their ability to analyse data and to publish.²⁰

These measures aim to help investigators reclaim their professional integrity and increase access to medical knowledge. Suppressing data from research is an affront to those subjects who underwent risk to support the research and to society’s quest to improve future treatment.

RESEARCH FRAUD

Research fraud is clearly unethical and unprofessional. Why is it committed? The professional kudos, the associated fringe benefits, such as trips to foreign conferences, and the ease of raising resources for empire building that accompany a coveted research record may be the motivating factors that lead some investigators down this path. Proposals have recently been made to establish a national organisation to investigate suspected cases of fraud and misconduct in clinical and biological research.²⁵

The need for this body has been highlighted by the case of the consultant obstetrician Malcolm Pearce. He published a paper describing a trial carried out in 191 women prone to miscarriage. They were treated with drug therapy, which he concluded improved the outcome of their pregnancy. He also published a report of a fictitious ectopic operation. His head of department, Professor Geoffrey Chamberlain, who was editor of the *British Journal of Obstetrics and Gynaecology*, accepted co-authorship of the paper. Following suspicions about the paper, Mr Pearce was unable to produce the notes, consent forms or the patients. No medical colleagues had heard of the research while it was supposedly in progress. The resultant scandal led to the sacking of Mr Pearce who was found guilty of professional misconduct by the GMC. Professor Chamberlain resigned as the President of the Royal College of Obstetricians

and Gynaecologists and as editor of the college’s journal.²⁶ This case also raises the issue of authorship.

AUTHORSHIP OF RESEARCH PAPERS

Authorship introduces various professional tensions including the academic need for publications, the necessity for commercially sponsored research to have respected names on the author list and the professional credibility that rides on the integrity of the results.

In academia, publications are a marker of academic success and appointments and promotions are often strongly related to the candidate’s bibliography. Research studies are often constructed with contributions from many people including those who conceive the study, others may design it, collect the data, analyse and interpret them. The writer of the final paper may have done little more than the actual writing. This raises the issue of who is the author? It is unclear to the reader what was the relative contribution of each author. It is traditionally recognised that the order of authors should reflect the rank order of contribution. Sometimes the first author has no input at all. The head of the team may insist on putting his name first; the junior who carried out most of the work will have no recourse, since he will be reliant on his superior for a reference necessary for career progression. A recent study in a UK medical school reported that “gift authorship” was common, promoted by a “publish or perish” environment. Reasons included motivation of research teams and maintaining working relationships.²⁷ Other reasons identified included that the authors were members of a publication syndicate or the additional author was being bribed or complimented.²⁸ Although the International Committee of Medical Journal Editors published guidelines for the criteria of authorship based on the principle that each author should be prepared to defend the work publicly, a study from 1997 showed that the guidelines were not working.²⁷

As previously discussed, when trials are undertaken with commercial sponsors, in some cases the first author may not have written the paper or had final input affecting the tone and emphasis of the paper. This practice erodes the fabric of intellectual inquiry and also makes the publishing journal party to misrepresentation, since the paper may not explain the extent to which the authors were powerless to control the contents of the paper that bears their name.

The major medical journals have recognised this weakness and now require authors to disclose their own and the sponsor’s role in the study. They may ask the responsible author to sign a statement indicating that he accepts full responsibility for the integrity of the data and the accuracy of the study

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results. The authors will be asked to describe the role of the study sponsor in the writing of the report.

STATISTICAL MISTREATMENT OF DATA

Statistics can be employed to misrepresent study results. This represents an abuse of professional expertise and power and undermines the principle of using research to develop understanding. It is beyond the scope of this article to describe in detail the methods that are used. Sometimes obscure statistical tests are used for data sets that are suitable for standard statistical techniques. Data dredging is common in the form of sub-group analysis. This can lead to false conclusions with serious consequences. For example, a study on the effect of aspirin to prevent stroke demonstrated a beneficial effect. A retrospective analysis reported that the beneficial effect was mainly confined to men. This led to aspirin being withheld in women for many years until this approach was discredited.²⁹

CONCLUSION

Fifty years ago medicine had little power to cure serious disease. Medical research has reshaped medicine giving health care workers substantial power to cure, palliate and reduce risk. The emphasis of evidence-based

decision making has reasserted the power of research to change health care practice. Market forces dominate the drug research agenda, driven by multinational conglomerates. The professional autonomy of the independent academic unit is being eroded. A deprofessionalised breed of contract investigators, who have surrendered autonomy and ownership of research, have flourished and are increasingly conducting trials. Patients are largely unaware of these currents and many agree to participate in trials out of goodwill or trust in their doctor's motives. It has been argued here that trial subjects are unable to give genuine informed consent because of coercive pressure to enrol and the absence of sufficient information to understand the real motives of the trial. The conflicting interests inherent in a doctor combining the dual roles of researcher and physician can undermine professional integrity and betray the doctor-patient relationship, which is built upon trust that the doctor will act in the best interests of the individual, current patient.

The academic world is fiercely competitive with a prevailing "publish or perish" culture, resulting in extreme pressure on researchers to recruit patients into clinical trials. A greater awareness and openness is needed to clarify issues such as authorship and ownership of research. Further safeguards are necessary to protect the patient in order to

counterbalance the uneven power balance between professional and subject. A helpful start would be for the GMC's advice to researchers to be put into practice, making clear to patients some of the factors at play that may influence the researcher's enthusiasm for recruitment. A patient advocate would help to balance power in the doctor-patient relationship. The Department of Health should attempt to co-ordinate research, focusing funds towards patient-need in the less glamorous and unprofitable areas.

The act of human medical research challenges many professional aspects of the researcher's work. Greater public recognition of these issues and tensions are necessary in order to counterbalance the pressure exerted on patients to enrol in clinical research. Eraut summarises this professional conflict:³⁰

"... whereas previously the State sought to protect its citizens from the unqualified practitioner; it now seeks to protect them from the qualified."

In the current climate, where issues of patient autonomy, openness and suspicion of the medical establishment dominate the health agenda, further safeguards are necessary in research, to protect the patient and to defend the trust and integrity that underpins the professional relationship between doctor and patient.

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