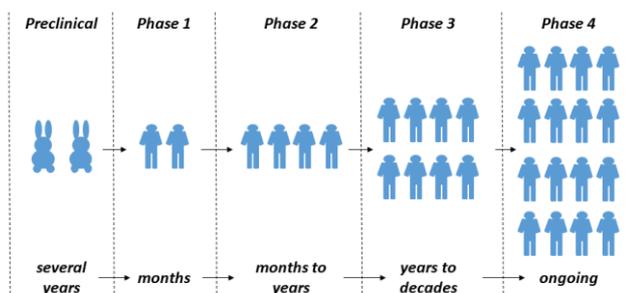


# Regulating Clinical Trials



Clinical trials are essential to establish the safety and efficacy of medicines and are strictly regulated in the EU. The current EU regulatory framework is due to be replaced by a new EU Clinical Trial Regulation in 2019. This POSTnote examines how this may affect the UK healthcare industry, including issues around clinical trial transparency. It also examines options for UK regulation of clinical trials post-Brexit, including a brief description of the more general issues facing UK patients and clinical researchers post-Brexit.

## Background

Clinical trials are studies to establish the safety and efficacy of new medicines in human populations. They can be used to obtain the 'market authorisation' needed to allow a medicine to be sold on the market. Such authorisations can be given centrally by the European Medicines Agency (EMA) or nationally by the UK's Medicines and Healthcare products Regulatory Agency (MHRA, see Box 1). Further clinical trials can be performed once market authorisation has been given. For a description of the different phases a medicine must go through prior to market authorisation, see the figure above and [POSTnote 390](#). Trials can be funded and performed by different organisations, ranging from large pharmaceutical companies, clinical research organisations through to charities, universities and Government.

## Current regulation

The EU Clinical Trials Directive (CTD) currently regulates (through UK legislation) clinical trials within the UK and across all EU Member States. It aimed to harmonise the running of clinical trials, improve patient safety and make it easier to run trials at multiple sites across the EU (multi-centre trials). However, full harmonisation was not achieved, as regulators across the EU implemented the CTD differently in their own legislation.<sup>1</sup> The CTD has also been

## Overview

- Clinical trials in the UK are currently regulated by the EU Clinical Trials Directive, which was transposed into UK law in 2004. The directive has been criticised for increasing the bureaucratic burden and cost of running trials in the EU.
- In 2014 a new EU Clinical Trial Regulation was agreed to address these issues. It includes a new EU-wide portal and database providing a single point of entry for all clinical trial applications in the EU.
- The new regulation aims to increase clinical trial transparency, simplify the application process and foster innovation.
- These changes are now likely to come into effect in 2019. It is not clear whether these changes will come into effect before the UK leaves the EU, but either way the UK will need to renegotiate clinical trial regulations.

### Box 1. Overview of key regulatory bodies for UK clinical trials

The agencies below are key players in regulating clinical trials and granting market authorisations in the UK and the EU.

- **International Council for the Harmonisation (ICH)** of Technical Requirements of Pharmaceuticals for Human Use publishes guidance on **Good Clinical Practice (GCP)**. These are a set of ethical and scientific guidelines agreed in 1997 between the US, EU and Japan for designing, recording and reporting results from trials that involve human subjects to get a drug registered for human use. These guidelines form the basis of many later regulations.
- **Health Research Authority (HRA)** is responsible for broad coordination of regulation relating to health research in England, working in partnership with sister agencies from the devolved administrations. It is a part of the UK Research Ethics Service, hosting the research ethics committees in England that provide ethical approval for running UK clinical trials.<sup>6</sup>
- **Medicines and Healthcare products Regulatory Agency (MHRA)** regulates medicines and medical devices. It acts as the UK's competent authority under the CTD, approves clinical trial applications and carries out GCP inspections.<sup>6</sup>
- **European Medicines Agency (EMA)** provides market authorisations for any new medicines to be sold across the EU, provides information on medicines to healthcare professionals and monitors the safety of medicines across their lifecycle.

**Box 2. UK issues with clinical trials regulation**

A 2013 House of Commons Science and Technology Committee inquiry into the UK clinical trials industry<sup>3</sup> highlighted issues both at the EU (the Clinical Trials Directive, see text) and UK levels. In the UK these included the lack of transparency in the registering and reporting of clinical trials (see [POSTnote 461](#)) as well as the complex system for gaining ethical approval for conducting UK trials. At the time of the inquiry, to gain ethical approval for conducting a clinical trial in the UK a decision was required from the National Research Ethics Service.<sup>7</sup> Permission from each separate NHS Trust involved in the trial was also required. Separate approval was also needed in some cases from other specialist bodies such as the Human Tissue Authority. To address this problem the HRA was given an expanded role providing a UK wide application service for ethical assessment and review.<sup>6</sup> In 2016 it launched a combined application service where assessment on behalf of the NHS is conducted in parallel with the ethical review process. A single HRA approval now confirms that all the necessary approvals are in place for a clinical trial in the NHS in England. The HRA suggest that this has reduced the time taken for approval, although it is difficult to accurately state whether the process has shortened due to the recent implementation of this service.

criticised for not differentiating between trials on the basis of the different level of risk they present (a “risk-based approach”) and for increasing costs.<sup>1</sup> The Directive has also been cited as one reason for the declining number of clinical trials being performed in the EU. For example between 2007-11, the number of trial applications fell by 25% and the average delay in starting a trial increased by 90% (to 152 days).<sup>2</sup> A 2012 House of Commons Science and Technology Select Committee examined issues concerning the EU CTD and its implementation in the UK (see Box 2).<sup>3</sup> Other similar criticisms led to a new Clinical Trial Regulation (EU 536/2014) being agreed in 2014.<sup>2</sup>

**The new Clinical Trial Regulation**

The new EU Clinical Trial Regulation (CTR) aims to ensure patient safety, improve clinical trial transparency and simplify the application process for clinical trials across EU Member States.<sup>4,5</sup> The CTR also introduces the concept of a ‘low-interventional trial’ (Box 3) allowing a more risk-based approach to the approval of clinical trials to be taken.<sup>4</sup> The regulation will apply directly in all EU Member States. This aims to stop regulators interpreting the regulation differently. Also included in the CTR is the formal recognition of ‘co-sponsorship’, whereby two organisations can share the responsibilities of the sponsor (the entity that takes legal responsibility for the trial). This may be more suited for the UK clinical research environment, where local NHS trusts and universities can work closely together to run clinical trials.<sup>7</sup> A key part of the new CTR is the EU-wide portal and database, which will provide a single point of entry for all clinical trial applications across the EU.<sup>4,5</sup>

**The new EU portal and database**

The EU portal will allow sponsors to submit a single application that can be accessed by the required competent authorities (Box 1).<sup>5</sup> This may shorten the amount of time taken to set up a trial, as a verdict given by the regulator will now apply to the whole country. A sponsor workspace will allow users to search for clinical trials, submit notifications during the trial and record results.

**Box 3. Definitions of clinical research trials used by the CTR**

The clinical trials regulation defines a clinical study as any investigation that aims to discover a clinical effect, adverse event or pharmacological property of one or more medicinal products to establish its safety and/or efficacy. Clinical studies are then broken down further on the basis of the risk presented by the trial:

- Clinical trial - any clinical study in which the patient has been assigned to a particular therapy in advance and the use of the medicinal product does not fall within normal clinical practice. An example would be a first in man trial of a new drug.
- Low-interventional trial - any clinical trial that fulfils all of the following: the medicinal product has market authorisation, poses no more than a minimal additional risk compared with normal clinical practice and the medicinal product is being used within the market authorisation (or the use is based on published scientific evidence). An example would be testing a medication that has market authorisation for a new indication.
- Non-interventional trial - any clinical study other than a trial. An example would be a behavioural study.

Sponsors are required to give notifications when:

- a trial begins
- a subject first visits the trial
- a trial is temporarily halted
- a trial is terminated early
- a trial ends.<sup>5</sup>

The CTR requires the registration of clinical trials (prior to initiation) and summaries of trials to be publically available within one year of trial completion.<sup>5</sup> These requirements may increase clinical trial transparency and patient safety, as trials that may have been stopped early and not reported will now be publically available. Competent authorities (the regulator in each Member State that oversees medicines regulation, see Box 1) will have access to the applications.

Regulators will be able to record the results of site inspections and receive notifications about the progress of the trial (see above).<sup>5</sup> The EU portal website will allow the general public to search for clinical trials and download pre-defined summaries (in the form of clinical study reports or an equivalent for academic researchers) of any trial conducted in the EU.<sup>4,5</sup> Detailed information on all clinical trials conducted in the EU will be available in all official EU languages.<sup>5</sup> The EU suggests that this level of summary is a compromise between confidentiality/commercial sensitivity and increasing public trust in the clinical trials industry. The database should help to ensure that clinical trials are not unnecessarily duplicated and may also foster innovation by allowing academic researchers access to clinical trial results that may not otherwise be published.<sup>5</sup>

**Potential issues with the EU CTR**

While there is broad support for the aims of the CTR, a number of potential concerns have been raised. These include whether the risk-based approach goes far enough, the potential for increased bureaucracy and the proposed timeframe for implementation.<sup>4</sup>

*Risk-based approach*

Different types of clinical trials can present different levels of risk to the patient (see Box 3).<sup>8</sup> Some organisations have

suggested that the new definition of a “low-interventional trial” introduced by the CTR could go further.<sup>7</sup> The NHS European Office lobbied for a more risk-based approach during the discussions for the new CTR (see page 4 for a more detailed discussion of this issue).<sup>4</sup>

#### *Bureaucracy*

The UK conducts more Phase I trials than any other country in the EU.<sup>9</sup> Such trials, and many other commercial and academic later phase trials, are often performed within a single Member State. Given that the UK recently took measures to streamline its procedure for gaining approval for clinical trials (see Box 2), there are concerns that for trials conducted solely in the UK, the portal may increase the bureaucratic burden. The increased number of events that require reporting during the trial (see page 2) may also increase the bureaucracy surrounding a clinical trial. Any increase in the time taken to plan or conduct a trial increases the cost of running that trial. The new regulation could thus act as a broader disincentive for trials to be conducted in the EU if the reporting procedures are thought to be too burdensome.

#### *Timeframes and technical issues*

Stakeholders involved in the audit process have suggested that the proposed timeframes (see Box 4) for the portal to go live in September 2018 were ambitious. EMA has since announced that this go-live date has been postponed due to technical difficulties (Box 4).<sup>10</sup> Its Management Board will discuss a new time frame in October 2017 and the CTR is now expected to come into application during 2019. Other concerns relate to how user friendly the system will be. As the new portal will be a large, complex EU-wide system that can store data for several years after a trial has been completed, there are fears that there may be further technical issues with its proposed implementation.

## **UK Clinical Research after Brexit**

The new CTR was originally due to come into force in October 2018, before the UK’s scheduled departure from the EU.<sup>11</sup> Technical difficulties with the portal now mean that it is not clear whether the CTR will come into application before or after the UK’s scheduled departure (Box 4). This, combined with the uncertainty over the UK timetable for leaving the EU, means that it is not clear whether the CTR will apply to the UK or whether the UK will have to negotiate new arrangements for clinical trials regulation with the EU. The following sections outline the challenges and opportunities arising from these uncertainties.

### **Challenges facing the UK post-Brexit**

#### *Staff recruitment and retention*

The NHS and the clinical research sector both employ a significant number of EU nationals. There are serious concerns in both sectors about staff recruitment and retention for UK positions post-Brexit and the potential impact of any visa requirements that may be introduced. Specific staffing issues relating to regulation include EU

#### **Box 4. Proposed timeframe for the CTR<sup>10, 11</sup>**

The EU CTR was agreed by the European Parliament in 2014. In December 2015, the EMA Management Board agreed the following time frame for delivery:

- **August 2017** - EU portal and database sent out for audit.
- **November 2017** - independent audit completed.
- **March 2018** - notice of audit completion published in the Official Journal of the European Union.
- **September 2018** - production version of the portal and database go live. Under this time frame the CTR would have come into application before the UK is scheduled to leave the EU. However, due to technical difficulties with the development of the IT system, the portal’s go-live date has been postponed.
- **October 2017** - the EMA Management Board will discuss a new delivery time date and the CTR is now expected to come into application “during 2019”.<sup>10</sup>

requirements that all staff that hold certain responsibilities must be based in the EU/EEA. These include:

- Market authorisation holders - individuals who are responsible for medicinal products cleared by the EMA for marketing in the EU<sup>13</sup>
- Qualified Person Responsible for Pharmacovigilance - the individual responsible for the safety monitoring performed once a drug has gone to market.

Post-Brexit any of the above staff residing in the UK will need to relocate to the EU/EEA, or the company in question will need to nominate new (EU-based) individuals.<sup>13</sup>

#### *Funding for clinical research*

The UK is one of the largest recipients of research funding from the EU.<sup>12</sup> Some stakeholders are concerned that any loss of funding through this pathway could threaten the UK’s position as a world leader in the life sciences.<sup>12</sup> Although the UK Government has committed to replacing any funding from the EU until 2019, stakeholders are concerned that this may not continue for funding rounds after 2019. Some UK academics have expressed concerns that their inability to act as lead investigators on large EU wide grants post-Brexit could reduce the opportunity for the UK to partake in cutting edge clinical research.

#### *The future roles of the EMA and MHRA*

Since the Brexit decision was announced, there has been speculation over where the EMA, currently based in London, will be located.<sup>14</sup> The EMA has stated it does not know how it will be affected by Brexit, including where it will be located in the future.<sup>15</sup> The Secretary of State for Health has stated that it is likely the UK will leave the EMA post-Brexit, although it is unclear what this may mean.<sup>16</sup> It has been reported that the MHRA conducts a large amount of work on behalf of the EMA and that this is a significant source of revenue for the MHRA.<sup>14, 16</sup> The MHRA is a leading regulator within the EU and is noted for driving innovative regulatory approaches and practices.<sup>14</sup> The MHRA has stated that playing “a full and active role in European regulatory procedures” is a priority after Brexit.<sup>17</sup> If the UK were to leave the EU regulatory system, this would require an existing institution (such as the MHRA), to provide market authorisation for new medicines sold in the UK.<sup>12</sup>

*Access to, and transparency of, clinical trials data*

If the UK leaves the European regulatory system, then regulator access to the EU portal and database may become restricted after Brexit, although this is unclear. The All Trials campaign, which advocates increased transparency, has indicated that this would be a retrograde step for clinical trial transparency (see [POSTnote 461](#)).<sup>18</sup> Reducing the ability of UK researchers to access data on clinical trials may also prevent research studies such as meta-analyses being performed, although other stakeholders dispute this.

*Access to new medicines*

Stakeholders have expressed concerns that the loss of an EU wide market authorisation procedure after Brexit could delay the availability of new medicines in the UK. This is because the UK is a smaller market for new drugs than the EU, so companies may prioritise gaining market authorisation for a new medicine in the EU rather than the UK. Switzerland is not inside the EU or the European Economic Area (EEA) and is thus not a member of the EMA.<sup>14</sup> Despite having a number of bilateral trade agreements with the EU, it is estimated that Switzerland gains access to new medicines on average 157 days later than the rest of the EU.<sup>14</sup> In Australia and Canada, which also have mutual recognition agreements with the EMA, new drugs come to market on average 6-12 months later than in the EU or USA.<sup>14</sup>

**Future Opportunities for UK clinical trials***A more risk-based system?*

The MHRA is a world renowned regulator that is respected for the risk-based approach it takes in relation to approving clinical trials.<sup>6, 8</sup> This includes implementing a three tiered system to categorising trials:

- Type A trials - no higher risk than standard medical care. This applies when a medicine is used within its market authorisation, or is used outside of its market authorisation but with published evidence for its use<sup>8</sup>
- Type B trials - somewhat higher risk than standard medical care. This includes dosage modifications or combinations with other medical products where an interaction may be suspected
- Type C trials - markedly higher risk than normal medical care. This would include trials for which a medicine has not been licensed in the EU

For Type A trials the MHRA has stated that it only requires notification of the trial, which it will acknowledge within 14 days (unless an objection is raised) to allow the trial to get underway.<sup>8</sup> The quicker a trial can be set up, the less it costs the companies to run, thus acting as an incentive to run trials within the UK.

*Collecting 'real world data'*

Clinical trials are highly structured studies where patients have been specially selected to take part.<sup>19</sup> This can mean that the data generated may not reflect a medicine's use in the real world. Trials that compare medicines in routine

clinical settings are highly valued, and are often referred to as providing "real world data".<sup>19</sup> With centralised data collection systems starting to be implemented by the NHS, and a more risk-based approach the UK could become a world leader in performing these types of trial.<sup>19</sup>

*End-to-end metrics*

A number of stakeholders have noted that, compared with some other EU countries, the UK has a relatively streamlined and centralised system for ethical and clinical trial application approval. Providing a timescale on the whole clinical trial process (i.e. from initial application through to trial initiation) has been referred to as "end-to-end metrics".<sup>6</sup> If the UK could provide reliable and accurate end-to-end metrics for clinical trial approval, this could be used to demonstrate that the UK provides an attractive place in which to perform clinical trials.<sup>6</sup>

*Developing a new UK regulatory system*

A 2017 industry-led strategy to strengthen the UK life sciences sector includes a proposal to increase the number of clinical trials conducted in the UK by 50% over the next five years.<sup>20</sup> The strategy suggests that the UK is well placed to conduct novel clinical trials compared with other EU countries because of its strengths in emerging technologies such as genomic medicine and gene- and cell-based therapies, as well as the increasing use of digital systems within the NHS. However, it notes that UK regulation of clinical trials (including market authorisation, pharmacovigilance, trial approvals and data sharing) will need to be aligned with EU regulation in these areas. Achieving such alignment might ensure that data generated by UK trials is of sufficient quality and integrity to be acceptable to EU regulators. It might also enable UK researchers and patients to participate in multi-centre trials (e.g. for rare cancers) located in both the EU and UK.

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