

Rule Britannia

Jörg Taubel, Keith Berelowitz and Ulrike Lorch at Richmond Pharmacology Limited look at the advantages of conducting first-time-in-human (FTIH) studies in the UK compared to other European markets

Recently, universities from the UK have been ranked the world's number one and two for the impact of their research in pharmacology, and six UK universities are among the top 10 in the European rankings (1). For decades the UK has had an outstanding reputation for its basic and clinical pharmacological research and is ranked second in the world for citations in pharmacology (2). The UK has a longstanding tradition of industry-sponsored and academic clinical trials, and this article discusses the opportunities available for cutting-edge early phase clinical research activities.

THE CHALLENGE

The regulatory environment and the facilities available for Phase I clinical trials in the UK have changed considerably in recent years. This was first achieved through the introduction of the Medicines for Human Use (Clinical Trials) Regulations in 2004, which introduced a regulatory approval that had not previously been necessary in order to commence a clinical trial in healthy volunteers. This regulation was triggered by the need to implement the European Clinical Trials Directive into national law. Secondly, the rules took another step forward through the introduction of a Phase I accreditation system; this became effective in 2008 and was triggered by the TGN1412 incident in March 2006 (3).

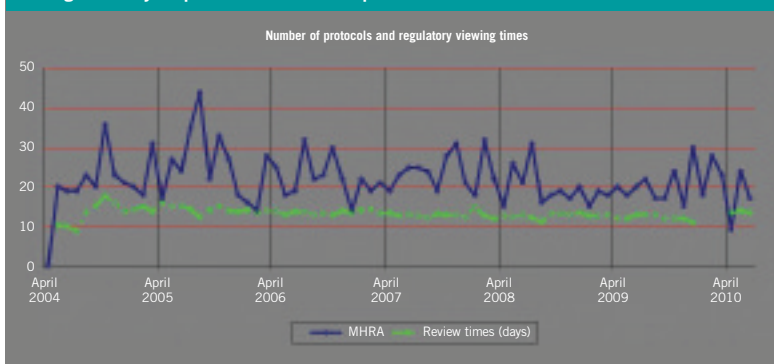
One might suspect that additional regulations would have an impact on the time taken from the commissioning of a clinical trial to the first participant enrolled. However, the legislation of 2005 has improved the early phase research ethics committee (REC) approval process through centralising, harmonising and streamlining the application and approval process. The time taken from submission to REC, all the way to final written approval is now predictable, typically taking about three weeks. There is a

group of appointed specialist Phase I research ethics committees in the UK – some independent and some NHS – with REC meetings taking place across the UK every week, allowing the applicant to start the clock from the moment a submission is ready. The regulatory approval timelines were designed to fit into this timeframe, and the Medicines and Healthcare products Regulatory Agency (MHRA) has an impressive track record of responding within 14 days – that is, one week below the legal target for Phase I trials in the UK.

Approximately one third of trials receive approval upon first review, whereas in two thirds of trials there are grounds for initial non-acceptance. In this instance it will usually take a further five days from the time the applicant replies to obtain full approval, meaning the time taken by the MHRA to review an application is typically under 20 days. Consequently, the agency is ahead of other European agencies that have longer review times, particularly for more complex studies.

The introduction of the expert advisory group (EAG) has established an additional cycle of expert review of proposed studies where the mechanism of action of the IMP necessitates consultation prior to the final study design, the specialist data review and possibly the exclusive use of a particular facility carrying supplementary accreditation. This supplementary accreditation is awarded only to clinical trials units (CTUs) demonstrating adequate safety provisions to deal with medical emergencies. This is to ensure that the risk of participating in a clinical trial is no more than minimal. However, only around one per cent of trials are approved through this process: five trials in healthy volunteers and patients (including FTIH trials with 'higher risk compounds') were reviewed in 2008, three in 2009 and one in 2010. The review times varied, but were generally below 60 days except for the period between September 2008 and September 2009 when they peaked at 120 days. The MHRA offers scientific advice meetings, which are relatively informal and can be booked well ahead of a clinical trials application. Such a meeting will ensure that the agency is aware of an intended submission and the applicant will have time to consider recommendations in their trial design prior to submission. This process facilitates the submission and approval process even in those rare instances where a referral to the EAG was deemed necessary. In comparison, the Paul Ehrlich Institut (PEI) in Germany, which is the

Figure 1: Number of Phase I clinical trials reviewed by the MHRA and the average monthly response time between April 2004 and June 2010 (5)



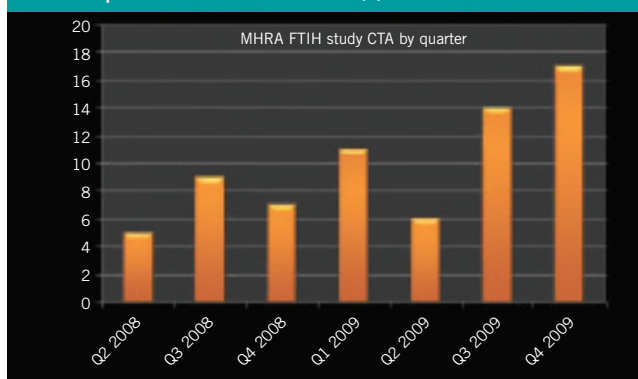


equivalent to the UK EAG, reviews around 30 trials per year, taking on average 130 days for their review.

Furthermore, the MHRA usually approves trials combining several steps in one, such as combined single ascending dose (SAD) and multiple ascending dose (MAD) protocols, often in combination with other aspects such as food interaction or the inclusion of an additional patient population. This approach, in combination with flexible escalation steps using pre-defined exposure levels and clinical endpoints as stopping criteria, has been proven to save time and cost. Between 2007 and 2008, clinical trials authorisation applications declined by about 20 studies, and decreased again from 2008 to 2009. This is consistent with the trend that many of the 30 to 40 FTIH SAD studies submitted each year will also now often contain a MAD part, which hitherto had been a separate application.

The UK is leading Europe in Phase I studies in accordance with a search performed in December 2010 on clinicaltrials.gov, ahead of its closest European rival Germany and well ahead of France, which occupies third place (4). This is, however, at odds with data published by the various regulatory agencies, which states that, in the five-year period from 2005 to 2009, 1,346 applications for Phase I trials were reviewed by the MHRA. During the same period, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Germany reviewed 1,696 applications for Phase I trials. The MHRA figures do not, however, take into account

Figure 2: Number of FTIH Phase I clinical trials reviewed by the MHRA between April 2008 and December 2009 (5)



Phase I oncology trials and this article assumes approximately 20 per cent of all Phase I trials listed by BfArM are oncology trials, which would reduce that number to approximately the same as in the UK. Data published by the Agence française de sécurité sanitaire des produits de santé (Afssaps) suggests that the volume of Phase I trials in France is about 75 per cent of that in Germany and the UK (5-7).

CHANGES IN THE MARKET

The above regulatory changes, either by themselves or in combination with the prevailing changes in the pharmaceutical industry, have led to a consolidation of the CTU marketplace through closure of smaller clinical trial units and the takeover of

long-established independent clinical trial units by larger global contract research organisations (CROs). In October 2010, the MHRA listed 17 accredited clinical trial units on their website two of which have since closed (5). Of the 15 remaining, 13 hold the highest accreditation status and two carry standard accreditation. Of the 15 clinical trial units, 13 are run by CROs, one is an academic site and the other is the only remaining industry running CTU in the UK. The number of clinical trial units in Germany is very similar, with 18 commercial CROs suggesting that in those two countries a similar supply is meeting a similar level of demand.

ACCREDITATION OF PHASE I UNITS

The Phase I accreditation scheme was introduced “to maximise subject safety and to create additional public confidence in the regulatory oversight of such trials...”, rather than to improve research *per se* (5). The emphasis has been on the overall safety of these facilities, their staffing and medical oversight of the trials conducted. That said, regular inspections against set standards invariably lead to common minimum standards, greater consistency in staff training and working processes, as well as accountability. The MHRA expects to see clearly defined and quality systems. Although seen by some as a hindrance to the entrepreneurial spirit, this scheme will undoubtedly achieve higher standards, which are likely to benefit the industry and society at large.

There appears to be a trend towards specialisation by CTUs: ICON use pain models in healthy volunteers; Pharmaceutical Profiles (now Quotient) focus on imaging and microdosing studies; Surrey CRC specialise in sleep studies; the Medicines Evaluation Unit concentrate on respiratory studies; and Richmond Pharmacology specialise in Japanese and cardiac safety studies.

SPECIALISATION OF CLINICAL TRIAL PROVIDERS

The clinical trials conducted in the UK have become more complex. A CTU must provide adequate facilities, state of the art assessment methods and processes to ensure participant safety, while harnessing meaningful high quality data. It is particularly the latter that has proven to be the stumbling block for many of the smaller CTUs; without specialisation it becomes difficult to maintain processes that are robust and most importantly scalable. For instance, it is relatively simple to produce high reliability ECG recordings in a small group of volunteers, but quite a different matter to achieve that consistent level of high quality in the much larger groups required for a thorough QT study. However, specialisation requires volume and that in turn may signal the end of the smaller generalists in the marketplace.

FREEDOM TO ADAPT IN EARLY CLINICAL TRIALS

In order to benefit from the freedom the regulators provide for the rapid conduct of FTIH studies using adaptive study designs, an adequate infrastructure has to be in place. This is to ensure rapid, continuous reporting and expert review, to monitor the study results against the study-stopping criteria and decide on appropriate dose escalation when using flexible protocols. This

Table 1: List of MHRA accredited Phase I units in the UK showing their accreditation status and the date of accreditation. Units 4, 9, 11, 12, 16 and 17 are based within an acute NHS hospital as recommended by the Duff Report (5)

	Name of unit and location	Type/date of accreditation
1	LCG Bioscience Bourn, Cambridge	Supplementary 9 June 2008
2	Simbec Research Limited, Merthyr Tydfil	Supplementary 20 June 2008
3	GDRU (Quintiles), Newcomen Street, London	Supplementary 18 August 2008
4	Richmond Pharmacology Mayday and St Georges Hospital, Greater London	Supplementary 14 October 2008
5	Quotient Clinical (formerly Charles River Clinical Services Riccarton), Edinburgh	Supplementary 14 January 2009
6	Hammersmith Medicines Research, Cumberland Avenue, London	Supplementary 11 February 2009
7	MDS Pharma Services, Lisburn Road, Belfast	Supplementary 25 March 2009
8	Quotient Clinical (formerly Pharmaceutical Profiles Ltd), Mere Way, Ruddington	Standard 17 April 2009
9	Parxel Clinical Pharmacology, Northwick Park Hospital, London	Supplementary 30 April 2009
10	Covance Clinical Research Unit, Leeds	Supplementary 30 June 2009
11	Medicines Evaluation Unit, Southmoor Road, Manchester	Supplementary 6 July 2009
12	GSK Clinical Unit, Addenbrooke's Hospital, Cambridge	Supplementary 23 July 2009
13	Bio-Kinetic Europe Ltd, Belfast	Supplementary 23 July 2009
14	Veeda Clinical Research Unit, Old Convent of Notre Dame, Plymouth	Supplementary 23 July 2009
15	Surrey Clinical Research Centre, Guildford	Standard 4 May 2010
16	Chiltern (Early Phase) Ltd, Ninewells Hospital, Dundee	Supplementary 26 May 2010
17	ICON Development Solutions Ltd, MRI Campus, Oxford Road, Manchester	Supplementary 5 October 2010

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requires the CTU to provide quality assured data within the shortest possible time prior to the assessment by expert reviewers.

The desire to move a clinical trial forward in swift fashion also requires quick responses and competence when dealing with unpredicted results and unforeseen adverse events. It is obvious that this can only be achieved if clinical trials are supported by rapid data capture, access to specialist medical assessment units and subsequent access to expert advice to help evaluate the findings in order to make rapid yet sound decisions.

Expert review relies on immediate competent medical investigation in the CTU in two steps. The first involves providing the necessary findings and background; the second looks at the essential contacts to initiate specialist review. This, however, is only widely available in the larger teaching hospitals. There needs to be existing, pre-arranged relationships leading to short referral times, but there also needs to be a continuum in a number of specialist areas where an ongoing arrangement leads to consistency and mutual trust, usually built on the relationship of leading medical experts in their respective fields.

Six of the 15 UK accredited Phase I units are now located within hospitals, and almost all the others are in close vicinity of an acute hospital. CTUs are moving or have moved their operations into hospitals, and it is likely that pharmacologists in the UK will in future focus more on complex specialist trials conducted in GCP compliant and accredited CTUs, thereby continuing a tradition in this field. Is it, therefore, surprising that there is such a significant upwards trend in the number of FTIH studies conducted in the UK? In 2009 over 20 per cent of all Phase I clinical trials in healthy volunteers reviewed by the MHRA (excluding Phase I oncology patients) were FTIH studies.

CONCLUSION

Clinical pharmacology continues to be a UK success story, as evidenced by the emerging data published by regulatory agencies. While the UK has moved forward from being one of the least regulated countries in Europe to a tightly regulated one, this has clearly led to an overall improvement of timelines and predictability as well as overall quality.

The UK now offers a simple and convenient application process, reviewed by one of the world's leading regulatory agencies, a robust and predictable system for regulatory and ethical approval, and possibly the most modern, safe, competent, varied and competitive clinical trials marketplace in the world. What else could one hope to find better elsewhere? Apart from good weather that is.

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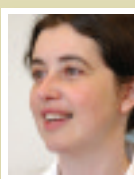
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