Improving Standards of Patient Recruitment and Retention in Clinical Trials

White Paper

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Introduction

The process of validating new treatments through clinical trials is one of the most significant yet essential costs encountered by the global healthcare industry. Not only are clinical trials expensive to run, they are notoriously time-consuming, as clinical research professionals endeavour to meet all of the associated regulatory criteria.

Many of these costs and delays are incurred due to inefficiencies associated with recruiting and retaining the patients necessary to successfully complete a trial. A 2003 report into patient recruitment opens with a series of damning statistics that illustrate the scale of the problem:

> Patient recruitment consumes 27% of the cost of development – that is US$5.9 billion annually around the world – [yet] only 1 in 20 recruited patients provides results that can be included in a regulatory dossier… Recruiting and retaining patients is a major cause of clinical trial delays. In fact, over three-quarters of all clinical trials currently fail to meet their recruitment deadlines.

The view taken by the IBM Institute for Business Value, who produced the report, is that:

> Inefficient patient recruitment processes will increasingly become a formidable barrier to pharmaceutical companies' success in launching new products. Improving the patient recruitment process is imperative to avoid wasted investments and eliminate costly delays in bringing new drugs to market – today and even more so in the not-so-distant future.

It is now more than ten years since the IBM report was written, but these issues are yet to be eradicated. The "formidable barrier" remains. In 2010, a Business Insights report examined the wider financial benefits that a more effective patient recruitment process might reap, arguing that:

> Recruiting patients is highly expensive exercise. As a result, effective patient recruitment can deliver significant R&D savings, which in turn can result in a greater return from sales over R&D… expediting recruitment campaigns to deliver timely trial results can help to bring drugs to market more quickly, where they can enjoy a longer period of patent-protected exclusivity.

The global healthcare industry is complex and multifaceted, creating many stakeholders in the success of clinical trials. In order to thoroughly understand the problem, and the range of different perspectives around it, One Research commissioned researchers at the University of Sussex's Innovation Centre to conduct interviews with 15 prominent experts – including presidents, VPs, C-level executives and company directors – operating within the clinical research sector.

These interviewees oversee a wide range of organisations across the UK, EU and US, including pharmaceutical companies, CROs, academic institutions, research sites and public health groups. Many are considered to be thought-leaders in the field of clinical research.

All of the interviewees have worked in multiple roles for different stakeholders across the clinical research community, with a combined 288 years of experience in the industry. The researchers also drew upon experience and data gathered by One Research from working with major pharmaceutical companies in the UK.

In this white paper, we will look to understand the series of challenges faced by clinical research and patient recruitment professionals. We will look to discover the factors that contribute to the successful management and execution of trials on time and within budget, and look towards a solution to common issues reported throughout the industry.

Research Professionals

Protocol

The complexity of trial protocols was mentioned by interviewees across all fields as a significant barrier to patient recruitment. Beth Harper, President and Founder of Clinical Performance Partners, told us that *"a lot of the recruitment patient problem is [actually] either protocol or a site engagement and relationship, or an education problem"*, a sentiment that was echoed by the majority of participants.

Reassessment of these protocols is usually one of the first things to happen should recruitment numbers be lower than required. Christine Pierre, President and Founder of the Society for Clinical Research Sites, says that *"you have to analyse the protocols, the therapeutic area and patient population you are trying to identify."*

While it is clear that the increasing complexity of protocols is hindering the effective execution of clinical research, it is a factor that can be expensive and time-consuming to remedy after the fact. Jim Kremidas, Lead Investigator at CenterWatch, says *"assume it's a protocol issue and they do an amendment. Tufts University just did a study about the cost and found it's about $450,000 on average."*

As a result, those tasked with recruitment will typically contact multiple sites in order to mitigate the risk of being unable to locate a suitable cohort. Aside from the likelihood that this reactive solution will cause delays, deferring exclusively to the sites is not an ideal approach.

Greg Koski, a co-Founder of the Association for Clinical Research Excellence and Safety (ACRES), says that *"the usual way a CRO or pharma company will go about trying to recruit is to try to identify investigator sites that have access to the desired populations. This is one of the major weaknesses in the system, because most investigators tend to over-estimate or over-represent their ability to enrol their patients."*

The healthcare industry must strive to be more proactive in addressing the dynamic between protocol and recruitment. In the Business Insights report mentioned above, a quote from Dr Ian Smith of Synexus Clinical Research suggests a solution:

> *"You should be looking at the patient recruitment strategy at the same time as when you are writing the protocol. In many cases the people who write the protocol do not have any experience of patient recruitment."*

In order for protocol and recruitment to be aligned in this manner, a secure central resource collating patient data would go some way towards providing the much-needed evidence that the suitable patient population is significant enough to meet the protocol criteria.

Retention

While the first hurdle faced by researchers is to recruit the appropriate numbers in order to conduct a study, efforts are further hampered because typically a significant percentage of patients will drop out of any trial before it is completed. Most researchers will *"factor in for the drop-out rate"*, in the words of Zaher El-Assi, President of Merge eClinical.

Not only does the problem of patient retention affect the time taken to gather enough volunteers for trials, it can also be a significant drain on resources. Harinder Chera, a VP at Anovo Inc., told us that in his view over-recruitment is not a sustainable practice: *"Study budget management is extremely important. In oncology...each patient is running $200,000 or $250,000 by the time you have paid an investigator, CROs, vendors and comparator drug."* However, there is little other option available to the industry according to Ross Rothmeier, a VP at Medidata Solutions. *"Clinical trial leaders seem to prefer to over-enrol because at least then you have sufficient data to make your claim. If you under-enrol then your data may become invalid and that's 100% loss"*, he says.

The consensus among the interviewees was that a drop-out rate in the region of 15% was widely accepted across their therapeutic areas, but many trials will be over-enrolled to an even greater extent, in order to mitigate against the risk of rendering the data invalid.

Kai Langel, Director and co-Founder of eClinicalHealth, told us that *"there was one company I was talking to and asked 'is patient retention a big problem for you if you lose 30% of your patients during the trial', and they said no, it's not really a problem because we recruit 50% more patients in the beginning to cover for that. I am sure it would be a problem for the people who are paying 50% more recruiting patients! They were not even considering what they do to actually minimise or reduce the 30% retention rate they currently had. They were just simply throwing money at the problem."*

Upon hearing these figures, one could be forgiven for questioning why – given the high costs associated with each individual patient – there is not more of a concerted effort to find ways of achieving higher patient retention numbers, and thus lessen the need for over-enrolment.

Healthcare Professionals

Often, the burden of recruitment is placed upon investigators and research sites, which are selected on the basis of their ability to recruit the desired patient population. As Greg Koski suggests above, the disconnect between investigator sites and protocol design can often result in recruitment numbers falling short.

Jim Kremidas emphasised that this typical recruitment method is not far-reaching enough. *"There just aren't enough investigators...they will recruit through the practice but that's not enough, you need to get patients outside of the practice too."*

Essentially, the problem is one of awareness; eligible and willing patients are simply not being reached with the message that clinical research opportunities are available to them. Bray Patrick-Lake, a Director of Stakeholder Involvement at the Clinical Trials Transformation Initiative, bemoaned the *"fragmented"* nature of the health system that leads to patients *"never becoming aware of appropriate clinical trials"*.

In the UK, a similar issue occurs when frontline healthcare professionals are tasked with promoting clinical trial participation to their patients. Understandably, many of these hard-pressed clinicians are too preoccupied with patients' primary care to consider recommending them to a trial, while patients themselves are frequently unwilling to trouble their busy general practitioner with questions about clinical research.

Last year, the UK House of Commons Science and Technology Committee issued an extensive report on clinical trials, stressing that the dependence upon primary care for the current system of referral warrants examination and reform. The following passage quotes Simon Denegri, the NIHR's National Director for Public Participation and Engagement in Research, and Chair of INVOLVE, a national advisory group for public involvement in research:

> Health professionals...appeared to be relatively uninformed about research opportunities, making it difficult for them to talk to patients about potential participation. Mr Denegri told us that a patient's relationship with their doctor was "pivotal" in influencing their decision about whether to take part in a trial but, according to the AMRC, a third of surveyed GPs and nurses said that they were not very confident talking about research with their patients, and 21% of health professionals were either unaware of, or failed to use, any of the tailored information resources available to support such conversations. A reluctance to discuss research also appeared to exist on the part of patients: a recent poll found that "only 21% of patients and the public said that they would feel confident asking their doctor about research opportunities". Mr Denegri considered that health professionals, who in the past had "not been very helpful" to patients wanting to find out about research opportunities, were gradually being excluded from the decision making process, as patients increasingly attempted to "self-refer to take part in research".

Evidently, frontline clinicians, whether from the research or primary care community, are not being supported with the resources they need to effectively reach and recruit willing patients.

Patients

Empowering Patients

If we are to relieve some of the burden that is currently being placed upon healthcare professionals, a good place to start would be by empowering patients to refer themselves for trials. One Research has explored motivations for clinical-trial participation through a nationwide sample of patients in the UK interested in late-stage diabetes research (958 registrants: 66% male, 34% female).

Most cited – by 34.2% of the poll – was altruism, followed by: improving understanding of diabetes (30.2%); access to new treatment (21.4%); curiosity about research (14%); and, with a marginal share, financial gain (0.1%). Although altruism is the most frequently cited, volunteers' motives are often interwoven. Anecdotally, almost all are motivated by a desire to help themselves and others.

So why, when a clear range of motivations to participate exist among patients, does this interest not translate into participation more frequently? The extract above, from last year's House of Commons report, indicates that patients are increasingly willing to self-refer. Clearly, the current process of clinical research referral is failing to empower this sub-group of interested patients. The report explains:

> Sharmila Nebhrajani, Chief Executive of the AMRC, agreed that there was "definitely a knowledge and access barrier" for people wanting to participate in a clinical trial, telling us that "patients want to do it, but they have no idea how". According to Professor Johnson [Peter Johnson, Chief Clinician at Cancer Research UK], "a much higher level of awareness among the general population would be enormously helpful".

Greg Koski points out that *"even if you look at oncology, which is one of the best developed areas in clinical trials, less than 7% of eligible patients ever participate. Patients are unaware, and in their lack of awareness of clinical trials, patients are concerned that they will be used as guinea pigs. They may not understand, and we have done a poor job of educating the public as to what a clinical trial is, and what it does."*

The industry needs to improve its communication to patients, not only to raise awareness of the available opportunities to get involved in clinical research, but to reassure them of the vital importance of their role.

Continuous Patient Engagement

During our interview with Jim Kremidas, he identified an often-ignored barrier to the success of clinical research – *"the final key element is communication with the patients"*. Several of our interviewees brought up the concept of patient-centricity – ensuring that the priority of research professionals is to work in the interests of the patients – and the need for them to engage with the person participating in a trial, rather than treating patients as a statistic or data point. This sense of disenfranchisement is a key contributing factor to patients' concerns that they are *"guinea pigs"*, as Greg Koski describes above.

A significant part of the problem is centred on the 'one size fits all' approach to recruitment and retention messaging, which risks leaving some patients to feel unappreciated or alienated. The 2010 Business Insights report insists that:

> Patient communication strategy must vary by geography in order to reflect the specific cultural and clinical differences between regions.

Jim Kremidas brought up the role that patient engagement specialists can play in tailoring communication with patients. *"You can't assume that you understand patients until you're directly interfacing with them. There are a lot of companies that think it's a waste of money…sometimes you need those tools, other times you don't. But it would be wrong to assume that you never need them."*

The issue is further compounded by inconsistent contact with patients following their initial engagement. Continuous contact with the cohort is vital in creating the sense that their contribution is highly valued.

Paul Wicks, VP of Innovation at PatientsLikeMe, told us that *"it's not clear that there is anything to keep people engaged in the trial other than the science...what happens if you get a side effect, do you stay in the trial? What will keep you convinced to stay in the trial? A better understanding and communication will contribute to this."*

It is clear that there is a need for a truly patient-centric model. However, it is understood that it will be difficult to manage ongoing relationships with patients effectively without the involvement of a third party, operating outside of the traditional structures of site, research organisation and sponsor.

Solutions

"There is no magic bullet." – Paul Wicks

"There isn't one magic bullet that is going to help a site reach its enrolment goals." – Christine Pierre

"The fundamental problem is that the industry looks for a silver bullet. They don't understand the complexity of all the factors that come into play in recruiting and retaining patients." – Beth Harper

Throughout the interviews, the same point was raised time and again, by experts with a range of different perspectives on the problem – that more than one issue is at play, and the 'magic bullet' does not exist. Whilst there may be no silver bullet, what we must aspire to is a 'gold standard' in patient recruitment. One facet of this gold standard must be clear and consistent communication with patients and the wider public.

It is obvious that no-one can claim a sweeping solution to the problem of successfully managing patient recruitment and retention for clinical trials. What is possible, and increasingly necessary, is a strategic approach that simplifies the process for each of the numerous stakeholders who must participate together in seeing a trial through to its conclusion. Such an approach must sit comfortably alongside existing methods, supporting both long-term planning, and inevitable short-term tactical changes.

For example, in order for protocols to be met consistently, there needs to be a greater emphasis on performing feasibility studies ahead of protocol design. Feasibility can be established quickly if geographically relevant data enables potential patients to be identified and contacted easily and in sufficient numbers. This is one advantage of establishing a cohort of volunteers to facilitate trial design, rather than trying to find volunteers after the protocol is written. In other words, the very same database of volunteers from which patients will be enrolled can allow feasibility studies to be conducted early in the design process.

Cohorts of patients can be designed and constructed according to medical and geographical requirements, supporting a succession of studies in the same disease areas. Reaching beyond local practices then becomes possible for researchers, because a broader pool of patients has been established in advance. Principle investigators are able to define realistic and achievable recruitment targets, and are able to reduce time from identification of participants to enrolment in the trial. And having access to a stable and consistent patient population can improve the potential for investment and repeat investment from sponsors.

A recurring theme of the interviews was the reluctance of senior figures within the industry towards radical change. Ross Rothmeier says that *"the process hasn't largely changed over the years until recently... what my colleagues in site assessment base their decisions on is not very scientific - it's much more emotional."*

Kai Langel expanded upon this prevailing attitude when describing his rationale for founding eClinicalHealth. He told us that based on his experience with electronic patient diaries, he felt that there were many more possibilities for better supporting patients in clinical trials: *"I really wanted to push the technology forward so it could be more supportive for the patients but also give something to patients, being more engaged and giving more information and feeding real-time information to the sites and that way you can really see what the patients are doing. In the end, we needed to set up our own company to finally turn that vision into reality."*

As discussed in the introduction to this paper, the issues outlined by IBM more than a decade ago persist; in fact many of the same recommendations are reiterated by the UK House of Commons report that was issued last year. It is clear that any proposed solution to the problems encountered by research professionals must sit within the existing framework for clinical research, if the transition to a more coherent approach is not to meet with resistance.

Recognising the complexities of patient recruitment, One Research has developed a methodology that complements and catalyses existing strategies and thereby reduces workloads for clinicians, as well as empowering patients to self-refer. Researchers are not presented with a whole new way of working, but instead with new resources. This empirical approach has been developed in dialogue with all stakeholders, most importantly the patients themselves.

When these guiding principles are adhered to throughout the process of engagement, recruitment and retention, the results speak for themselves. One Research consistently sees upwards of 85% of patients that declare interest in clinical research registering to join their cohort. Registration rates have remained at this level since the recruitment programmes were launched, 5 years ago. In addition, sustained and personal contact with patients has been shown to maintain a stable pool of volunteers – over 97% are retained in the cohort for more than 12 months.

A stable base of patients allows recruitment targets to be achieved more efficiently and cost-effectively. This additional resource can be referred to by investigators as soon as recruitment commences, supplementing their existing patient population to help achieve randomisation targets more efficiently.

A volunteer's first impression of clinical research is critical to the entire process. Retention begins with recruitment, and all of the anecdotal evidence suggests that good, continuous communication can have a hugely positive effect in helping to reduce attrition.

Patients must be able to ask questions and voice concerns. One Research provides the time and space for them to do this – a link to make sure researchers are fully informed about how volunteers feel before, during and after their participation. Similarly, through interviews with researchers during the trial process, One Research can feed back to sponsors which retention initiatives are working best. This has particular value across multiple sites in international studies, allowing sponsors to aggregate feedback and confront the challenge of retention at a strategic level.

But dialogue with patients is not just important during studies. The relationship must be long term if it is to be far reaching. Every trial participant is potentially an ambassador for clinical research, and every opportunity must be taken to engage them. The progress of the study, its outcome, and the impact of the research on healthcare should all be offered back to volunteers with thanks for their contribution. The One Research methodology allows all this to happen seamlessly, without burdening researchers with the responsibility.

If you'd like to find out more about One Research, or contribute to further discussion about patient recruitment and retention, connect on LinkedIn, or email info@oneresearch.co.uk.

References:
Extracts 1 & 2: IBM Global Business Services / IBM Institute for Business Value – Delay No More: Improve patient recruitment and reduce time to market in the pharmaceutical industry (Wang/Drayton/Fraser, 2003), p.1
Extract 3: Business Insights: Outsourcing – Clinical Trial Recruitment Strategies: Optimizing patient recruitment and retention in late stage clinical trials (Seget, 2010), pp.21-22
Extract 4: ibid. p.139
Extract 5: House of Commons Science and Technology Committee – Clinical Trials: Third Report of Session 2013-14, pp.24-5
Extract 6: ibid. p.24
Extract 7: Business Insights: Outsourcing – Clinical Trial Recruitment Strategies: Optimizing patient recruitment and retention in late stage clinical trials (Seget, 2010), p.145