

# **Breaking the patient recruitment logjam in clinical trials**

July 2010



## About the sponsors

Breaking the patient recruitment logjam in clinical trials has been commissioned by Citeline, an Informa company specialising in the provision of information to the medical and scientific communities.

Citeline is the premier provider of real-time data and intelligence to the global biopharma industry, and delivers a range of products and services to research departments, scientists, and information libraries.

Citeline provides the most comprehensive and detailed trials information, on average up to 3x as many as mandatory sites such as ClinicalTrials.gov.

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## Summary

### **Clinical trials - Over costly, Over lengthy, and over-regulated?**

Perhaps more than any other single issue, difficulties in recruiting patients are cited as the primary factors driving up cost, causing delays and leading to postponed and failed clinical trials as sponsors struggle to find, and deliver successful outcomes.

But is this view of the situation true right across the industry? Or indeed globally? Or is it just a reflection of what is happening within a tightly defined sector, a specific geography, or even just in their own records, which is affecting trial sponsors' view of patient availability?

There are grounds to dispute the claim - for every sponsor claiming difficulty, there seem to be just as many, if not more, CROs and investigators claiming that they have 'no problem' executing trials successfully, and all you need to do is give them your business and your worries are over.

Or is that just marketing hype?

This white paper sets the process in context by examining some of the factors underlying the patient shortfall, looking at some of the current methods used for identifying investigators and recruiting patients, and comparing these with the best practices made possible by new technologies.


It explains opportunities made possible by these new technologies, as well as examining the costs and benefits and setting them in context with current practice.

Several key factors affecting the patient recruitment situation are clear:

The current process for the recruitment of clinical investigators to conduct clinical trials is disjointed, inefficient and expensive.

Although protocols, such as the ICH/GCP standards, strive to provide a climate that is fair to both investigator and patient, the environment for carrying out trials is often seen by doctors as hostile, especially in the US, where high risks of malpractice litigation have become a positive deterrent to many physicians.





Emerging markets, such as India, the Far East and Russia all offer opportunities to replace the lost trials participants. Trials activity is enjoying double-digit growth in all these regions, but the local environments and language barriers are posing significant cost and management challenges.

Effective trial planning, from conception through to protocol and monitoring is a key factor in reducing the cost of trials that is often overlooked.

Outsourced trials are just as much at risk as those conducted in-house.

Opportunities exist to reduce cost and trial duration, through more effective selection of investigators and development of trial protocols that are sympathetic to the environment in which the trial is conducted. However, these are not yet being optimized right across the industry.

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## Where have all the patients gone?

With an entry-level budget of at least \$1bn to develop a new drug, anything that causes the development period to run over time will have a dramatic impact. This will come not just in terms of additional trial costs, but even more dramatically delays at trial affect the length of patent-protected sales, which some analysts claim can be as valuable as \$40million per month.

The cost of running clinical trials makes up a substantial percentage of the total drug development cost, some estimates put the proportion as high as 80%, so there is a powerful motivation to keep trials as short and effectively-run as possible, and minimize any delays and interruptions.

Delays and failures not only impinge on the viability of the trial, but in worst-case scenarios, the ability of the sponsor to continue funding. Trial delays can even destroy the viability of the compound under test.

Many in the industry point to the methodology being employed as too demanding and proscriptive. Although Randomized Controlled Trials (RCT) are recognised as the most effective method for evaluating the likely efficacy of a new drug, it can also be argued that one of the major contributors to the high drop out of trials achieving Phase IV is the difficulty of completing RCTs to an adequate level of accuracy.

This problem is particularly prevalent in cases where there are high demands on the patients – such as the need for frequent assessments, or lengthy study durations, or indeed just the location of the investigator and its distance from the patient.

Significant challenges have also been widely reported in cases where the subject group is less than reliable. An obvious example of a sub-group where this prevails is among those being treated for substance or alcohol abuse, or whose mental conditions may render them less than wholly reliable.

None of this is news, and these hurdles are regularly cited by the proponents of in silico research as a replacement for in vivo research.

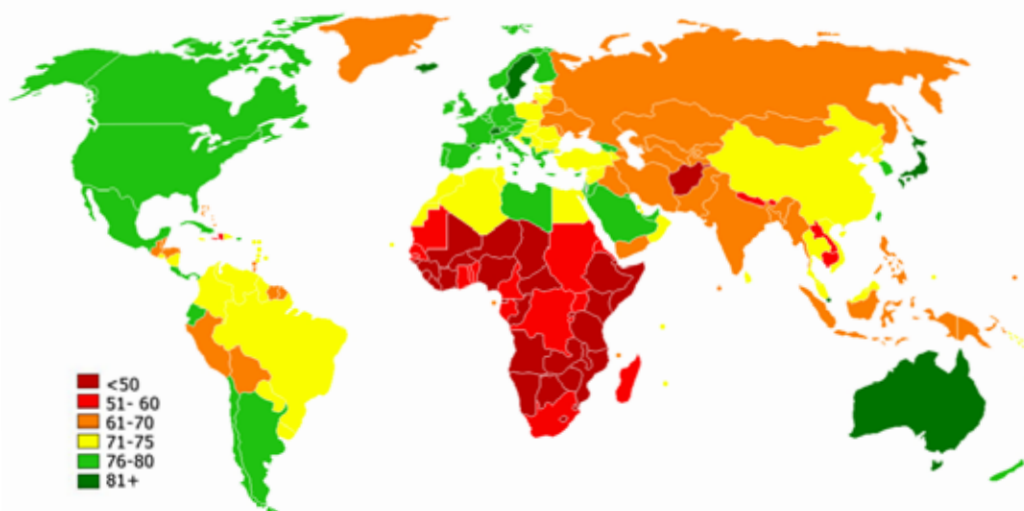
They gleefully point to the successful first flight of the A380 as a fully developed airplane, conceived, designed and tested entirely in a virtual world. However, the human being is a far more complex mechanism than even the most sophisticated airframe, and despite the highest aspirations of the computer industry, the reality is that RCTs are going to remain the industry standard for well into the foreseeable future.

One of the biggest challenges with running RCTs is finding a large enough pool of volunteers. Even those who enroll are aware that as many as half of them may be given a placebo, so are often uneasy about entering the test for fear that their condition will not be ameliorated in any way.

A growing cynicism about the potential of being part of the double blind is particularly affecting recruitment in those geographies where patients have become familiar with the conduct of drug trials, so it comes as little or no surprise to anyone involved with trials, that one of most frequently-recurring comments among those interviewed for this white paper is that the supply of willing volunteers in the English-speaking world is drying up.


There are several other key factors, not least the increased complexity of running clinical trials, and it also needs to be remembered that the populations of the western world are generally much healthier, live longer and have far better access to preventative medicine than those in emerging economies, where many diseases that have been wiped out in the west remain commonplace.

### Average life expectancy



Source: CIA World Factbook 2008

Despite continual claims by the healthy eating lobby that our diet of processed food and pre-packed meals is damaging our life expectancy, average mortality ages in the Western world have been steadily rising for many decades. This situation does not hold true in the less-developed world.



The 2008 CIA world factbook points out that while the average North American citizen can reasonably expect to see their eighth decade, and indeed enjoy it in relatively robust health, such longevity is nearly half as much again as that of the average African male.

So, faced with an increasingly healthy population, where many of the most acute, life-threatening conditions of the 20th and preceding centuries have been eliminated, sponsors are increasingly turning to developing economies to run their trials.

This can be a sound move, especially as developing economies often provide a much more lenient regulatory and economic environment, together with much more compliant patients. But running trials in a distant geography introduces a complete new set of dynamics, which many sponsors see as all but custom-designed to add to the complexities and challenges of trials management.

In theory trial protocols should be repeatable, but in practice it's not often so easy - How reasonable is it to expect a hard-pressed GP in Africa with a bush practice covering an area the size of New Jersey, to conduct a trial following the same disciplines as his counterpart in leafy Princeton?

This brings the problem full circle - in the ideal world the conduct of clinical trials should be in the natural language of the company sponsoring the trial, every element of the process should be fully documented and capable of standing up to the most rigorous scrutiny, and the results unimpeachable. But experience is beginning to demonstrate that this ideal scenario is increasingly difficult to obtain when working out of the home territory.

Many sponsors' response is to bring the trials back to the First world, where they promptly come head-to-head with the situation of an apparent decline in volunteers.

However, not everyone believes the industry view, and interviewing practitioners in the field reveals that despite the cynicism of some patients, the apparent disconnect between sponsors' needs and patient availability can often be more perceived than real.

## **How big is the decline?**

Elliot Barber, Vice President of Editorial Operations at SiteTrove, believes that the patient shortage is not universal, and that by careful choice of investigators it is perfectly feasible to recruit a more-than adequate pool.

"SiteTrove is one of very few independent sources of information that allow sponsors to see at-a-glance which investigators have the necessary experience in running similar trials, and which are available. While it does not show their ability to access specific patient numbers, past experience in this case usually is a good guide to future capability. It's a relatively new solution, which offers a very different approach to simply relying on sponsor's past experience and contacts.

"Although looking at past experience is the widely-used standard approach, it inevitably will lead to a diminishing pool of subjects, as either they move out of the pool, or investigators give up their work. The only effective solution is to have access to a comprehensive, external dataset of trials and investigator information."




Source: TrialTrove July 2010

Karen Jersey, a clinical trials specialist in San Diego, California, agrees that in many cases, the lack of patients can often be better described as 'lack of looking', "We have pages of advertisement in just one local newspaper, for patients to take part in trials, and in 20 years of running trials have never had a problem placing trials or achieving the desired number of patients.

"We use a variety of methods to recruit, not least advertising on local radio, or through internet forums and websites. There are plenty of people out there willing to take part in trials, it's just a case of knowing where and how to find them."

Elliot Barber also confirms that geography plays a critical role. "While on a large scale it is fairly obvious that there are unlikely to be many malaria sufferers in the US, often 'Western' diseases can have a very tightly confined locus.





“For example, in Arizona there are just two investigators currently conducting trials on treatments for Schizophrenia,” he continues, “but there are nearly 120 in California, and 96 in New York. Clearly if you were wanting to trial a new medication for this condition, you could save a lot of time and money by starting out on the East or West coast!”

Dr. Barber also points out another common factor that appears to exacerbate the perception of patient shortage is sponsors underestimating the volume of sites needed to deliver an adequate number of patients. “If you’re running Phase III or IV trials on a vaccine, and you need to get results on thirty or forty thousand patients, it would be grossly unrealistic to expect to get that volume from just a few investigators. Too frequently sponsors underestimate the number of sites they need, so find themselves running out of subjects and having to rush into recovery mode.”

### **Does trial execution influence patient availability?**

According to the Drug Information Association around one third of all trials are now managed by CROs, but they have a preference for the more profitable, early stage trials. This leaves the sponsor companies with the responsibility, and often the larger challenge of finding the patients to run the very large samples required for Phase III and Phase IV.

Shireen Kaur, a Clinical trials consultant at Imprimis Life in New Delhi, believes that CROs play a valuable role, especially in emerging economies, with their ability to act as a bridge between patient and sponsor.

She also believes that the industry as a whole is not doing an adequate job of communicating with its target market – the prospective trial patients. “India is managing all sorts of global clinical trials and all sorts of languages being used, so it is critical that the sponsors of Clinical Trials should communicate more with the general public. One of the first things the industry needs to do is to build awareness of clinical trials and help them get an insight that they are not being used as guinea pigs.”

She also cites a useful checklist for companies running trials in foreign geographies:

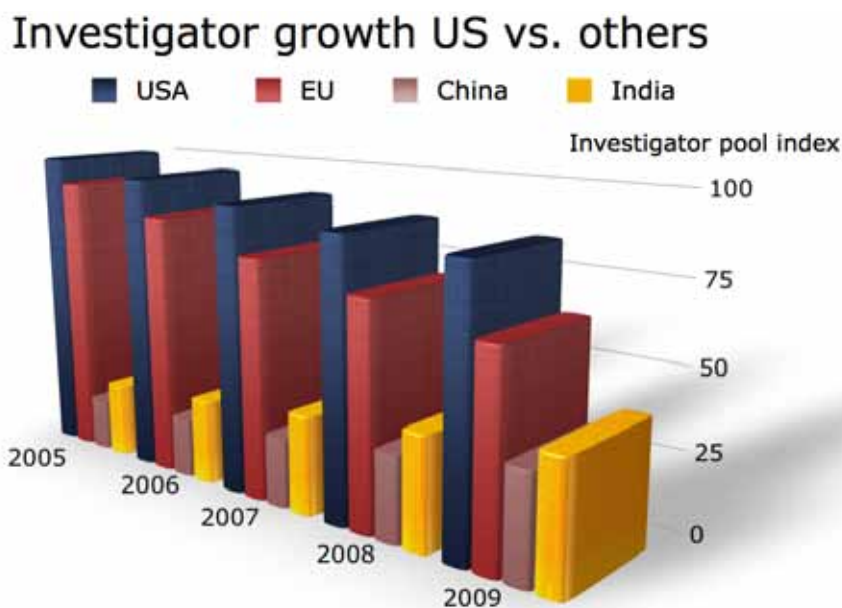
- Train the investigators properly to have a full understanding of what you are trying to achieve.
- Train the site staff and make them understand how to deal with patient questions specific to study protocol.

- Translate all study specific documents in regional languages for ease of understanding, and use native language speakers for the task.
- Make sure that enough time is devoted to ensure patients receive proper care.
- Explain the importance of compliance with the study requirements and most importantly making them understand that this will not only benefit them but also society at large.

Her own experience, widely shared by others interviewed for this document, is that if you get the basics right, and have a sound, well-prepared and well-communicated plan, finding and retaining patients becomes much less of a challenge.

## Is there a Doctor in the house?

One very concerning factor affecting the running of clinical trials investigations, is a continuing reduction in the number of clinicians in the US and taking part in clinical trials investigations.



**Source: ACRO 2010**

In June 2010 The Association of Clinical Research Organizations (ACRO) unveiled that over the past decade, the number of physicians participating in clinical research has continued to decrease in the U.S. and countries in Western Europe, while participation increased at double-digit rates in Asia, Latin America and Central/Eastern Europe.

The survey found that 70 percent of all respondents in both the U.S. and Western Europe believe that the current regulatory environment makes clinical trials difficult to manage - with little variation between U.S. and Western European investigators.

This includes concerns around medical liability, conflict of interest rules and mandates that physicians disclose financial relationships with drug industry partners.

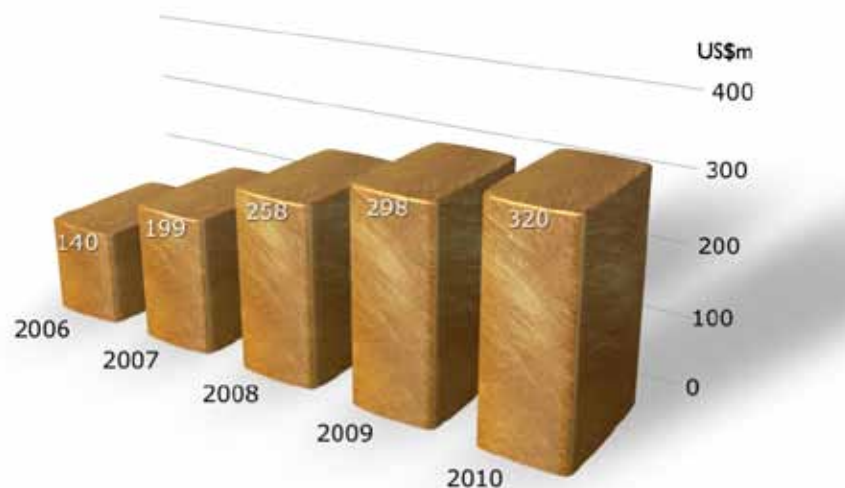
Another highly relevant finding, was that a lack of standardized information about research opportunities deters eligible physicians from participating in research.

Roughly half of respondents believe that a more comprehensive online marketplace or clearinghouse would help to increase physician participation.

### **The challenges of going overseas**

To many organisations India has become a primary market for carrying out clinical trials. With the bulk of the average \$1bn cost of bringing a new drug to market being eaten up by human trials costs, the Indian government's 'open for business' approach to welcome clinical trials has many attractions.

#### **Indian trials market value 2006 - 2010**



*Source: Indian Department of Biotechnology*

Clinical trials in India have become a multi-million dollar business, as the chart shows the Indian government's Department of Biotechnology has been very successful in supporting the growth of the industry whose value in 2005/6 of US\$140m is expected to hit US\$320m in 2009/2010.

Running clinical trials in India is a very attractive option. Apart from the cost benefits, companies are supported by a very favourable legislative environment, and the sub-continent

provides a large pool of qualified, English speaking doctors and patients.

The country's lower employment costs mean that the remunerations needed to deliver a trial are far less than those called for in mainland Europe or North America, and costs can in some case work out at less than half of the cost of running a similar trial in the First world.

It is also interesting to correlate the fact that in the US, according to the ACRO research, just over two-thirds of the physicians taking part in clinical trials had trained in GCP. The percentages of similar training in developing countries were not measured, but it is generally expected to be much lower.

## **How improving the selection process reduces cost**

The one theme that has been repeated by interviewees throughout the preparation of this backgrounder is the need for good preparation and research before a trial is commissioned.

While it is not practical to expect a very close working relationship with each individual investigator conducting a trial, it is critical to ensure that the most minute details are covered within the trial protocol, even down to the flexibility available for paying travel and accommodation costs for those not close to the site.


But a great deal of money can be saved, and trial length reduced considerably, by careful selection of investigators before a trial is commenced.

Dr. Jamil Hussain, VP of Clinical Solutions at Citeline, explains some of the common pitfalls that trial sponsors can overcome. "There are several key challenges in finding investigators to deliver a trial – not least are experience, their patient pool, and availability. For example, there is little value in finding an investigator with access to several thousand patients, if they do not have experience of running similar trials.

"Equally, finding an investigator with the patients and experience will be even more frustrating if they are right in the middle of running a trial that competes directly with your own," he continues, "However, with just a little research it is possible to narrow the field down dramatically and shortlist sites for a pre-study visit, which can sharply reduce the time taken, and costs to get into trial."

Finding this information can be a very lengthy process. Although the Internet hosts millions of sites claiming to offer information about clinical trials investigators, many of these have very limited data.





For example, ClinicalTrials.gov, which is widely used as one of the primary sources for research, offers little information about the investigators, and extremely limited search capabilities

It has been clear for some time that the market needs a better solution, which was one of the driving factors behind the launch of Citeline's SiteTrove product, which now offers the most advanced independent sources of investigator information.

Linda Blackerby is SiteTrove's president. "SiteTrove lists over 200,000 investigators globally and keeps track of all their ongoing and completed investigations, as well as linking to TrialTrove to give a complete picture of each clinical trial, and the range and depth of each investigator's experience

"This breadth of information, which is fully-searchable, helps sponsors build a very accurate list of investigators with availability as well as relevant experience," she continues. "The ability to build an accurate and effective investigator shortlist from one's desktop in a matter of minutes is unique and can save hundreds of thousand of dollars."

One example of the potential saving from using SiteTrove came from comparing a trial that was run in the US in 2009. Naturally the company concerned does not wish to be named, but the retrospective analysis showed that by using a selection from SiteTrove, the sponsor could have saved nearly half a million dollars just by eliminating potentially unsuitable sites before the outset of the trial.

In an article in the November 2009 issue of Pharma Exec, Diego Glancspigel of PAREXEL suggests a typical planning time for setting up each investigator as being anything up to 12 working days. When you consider how many investigators it takes to run even a Phase II trial, let alone phase II or Phase IV, the ability to remove the time taken to approach potentially unsuitable investigators, even if only to discount them, can dramatically reduce the time taken to set up a trial, potentially by as much as half.

This of course does not just yield benefits to the cost of running the trial, both in terms of time and external cost, but can also significantly reduce the overall time taken to conduct the trial, especially if it manages to avoid the trial being delayed or even suspended.

## Conclusion

Is there a true patient shortage?

Certainly in some areas this is so, but whether this means that companies need to move all their trials overseas just to find the appropriate pool remains a moot point.

New trials regimens do offer a solution to the problem of finding appropriate patients, but this has to be balanced with the challenges of operating in unfamiliar markets, and different trials conditions.

Certainly the key impression to come from the research undertaken for this backgrounder is that the lack of a comprehensive directory of trial sites and investigators has been a driving factor in sponsors seeking new markets in which to run trials.

The arrival on the market of a comprehensive, fully-searchable, Site and investigator intelligence solution looks set to bring many changes and help sponsors substantially reduce trials costs and time to market.





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