Executive summary

The delivery of the clinical study programme is the most costly, labour-intensive and time-consuming component of the drug development process. Delivering the clinical study programme successfully is getting harder as the operating environment has become more complex. There is increased competition for and continued geographical spread of clinical study sites; more complicated clinical study protocols; increased regulatory agency expectations; stringent post marketing commitments and continuing adoption and adaption of industry standards and best practices. Although clinical development timelines have remained stable, this stability has come at the expense of spiralling costs per patient and a decline in data quality.

The Clinical Operations department manages the operational delivery of the clinical study programme. Given the increasing complexity of the operating environment, one might expect that Clinical Operations be at the top of the agenda for R&D executives. However, what we find is that Clinical Operations is often not treated as a key partner by the rest of the organisation. This is shown by a lack of investment in Clinical Operations. Specifically there is:

- A lack of an uninterrupted, Clinical Operations line of accountability from Clinical Study Management to Site Operations and therefore from central sponsor directly to individual study sites
- A lack of Clinical Operations representation on key development teams
- A highly fragmented and overly diverse network of external suppliers providing services to Clinical Operations and
- A limited/restricted talent pool within Clinical Operations. As it has not been traditionally seen as an area for significant career advancement in clinical development, individuals often leave Clinical Operations to join other functions where the prospects may seem brighter.

Pharmaceutical Companies can enhance the successful delivery of their clinical study programmes by recognising Clinical Operations as a key partner in the drug development process. They need to make meaningful investment in Clinical Operations, specifically they need to:

1. Group clinical study delivery functions into one cohesive, delivery excellence unit
2. Ensure Clinical Operations representation and participation in the three key development teams
3. Rationalise the number of external suppliers to Clinical Operations
4. Up-skill the capability of Clinical Operations staff and management through organizational recognition and the provision of tangible career advancement opportunities.

Only by empowering Clinical Operations in this holistic way, can Pharmaceutical Companies get the performance that customers and partners expect from Clinical Operations - high quality clinical data and study reports delivered on time and to budget.
Clinical development times have remained stable but at the expense of spiralling costs and an increase in poor data quality.

The delivery of the clinical study programme is the most costly, labour-intensive and time-consuming component of the entire drug development process. Issues with the clinical study programme have serious consequences for the drug asset in terms of timelines, regulatory approval, revenues and patient access. Delivering the clinical study programme is getting harder as the operating environment has become more complex (see SIDEBAR). Publically available datasets suggest that the industry has been successful in holding clinical development timelines stable between 5.5-6.5 years (see Figure 1).

### Mean clinical development timeframes for NDAs submitted to FDA

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### Mean clinical phase for RBI Oncology drugs submitted to FDA

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### Mean phase lengths for FDA-approved novel recombinant proteins & mAb Therapeutics

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**Figure 1: Illustrative Clinical Development Timeframes**
However, this stability has come at the expense of spiralling costs per patient (see Figure 2) and a decline in data quality (Figure 3). Whilst the mean cost per patient in a Phase 4 clinical study has remained around US $5,000, the costs per patient in Phase 1, 2 and 3 clinical studies have approximately doubled between 2001 and 2010. Similarly, the percentage of sites and investigations found to have conditions that represent “significant departure from regulations” has approximately doubled between 1977 and 2010. (We accept that this may also be a result of a more demanding standard of inspection.)

Figure 2: Mean cost per patient worldwide, in clinical trials by clinical phase

Figure 3: CDER Clinical Investigator inspection classifications
SIDEBAR: The clinical study environment has become more complex. There has been:

1. Increased competition for study sites and subjects.
The number of worldwide active R&D projects in development has doubled between 1999 and 2011, from 5,990 to 10,351 (Figure S1). This means it is harder for Clinical Operations to access the patient pool to conduct studies.

2. Increased clinical study protocol design complexity.
Between 2000 and 2007, the median number of unique and total procedures increased by 38 and 49% respectively and the median number of case report form pages per protocol increased by 227%. The patient enrolment rate and retention rate fell 20% and the knock-on effect was that the time from protocol ready to Last Patient Last Visit increased by 70% (Figure S2). This means that Clinical Operations must do more ‘work’ per study and spend more resources ensuring GCP compliance and oversight due to more complicated procedures.

3. Continued internationalisation of clinical sites.
The percentage of worldwide clinical trials conducted between 2006 and 2010 has fallen or remained stable in traditional regions such as North America and Western Europe but has significantly increased from 25.4 to 31.1% for Asia, with Japan and Korea growing >13% each (Figure S3). This means Clinical Operations needs to run operations in a larger number of countries.

4. Increased regulatory agency expectations and continued stringent post marketing commitments accompanying marketing authorisations.
The percentage of New Molecular Entities approved by the FDA which had post marketing commitments and/or Risk Evaluation and Mitigation Strategy requirements has been more than 90% since 2006 (Figure S4). This means Clinical Operations must continue to support products post approval.

5. The adoption of different technologies and industry standards.
In the last decade there have been three major trends (a) to move from paper-based to computer-based systems (e.g. IVRS/IWRS, electronic medical records, electronic data capture, web-based site training and qualification, clinical trial management systems, electronic patient diaries, electronic document storage and electronic processes for recording biospecimens) (b) in the continuing evolution of science (e.g. biomarkers) and (c) in best practices in key clinical study activities (e.g. feasibility practices and patient enrolment and retention practices). This means Clinical Operations must continually adapt and innovate in order to stay competitive.
Clinical Operations manage the most expensive part of the drug development process but are often not treated as a key partner

Clinical Operations is the group of functions that manages and executes the operational rather than the strategic aspects of the clinical study programme and the individual clinical studies contained within it. Clinical Operations is accountable for ensuring that clinical data demonstrating that a drug asset is bioavailable, effective, safe and value for money, is delivered on time, to budget and to the required data quality. Clinical Operations is unique in the pharmaceutical development process in that it relies on an international network of independent clinical investigators, operating outside the management structure of the Pharmaceutical Company, to execute clinical studies.

Clinical Operations fundamentally divides into three parts:

1. **Clinical Study Management**
   - This function is responsible for the planning, coordination and oversight of clinical studies, often referred to as the ‘global’ or ‘central’ group.

2. **Site Management**
   - This function is a regional and country structure whose role is to identify, manage and monitor investigators and institutions with whom and where clinical studies will be conducted.

3. **Support Services**
   - This group is responsible for the other key activities needed to execute clinical studies and to determine their outcomes: Clinical Supplies, Biostatistics, Data Management, Medical Writing and Archiving. This group also includes functions involved in enhancing and controlling quality and compliance.

Pharmaceutical Companies take great care in getting the science of the clinical study programme right. The Clinical Science/Medical function rightly enjoys high standing, prestige and influence within the organisation. However, the same cannot be said for the function accountable for the execution side of the clinical study programme. Clinical Operations is often seen within a Pharmaceutical Company as a service provider rather than as a key partner. This means that Clinical Operation’s contribution to the science and to decisions regarding the clinical study programme and elements within it, are seen as non-critical. This is evidenced by a lack of organisational investment in Clinical Operations. Specifically there are four main issues:

**Issue 1:** A lack of an uninterrupted Clinical Operations line of sight from Clinical Study Management to Site Operations.

Clinical Operations must demonstrate and work in compliance with Good Clinical Practice (GCP) as part of its day-to-day business. A key part of GCP compliance is having consistent and clear accountabilities for Clinical Operations roles. Without a single clear line of sight from central sponsor directly to individual study sites, it is hard for Clinical Operations to be GCP compliant. This is because there will be inconsistent and potentially poorly understood Clinical Operations roles, responsibilities, reporting relationships and therefore, decision making authority and accountabilities across different parts of the business. This situation also significantly limits the ability of Clinical Operations to be operationally excellent in delivering clinical data.
**Issue 2:** A lack of Clinical Operations representation on key development teams.

The successful development of a drug asset, with its associated clinical study programme is a complex business and involves the coordination of up to 17 distinct disciplines and skillsets. These are typically brought to bear through three cross-functional teams. At the highest level, an Integrated Global Development Team (IGDT) is charged by the organisation to successfully guide the drug asset through drug development. A Clinical Programme Team (CPT) is charged by the IGDT to design and successfully execute clinical study programmes for each drug asset. Finally a Clinical Study Team (CST) is charged by the CPT to design and successfully execute individual clinical studies. Widespread functional representation on these teams is shown in Figure 4. Without membership on these teams, the ability of Clinical Operations to positively influence key development decisions is severely limited as a Clinical Operations informed view of matters never makes it to decision makers.

![Figure 4: Widespread functional representation/make up in the three key Development Teams](image)

**Issue 3:** A highly fragmented and overly diverse network of external suppliers to Clinical Operations.

Similar to other pharmaceutical functions, Clinical Operations has used a variety of outsourcing models to help reduce its cost base, provide resource flexibility and provide access to skills and capabilities not available in-house. Unfortunately there is often no unifying company-wide strategy around outsourcing which means that there could be a different external supplier by function, process, geography or asset. A single study may have five or more external vendors working on it at the same time.

**Issue 4:** A limited/restricted talent pool within Clinical Operations.

Although clinical operations roles have existed since the advent of clinical studies, formal recognition of Clinical Operations the function, has been a relatively new phenomenon—perhaps only for a decade or so. Although it has often been the first career choice for many individuals in clinical development who lack medical degrees, it has traditionally not been seen as an area for significant career advancement in clinical development and individuals often leave to join other functions where the prospects seem/are brighter. This means there is often a limited pool of talent and experience to draw from. Across the industry, this has significantly limited the capability of Clinical Operations to lead, to innovate and to renew itself (e.g. through adopting new technologies, processes, management tools and metrics, operating, resourcing and geographical strategy) to keep pace with the changing challenges of the external operating environment.

These four problems result in an inability to produce the performance that customers and partners expect from Clinical Operations – high quality clinical data and study reports delivered on time and to budget.
How do we position Clinical Operations so that it makes its full contribution to the development process?

Companies need to value Clinical Operations as a key development partner. They need to make investments in Clinical Operations so that all four of these issues are all properly addressed.

**Solution 1.** Group clinical study delivery functions into one cohesive GCP compliant and delivery excellence unit.

Core clinical study activities need to be grouped into a single, seamless, integrated and scalable Clinical Operations function. Our ideal clinical study delivery excellence organisation is shown in Figure 5.

![Figure 5: A seamless, integrated and scalable Clinical Operations group](image)

This organisation should be accountable for all operational activities that take place between the finalisation of the Clinical Study Protocol and for the submission of the Clinical Study Report, (as well as being responsible for providing other key inputs as outlined in Section 2 below). Clinical study delivery excellence is ensured through the close integration of Clinical Study Management, Site Operations, Data Management, Statistics, Medical Writing and Quality Assurance, Compliance and Risk Management within a single organisational structure. In particular, there needs to be a direct functional reporting line from Site Operations through to Study Management which allows for a coherent, unbroken chain of command and line-of-sight from the Study Management group through to Study Monitors and thereby to individual sites within countries.

This single way of working allows for the creation and management of consistent, easy to follow and organisationally transparent processes, roles and responsibilities throughout Clinical Operations. This helps ensure GCP compliance as there are clear role accountabilities. It should also allow early and appropriate corrective action to ensure patient safety and data quality and allow for industry median (or better) study completion times.
**Solution 2. Ensure Clinical Operations representation and participation in the three key development teams.**

At the highest level, the Integrated Global Development Team is accountable for the successful development of the drug asset and bringing it to a position where it can be brought onto the market. We have frequently observed that Clinical Operations is omitted from representation in this team. We contend that this is a serious oversight. It is worth reiterating that the most costly, labour-intensive and time-consuming component of the drug development process is the delivery of the clinical study programme. While the Clinical Science representative provides expertise in the scientific rationale and design of the development programme, that development programme must be operationalised in the real world, in countries, in sites with investigators and patients. The laudable intent of creating a ‘scientifically perfect’ clinical study programme always needs to be counterbalanced by an understanding of the operational reality, which is the domain of Clinical Operations. More effective and efficient decision making by the Integrated Global Development Team will happen if the experts in the process, the Clinical Study Management group, are active participants. In our experience, best practice development organisations frequently appoint a Clinical Operations Head for each Therapy Area. These individuals are members of the relevant IGDTs and are accountable for all of the Clinical Operations activities in that therapeutic area.

At the next level, the Clinical Programme Team is accountable for the design, oversight and successful execution of the clinical study programme for the drug asset. We have observed that while companies frequently have Clinical Operations representation from the Biostatistics function, they frequently omit Study Management representation from this team which is a second serious oversight. The design of the clinical study programme is of strategic importance and involves trade-offs between scientific and operational needs as well as commercial fit, and regulatory and legal needs. Key operational assumptions are based on available patient populations, the accessibility of those patient populations, the compatibility of different medical practices in different countries, the feasibility of protocols and the impact of these factors on enrolment and recruitment timelines. Effective and efficient decision making is more likely to happen if the experts in the process, the Clinical Study Management group, are present and actively participating. Indeed, in best practice development organisations, a Programme Manager from Clinical Operations leads the Clinical Programme Team and that Programme Manager is accountable for the delivery of the studies making up the clinical study programme.

Finally, we would emphasize that the Clinical Study Team needs to be accountable for the successful design and execution of a single clinical study and a Clinical Operations Study Manager should (and usually does), lead the team and is accountable for the delivery of the study, from finalisation of the study protocol to the finalisation of the study report. Our thinking is summarised in Figure 6.

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**Figure 6: Ideal, best-practice composition of the three key Development Teams**
Solution 3. Rationalise the number of external suppliers to Clinical Operations.

For the reasons outlined earlier in the paper, it is vital for Clinical Operations to continue to access external skills and resources. However, companies must utilise a common global strategy and reduce the number of external vendors in order to accrue the benefits of external sourcing. Many Pharmaceutical Companies have now settled on using preferred partnership deals with Contract Research Organisations (CROs) to deliver their clinical study programmes. This makes sense, within CROs:

- The need to maintain relationships with multiple clients makes them responsive to customers
- Lean margins has made them efficient and
- They have the size to access a talent pool which is considerably bigger than one which a single Pharmaceutical Company could have.

Utilising a limited number of one or two external vendors makes the management of them far easier and allows meaningful performance incentives for both parties due to the volume of work for each preferred partner.

In our experience there are two critical success factors to consider when thinking about this. First, choosing the right clinical operations activities to outsource and which to maintain in-house is key. Our preferred method is to map activities on a three-axes framework: a) the strategic added value of the activity to the company; b) the performance of the company in conducting that activity and c) the capability of CROs and the potential for cost savings if the activity was to be outsourced – see Figure 7.

Since the strategic value of an activity is a key consideration in our framework, activities that an individual company considers strategic will never fall under Q1 or Q2. In the example map shown in Figure 8, non-strategic data management activities fall under Q1 and Q2, but strategic activities are not candidates despite poor internal performance. They are in fact, candidates for internal upgrade.

Figure 7: Kinapse framework for determining if activities should be outsourced or kept in-house

The second factor to consider is that outsourcing will not by itself, solve Clinical Operations performance issues. You can have the best delivery organisation in the world staffed with the world’s best talent, but if that organisation has no influence at key decisions, it will still not be able to consistently deliver high quality clinical study reports on time and to budget. Pharmaceutical companies still need to give their clinical programme delivery arm, be that their internal Clinical Operations function or a CRO, the ability to participate in development teams and positively influence development decisions.

Figure 8: Illustrative data management activities mapped on Kinapse framework
Solution 4. Up-skill the capability of Clinical Operations staff and management through organizational recognition and the provision of tangible career advancement opportunities

Clinical Operations staff need to be proactive, collaborative and willing to push beyond current practices and ways of working. The operating model is a shop floor to factory manager progression. This should be based on in-depth knowledge of clinical research methodology, combined with hands-on experience of managing studies at site level, progressing to project management of studies at regional and global levels, including the matrix management of multiple functions.

Individuals need excellent skills as communicators, presenters, trainers and project managers. They need to be delivery focused and be strong influencers, tough enough to fight their corner in the development team environment and upwards to senior management. Although therapy area expertise is useful, it is secondary to the above outlined skillsets.

The best way to enhance the pool of talent in Clinical Operations is to build a recognised and rewarding career path. In our experience, there needs to be a direct and recognised career progression from Clinical Research Associate (Study Monitor) through to Clinical Operations Study and Programme Management and then up to senior management roles. Our roadmap is shown in Figure 9. Hand-in-hand with the career path, companies must have a willingness to promote and grow talent and provide as much training and support as is required.

The second way to increase the pool of talent in Clinical Operations is to embrace technology and virtual working practices so that your workforce does not need to be co-located in a central geographical hub. Having global/central Clinical Operations staff in countries across the world gives the organisation a better knowledge base which in turn helps make better decisions. The third way to attract world-class talent into Clinical Operations is when leadership career paths are established into other parts of the organisation.

Only by making these four investments and empowering Clinical Operations in this way, can Pharmaceutical Companies ensure the performance that customers and partners demand of Clinical Operations—high quality clinical data and study reports delivered on time and to budget.
About the authors

Dr James Man
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James has over 10 years of business consulting, medical education and discovery research experience within the pharmaceutical industry. He has successfully delivered a number of programmes diagnosing, developing and implementing new ways of working in clinical development. He recently completed a project to integrate the Global Development and Global Clinical Operations departments of a top 10 pharmaceutical company into a more effective and efficient new combined organisation; helped the global clinical operations function of a top 5 pharmaceutical company to improve its performance in executing clinical studies on time, on budget and to quality; helped the EU clinical operations group of a top 20 pharmaceutical company be ready to deal with an expected 4-fold increase in workload over a 3 year period and established and implemented new processes for the conduct of clinical studies for a newly created top 20 pharmaceutical company in the immediate post-merger environment.

Dr Steve Coles
Kinapse Consulting Partner

Steve has over 25 years cross-functional experience in the pharmaceutical industry with particular focus on Clinical Operations. Most recently he was Managing Director of the European clinical development organisation of a top 15 global pharmaceutical company. Steve has extensive experience of designing and implementing process and organisational changes, particularly in Clinical Development and Clinical Operations organisations.

Dr Mike Emanuel
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Mike has over 30 years experience in the pharmaceutical industry across multi-divisions and departments from early phase clinical development to post marketing support. Most recently he was UK and International Board Director and Vice President of Clinical Trials for Europe, Middle East & Africa region for a top 15 global pharmaceutical company. Mike has extensive experience in design of Clinical Development functions infrastructure and its implementation, at a global and regional level including creation of global coordination and many critical regional roles.
About Kinapse

Kinapse provides consulting and outsourcing services to life sciences organisations. Our mission statement is: ‘Collaborating with our clients to innovate for exceptional results’. Kinapse clients include many of the world’s leading pharmaceutical, biotechnology, medical device and specialty pharmaceutical companies, government organisations and life sciences service providers. Our key advantages are:

• Focus on the life sciences industries
• Deep industry experience and technical acumen
• History of successful project delivery

During 2013 Kinapse facilitated focused discussion groups which addressed ‘patient centred pharma’ and specifically what is required to move the concept forward at an operational level. Forum attendees included patient representatives, pharmaceutical company executives, and technology providers.

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