Ethics in clinical trials

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Abstract

Although one of the first pieces of legislation to address ethical issues in clinical trials was drawn up following the findings from the Nuremberg Trials, only in the most recent clinical research have the principles of beneficence, non-maleficence, autonomy and justice been considered and informed consent plays a major role. In the UK, the National Research Ethics Service and the Medicines and Healthcare Products Regulatory Agency require compliance with Good Clinical Practice. Patients are unlikely to participate in, or clinicians consent their patients to, trials where they do not feel safe or protected – data and safety monitoring assess for loss of clinical equipoise thus ensuring the most efficacious treatment is always available. Honesty and trust are crucial and place an obligation on investigators to disseminate even less favourable trial results, with the ultimate aim being partnerships between patients, their families, and those delivering the research which are mutually beneficial and respectful.

Keywords Clinical trials; equipoise; good clinical practice; informed consent; legislation; research; research ethics

Royal College of Anaesthetists CPD Matrix: 3J03

Learning objectives

After reading this article, you should be able to:

- identify the 10 ambitions set out by the Department of Health to ensure the NHS remains world-leading in the delivery of healthcare
- recognize significant historic and current legislation for clinical research and summarize the connecting principles
- discuss clinical equipoise

Clinical research has been around, in one form or another, since the biblical era. However, it is only in far more recent times, since World War II, that concepts such as Beauchamp and Childress's four principles of beneficence (providing benefits to persons and balancing those against risks and costs fairly), non-maleficence (the obligation to avoid inflicting intentional harm), autonomy (a person's right to make choices, to hold views and to take actions based on personal values and beliefs) and justice (treat all equitably and distributing benefits and burdens fairly) have been taken into consideration.[1]

The Department of Health: Shared Delivery plan 2015–2020 sets out ten ambitions (see Box 1) for ensuring the NHS is world-leading in all it does, by being well-led, always learning to improve and is more efficient – reducing waste and making sure public money is spent wisely.[2]

Each of these ambitions has been laid down with the vision of ensuring each person can access the health and care that they need when they need it, that people are supported throughout life to stay in good health or to be supported in living as independently as possible.

These bold intentions can also be applied to clinical trials. Clinical trials provide us with the knowledge required to determine the most precise course of treatment for a specific health condition, which in turn enables us to fulfil the above ambitions.

One of the first pieces of legislation to address ethical issues in clinical research was the Nuremberg Code. This was drawn up following the findings of the Nuremberg Trials – the tribunals which brought retribution for some of the atrocities inflicted during World War II. A main criticism is that it was very closely based on the guidelines for therapeutic and scientific research on human subjects – originally published as Circular of the Reich Minister of the Interior on February 28th, 1931 – without any credit or reference being given. Another criticism is that The Nuremberg Code is not regularly reviewed or updated – unlike the Declaration of Helsinki.[3,4]

Informed consent

Informed consent was the main clause of The Nuremberg Code and is a major element of trial safety today, as the key motivation is to inform and protect participants of clinical studies.[5] There are numerous aspects to the concept of informed consent – each participant MUST be informed, competent and a volunteer. To this end, they must be free and able to make an informed choice, having had appropriate access and sufficient time to digest all the available information regarding the trial. Participants must also be made aware of their right to abstain from participation, as well the ability to withdraw at anytime without reprisal. Documentation of consent is fundamental and strict adherence to the requirements is essential.

Consent is not a single procedure – it is an active and ongoing process which should be sought and updated appropriately and additional safeguards may be required, depending upon the circumstances and the vulnerability of each individual. This would include those who are not able to be completely autonomous; those who are unable to read or write, children under the age of 16, adults with incapacity and those requiring emergency procedures.[6]

Those unable to give informed consent

Those requiring emergency treatment or who are critically ill are, in most instances, unable to give informed consent due to their lack of capacity and this gives rise to concern in the participation in clinical trials. However, it can be argued that to deny these

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The ten ambitions from The Department of Health: Shared Delivery plan 2015–2020

1. Improving out-of-hospital care
2. Creating the safest, highest quality healthcare services
3. Maintaining and improving performance against core standards while achieving financial balance
4. Improving efficiency and productivity of the health and care system
5. Preventing ill heal and supporting people to live healthier lives
6. Supporting research, innovation and growth
7. Enabling people and communities to make decisions about their own health and care
8. Building and developing the workforce
9. Improving services through the use of digital technology, information and transparency
10. Delivering efficiently: supporting the system more efficiently.

Box 1

patients access to new therapies under investigation is also unethical. In these situations, and given satisfactory ethical and scientific justification, next of kin can accede to requests for consent and this will allow access to the trial. The same is also true for research which is for the participation of children. For adults with incapacity due to mental health conditions, The Mental Capacity Act (2005) seeks to limit situations in research which may cause ethical concern.[7]

The abuses of vulnerable people, such as those which took place in the name of research at Nuremberg, Joliet and Tuskegee (amongst others), have had a part to play in the forming of the modern legislation which governs clinical trials. The malfeasance of these now notorious trials necessitated a process for informed consent and the responsibility of the researcher to ensure that any risks taken by the participant were commensurate with the anticipated gain.

Current legislation

Despite its criticisms, The Nuremberg Code has helped shape future legislation. Nowadays, there have been a great many safeguards put in place to ensure that clinical trials are run with the health and privacy of the participants at the forefront; such as the Declaration of Helsinki, in 1964, which is updated regularly and sets down fundamental ethical principles core to clinical research.

Within the UK, two bodies which govern the approval and monitoring of clinical trial are the National Research Ethics Service (NRES) and the Medicines and Healthcare Products Regulatory Agency (MHRA) and both enshrine the principles of the Declaration of Helsinki.

All clinical research carried out within the NHS in the United Kingdom, also demands compliance with a set of principles called Good Clinical Practice (GCP). The International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use issued guidance for GCP in 1996. GCP contains 13 principles, which are widely accepted across the world and set out guidelines for how clinical trials should be conducted – although it is worth noting that, in the UK, the MHRA inspect sites against the various UK legislative documents, not the ICH-GCP.

Renowned bioethicist David Resnik summarized the principles he found to be addressed in many of the pieces of global legislation, guidelines, codes and policy documents in his 2015 essay *What is Ethics in Research & Why is it Important?* and produced 16 key points (Box 2).[8]

Avoidance of harm

It is imperative that trial participants must be kept safe from all avoidable injury and harm. In order to avoid harm, the Declaration of Helsinki has previously been amended to include the stipulation that where possible, all trials should be tested against current best therapies.

The use of placebo within a randomized controlled trial is a questionable element of this. Randomized controlled trials are generally considered to be the 'gold standard' when it comes to the testing of new therapeutic products; however, whether to use a placebo or a currently licensed drug to test against is a significant consideration. It has often been asked if it is ethical to treat patients with the same disease with different treatments.

Clinical equipoise

This is where the concept of clinical equipoise comes into play. Clinical equipoise is when genuine uncertainty or conflicting opinion exists regarding the therapeutic merits of treatment arms in a trial. No patient on a trial should ever receive less that the current standard of care, thus clinical equipoise ensures that no trial arm (or placebo) offers treatment which could be considered inferior to available alternatives.

Patients are unlikely to participate in trials where they do not feel safe – where the risks outweigh the benefits – and clinicians will not enrol patients to trials where they believe the participants to be receiving inferior therapy. This can cause conflict if a course of treatment for a patient means the choice between proven therapies or participation in a randomized clinic trial and equipoise has been proposed to address this. If investigators have a genuine belief that one treatment option is superior, they would be ethically obliged to offer that treatment to patients above all else, but by ensuring that treatment arms (including placebo) of a trial have equal therapeutic merits, randomization can become less unappealing.

One criticism of equipoise would be that there is a predilection to the early closure of trials with the loss of equipoise. In large multi-centre trials that are ongoing over a number of years, there is a need for interim data analysis and monitoring. This allows for the evaluation of early evidence of interventional differences. If significant differences come to light, it may be necessary to halt the trial to allow for further safety reviews and protocol appraisal.

Data and safety monitoring of clinical trials attempts to negate any ethical concerns regarding a shift in the equipoise of treatment arms, although there will always be a degree of uncertainty. Given that uncertainty, the safety monitoring of any participant is of utmost importance and written into legislative documents. It also covers the pharmacovigilance of pharmaceutical trials; that is the science of collecting, monitoring, researching, assessing and evaluating information on the adverse effects of medicines with a view to identifying information about potential new hazards and preventing harm to subjects. If the regulations laid

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