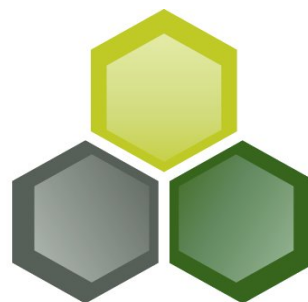


# Kinapse



Life Sciences Consulting and Outsourcing

**Kinapse White Paper**

**Improving Clinical Site Productivity**

**Expertise ► Collaboration ► Innovation ► Results**

There are a number of factors in the industry that make clinical trials more costly, more time-consuming and requiring more patients than in previous years. More than ever, sponsor companies are being pushed to deliver clinical trials quicker and more cost effectively. The purpose of this paper is to look at ways in which clinical trials can be run more effectively and thus improve productivity. The paper introduces the Kinapse Clinical Site Productivity Framework as a mechanism to evaluate seven key areas in the patient recruitment process. By assessing each key area, issues can be identified, prioritised and solutions designed and improvements made.

## Introduction

In 2005, there were twice as many patients required for a new Phase II study than there had been in 2001<sup>1</sup>. New and inexperienced sites were needed to identify and recruit these additional patients, incurring greater costs for the study. In an internal Pfizer analysis of the clinical studies it conducted from 2000 to 2006, the Director of Clinical Trial Recruitment Services found that 80% of the participants in Pfizer studies were enrolled by 26% of the participating clinical sites<sup>2</sup>. In addition, 8% of sites failed to complete a single patient<sup>2</sup>. Schultz *et al.* (2007) similarly reported that 254 out of approximately 2000 clinical sites also failed to recruit a single patient<sup>3</sup>. In a recent assessment within a leading specialty pharmaceutical company performed by Kinapse in 2007, those sites which failed to enroll one patient ranged from 0% to 8% depending on the specific study assessed<sup>4</sup>. In addition, increasing the number of countries used in studies often delivers fewer patients per country and drives up costs and complexity<sup>4</sup>. Costs are also impacted by delays during study start-up, maintenance and close-out phases.

Improving clinical site productivity within a global pharmaceutical or biotechnology company is much more

complex than is first apparent. The complexity is compounded by a number of factors not limited to the execution of the clinical study at site. It is commonly thought that high quality support from a Clinical Research Associate (CRA), a strong trust-based relationship with the investigator and site staff and the proactive support of the sponsor organisation will be enough to deliver the necessary patient numbers at the regional and global level. However, this is not the case. It is also imperative that resources are invested early in protocol development to ensure that the protocol is deliverable and the right countries and sites are selected to participate in these studies so as to prevent, or at least limit, delays to timelines (Table 1).

The paper will examine the critical relationship between the Clinical Development and Clinical Operations functions and will introduce the Kinapse Clinical Site Productivity Framework (Figure 1) as a mechanism to identify process improvements which will impact clinical site productivity<sup>3</sup>. This framework, which is discussed in detail below, aims to provide a basis for the effective delivery of patients into a clinical study in a more productive manner than is often employed.

Table 1: Explanations given for delays in clinical trials in the European region<sup>5</sup>

Cause of Delay	% Cited
Contract and budget negotiation and approval	47%
Patient recruitment and enrolment	42%
Availability of study drug	41%
Ethics Committee review and approval	40%
Investigator selection	39%
Correction of case report from enquires	38%
Protocol development and refinement	37%
Legal review	36%

### 1. Protocol Feasibility

Central to the delivery of a clinical study is a robust protocol written collaboratively between the medical function, responsible for the development of the protocol synopsis, and those representatives of the clinical operations function, who will be given the responsibility for executing the clinical study. Excellence in medical science and the development of an innovative protocol provides the opportunity for patient stratification or data which will support a strong regulatory submission.

The input from experienced operational colleagues early in protocol development, in an advisory capacity, enables these innovations to be grounded in the real world practicalities of executing a clinical study within the primary or secondary care setting. This interface between the medical function and the clinical operations function can be challenging and unless company culture reinforces a collaborative approach through appropriate objectives and measures for the individual and the team, the resultant protocol may be difficult to execute to time, cost and the necessary quality.

### 2. Country Feasibility

Relevant, up to date information from a commercial, clinical and regulatory perspective is critical to support effective decision-making. A challenge here, particularly outside of the US, is that this knowledge resides at the country or sub-country level and without a clear, timely and routine process for delivering information between the countries, the regions and the global level, important data which may impact regional or country selection may be unavailable, not up-to-date or used to its full potential.

Most pharmaceutical companies operate a feasibility process which requests either regions or countries to

provide a provisional patient commitment and cost for completion of the study within in a given timescale. The source and accuracy of this information is often country-dependent whether this is an existing or new therapy area to the country. Sources for this type of information range from user-friendly, real-time global databases, local investigator databases in Microsoft Access, commercially available databases, clinical research networks, clinical site feasibility questionnaires/interviews through to the opinion, experience and knowledge of a clinical project manager within the country. Critical to this process is the reinforcement of good behaviours, rewarding individuals and the country-level organisation for the accuracy of forecasting patient, cost and timelines. Poorly devised metrics can contribute to bad behaviours with countries provisionally committing low numbers of patients to ensure that their targets are always met, however, an overall low provisional patient commitment collated at the global level requires additional countries and clinical sites to be approached resulting in an increased overall cost per patient for the study.

### 3. Clinical Site Patient Feasibility

Depending on the pharmaceutical company, the term clinical site feasibility can have different meanings. In some, this is a general term which describes the entire process of setting-up a clinical site, the period from receipt of a finalised protocol within the country through to a site initiation meeting. This all-in-one approach to the pre-study phase can lead to ambiguity, unfocused effort and wasted time and cost, as it makes the assumption from the start that every investigator site will be included in the study.

In contrast, we advocate a staged approach, with the initial stage focusing on how many patients the clinical sites within a country can deliver in the terms of patients/site within a time period and if each has access to specific, technical equipment necessary to conduct the study in question . Only once this has been assessed

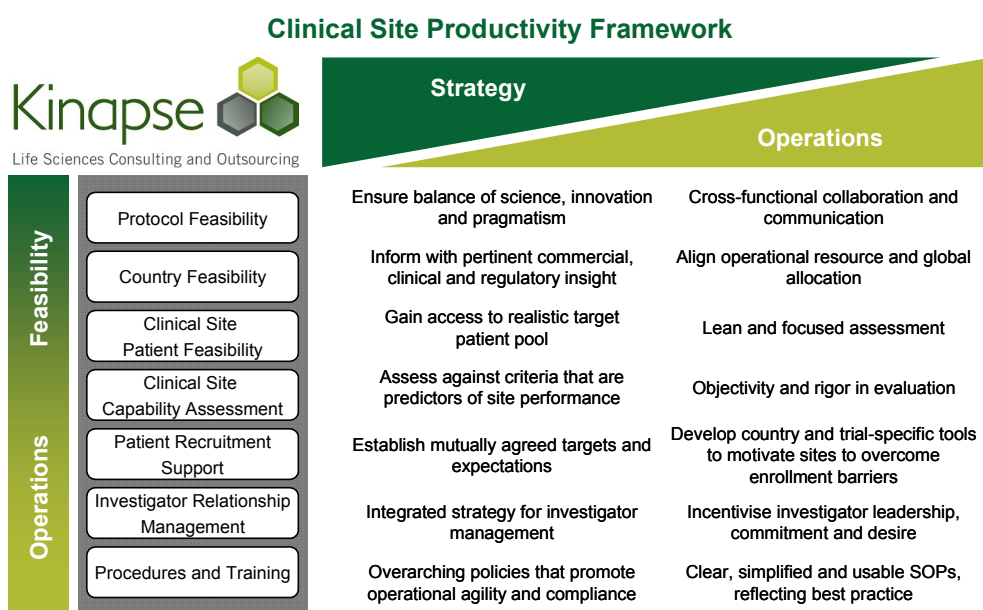


Figure 1: The Kinapse Clinical Site Productivity Framework

would a more detailed capability assessment occur (see point 4). This approach quickly identifies the provisional inclusion of the site in a study and informs the country-level forecast or commitment (as described in the previous section).

#### 4. Clinical Site Capability Assessment

Once the country has been selected to take part in a study, there needs to be a robust assessment of each provisional investigator site to determine qualification or selection to be involved in the study, which is the next stage gate. The purpose is to derive a thorough understanding of the capability of the investigator site and to inform decision-making around its selection or exclusion from the study. Examples of criteria to be assessed are included in Table 2.

Organisations benefit from a robust and routine process as this focuses the time during the assessment and over time through experience and familiarity. Critical to this approach is the need to only procure information relating to the selection or exclusion of the site from the study. This lean approach is time-efficient during the assessment and also reduces the complexity and time associated with the actual decision to select or exclude. In addition, for investigators and clinical sites which are currently working with the sponsor or have just completed a study, information relating to site capability will be readily available and negates the need to conduct a formal assessment at the site, which also adds to efficiency gains.

#### 5. Patient Recruitment Support

Sponsor support to staff involved in patient recruitment is often critical to achieving patient numbers within a desired timeframe. The sponsor has a number of opportunities to provide this support and an optimal mix should be defined for a particular study. These include providing education directly to the patient through clear and understandable patient information sheets, newsletters and identifying support networks in their locality. When an organisation is embarking on a study in an unfamiliar TA or indication the use of clinical

research networks also provide the opportunity to identify new patients.

Support to clinical site staff, such as nurses, may include teleconferences with other sites to share best-practice, training in finding and consenting patients as well as creating awareness of the study within the broader care facility. More creative ways which require greater time and cost to the sponsor are the development of study specific websites to generate awareness and to keep patients in touch with the status of the study. There are a number of successful engagements reported by companies such as Rapid Trials who focus specifically on the investigator site and supporting recruitment, often under challenging circumstances. In addition to the specific activities, the building of rapport and the natural development of the relationship with the site staff can be motivational in itself, for both sponsor and clinical site staff.

#### 6. Investigator Relationship Management

A focus of activities at the local operating country level is the effective management of the relationship with investigators. There are a number of roles that may be involved in this relationship and these benefit from coordination on behalf of the sponsor company. Sponsor company staff need clarity of role and responsibilities in order to manage the investigator effectively, and there is unlikely to be a “one size fits all” approach which can be applied to a pharmaceutical company due to their differing size, organisational structures and culture. That being said it is relatively easy to map relationship management responsibilities at each step of the process, be it investigator meetings, monitoring visits or motivational visits.

Sponsor organisations benefit from moving away from a transactional approach to the relationship with the investigator and the broader clinical site, approaching the relationship as a trust-based partnership. In a competitive market place, where investigators can choose or prioritise the sponsor companies he/she works with, it is important to invest time in the relation-

**Table 2: Clinical Site Capability Assessment**

1. R&D Office (contract, procedures, timelines, financials)	10. General and specialist equipment availability
2. Ethics committee meeting dates and deadlines for submission	11. Investigator eligibility to receive and dispense Investigational Medicinal Products (IMP)
3. Principal investigator experience within the specific indication	12. Medical license and expiration dates for the Principal and sub-investigators
4. Clinical site staff experience of involvement in clinical research	13. Time commitment expectations during monitoring visits
5. Pharmacy assessment and experience	14. Source data and access during monitoring, audits and inspections (as applicable)
6. Review of Principal Investigator and other site staff CVs to determine appropriate medical knowledge, experience, GoodClinical Practice (GCP) and patient confidentiality training	15. Motivation and enthusiasm of investigator and site staff to be involved in this specific investigation
7. Dedicated coordinating research nurse	16. Inspection findings, serious breach (UK) associated with the clinical site
8. Specialist departments e.g. pathology's availability to process samples in accordance with the protocol	17. Dedicated workspace, IT connectivity during monitoring visits
9. Knowledge and ability to do electronic data capture (EDC)	18. Awareness of ongoing competitive studies and their recruitment close-out dates

-ship to ensure that the partnership is a rewarding experience for the investigator and clinical site staff.

Investigator needs must be understood and met. Investigator perceptions of a sponsor company, and their requirements can be obtained by a number of mechanisms including subscribing to an industry-wide survey such as that provided through CenterWatch, commissioning a survey from within the sponsor company, focus groups (representing a cross-section of investigators), one-to-one interviews and, more informally, feedback from investigator-facing staff. Through investment in these types of approaches a sponsor company will be able to reflect on the relative success of its investigator management tactics, identify unmet investigator needs and opportunities for improvement. Justification for the investment in investigator relationship management should be sought through improvements in recruitment numbers, timelines and quality. Indeed these data can also influence the decision of an investigator to take part in a future clinical study.

## 7. Procedures and Training

The interpretation of what a good GCP-compliant procedure is differs between pharmaceutical organisations and is often influenced by the strength of regional *versus* global organisational culture. In addition, in an attempt to be all encompassing these procedural requirements can often be large and unwieldy. Whilst it is difficult to proscribe how an organisation should structure its document hierarchy e.g. policies, standard operating procedures, work instructions etc. it is important to clearly articulate roles and responsibilities within a procedural document. Focused procedures which are written clearly, simply and in a logical, stepwise manner and reflecting current best-practice within the organisation are beneficial to the reader.

The CRA is increasingly becoming the major investigator-facing representative of a pharmaceutical organisation during the execution of a clinical trial. Investment in training (therapy area, indication, protocol, negotiating and influencing, communication, project management and GCP compliance) is not an insignificant cost to a sponsor. Whereas an organisation must provide and document certain compliance training and that TA/DA and protocol training continues to occur through the study team network, at times of economic uncertainty and cost control it is often the “softer skills” budget which is under the greatest scrutiny and pressure. New CRAs or those undergoing refresher training also benefit from training provided by individuals more experienced in their role, mentoring, co-monitoring visits and the opportunity to discuss challenges they face with their peers.

## Conclusion

Pharmaceutical and biotechnology companies are under ever-increasing pressures to cost-effectively recruit patients to clinical studies at a time of increasing ethical, regulatory and contractual scrutiny. Speed needs to be balanced with quality and the time available for patient recruitment maximised through the timely conclusion of

contracting and budgeting negotiations in addition to regulatory and ethics submissions during the study start-up phase.

The Kinapse Clinical Site Productivity Framework (Figure 1) provides a mechanism to evaluate seven key areas in the study recruitment process and, by assessing each using lean tools and techniques, the sponsor can quickly identify and prioritise issues and design and implement solutions to the same. Whereas interventions in one area can achieve improvements, it is only through the holistic assessment of the end-to-end process, with internal and external stakeholders, that the patient recruitment process can be fully optimised and clinical productivity improved.

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5. Source: Thomson CenterWatch (2006) European Survey (n = 306)

## About the author

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Steve has 9 years of management and business consulting experience within the pharmaceutical, biotechnology and medical device industries in the US and Europe.



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