OVERVIEW

- Patients might access experimental treatments if other treatments have not worked or are not available.
- There are several ways in which experimental treatments can be offered legally to UK patients, or patients may travel abroad to access treatments not offered in the UK.
- The use of experimental treatments can raise ethical issues such as: difficulties in assessing efficacy and safety; ensuring fairness of access; challenges around decision making and consent; potential impacts on knowledge generation; and ensuring healthcare professionals act responsibly.
- Particular issues are raised in the context of experimental advanced therapies (such as gene and stem cell therapies), fertility treatment ‘add-ons’, and innovation in surgery.
- A core challenge is balancing the interests of patients in accessing experimental treatments and the need to support innovation, with ensuring there are sufficient safeguards to protect patients from potential harm(s).

INTRODUCTION

In some circumstances, patients can access medical treatments before they have been subject to rigorous testing and approved by medical regulators, which are often referred to as ‘experimental treatments’. Patients might access these treatments when they are in a desperate situation, have exhausted all other options, or are not able or do not want to wait for the approval process.¹

This briefing note considers why, and in what contexts, patients might access experimental treatments, how they are regulated in the UK, and ethical questions raised by their use.
WHAT DO WE MEAN BY ‘EXPERIMENTAL TREATMENTS’?

We use the term experimental treatments, but terms used elsewhere include innovative, novel, unproven, unvalidated, non-standard, and unlicensed treatments. There is a spectrum of treatments that might be considered to be experimental, from those which have never been used in humans, to those which are used routinely but are not licensed for the condition in question. Experimental treatments include medicines, surgery, the use of medical devices and implants, stem cell and gene therapies, and fertility treatments.

This briefing note does not consider treatments that are being tested in clinical trials, as these are subject to specific regulatory frameworks. The use of complementary medicine is explored in a separate paper by the Nuffield Council on Bioethics.

WHY MIGHT PATIENTS CONSIDER EXPERIMENTAL TREATMENTS?

Patients and their families might consider experimental treatments if proven treatments have not worked or are not available. While some patients can access experimental treatments by participating in clinical trials, not all patients are eligible for or able to take part in trials. In addition, the process of testing and approving new treatments through clinical trials is often complex and lengthy, particularly for medicines.

Patients’ decisions about experimental treatments might be influenced by a range of factors including their own values and goals, the views of their family and community, advice from healthcare professionals and others, marketing activities of companies offering treatments, and available funding.

REGULATION AND GOVERNANCE

There are several ways in which experimental treatments can be supplied and offered to patients within the UK legal and regulatory framework. There is uncertainty about how some medical treatments will be regulated when the UK leaves the EU, although the UK regulatory body for medicines and devices has stated a commitment to continuing close working relationships with European partners.

REGULATION OF PRODUCT SUPPLY

Medicines must have marketing authorisation (a licence) before they can be supplied in the UK, from either the UK authority - the Medicines and Healthcare products Regulatory Agency (MHRA) - or the European Commission (EC) after assessment by the European Medicines Agency (EMA). The licence is issued following evidence gathering and clinical trials to assess a medicine’s safety, quality, and efficacy, and commits the manufacturer to ongoing drug safety monitoring. However, EU Regulation includes a provision for compassionate use of unauthorised medicines. In the UK, the specials exemption allows the supply of an unlicensed medicine on request from a healthcare professional in order to treat a patient in their care where no equivalent licensed treatment is available. The early access to medicines scheme (EAMS) gives UK manufacturers a route to offering medicines 12-18 months before they have been licensed. Manufacturers can apply if they have promising scientific evidence on efficacy, and there is a clear unmet medical need.

Medical devices and implants must have a CE mark, which certifies that they meet European safety and performance standards, before they can be supplied in the UK. However, clinicians and manufacturers can apply to the MHRA for exceptional use of a medical device that has not been CE-marked if there is no certified device available that meets the needs of an individual patient. The device manufacturer must provide evidence of safety and the clinician must provide justification for its use. Under the in-house manufacture exemption, devices that are made in a healthcare establishment can be used for patients within that establishment without certification.

Advanced therapies, such as stem cell and gene therapies, must have a centralised European marketing authorisation, granted by the EC following assessment by the EMA, before they can be supplied in the UK and Europe. However, the hospital exemption allows ‘non-routine’ use of custom-made advanced therapies provided they are manufactured in authorised facilities and used...
in the same member state. There is no requirement to notify the MHRA of treatments offered under the hospital exemption.20 The specials exemption can apply to advanced therapies as well as medicines, where no equivalent licensed treatment is available.21

REGULATION OF MEDICAL PRACTICE

General Medical Council (GMC) guidance states that healthcare professionals must provide effective treatments based on the best available evidence, and that patients must be told whether a proposed treatment is experimental and about any additional risks or uncertainties.22 Beyond this, and within the constraints of available funding, it is up to healthcare professionals to judge what treatment to offer based on their knowledge of the patient. This can involve administering or prescribing unlicensed treatments, or prescribing licensed medicines or CE-marked medical devices ‘off-label’, which means for a use or purpose different to that for which they have been licensed.23 This could include use for a different dosage, a different duration of treatment, or in a different patient group, such as a drug which has only been licensed for adults being prescribed to a child, or a different disease.24

Following a legal challenge mounted by two pharmaceutical companies, a UK Court recently affirmed that the drug Avastin, a licensed cancer treatment, can be prescribed off-label for a common eye condition which it is also known to be effective for.25

EMERGENCY SITUATIONS

In a rapidly spreading epidemic or other emergency situation with high mortality rates it might not be possible to initiate clinical trials immediately, and national authorities can allow experimental treatments as part of the emergency response.26

FUNDING OF EXPERIMENTAL TREATMENTS

According to NHS commissioning policy, it is standard practice not to fund treatments that are considered to be experimental, however, exceptions can be made.27 The NHS Cancer Drugs Fund can be used to fund access to promising and newly-licensed cancer drugs while further evidence is collected.28 As part of compassionate use schemes, manufacturers might offer experimental medicines free-of-charge to eligible NHS patients until there is sufficient evidence to decide whether its use should be funded across the NHS.29

When patients or those caring for them seek treatments outside the NHS or abroad, they will usually have to source their own funding. Crowdfunding websites have emerged in recent years as a way to raise funds for costly medical treatments.30 According to a recent study, more than 540 crowdfunding appeals have sought to raise money for UK patients to have experimental or alternative cancer treatments since 2012, most of which were offered abroad.31

ACCESS TO EXPERIMENTAL TREATMENTS IN DIFFERENT CONTEXTS

How patients access or are offered experimental treatments varies in different areas of healthcare. Below are some examples.

ADVANCED THERAPIES

Advanced therapies, such as stem cell and gene therapies, is a developing area of research.32 Treatments in the pipeline are often aimed at conditions for which there is currently no effective cure, such as some cancers, multiple sclerosis, and muscular dystrophy.33 Some advanced therapies have already been approved and are available to NHS patients, but they are mostly offered on a small scale bespoke basis to individuals and in research contexts.34 These therapies can be highly expensive to develop, to bring to market and, once approved, to provide to patients.35

UK patients can access experimental advanced therapies in other countries such as the US, Australia, and Germany.36 Different regional or national authorities might apply different standards of evidence before a treatment is approved. UK regulators have no power over clinics outside the jurisdictions of the UK, and are limited in the ways they can support patients travelling abroad for treatment.37 Concerns have been raised about the
marketing practices of unregulated and sometimes unscrupulous clinics, the influence of overly optimistic media reports, and public campaigns for access to very early-stage therapies.\textsuperscript{38}

**FERTILITY TREATMENT**

Within the private fertility treatment sector, patients are increasingly offered ‘add-ons’ alongside their main fertility treatment with the aim of improving the chance of a successful pregnancy.\textsuperscript{39} There are strong incentives for patients to consider add-ons to maximise their chance of conceiving, given the cost and emotional and physical stress of fertility treatment.\textsuperscript{40}

Typically, add-ons cost between £50 and £8,000.\textsuperscript{41} There is limited evidence to support their use. Over 70\% of fertility clinics in the UK offer add-ons which have been rated by the Human Fertilisation and Embryology Authority as having insufficient or no evidence to show that they are effective and safe. A recent study found that some clinics in the UK provide misleading or inconsistent information about the available evidence for add-ons.\textsuperscript{43}

**SURGERY**

There is a strong culture of innovation in surgery.\textsuperscript{44} The Royal College of Surgeons emphasises that the use of surgical techniques that deviate significantly from established practice must be underpinned by rigorous clinical governance processes.\textsuperscript{45}

However, it has been reported that surgical procedures are frequently used without first being tested in clinical trials, and with no long-term follow-up of patients, systematic outcome reporting or information sharing.\textsuperscript{46} There is a lack of systematic oversight of new surgical procedures in NHS hospitals.\textsuperscript{47} There have been cases of patients not being informed that the surgical procedure they are being offered is non-routine.\textsuperscript{48}

Testing surgical procedures in traditional clinical trial models can face both practical and ethical challenges.\textsuperscript{49} There is a lack of clarity about what constitutes a new intervention and what is a modification.\textsuperscript{45} Initiatives such as the IDEAL Collaboration are seeking to create a framework for surgical innovation and encourage systematic outcome reporting as a professional duty for surgeons.\textsuperscript{51}

**ETHICAL ISSUES ARISING FROM THE USE OF EXPERIMENTAL TREATMENTS**

**SAFETY AND EFFICACY**

Assessing the efficacy and safety of a treatment is a challenge when there is limited research evidence and little or no clinical experience of use, creating high levels of uncertainty. Factors that might be undetermined before clinical research has concluded include the appropriate dosage and other interventions required to make a drug safe and effective.\textsuperscript{52} A previous Nuffield Council on Bioethics report highlighted the particular uncertainty around safety and long-term effects of the use of novel technologies that intervene in the brain.\textsuperscript{53} Safety concerns have also been raised about the use of some off-label medicines in children – see Box 1.

For patients who have limited options, uncertainty about safety and efficacy may be outweighed by the possibility, even if very slight, that the treatment could be effective for them.\textsuperscript{54}

**BOX 1. UNLICENSED USE OF MEDICINES IN CHILDREN: CISAPRIDE**

By 1999, the drug Cisapride had been prescribed to over 36 million babies and young children worldwide to treat reflux, even though it had not been licensed for children under 12 years old.\textsuperscript{55} It was withdrawn from routine use in the UK in July 2000 because of concerns about rare but very serious adverse effects, including sudden death, death from cardiac arrhythmia, and serious non-fatal arrhythmia. A later review found no clear evidence that Cisapride had significant benefits compared with placebo.\textsuperscript{56}
BOX 2. DISAGREEMENTS ABOUT THE USE OF EXPERIMENTAL TREATMENT IN CHILDREN: THE CASE OF CHARLIE GARD

Charlie Gard was a critically ill infant who had a rare degenerative condition. His parents wanted him to have experimental nucleoside therapy in the US and raised the necessary funds through crowdfunding. This therapy had never undergone a clinical trial, nor been used to treat this particular disease, but a US neurologist believed it might offer a small chance of improvement to his quality of life. Disagreement arose between the parents and Charlie’s medical team, who thought that having the treatment would not be in Charlie’s best interests. Following a protracted and high profile series of court cases, judges ruled that Charlie should not have the treatment. Life support was withdrawn and Charlie died in July 2017.64
experimental treatments include: responsibility in avoiding hype and false promise; humility in acknowledging the limits of current knowledge; and trustworthiness.\textsuperscript{70}

While their primary duty is to offer the best possible treatments for their patients, healthcare professionals also might be driven by financial incentives, the desire to advance medical knowledge in the interests of future patients, and enhance individual or institutional reputation.\textsuperscript{71} Studies in the US and Australia have highlighted conflicts of interests arising from relationships between surgeons and medical device providers, which incentivise innovative uses of medical devices.\textsuperscript{72} Guidance on conflicts of interests has been published by the British Medical Association, and the Association of the British Pharmaceutical Industry.\textsuperscript{73} Professionals have a responsibility to report adverse effects of any medicines or medical devices, including those that are unlicensed or used off-label, to the MHRA or to the manufacturer who has an obligation to notify the MHRA.\textsuperscript{74}

EQUITY AND FAIRNESS

Access to experimental treatments is unequal. Not everyone can afford treatments that are available privately or abroad, and there are differences between and within European countries in how compassionate use schemes are used.\textsuperscript{75} How quickly patients can access experimental treatments also can vary, for example, between Scotland, England and Wales.\textsuperscript{76}

Moreover, while manufacturers might be allowed to offer experimental treatments, there is no guarantee that they can or will offer them to all the patients who might benefit – see Box 3.\textsuperscript{77} Early access to expensive treatments might also raise questions of distributive justice if resources are diverted from elsewhere in the NHS without strong evidence of their benefit.\textsuperscript{78}

IMPACT ON RESEARCH AND KNOWLEDGE GENERATION

When experimental treatments are provided outside of a clinical trial, information about their efficacy and side-effects might not be recorded and shared, hampering knowledge generation.\textsuperscript{81} For example, while adverse reactions must be reported to the MHRA when an experimental medicine is supplied under the specials or hospitals exemption, there is no obligation to report other outcomes.\textsuperscript{82}

Efforts have been made to ensure that the outcomes of experimental treatments are recorded. NHS Commissioning policy requires that any experimental treatments funded should contribute to the knowledge base, for example by requiring that data are submitted to clinical databases.\textsuperscript{83} The World Health Organization has developed an ethical framework for Monitored Emergency Use of Unregistered Interventions, which includes an obligation to collect and share meaningful data.\textsuperscript{84} In the UK, the Access to Medical Treatments (Innovation) Act 2016 proposes a register of experimental treatments provided by doctors in England.\textsuperscript{85} However, no such register has been set up and what purpose it might serve is debated.\textsuperscript{86}

A separate concern is that healthcare professionals might offer experimental treatments to patients as a way of bypassing research, given real and perceived challenges and obstacles to initiating clinical trials, such as lengthy timelines, a lack of eligible patients, and a lack of support from funders.\textsuperscript{87}

BOX 3. COMPASSIONATE USE OF EXPERIMENTAL TREATMENTS: HIV DRUGS IN FRANCE

When French authorities allowed compassionate use of experimental anti-retroviral drugs for HIV patients in early 1996, manufacturers could initially only produce enough of the drugs to treat a small proportion of the 18,000 potential patients, and the national ethics committee recommended drawing lots to randomly allocate treatments.\textsuperscript{79} Eventually, 11,000 patients were able to access the drugs through the compassionate use programme, which is estimated to have led to a significant drop in hospitalisation rates and deaths. The drugs were given marketing authorisation later that year.\textsuperscript{80}
CONCLUSIONS

Patients who have limited options might wish to access experimental treatments despite uncertainties about safety and efficacy and the often substantial financial costs involved. Healthcare professionals have important responsibilities to support patients to make informed decisions about treatments for which evidence is limited. Particular issues arise when making decisions about the use of experimental treatments in children and others without capacity to decide for themselves. A key challenge is balancing the interests of patients in accessing experimental treatments with ensuring protection from harm, particularly when treatments are offered outside the UK regulatory framework. Further questions are raised about how best to capture the knowledge gained from the use of experimental treatments, and ensure that their offer does not undermine research that might benefit patients in the future.

REFERENCES

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21   Medical Research Council Regulatory Support Centre; The Association of the British Pharmaceutical Industry; Committee of Advertising Practice; and Tsachi Keren-Paz, University of Sheffield.

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