Legal reviews

This issue of the *Annals* sees the first in a new series of reviews dealing with legal aspects of surgical practice. We have asked several distinguished authors, expert in their field, to contribute to this series. Our aim is to provide up-to-date guidance for surgeons in potentially difficult areas of their practice and academic work, whilst at the same time re-affirming the legal boundaries within which they work.

The first in the series deals with the legal aspects of surgical research. It is written by Dr Tom Woodcock, who has much experience as the chair of a local clinical ethics committee and a continuing interest in the legal aspects of research on incapacitated patients. With a postgraduate qualification in medical ethics, he writes and lectures regularly on these topics.

Future articles will cover proxy consent, confidentiality and data protection, the genetic implications of surgical disease, the reasonable standard of care, the particular problems relating to children's surgery and the legal implications of tissue and its retention.

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Surgical research in the UK

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This review focuses on the history of, and recent developments in, the law and ethics of research with practical advice for surgeons conducting clinical research. Legal references apply to England and Wales or to Scotland, but the underlying ethical principles reflect modern approaches taken internationally.

KEYWORDS

Law – Ethics – Consent – Retained tissue – Publication – Research

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An historical perspective

The Nuremberg Doctors' trial had proven the need for guidelines on ethical research in 1946.¹ The World Medical Association adopted The Declaration of Helsinki in Finland in 1964. Physicians were to obtain consent from research subjects (or proxy consent) 'if at all possible'. In the light of the Declaration, contemporary examples of unconsented research were sought and soon found. Maurice Pappworth

exposed some practices in a 1966 magazine article and his book *Human Guinea Pigs: Experimentation on Man* in 1967.² He called for formal regulation of research with lay representation and clear accountability. In response, the Royal College of Physicians issued a Report and the Minister of Health requested health authorities to establish research ethics committees in 1968. The Department of Health first issued national guidance on research ethics committees in 1991.

Following Professor David Southall's publication in 1998 of a randomised, controlled trial of ventilation techniques for newborns with respiratory distress, an action group of parents alleged research misconduct and the UK Government commissioned an inquiry led by Rod Griffiths.³ Published in 2000, the report was critical of Southall and his colleagues and prompted the Department of Health to publish its first Research Governance Framework document in 2001.⁴ The Griffiths Report, in turn, was heavily criticised. It is now claimed that Southall has been exonerated of the allegations against him concerning that study.⁵

European legislation (Directive 2001/20/EC) obliged the Government to put in place the *Medicines for Human Use (Clinical Trials) Regulations (2004)*.⁶ At first, neither of these instruments allowed for unconsented research even for emergency treatment. An Amendment in 2006 addressed this problem.⁷ Directive 2005/28/EC provides detailed guidelines on good clinical practice and will be integrated into UK law. Good clinical practice is the standard provided by the tripartite (USA, EU and Japan) International Conference on Harmonisation. Curiously, the European Union only recognises the fourth revision of the Declaration of Helsinki (1996), ignoring the controversial fifth revision of 2000.⁸ The EC Directives and UK Statutory Instruments only apply in law to trials of medicines, but they form the basis of all research policies and are, therefore, enforceable by the requirements of the researcher's employer or professional body. They include regulations about the process of independent ethical review of any research proposal and the monitoring of adverse events. The General Medical Council issue specific guidance on research⁹ and their Indicative Sanctions Guidance (April 2005) states:

Research misconduct ... undermines the trust that both the public and the profession have in medicine as a science, regardless of whether this leads to direct harm to patients. Because it has the potential to have far reaching consequences, this type of dishonesty is particularly serious.

The Bristol Royal Infirmary Inquiry (Ian Kennedy) and the Royal Liverpool Children's Inquiry (Michael Redfern) published critical Reports in 2000 and 2001 and inspired Parliament to deliver the *Human Tissue Act (2004)*.¹⁰ Most recently, the disastrous experiments at Northwick Park Hospital with an antibody called TGN1412 have led to new advice on the management of Phase I trials.¹¹

The duty to obtain consent

The law on consent in healthcare is mostly derived from cases involving surgical practice, and so the process of consent to surgery has become extensive and formalised. A similarly meticulous and well-documented approach to

consent to trial participation is necessary. A particular difficulty in randomised trials is that the researcher must explain, and the patient must comprehend, each of the possible treatments before randomisation determines which will be provided. In non-blinded trials, a patient disappointed with the outcome of randomisation might choose to withdraw, to the detriment of the power of the trial. It has been argued that the research subject's altruism deserves an even more detailed presentation of relevant information, and the argument is especially strong where the subject is to receive treatment that might not otherwise be offered. The outcome of the TGN1412 trial reminded us of the need for subjects to understand that any medical intervention can rarely cause death or serious morbidity. The potential subject must be given as much information as is necessary in order to make a choice about participation. The consent process will involve both verbal and written information provision, with sufficient time allowed for consideration and deliberation. The research concepts of standard, control or placebo treatments for comparison with the experimental candidate, and the principle of equipoise which morally justifies randomisation and blinding are often difficult to explain. People with serious or life-threatening diseases may hold unrealistic hopes of benefit from participating in trials of 'new' drugs or procedures and they will need careful and compassionate counselling. It would obviously be of dubious morality to allow a desperate patient to consent to a trial in false hope of a cure.

The other form of coercion to consent is financial. The boundaries between reasonable expenses and financial incentives are obviously grey. It remains a fact of life that poorer people can earn a significant income from 'volunteering' to research projects, and advertisements for 'volunteers' are regularly placed in the street magazine *Big Issue*. The *Adults with Incapacity (Scotland) Act (2000)* gives power to guardians, attorneys, or close family members to provide proxy or surrogate consent to research,¹² but there is no legal basis for proxy consent to research on behalf of an adult who lacks capacity (the incapax) to make the decision in England and Wales. This inconvenient fact did not prevent research being approved and conducted on the incapax, sometimes with a 'waiver of consent' and sometimes with proxy consent, which some referred to as assent in recognition of the fact that the law did not embrace proxy consent. Such practices were justified by being compatible with international guidelines on good clinical practice, and approved by a research ethics committee. The *Mental Capacity Act (2005)* requires the researcher to identify somebody close to the patient who knows the potential subject well and is prepared to accept the duties and responsibilities of a 'Personal Consultee'. Where there is a patient-nominated Attorney or Court-appointed Deputy, this person may undertake the role of Consultee. In cases where no

such person can be identified, the researcher may instead invite someone to accept the duties of a 'Nominated Consultee'. The Consultee is given all the relevant information about the proposal to enlist the incapax, and his duty is to advise the researcher whether the incapax would have consented or refused. Guidance emphasises that the Consultee should put to one side any personal views on the proposal, and should understand that he or she is not giving or withholding consent. Nonetheless, Consultee advice will be determinative of whether or not the incapax participates and is self-evidently equivalent to the proxy consent required by international standards. It is recommended that the Consultee be given access to 'independent' advice about their duties and responsibilities in law.¹⁵ There are regulations addressing the rare instance of unanticipated loss of capacity during a research project, which reflect the principles applied to the care of the incapax.¹⁴

Where the investigation is into emergency interventions which preclude prior involvement of a Consultee, the Act requires the researcher to identify one or more doctors who are knowledgeable about, but not connected with, the trial, and who are willing to accept the responsibility to decide whether or not to agree to the inclusion of each patient into the trial. Recruitment will only be lawful with an agreement. In trials where there is no opportunity for agreement by an independent doctor, the research ethics committee may grant a waiver of the requirement for advice by a Consultee or agreement by a doctor, though consent of the patient or the advice of a Consultee must be sought at the earliest possible opportunity after the emergency. The guidance is silent on what to do in the case of fatal outcome, though common sense dictates that 'next of kin' and the Coroner should be appraised of what happened.

Patient information and retained tissue

Law normally requires consent from the individuals concerned before 'sensitive' data concerning their health are acquired and processed, or before the removal, storage and use of their tissues. The relevant Statutes are the *Data Protection Act (1998)*,¹⁵ the *Human Tissue Act (2004)*,¹⁰ and the *Human Fertilization & Embryology Act (1990)*¹⁶ concerning live gametes and embryos. The law does, however, permit ethically-approved research access to anonymised medical data and to 'residual' tissue. For England and Wales, Section 60 of the *Health and Social Care Act (2001)* confirmed that patient information can be shared for medical purposes, which include research and the establishment of disease registers, in the interests of improving patient care.¹⁷ The Patient Information Advisory Group (PIAG) was established as a statutory committee to be consulted about the regulations under Section 60. Researchers wishing to use patient information must obtain research ethics committee

approval before submitting an application to the PIAG. The *Health and Social Care Act (2008)* establishes the National Information Governance Board to replace the PIAG.¹⁸ Privacy advisory committees in Scotland and Northern Ireland fulfil a similar function in those countries. Anonymised data can be linked to the appropriate tissue, but there must be nothing in the information supplied to the researcher which would allow an individual 'donor' to be identified. Coding (that is, substituting the individual's name for a number linked to the name) is not an adequate anonymisation.

Publication ethics

Editors, reviewers or readers may notice in submitted or published articles unethical research conduct which has escaped the initial ethical review process. They may feel they have a duty to report this to an appropriate authority. There are also a number of areas of misconduct specific to the publication process.

Redundant or duplicate publication

Researchers must take care to identify in their manuscript any data or analyses which have been previously published in any format.

Plagiarism

From short, unattributed phrases to substantial paragraphs of text lifted from any source. In 2008, the General Medical Council found Rajendra Persaud guilty of dishonesty and of bringing the profession into disrepute for inadequately acknowledging the work of others in his books, articles and other media. Dr Persaud is a well-known broadcaster and author of books on psychiatric topics for the public.¹⁹ The non-professional nature of these media does not reduce the obligation to give clear acknowledgement of the work of others.

Fabricated data

Examples go from total fabrication of data to selective use of data whose aggregation results in unwarranted statistical results. Dr Julio Cruz escaped disciplinary action because he died before his fraud was discovered. He published three papers on the treatment of head injury with high-dose mannitol between 2001 and 2004. He died in 2005. Doubts were raised about the veracity of his reports in 2006, and enquiries found no evidence that he had conducted such research in any of the hospitals he had worked at.²⁰ A British cancer researcher was removed from the Medical Register in 2007 for plagiarism and misrepresentation.²¹

Unwarranted authorship

Doctors who claimed authorship of the papers describing Dr Cruz's experiments had no evidence that the work was 'real'.

Undisclosed conflict of interest

Researchers will benefit from the publication of their work, but it is to be expected that they will present their results objectively and that their conclusions will be uninfluenced by financial or commercial considerations. The extent to which a sponsor's generosity towards researchers can influence their objectivity is debatable. Any affiliation which could be seen to be a conflict of interest must be declared to the journal editor.

Publication ethics is increasingly formalised with guidance from bodies such as the World Association of Medical Editors²² and the Committee on Publication Ethics.²³

So you still want to do research?

There are now many hurdles to clear in planning and executing a research project. It can be tempting to attempt to answer a research question by 'audit' of existing practices in order to bypass many of the hurdles, and there can be no doubt that young surgeons are conducting 'audits' where they would have carried out 'research' in times gone by. The distinctions between clinical audit and clinical

research can be very unclear.²⁴ A defining characteristic of research is that its results can be trusted to inform evidence-based practices, and so there is an imperative to help researchers through the jungle of regulations. A number of organisations provide useful websites.

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Table 1 Useful websites relating to research ethics

Research reports from The Royal College of Surgeons of England
<http://www.rcseng.ac.uk/surgical_research_units/report.html>

Clinical Trials Toolkit from the Department of Health and the Medical Research Council
<<http://www.ct-toolkit.ac.uk/>>

Using personal information and human tissue samples in healthcare research, from the Medical Research Council
<<http://www.dt-toolkit.ac.uk/home.cfm>>

UK Clinical Research Collaboration
<<http://www.ukcrc.org/>>

Research Regulatory & Governance Advice Service
<www.ukcrc-rgadvice.org>

Good Practice in Research, General Medical Council
<<http://www.gmc-uk.org/guidance/current/library/research.asp>>

Medical Research Council's Ethics and Governance page
<<http://www.mrc.ac.uk/PolicyGuidance/EthicsAndGovernance/index.htm>>

The National Research Ethics Service at the National Patient Safety Agency
<<http://www.nres.npsa.nhs.uk/>>