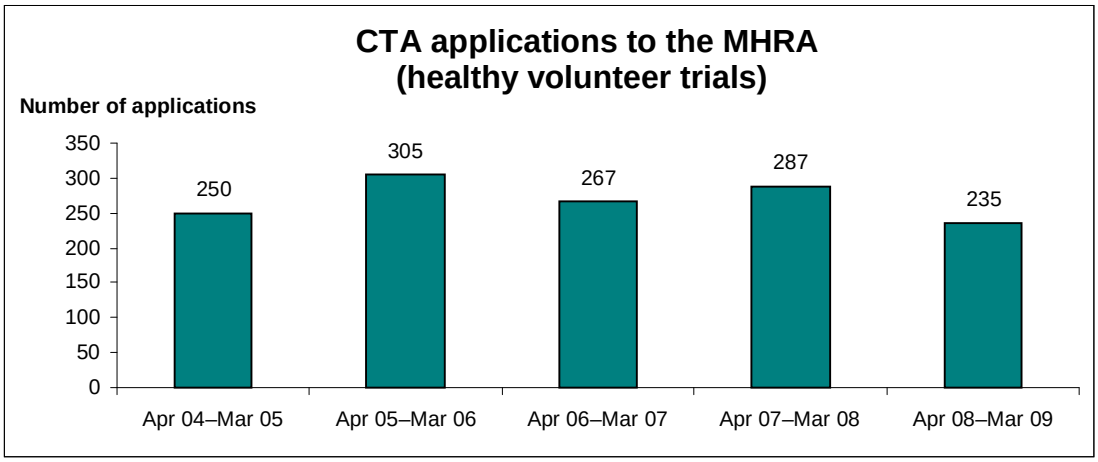
Part A: General comments

1. Evidence for a reduction in the number of trials

A survey of 29 UK phase 1 units in 1999–2000 (Calder *et al* 2004), showed that about 600 phase 1 trials were done in the UK each year. The number of CTA applications to the MHRA for phase 1 trials for the period Apr 2004 to Mar 2009 is shown in Figure 1.

Figure 1



Thus, the number of phase 1 trials being done in the UK more than halved after implementation of the CTD. There are several possible reasons.

(a) Phase 1 trials were unregulated in the UK before implementation of the CTD, so the UK had an advantage over other EU countries and the USA.

(b) In recent years, some sponsors have applied for a CTA with several parts, such as single-dose and repeat-dose rising parts, and a fed-fasting part. However, although 'bundling' of trials may have contributed partly to the fall in the total number of CTA applications, it would not account for all of it.

(c) UK units lost phase 1 trials to other countries – such as France, Belgium, Holland and Canada – in the first year after the CTD was implemented in the UK. France was slow to implement the CTD, and Belgium and Holland have interpreted the CTD less strictly. Holland has a 'one-stop shop' approach to the CTD. The turnaround time for phase 1 trials in Canada is faster than the UK. Most pharmaceutical companies are international and can do their phase 1 studies in whichever country they choose.

(d) The Pound Sterling exchange rates were unfavourable in the early period after implementation of the CTD. However, although the Pound has weakened substantially in the last year or two, the total number of CTA applications per year has not improved during that time. If anything, the reduction appears to be progressive. More importantly, the number of phase 1 trials done in EU countries such as Belgium and Holland has increased.

(e) Several reports have highlighted the worldwide reduction in phase 1 trials over the past 12–18 months because of the recession.

Thus, although various factors influence the number of phase 1 trials done by the UK, overall the evidence strongly suggests that the CTD, and the way in which it was implemented, has adversely affected phase 1 trials in the UK. Several UK phase 1 units had to close for financial reasons in the wake of the CTD. They held the CTD responsible for their closure.

Part A: General comments

2. Lack of evidence that the CTD has improved safety of trial participants

I know of no good evidence that the CTD has improved safety of participants of phase 1 trials in the UK. Subjects who volunteer for phase 1 trials get no therapeutic benefit from the IMP, so the risk of harming the subjects must be minimal. Reviews of the safety of phase 1 trials show that they have a good safety record. Overall, the incidence of serious adverse events related to the IMP was about 0.02% (ABPI, 2007). Over the years, the Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI) has monitored reports of adverse effects in phase 1 trials. There has been no change in the low level of reports since the CTD was implemented. Sadly, the CTD did not prevent the TGN1412 incident, in which six volunteers experienced serious adverse reactions.

3. *Increased administrative costs*

The CTD has probably led to at least 10% additional costs to a phase 1 trial. The main reasons are:

(a) The procedures for applying for, setting up and maintaining a phase 1 trial have become much more bureaucratic since the CTD was implemented. More staff are now required to cover a phase 1 trial.

(b) The CTD has prolonged and increased the uncertainty for set-up times for phase 1 trials, which often results in postponements and loss of revenue to the phase 1 unit.

(c) MHRA GCP and GMP inspections are costly.

4. Impact of substantial amendments

Many phase 1 trials require amendments to the protocol to complete them satisfactorily (Boyce and Warrington 2002). Substantial amendments, which must be reviewed by the MHRA and/or the research ethics committee (REC), are the most common type. The MHRA and REC are both allowed 35 days to review a substantial protocol amendment. Many amendments for phase 1 trials need to be reviewed quickly to keep the study running smoothly. Delays in obtaining approval can cause considerable inconvenience to everyone directly involved with the study – sponsor, investigators and their staff, and the volunteers. The review procedure for the competent authority and/or the ethics committee should be streamlined and speeded up. In other words, there should be a procedure for expedited review of a substantial amendment to the protocol of a phase 1 study. Also, sponsors are inconsistent about which amendments they consider substantial, so they need more guidance about what is and is not a substantial amendment.

5. Clinical trials by 'academics', and 'low-cost' countries

If concessions are to be made for 'academic' clinical trials, they should apply to commercial trials as well. The regulations for phase 1 trials should be the same whether they are done by 'academic' or commercial units. The same applies to phase 1 trials in low-cost countries, such as India. The EU should not accept phase 1 data from sponsors that use low-cost countries unless they can show that the GCP and GMP standards match those of the EU.