



Clinical Trials



Clinical trials benefit the health and safety of patients by making proven new treatments available more quickly. This industry is also very important for the UK economy. However, recent years have seen a drop in the number of trials held in the UK. This POSTnote summarises some of the most important reasons behind this decline, and the actions being taken to improve the situation. It also highlights areas identified by key industry partners as opportunities for growth.

Clinical Trials

Purpose

Clinical trials are studies designed to test whether medical interventions are safe, effective, and work well in the intended patient population. In the EU, no new medicine can reach the market without being clinically tested and proven in humans. Globally, regulations vary for proving a treatment's medical safety and "efficacy" (capacity to produce the intended effect). Non EU producers must ensure that equivalent principles and standards have been met in their trials prior to being marketed in EU member states. With its academic and industrial science base, the National Health Service, and a high proportion of patients who are keen to participate, the UK has a strong basis for conducting high quality clinical research.

Design and Regulation

Different legislative instruments control how various medical treatments are regulated and tested in the EU. This POSTnote focuses on clinical trials of "Investigational Medicinal Products" (IMPs), which fall under the European Clinical Trials Directive 2001/20/EC (the CTD). These

Overview

- The UK is losing its global allocation of clinical trials, with negative effects for patients, the economy, and support for innovation in the NHS.
- To improve the situation, reforms of clinical trial regulation and governance are planned or already under way, at UK- and EU-level.
- A key aim is to make regulatory requirements proportionate to the risk posed by a trial, and to make the process of gaining trial approval faster to complete.
- A Health Research Authority (HRA) will be set up in 2011 to oversee all health research regulation in England.
- There will be an increasing need for changes in trial design and in the type of evidence required by regulators, to reflect both the changing nature of medicinal products, and the specific make-up of populations who use the medicines.

include traditional pharmaceutical medicines and also "biologics" (or "biopharmaceuticals"), derived from organisms or biotechnology processes. They include vaccines, monoclonal antibodies (immune system proteins), and recombinant proteins (artificially produced proteins such as human growth hormone). In some cases, stem-cell and gene therapies ("advanced therapies") are considered to be IMPs and therefore fall under the regulation of the CTD.

Clinical trials progress in phases, providing the results of each phase are favourable. First, "pre-clinical" studies are performed to test potential new treatments in animals, and sometimes also on cells in the laboratory. If those steps indicate that the treatment shows efficacy and no obvious medical safety issues, phases I-IV of clinical trials in humans follow (see Box 1).

Each EU state implements the CTD through its own national regulatory system. To carry out a clinical investigation in the UK, a strict pathway of regulatory and governance approvals must be followed (see Box 2). Steps along the

Box 1. Clinical Trial Design and Phases

Clinical trials are carefully designed and highly controlled to minimise bias and to generate statistically reliable evidence with which to measure a treatment's efficacy and safety. This is achieved by selecting an appropriate number of patients, and by comparing the new treatment (or combination of treatments) against either a placebo or the current standard treatment.

Phase I trials include the first in-human tests, so their main aim is often to test the safety of the treatment. These typically use small numbers of healthy volunteers (often fewer than 10), or patients who are ill and have few other treatment options.

Phase II trials use about 20 to a few hundred volunteers or patients. Phase IIA trials test dosage levels, and phase IIB trials assess efficacy (the ability of the medicine to treat the disease or symptoms).

Phase III trials may involve up to several thousand patients to definitively assess efficacy of the treatment. Large numbers of participants are necessary to provide statistically reliable evidence, and to spot less common side-effects.

Phase IV occurs after the treatment is licensed for marketing. These trials are for safety surveillance ("pharmacovigilance") to detect any rare or long-term adverse effects in the wider patient population, and to compare against competitors' products or current medical practice.

pathway check the soundness of the trial design, associated ethical issues, funding, capability of the sites involved (often hospitals), and any necessary licences or approvals for specific activities (such as using human tissue, radiation therapy, or gene therapy).

Falling Numbers of Clinical Trials

Historically, the UK has been a world leader in medical research. However, in recent years the UK's standing in the clinical trials market has slipped. In particular, between 2002 and 2006, the UK's global share of patients in trials fell from 6% to 2-3%, a trend that has continued since then.¹ A similar trend has recently been seen throughout other EU member states. Professional bodies attribute this to different factors at international- and UK-level.

International Context

Clinical trials have been moving away from Western Europe due in part to a combination of EU legislation and the emergence of new pharmaceutical markets elsewhere.

The EU Clinical Trials Directive (CTD)

Multi-centre trials (using patients at multiple locations, often in multiple countries) are important because of the need to recruit large groups of patients for late phase trials. The CTD was implemented in 2004 to simplify and harmonise the administrative requirements for clinical trials across the EU.² However, it has been widely criticised for its non-proportionate "one size fits all" approach to regulatory requirements. For example, there is a perception that under the CTD all studies must fulfil demanding "Good Clinical Practice" (GCP) requirements, regardless of the risks a trial poses. In addition, some aspects of the CTD's rules are open to interpretation, which has led to differing implementations across EU member states. This has

Box 2. Regulatory and Governance Bodies for UK Clinical Trials

All trials need approval from:

- the **Medicines and Healthcare Products Regulatory Agency (MHRA)**, the UK's "competent authority". This authorises trials based on their purpose and soundness of scientific design. (It also evaluates and licenses treatments following the evidence from trials);
- the **National Research Ethics Service (NRES)** in England, or equivalent research ethics services in the devolved nations. These grant ethics approvals via recognised Research Ethics Committees;
- **Research and Development offices** (of NHS Trusts for example). These grant site-specific permissions and agreement on payment contracts at locations of trials.

Depending on the nature of the trial, other approvals might come from:

- the **Human Tissue Authority (HTA)**. This licenses premises where human tissue is obtained, manipulated, stored, distributed, imported or exported;
- the **Human Fertilisation and Embryology Authority (HFEA)**. This grants project licences for trials involving human embryos;
- the **Administration of Radioactive Substances Advisory Committee (ARSAC)**. This certifies doctors to administer radioactive therapies.

For a licensed treatment to be accepted for use in the NHS, its evidence must be evaluated and approved by the **National Institute of Health and Clinical Excellence (NICE)**. In addition to the controls of each EU member state's competent authority, the **European Medicines Agency (EMA)** and its scientific committee evaluate certain medicinal products, such as new active substances and "advanced therapies" (e.g. cell- or gene-therapies), and can issue Europe-wide marketing authorisations.

complicated the process for arranging multi-centre trials, incurring unnecessary costs and delays.

Global Markets and Patient Recruitment

Increasingly, trials are being conducted in Asia (particularly China and India), South America (Brazil), Russia and Eastern Europe (Poland and Hungary). One reason for pharmaceutical companies to place trials in Asia and South America is the emergence of large markets for their products. Genomic differences can lead to drugs being more or less effective in different ethnicities. It is therefore reasonable that different nations expect evidence of the safety and efficacy of these new products in their own populations. The costs and timelines for trials in these countries can also be significantly lower than in the EU, and the quality of some of their research facilities now rivals the best in Western Europe and the USA. Large population sizes make it easier to recruit adequate numbers of participants as well, enabling a large trial to be conducted within the regulatory framework of a single country. In addition, more volunteers and patients in poorer or less medically-developed countries are "treatment naive". That is, they have not taken other treatments which might confound the results of the study.

UK Context

Within the UK itself, some specific problems have been identified:

- the time to start-up trials: There is wide agreement that this is the largest obstacle to clinical research in the UK.

Numerous regulatory bodies are involved, as outlined in Box 2. It can take years to complete the approvals pathway and recruit enough participants. The steps managed by the Medicines and Healthcare Regulatory Agency (MHRA) and the National Research Ethics Service (NRES) are processed within defined approval timelines. By far, the most criticised step in the pathway is obtaining Research & Development (R&D) permissions, where the participating trial sites assess the feasibility of conducting the study there. Because every NHS site is a separate legal entity, each one involved must complete the R&D permission. For many trials, that process has lacked oversight, with no agreed timeline, no incentive for completion, and often inconsistency between NHS sites in their interpretation of checks. Consequently, a trial may already be underway in other countries while the UK is yet to start;

- the UK's interpretation of the CTD: In the UK, the CTD is implemented through the Medicines for Human Use (Clinical Trials) Regulations 2004.³ The Regulations closely reflect the wording of the CTD, but their day-to-day interpretation can involve a stricter approach to some requirements and definitions than in other Member States. The UK is therefore perceived to have "gold-plated" the Directive.

Reforms of Clinical Trials Regulation

Over the past few years several actions have been taken to improve the situation, at both UK- and EU-level.

Reforms at UK Level

In addition to the initiatives outlined in Box 3, significant efforts have been made to assess and improve UK clinical trial regulation and governance.

The Academy of Medical Sciences' Report

In response to a request from the government, the Academy of Medical Sciences (AMS) published a report assessing the barriers to health research in the UK in January 2011.⁴ It made a series of recommendations for improvements, the most notable of which being the establishment of a single health research agency. The AMS proposed the agency should:

- provide a single system for both general and specific ethical approvals and licences, thereby bringing together the functions that are currently fragmented across NRES and multiple other bodies;
- oversee a streamlined, common process for NHS R&D checks to agreed timelines. The agency would undertake study-wide checks centrally, to ensure consistent national standards and interpretation of requirements, while local R&D feasibility and delivery checks would be performed by the NHS Trusts involved;
- work with the MHRA to improve the regulatory environment for clinical trials.

The Plan for Growth and the Health Research Authority

Several of the AMS' recommendations were taken forward by the government in the Plan for Growth,⁵ published

alongside the 2011 Budget. As well as pledging to "reduce perceived gold-plating and increase the proportionality" of the EU CTD, the government announced its intention to form a single health research agency, to be known as the Health Research Authority (HRA). This will be set up in 2011, aiming to "create a unified approvals process and promote proportionate standards" for health research. Initially, it will be set up as a special health authority with NRES at its core, to allow for a single system for ethics approvals and licences. Later on, the HRA will be established through primary legislation, when it may also take on the research approvals or licensing functions of other regulatory bodies, such as the Human Tissue Authority (HTA) and the Human Fertilisation and Embryology Authority (HFEA). The government intends to consult on this in late 2011.

Current plans mean that the HRA will not directly manage any NHS R&D permissions, contrary to the AMS proposal. It will instead oversee a national system of research governance, within which the permissions process will be coordinated and monitored by the National Institute for Health Research (NIHR). Some initiatives exist to increase the speed and efficiency of the permissions process. Since May 2011 the NIHR has provided its Research Support Services as a framework of good practice and standard procedures for the permissions process. From 2013, NIHR funding for providers of NHS services will be conditional upon several performance criteria, including a benchmark of 70 days from the receipt of the "valid protocol" for the R&D application to the recruitment of the first trial participant.

Reactions to the Plan for Growth

Some stakeholders harbour concerns about these announcements.

- On the proposed 70-day timescale for recruiting first patients, timely recruitment of the *full target* number is envisaged as being more important; additionally, in the case of rare diseases, it can take a long time to find a suitable patient.
- The Plan also states that the government will "build a consensus" on the use of electronic "e-Health" records, and publish plans by Autumn 2011 for a secure data service linking large healthcare data sets. e-Health records, piloted by the previous government, could help researchers to identify potential trial participants. There are currently plans to implement a less comprehensive service. According to the Department of Health (DH), this will prioritise the data sets of most significance for the UK's international competitiveness, but many professional bodies feel that these plans, which they perceive as providing only basic functionality, miss an important opportunity for UK medical research.

Reform at EU Level

Between January 2010 and May 2011, the European Commission (EC) launched public consultations to assess how the CTD could be improved. Key questions concerned how to process authorisation requests for trials in multiple member states, how to take a more risk-proportionate

approach, and how to clarify definitions to avoid an unnecessary regulatory burden. The EC is expected to put forward a revised draft of the Directive in 2012.

The UK's official response, published by the MHRA, the Department for Business, Innovation and Skills (BIS) and the DH, stated that the UK:

- strongly urges the EC to prioritise the redraft of the CTD with a view to early implementation (the revised CTD is unlikely to be implemented for several years yet);
- strongly supports the adoption of a risk-adapted approach to approval of all trials under the CTD;
- supports an optional co-ordinated assessment procedure (CAP) to assess trial risk and benefit, rather than every member state duplicating that process.

Box 3. Other UK Initiatives

Some initiatives are already being piloted in the UK. In particular, other EU member states have shown interest in the UK's new risk-proportionate systems for trial notification and ethics review:

- **MHRA Notification Scheme:** launched in April 2011, this is a proportionate scheme whereby trials which pose no greater risk than standard treatment can notify the MHRA of the trial details, and assume tacit approval if the MHRA has not raised an objection within 14 days, compared with the standard 30 days for initial assessment;⁶
- **NRES's Proportionate Review of ethics:** for studies with limited ethical issues, a smaller sub-committee can be used instead of a full research ethics committee, and approval given within 14 days.

The **National Institute for Health Research (NIHR)** has schemes to help deliver NHS trials in England to time and recruitment targets:

- trials adopted into its **Clinical Research Network (CRN) portfolio** are eligible for assistance in trial set-up, including obtaining R&D permissions. The devolved nations also have network portfolios;
- the NIHR's "**North West Exemplar Programme**" has demonstrated that improved set-up performance is possible within the current system when the CRN, the NHS and trial sponsors work closely together.⁷ Monitoring 20 projects, the programme has successfully reduced start-up times and increased recruitment levels.

Future Challenges

With an ageing population, advances in electronic data analysis, and increasingly advanced medicines, several challenges and opportunities exist for clinical research.

Reflecting Real Patients

A common criticism is that data from highly controlled trial situations do not reflect a treatment's effects in real-life use, failing to account for human variability:

- for ethical, liability, and practical reasons some groups of people tend not to be recruited into clinical trials, including children and the elderly. This means the picture of potential side-effects and limitations is incomplete at the licensing stage. In early 2011, the European Medicines Agency (EMA) announced strategies⁸ and networks⁹ to promote the appropriate testing of geriatric and paediatric medicines in trials involving those populations;
- building a full understanding of health outcomes, to identify the safest, most effective and most cost-effective

treatments, will need additional sources of evidence. The USA's Food and Drug Administration (FDA) is developing a system to monitor medical data from tens of millions of Americans;¹⁰ so-called "Real-World Data", about the day-to-day use of treatments, reflect patients' different lifestyles, ages, multiple medical conditions and more. Using these studies to complement clinical data, even prior to phase IV trials, is an opportunity the UK could build on, tapping into the wealth of comprehensive patient data associated with the NHS. The challenge is to develop UK electronic systems, and to evaluate treatments using this data.¹¹

New Types of Medicines

The evidence needed to assess new medical treatments is likely to change in the near future, implying modifications to the design of their clinical trials. This reflects both a move toward "value-based pricing" (see POSTnote 364), and a change in the types of medical treatments themselves. Some particularly promising new areas of medicine involve treatments that are technologically advanced, or are prescribed in a more targeted way than traditional pharmaceuticals (See POSTnote 333 on Regenerative Medicine and POSTnote 329 on Personalised Medicine). Consulting with the National Institute of Health and Clinical Excellence (NICE) and the MHRA early in the trial design process will help trials to address the challenge of how to demonstrate value, safety and efficacy, particularly when it is hard to recruit large numbers with the same personalised- or regenerative-medicine needs.

Endnotes

- 1 NESTA, 2011, *All together now: Improving cross-sector collaboration in the UK biomedical industry*, http://www.nesta.org.uk/library/documents/Report_67_Biomed_web.pdf
- 2 EU Clinical Trials Directive 2001/20/EC, http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm
- 3 The Medicines for Human Use (Clinical Trials) Regulations 2004. <http://www.legislation.gov.uk/ukSI/2004/1031/contents/made>
- 4 The Academy of Medical Sciences, 2011, *A new pathway for the regulation and governance of health research*, <http://www.acmedsci.ac.uk/p47prid88.html>
- 5 Department for Business Innovation & Skills, 2011, *The Plan for Growth*, http://cdn.hm-treasury.gov.uk/2011budget_growth.pdf
- 6 Medicines and Healthcare products Regulatory Agency (MHRA) website <http://www.mhra.gov.uk/>
- 7 National Institute for Health Research (NIHR), North West Exemplar Programme http://www.crnc.nihr.ac.uk/Life+sciences+industry/tools/nwe_prog
- 8 European Medicines Agency (EMA), 2011, *Geriatric medicines strategy*, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf
- 9 European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA), <http://goo.gl/ik2uw>
- 10 United States Food and Drug Administration's (FDA) Sentinel Initiative; <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>
- 11 Association of the British Pharmaceutical Industry (ABPI), 2011, *Demonstrating value with Real World data* <http://www.abpi.org.uk/our-work/library/guidelines/Pages/real-world-data.aspx>