

Identifying and Reducing Barriers to Oncology Clinical Research at the Site Level



Abstract

In a field where improvements to standards of care are sought amongst ever smaller patient sub-populations, as defined by the evidence of specific molecular alterations, oncology poses an ever greater challenge for the effective development of new cancer treatments. Key opinion leaders (KOLs), academics and healthcare professionals in regional tertiary centers have oncology clinical development vying for the researchers' attention with the ever more complex demands of patient care, mounting burden of health administration and increasingly limited resources.

Whatever motivations busy and dedicated physicians may have to participate in the conduct of clinical trials, studies are time consuming and demanding on research teams. The pharmaceutical industry is acutely aware of this. If clinical research is to be successful and generate new treatments that really make a difference to cancer patient's lives and those of their friends and families, industry and clinical teams need to optimise their working relationships.

This paper provides some talking points, specific ideas and innovative approaches that can make a real difference to the successful conduct of industry-sponsored clinical trials by improving the 'Research Team Experience'.

Current State of Oncology Clinical Development

Clinical trials, specifically in the field of oncology, allow access to effective treatments and improved individual patient care for all participating patients. The development and approval process for a new compound may take 10–15 years and requires multiple clinical trials involving hundreds if not thousands of patients. While the Tufts Center for the Study of Drug Development (CSDD) (2013) suggested that 9 out of 10 trials will reach enrollment goals, only 6% of trials will be completed on time according to the Food and Drug Administration (FDA). Even a single day of delay can potentially cost Sponsors millions of dollars in revenue. Within the field of oncology, there are almost 800 medicines currently in clinical development (PhRMA Cancer Medicines in Development Report, 2014), translating to over 3,100 active cancer clinical trials in the US alone. Of these, 1,824 are now seeking volunteers to participate or have not yet started recruiting patients. In order to be successful in the development of new cancer therapies, Sponsors and Clinical research organisations (CROs) need access to sufficient numbers of trained and interested investigators, with highly trained staff and resources to offer those clinical trials to patients. Unfortunately, not only has there been effectively no growth in the number of active principal investigators (PIs) since 2000, 40% of participating PIs are predicted to decide not to continue conducting FDA-regulated clinical trials on an annual basis.

Without a motivated investigator, the process of getting patients to the door for an active trial becomes much more difficult. Despite a large number of trials available to investigators, only about 3% of cancer patients choose to participate in the US (Seruga et al, 2014). However, initiatives taken by organisations such as the National Cancer Research Network in the UK demonstrate the impact that providing support to sites can have on the success of trials, including an increase in accrual rate to clinical studies to more than 17% of patients (Rodbard, 2013). CROs need to identify mechanisms to support investigators and site staff and to reduce barriers in order to increase their level of interest and involvement.

Understanding Investigator Motivation & Barriers to Involvement

The motivating factors for many investigators to participate in clinical research include the opportunity to be involved with cutting-edge science, gain access to new therapies to offer to their patients, the financial support that helps fund the clinical research programme at their site and academic kudos. However, despite these motivations, significant barriers exist at an investigator and site level that often limit participation in clinical research.

According to a recent article in PharmaVoice (Sears, 2014), sites and investigators reported the following barriers to participating in research:

- Constrained site and staff resources impact the ability of sites to manage the contractual and regulatory process, often limiting the number of studies that they are involved with
- Competing priorities at a site level and a lack of feeling engaged with the trials they are involved with
- Limited access to training to allow investigators and staff to navigate the increasingly complex research environment

This data is supported by feedback received directly from sites and networks such as the Sarah Cannon Research Institute (SCRI) UK, which highlights the need to streamline processes, improve communication and support the training needs of investigators and site staff. "One of the main reasons to open a dedicated early clinical trials unit like SCRI in the independent sector was to reduce the burden of competing interests, i.e. Standard of Care Oncology service versus clinical trials, streamlining R&D processes, including contract and budget negotiations with our Pharma partners and ultimately focus in executing trials in a competitive fashion" said Dr Arkenau, Executive Medical Director, SCRI UK.

Optimising Oncology Clinical Research Through Site Partnership & Investigator Support

CROs must acknowledge and address investigator concerns in order to reduce investigator turnover, thereby saving valuable time and money. In order to increase trial participation at the site level, there is a critical need for infrastructure to support investigators and staff (Somkin, 2006) and make the process more efficient. In addition, by ensuring that physician attitudes and values align with the programme goals and providing support for physicians' research activities, Sponsors and CROs can reduce the barriers to investigator participation in oncology trials.

Addressing Limited Staff Resources Through Process Efficiencies

Direct Enrollment & Feasibility

Alleviating the site burden of identifying patients for evermore exacting protocols, which require more specific and heavily competed for sub-populations is an aspirational jumping off point. Now smart technology which intelligently interrogates Electronic Health Records has become accessible. ICON is running a pilot study with IBM Watson making it a reality to present the right patient for the right study directly to the investigator team. This not only affords us greater predictability of enrollment dynamics in clinical trials but also serves sites as they can concentrate efforts on the patient treatment in the study as opposed to manually searching for eligible patients. Complimentary to this, TriNetx and EH4CR partnerships that make use of patient trial eligibility algorithms to trawl HER, support improved feasibility and increase the chances of singling out those sites for which any given trial can offer most benefit to the investigator team and their patients as well as the trial sponsors.

Lightening the Administrative Burden

Managing the conduct of clinical trials requires a tremendous amount of administrative activity at the site level. In order to identify which sites are interested in participating in a particular clinical trial, Sponsors or CROs will often conduct feasibility assessments. These assessments often take the form of questionnaires that are sent to sites to be completed and can be quite time consuming for staff. In addition, sites often complain that after initial feasibility information is provided (perhaps during the proposal phase), there is no or delayed feedback to the site as to the status of the project. CROs must identify opportunities to standardise the approach they take to the feasibility and site identification process and maintain internal systems that minimise the repeated requests for information.

The administrative workload for a site can also increase once they have been selected to participate in a trial.

Collection of all required regulatory documents, as well as the negotiation of contracts between Sponsors and sites, often requires a number of telephone contacts, as well as numerous email exchanges. Employing systems that clearly outline the administrative tasks that need to be completed, set expectations on both sides for timelines, identify the current status of all tasks and track all communication exchanges through a single portal can reduce the number of exchanges between Sponsors and site staff. The 'Activate' system used by ICON provides site staff with a centralised point to manage all communication and document exchange.

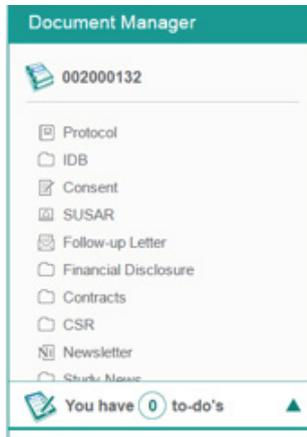
Establish a Single Point of Contact

When working with research networks such as the SCRI, having a single point of contact, e.g. a Site Network Coordinator, can simplify feasibility and site identification activities conducted through the network. Having key documents such as master Confidential Disclosure Agreements (CDAs) in place can help to facilitate the sharing of specific clinical trial information with the network. This also allows the CRO to access information regarding site profiles and investigators within the network and ensures accurate and timely responses so that timelines can be significantly reduced. Coordinators can develop strong relationships with key network personnel and conduct regular partnership meetings to discuss study status, contract issues, upcoming studies and any potential partnership concerns. In addition, placing trained people in targeted regions to maintain communication with sites, trouble shoot and train for patient recruitment will support the timely completion of clinical trials, ultimately getting these new therapies to patients.

Reducing the Need for Re-monitoring

Increasing efficiency at the site level not only reduces administrative time but can also lead to increased quality and a reduction in protocol deviations in clinical trials. Protocols have become increasingly complex, with a large number of tests and procedures that must be completed. Traditionally, much of the documentation for a protocol is stored in large study binders and specific information may be difficult to find. One innovative approach that improves access to information is Firecrest, which was conceived by a team of PIs and online-education experts. Firecrest incorporates a Visit-by-Visit Guide, combining information from the protocol, case report form (CRF), laboratory manuals and other sources. It serves as a support tool for investigators, site coordinators, study monitors and other study personnel. With the Visit-by-Visit Guide, updates to procedures can be rolled out quickly and simultaneously across all sites and it is also a place where all study personnel can go 24/7, 365 days a year to find answers to any questions they may have regarding the study.

Firecrest Improves Access to Study Information & Documents



Patient ID	Version	Date/Time Signed	Patient Name	SDV	View
Assign	1.0	19/01/2015 03:11	Adam Cole	N	View
Assign	1.0	19/01/2015 03:16	Earl Simmons	N	View
Assign	1.0	19/01/2015 03:45	James Smith	N	View
Assign	1.0	19/01/2015 06:33	Chris Raymond	N	View
Assign	1.0	19/01/2015 06:53	Edin Walters	N	View
Assign	1.0	19/01/2015 07:10	Christine Williams	N	View
Assign	1.0	20/01/2015 10:36	David Black	N	View
Assign	1.0	20/01/2015 10:51	John White	N	View
Assign	1.0	21/01/2015 08:08	Janine Fournie	N	View

Another benefit of Firecrest is that it provides a mechanism for sites to utilise an e-consent process, greatly reducing the protocol findings and data queries that are often associated with consent forms. According to the FDA, 9% of all deviations in clinical trials are related to incomplete or incorrect consent forms, despite intensive and costly monitoring. Adding to the complexity of oncology clinical trials is the frequent need for multiple patient consent forms for additional imaging, laboratory or tissue testing. In the majority of cases, the errors are largely administrative, e.g. an incorrect date or a signature on the wrong version of the consent form. However, these errors are significant enough to invalidate the form and require that the subject returns to the clinic in order to resign the form and reconfirm their willingness to participate. In the worst-case scenario, the consent forms cannot be located because they have been lost, misfiled or simply not completed, thereby making it

impossible for the clinical trial monitors to confirm that the participant had consented at all. The inability to locate a complete, current and signed consent form is considered to be one of the most serious violations within a clinical trial, supporting the need to maintain high-intensity monitoring processes despite their apparent limited success. This high-intensity approach to monitoring results in more time on site for the clinical research associate (CRA) and more time for site staff to re-consent patients and respond to queries. Firecrest eConsent is a next-generation, electronic, informed-consent solution that incorporates key recommendations from the FDA's recent draft guidance on informed consent and has been designed to be compatible with sites' existing IT infrastructure, enabling sites to adopt the Firecrest eConsent solution quickly and efficiently. By utilising e-consent, deviations can be reduced, resulting in increased efficiency of site resources.

Firecrest Econsent Simplifies the Patient Consent Process

Title	Version	Published Date	View	Action
Study Consent Form for Ireland	1.0	11-Dec-2014	View	Sign
Test Consent form	1.0	10-Dec-2014	View	Sign
softball	1.0	10-Dec-2014	View	Sign
Printable Consent V2	1.0	18-Dec-2014	View	Sign
Consent Form	1.0	12-Feb-2015	View	Sign

INFORMED CONSENT FORM FIRECREST

I understand that I will be given a copy of this consent form after signing it.

John Smith
Patient Name (print)

John Smith
Patient Name (signature)

01/01/2015
Date

I, the undersigned, have fully explained this informed consent to the patient named above and/or the patient's legally authorized representative.

Alan Rice
Name of person conducting Informed Consent (print)

Alan Rice
Name of person conducting Informed Consent (signature)

01/01/2015
Date

FIRECREST [Cancel] [Print]

Access to Training

Another barrier to research identified by sites and investigators is limited access to training. As clinical trials become more complex, an increasing burden is being placed on investigators who have to deal with frequent protocol amendments, more complex procedures and an ever expanding CRF. Ineffective training, inadequate communications and poor data-capture methods contribute to poor trial performances, which inevitably result in delayed recruitment, frequent non-compliance with protocols and, ultimately, delayed study close-out and market approval. On average, the FDA receives 250 complaints about PI non-compliance on an annual basis, with protocol non-compliance being one of the top reasons cited (Tufts, 2013).

Traditionally, training of site staff occurs during the site initiation visit (SIV) for a particular study. Unfortunately, additional training is often required as a study continues, due to protocol amendments, staff changes at the site or the availability of emerging data. These training needs are usually addressed during future monitoring visits by the CRA or through web-based programmes but are often limited by scheduling issues. In addition to simplifying study processes, Firecrest also offers an innovative approach to training. Each Firecrest module is customised to enhance specific trial, protocol, site array and study team needs, allowing site personnel to receive standardised instructions on key aspects of the trial, such as Response Evaluation Criteria in Solid Tumors (RECIST), Good Clinical Practice (GCP), drug mechanism of action, assessing efficacy, managing toxicities and reporting outcomes on the Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS). Training is available on demand to all site staff, making it more convenient and easier to access whenever the site needs it. The system also provides a mechanism for tracking the completion of training by site staff, increasing compliance with the protocol. An ICON analysis of the benefits of incorporating Firecrest into clinical trials has shown a reduction in both protocol deviations as well as data queries, thereby freeing up valuable site resources.

Increasing the Involvement of Investigators & Sites

Sites including the SCRI UK have suggested that early discussions with the entire site team, including team members such as investigators, pharmacy and nursing, during protocol development can help avoid impractical study schedules while still retaining scientific validity and increasing site 'buy in' to the study design, specifically for the increasingly complex inclusion and exclusion criteria.

In addition, ongoing discussions with investigators and site staff during a study can provide valuable information about how the protocol and broader clinical development programme is progressing, keeping the study top-of-mind for the site and adding a broader perspective to why the study is important. A recent report from the Tufts CSDD (Tufts, 2015) gathered similar feedback from members of the CSDD Executive Forum, which suggests that Sponsors and CROs can minimise challenges at the site level by soliciting feedback from sites throughout the process and allowing sites to provide feedback through scorecards that utilise quality metrics.

Developing and maintaining relationships with investigators and Key Opinion Leaders (KOLs) allows for Sponsors and CROs to gather feedback directly. For Sponsors, these relationships are often managed by field-based personnel such as Medical Science Liaisons (MSLs). MSLs build relationships with KOLs and investigators through scientific discussions and participation in clinical trials. The two-way scientific exchange between MSL and KOL allows investigators to be involved with the design and conduct of clinical trials, while allowing MSLs to gather competitive intelligence and valuable feedback. The result is physicians who feel involved with the overall clinical development process and want to continue working with the Sponsor organisation.

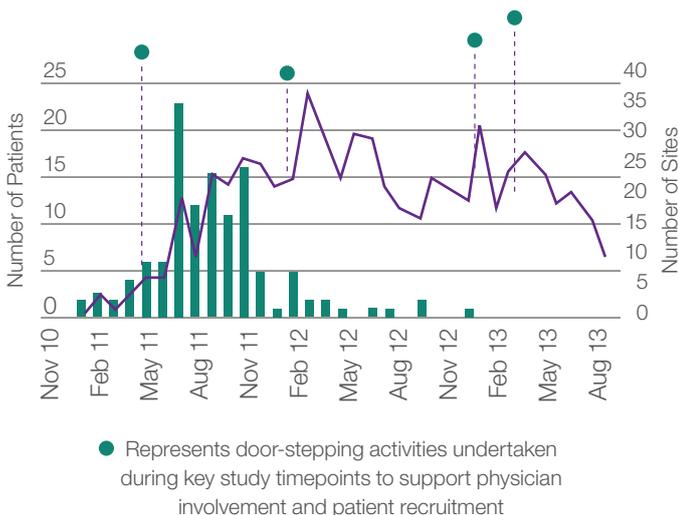
While CROs work with a large number of physicians, the relationship between the CRO and the investigator/KOL does not usually have the depth that is seen between the MSL and KOL. Unlike the specialised MSL role that is focused on developing and strengthening the relationship with investigators, within the CRO industry, this relationship is often managed by the CRA. The primary focus for CRAs is monitoring and evaluating data at a site level and they may have limited resources for scientific discussions with investigators. Communication is often one way, from CRO to investigator, and may come in the form of quarterly newsletters that provide status updates on clinical trials, rather than face-to-face meetings, limiting the depth of the relationship.

CROs have the opportunity to adopt a model similar to that used by Sponsors in order to strengthen their relationship with KOLs and investigators. Utilising clinical and scientific experts to have face-to-face meetings with investigators on a regular basis, initiatives such as ‘door stepping’ allow CRO experts to do the following:

- Clarify and discuss the scientific considerations of the study
- Gather feedback on how best to improve the physician experience of the study
- Disseminate key information directly to participating investigators

Through this initiative, the study is kept at the front of the investigator’s mind by building a credible ‘personal’ working relationship with physicians, leading to an increase in patient enrollment. An example of the impact that door stepping can have on patient recruitment is seen below. During a recent global oncology study, door stepping activities were undertaken at key points in the study, leading to increases in patient recruitment. These activities included face-to-face meetings and quarterly calls between ICON clinical experts and the investigator, as well as programmes held during major medical conferences that allowed the study team to provide updates to investigators and gather feedback.

Fig. 1: The Effect of Door-Stepping on Enrollment During a Global Oncology Study



Conclusions

The goal of oncology drug development is to bring effective treatments and improved individual care to patients suffering from cancer. The process to get a new therapy approved by the FDA may take 10–15 years and requires the timely completion of numerous clinical trials. The success of the process rests on finding and supporting the investigators and site staff that ultimately recruit the patients for the studies. By finding ways to create administrative efficiencies, keep investigators engaged throughout the process and provide ongoing access to training, CROs can reduce barriers to clinical research participation for sites.

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A Symbol of Excellence

ICON plc Corporate Headquarters

South County Business Park
Leopardstown, Dublin 18
Ireland
T: +353 1 291 2000
F: +353 1 291 2700

info@ICONplc.com
ICONplc.com