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Early phase clinical trials in the United Kingdom

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The UK remains the European leader, and only second to the USA, when considering trials registered on the *ClinicalTrials.gov* database. In April 2014, 6,890 Phase I clinical trials in healthy participants were registered on this database and of these, two thirds were conducted in the USA and Europe, and one third in the rest of the world: 2,921 (42%) were registered in the USA, 591 (9%) in the UK and 1,271 (18%) in the rest of Europe. Of the above total, 710 were listed as ongoing or due to commence, 276 (39%) were registered in the USA, 77 (11%) in the UK and 115 (16%) in the rest of Europe[1,2].

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Approval process

Setting up and conducting Phase I clinical trials in the UK is transparent, simple and predictable: a government-regulated approval process for both ethics and regulatory review grants approval within a 30-day time frame. MHRA published data[3] shows that the clinical trials assessment unit consistently provides a response to applications within 12 days on average. Of the most recent 146 applications, 43% received full approval within 11 days of the first application. Those with grounds for non-acceptance, received approval within a further six days from submitting a response to the MHRA; less than the 12 days on average applicants took to submit the additional information requested.

Sponsors can receive detailed advice on their application requirements through the MHRA Innovation Office. The office was launched to help innovative organisations understand and follow the regulatory requirements applicable to the development of their innovative products. The response is to be expected within 20 working days and it may consist of both regulatory and scientific advice. The process of obtaining advice is unbureaucratic, the cost is reasonable and the use of this facility will help with more complex studies, usually resulting in a faster approval of any subsequent clinical trials application.

Ethics review

Ethics review is performed in parallel with the MHRA assessment and usually takes 30 days: 14 days of submission prior to the Ethics Committee meeting and up to a further 14 days to receive final approval. Meetings are booked through a central system, but applicants can chose a committee that fits the required time frame for approval[4] and that is within reasonable travel distance allowing the Principal Investigators to attend those meetings and answer any questions to minimise delay.

The quality of studies performed in the UK is generally very high. In April 2008, the MHRA developed a scheme to maximise subject safety and to create additional public confidence in the regulatory oversight of Phase I clinical trials. The MHRA and associated key stakeholders undertook a review of the scheme in 2013. The updated scheme gives assurance that accredited units not only meet, but surpass, the basic regulatory GCP (Good Clinical Practice) aspects. Accredited units have to implement additional 'best practice' procedures that encompass the highest standards for avoiding harm to trial subjects and for handling medical emergencies should they arise, thus making significant contributions to enhancing the safety of volunteers[5]. Currently, 15 units hold standard and supplementary accreditation. The scheme involves periodic inspections by the MHRA every two years and the accreditation is revocable at any time, should there be a serious breach or any major changes to staffing or the facility.

One of the most exciting opportunities is the option to obtain approval for adaptive protocols. This allows researchers the flexibility to make

protocol amendments without ethics or regulatory submission/approval and which do not require interim updates of safety information to either MHRA or Ethics Committee, provided researchers and sponsors stay within the approved specifications defined in the protocol. The European Medicines Agency (EMA) published a reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design (CHMP/EWP/2459/02) in 2007[6], followed by a draft *'Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics'*, which was published by FDA in 2010[7], but UK is currently the only country to have adopted this innovative approach in early-phase exploratory studies. This provides a considerable competitive advantage over other countries' legislations. Adaptive study designs save significant time, of approximately two months on average, in individual studies and have been shown to save over six months in early phase research programmes[8].

The flexibility of adaptive design avoids delays caused by changes in conventional, non-adaptive studies and further maximises potential time savings by overlapping of study parts. In addition, such a design provides better value for the funds invested as it allows the prompt removal of unnecessary tests from the study conduct and substituting them with additional assessments, thereby enriching the re-directed analysis.

The UK has at its core the NHS looking after the health and wellbeing of its citizens. This is a huge advantage for the conduct of clinical trials. "The UK is the only country in the world where data has been recorded, since the 1940s, for every person registered with the health service – from birth to death."[9]

When conducting early-phase clinical trials, having access to a volunteer's comprehensive health record, through the general practitioner's medical records, not only ensures the safety of the healthy volunteer but also allows the researcher to identify and pre-qualify participants with relevant disease or biomarkers prior to actual screening.

The government is actively promoting clinical trials in the UK and volunteer participation is growing significantly for both commercial and non-commercial clinical trials and has tripled in the last five years.

In summary, the UK has:

- A well-regulated clinical trials industry with predictable and rapid approval times.
- Access to regulatory and scientific advice from the MHRA.
- High quality clinical research institutions underpinned by the MHRA Phase I accreditation scheme.
- Regulatory 'buy-in' for adaptive clinical trials.
- Access to the most comprehensive clinical volunteer/patient database in the world.
- Increasing participation by clinical trials volunteers.

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