Restricting Regulations

Clinical trials are significantly affected by rules and regulations that slow the process from laboratory to consumer. The 2001 EU directive only worsened this, resulting in third-world country outsourcing. Is there any hope for studies in Europe?

Craig Morgan at goBalto

Contemporary medicine has come a long way since the days of snake oil salesmen. Today, patients can be assured that prescribed medicine has been vetted for safety and efficacy through a long and arduous process, guided by governmental regulatory agencies. The central pillar of this rigorous process for current drug approval is the human clinical trial, the success of which has resulted in a proliferation of studies worldwide. Since the international committee of medical journal editors established trial registration requirements in 2005, enrolment has increased fivefold (1). In the US alone, clinical trial registration has increased tenfold during this same time period, but, against this backdrop, the EU recorded a concerning 25% decrease in clinical trial applications (CTA) from 2007 to 2011 (2).

Global Trials

One of the issues affecting the number of EU studies is a growing trend towards globalisation, with a recent rise in those conducted in developing countries. For example, the number of countries serving as study locations outside the US has more than doubled in the last 10 years, and the proportion of trials undertaken there and in Western Europe has reduced significantly (3,4).

Several factors drive this globalisation trend – one of them being the spiralling drug development costs. A 2013 study by the Tufts Center for the Study of Drug Development estimates the average expense to develop and gain market approval for a new therapeutic is $2.6 billion – up 145% from a similar investigation conducted in 2003 – with time costs accounting for half of that amount. The time and investment required to conduct trials is the largest contributor to these increases, and, given that the success rate for medications moving through clinical trials to FDA approval is a mere 10%, the pharmaceutical industry is struggling to sustain profitability (5).

This has resulted in a variety of aggressive actions to minimise clinical study delays and costs, including shifting trial locations to developing countries. The large pool of potential participants available to accelerate patient recruitment in countries such as China and India are fuelling the move. Additionally, developing countries often offer lower salaries for workers, reducing trial expenditures up to 60% (4).

Another important motivation of this globalisation trend is the increasingly bureaucratic and expensive regulatory environment in places such as the US and the EU. Government of clinical research conduct in these areas has become more complex over the last several decades, resulting in a larger burden on investigators in terms of documentation, compliance and training. All of this serves to increase trial and drug approval timelines and expenses. For example, in the US, an experimental drug takes an average of 12 years to travel from the laboratory to a medicine cabinet, and the costs of running clinical trials have outstripped funding for clinical research and strained the industry's research budgets (6).

Many people, not the least of which are patients awaiting new life-saving medicine approval, feel that a 12 year development and approval cycle is just too long. In response to this, the US congress recently passed the 21st Century Cures Act by an overwhelming majority. This bill, supported by pharma companies and patients, serves to reduce regulations and speed the approval process for new drugs and devices.

EU Directive

The EU may very well have the most burdensome regulations. The EU clinical trials directive was passed by the European parliament in April 2001 to facilitate the implementation of Good Clinical Practice (GCP) across the continent in clinical trial conduct for medicinal products. This directive's original intention was to simplify and harmonise the administrative provisions governing study regulations – it merely provides guidance on clinical trial applications and conduct, and member countries must translate this directive into their own national legislation. Given that each EU country interpreted this directive in its own way, all developed their own unique submission requirements, timelines, classifications and safety reporting. While the directive has facilitated important improvements in the safety and ethical soundness of studies in the EU, it has been widely criticised for serving to increase both the time and costs of conducting clinical trials (7). Since this directive's passage, the following has occurred (2):

- Staffing requirements for the authorisation process for sponsors has doubled
- Insurance fees have risen by 800% for industry sponsors
- Administrative costs for non-commercial sponsors increased by 98%
- Clinical trial launching delays elevated by 90% to 152 days

Therefore, many sponsors have chosen to conduct trials elsewhere, given the heightened cost in running EU clinical trials.

Harmonising Requirements

As one potential solution to this problem, efforts are being made to harmonise standards within and between member countries. In 2014, the European commission adopted a new regulation – number 536/2014 – with the intention to streamline the application dossier submission for trial authorisation and harmonise the procedures for conducting clinical trials across member countries. This new regulation is binding across all member states and is expected to come into effect in 2018.

Several important simplifications inherent in this regulation are expected to make major improvements over the directive currently in use:

- A single portal for clinical trial application submissions, no matter how many countries are involved
- A sole decision on the CTA submitted through the EU portal, as opposed to separate decisions from each member state
- A national level body will review the documents as per the applicable law, but with only one contact point and one fee per country
- Review timelines have been established – a total maximum time of 106 days is allowed for the initial submission, although advanced therapy trials can take up to 156
- Clinical trials regulations throughout the member states is unified
- Simplified reporting procedures
- Increased clinical trial result transparency

The first simplification listed above is perhaps the most significant, as it effectively reduces what might have been a total of 28 required application dossier submissions (one for each member state) down to just one.

Looking Ahead

The trend towards clinical trial globalisation has led sponsors and CROs to adopt cloud-based solutions, such as study start-up (SSU) solutions that serve to expedite the multi-site trial process across countries with disparate requirements. These simplify the complicated site activation activities encountered by global studies with standardised country-specific workflows and streamlined document management. Cloud-based SSU approaches have the potential to realise what the EU directive failed to accomplish: improve the ease and efficiency of the clinical trial approval process.

As clinical trials have gone global, legitimate questions have been raised as to whether those conducted in developing countries are ethical or scientifically valid. Regulatory bodies in places such as the US and EU often have limited information on many research aspects conducted outside their jurisdictions and cannot judge the research quality administered elsewhere effectively.

As the pace of change accelerates, governmental agencies creating a robust, yet efficient, regulatory framework that protects patient rights, speeds the development of life-saving medicines and protects the integrity of research – no matter where it takes place – is essential.

In response to the decline in clinical trials across the EU, the European commission has adopted regulation number 536/2014. Hopes are high that this will serve to reverse the decline in study applications and attract more of them to the EU. As clinical trial globalisation continues to expand, even the harmonised procedures in the new EU regulation may not be enough to completely reverse this trend.

Regardless, efforts by governmental agencies around the world to unify and simplify regulations towards the goal of expediting clinical trials are important and must continue. While protecting patient safety and assuring medication efficacy remains paramount, excessive regulations only serve to slow the release of valuable, life-saving therapies to patients.

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About the author

Craig Morgan is Head of Marketing at goBalto, a life sciences software as a service technology organisation. He works with sponsors, CROs, medical device manufacturers and sites to reduce cycle times and improve collaboration and oversight in clinical trials. Craig is a technology and life sciences management professional, with over 15 years' experience in informatics and bioinformatics applications to drug discovery. He holds degrees in analytical chemistry, information systems and business administration and is a certified project manager with the Project Management Institute.

Email: cmorgan@gobalto.com