White Paper

INTRODUCING A COMPLEXITY SCORING SYSTEM IN CONTRACT NEGOTIATION
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1. **Introduction**

The great majority of clinical trial professionals will acknowledge that the start-up phase is the most challenging and important stage of any clinical trial. Indeed, recent publications also point to the critical nature of this phase of trial management, and specifically the importance of the process of contract and budget negotiation with sites.\(^1,2,3\)

It has been reported that contract review to contract execution period represents the greatest proportion of cycle time (30%) in the site start-up process.\(^3\) Interestingly, a recent report based on on-line questionnaires completed by 65 clinical trial managers indicated that team performance during study start-up had the lowest performance score and the greatest variation in performance compared to any of the other stages of clinical trials.

Here, Davide Garrisi and Cinzia Bernini share their experience of management of multinational clinical trials to recommend a new risk mitigation strategy for successful site contract negotiation during the start-up phase.

2. **The Key Drivers For Study Startup Performance**

Several factors have been proposed which could influence successful and timely site start-up. These include length of operational timelines (including factors such as time to create study specific operational plans, time to create study specific forms, IT system set-up and time to conduct Feasibility analysis.), ability to identify qualified investigators, performance of the project manager, knowledge and interpersonal skills of the project manager, and CRA performance.\(^1\)

As might be expect, analysis of surveys relating to the above factors indicated that adherence to operational timelines had the highest correlation with study start-up performance (\(r=0.81\)).

As noted above, adherence to operational timelines is a composite indicator comprising different activities like projects and operational plan, study specific convention, forms and documents, and the regulatory submissions.

Among these parameters we believe that financial negotiation and contracting with the investigational sites is a critical step to ensure successful initiation. This is reinforced by findings which indicate that investigator sites in the United States reported that nearly 50% of delays in site level subject recruitment were attributable to delays in the contracting process in study start up.\(^2\)

This is because even with full regulatory and ethical approval investigational sites cannot start recruitment in the study if a fully executed contract is not in place.
3. **Contracts Negotiation – Parallel or Approval-Dependent?**

The process of negotiating agreement on budgets, contact wording and contract execution is typically study, country and indeed site specific. Terms, templates and financial arrangements can be different for each study, in each country and in each site.

However in our opinion common features can be identified starting from the type of negotiation and its correlation with the approval process.

Generally three different scenarios apply for contract negotiation procedure:

1. **Parallel contract negotiation, independent from regulatory and ethic approval;**
2. **Parallel contract negotiation but approval-dependent (i.e. the contract is negotiated during the approval period, but the final version is approved and signed (by the site) only after regulatory and ethical approval are granted);**
3. **Approval-dependent contract negotiation (i.e. contract negotiation is started only after full approval is granted to the trial).**

4. **Parallel Contract Negotiation - Independent**

Among these different options the first one is the best case, while the third is the worst case. Parallel contract negotiation which is independent from regulatory and ethic approval allows project managers and CRAs to fully utilize the time taken for study review by the Competent Authorities and/or Ethics Board.

Considering a standard review time between 60 and 90 days after application, 2 to 3 months are available to negotiate the contract with the investigational site and agree a final version for signature.

5. **Parallel Contract Negotiation - Dependent**

In this second option the contract with the investigational site can be negotiated in parallel during the study review period, but release and signature of the final version is granted only after a full regulatory and ethic approval are released.

This is similar to the first case, but because there is more time available (due to signature occurring after regulatory approvals are in place), there is an increased risk that modifications may be requested.

6. **Approval-Dependent Contract Negotiation**

Though not common there are cases especially with public institutions, where the contract is not negotiated until the final regulatory and ethic approval is granted. Mitigation
strategies are mostly useless under these circumstances, and if included such sites should not be relied upon to recruit strongly to the study.

We recommend analyzing closely the type of sites (public/private) and the contract negotiation process in place during site selection process. This allows the project team to focus attention appropriately during start up to place suitable resources on sites with varying difficulty of contract negotiation.

7. Private or Public?

Another criterion to be considered is the type of hospital/clinic, if a public institution or private. Private clinics/hospitals are more flexible in contract negotiation and are more likely to accept the contract template provided. Also the cycle time of the review process is usually shorter.

Public institutions usually prefer to negotiate on the standard template of the institution, with few possibilities to modify the clauses and terms of the standard contracts they provide.

If these (standard institution templates) are modified substantially, time to final contract can be prolonged to an unpredictable extent as changes proposed will be reviewed by legal departments within the institution or sometimes via external consultants.

8. Separate or Combined?

In some countries separate contracts for the same study with the Principal Investigator and his/her study team for the clinical work, and the Institution for the utilization of facilities and premises during the study conduct are required.

Separate contracts can be negotiated directly between the Sponsor/CRO and Investigator/Institution, thus simplifying negotiation.

Under an increased transparency about payments in clinical trials there is an increased tendency is for combined contracts where the agreed fee for clinical work under the scope of a sponsored trial is described in a single financial document, signed by Sponsor, Institution and Investigator.

Combined contracts should be negotiated with Investigator and Institution in parallel. This requirement is associated with an increased risk of delay due to the need for both parties (Investigator and/or Institution) to review any proposed changes before agreement can be reached.

In some other cases signature by the Sponsor and any third party (CRO) delegated for project-related tasks is also required, as in the case of the NIH-ABPI standard template in
the UK. Typically in this case, however, the investigator does not sign. The signatories of these agreements are Sponsor, CRO and Institution.

9. **Local Legislation**

Sponsors and delegated CROs may often commence contract negotiation on the assumption that standard templates complying with the regulation/legislation of their country of origin will be acceptable to sites internationally. This approach is likely to be rejected by the investigational sites, especially public institutions, and therefore immediately introduces delays.

Investigational sites, whether private or public institutions, want to be protected by the local regulations enforced in their own country and are understandably reluctant to accept extensive clauses and terms referencing the laws and regulations of other countries.

A typical example is the attempted application of US contract templates to sites located in the Europe. Often these templates require the sites to comply with US law and regulation, and negotiation starting from these templates is typically lengthy.

We strongly recommend all applicable clauses and terms to reference local legislation are to ensure a successful and smooth negotiation process.

10. **Contract Language**

Contracts are always required in local language. English outside the US and UK is sometimes usually accepted by private institutions, even if the prevalence is always given to the local language version, for contracts in double-languages, i.e. local language and a second one to facilitate negotiation by the clinical/legal team, usually English.

11. **Introducing Complexity Mapping In Contract Negotiation**

We analyzed several factors impacting on the contract negotiation process, namely:

- Parallel or Approval-dependent negotiation
- Private or Public Institution
- Separate or Combined Contract
- Adherence to local legislation
- Contract Language requirements

For each of those aspects a “best” and a “worst” case scenario was described, based on the increased complexity (= more time) of contract negotiation.

Accordingly a very simple scoring system can be built, where the lowest score corresponds to the lowest complexity and the highest score to the highest complexity.
Table 1: Proposed scoring system to measure contract negotiation complexity

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>SCORE</th>
<th>CUMULATIVE VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Type of Negotiation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Parallel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval-dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Type of Institution</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Private</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Type of Contract</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Separate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Accepted Legislation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Sponsor/CRO(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local Legislation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Language Requirements</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>English only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>English and local</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SCORE \(\Sigma(\text{Rows 1 to 5})\)

We believe the proposed scoring system to map contract negotiation process is particularly helpful in a multicenter, multinational and global project in building up a priority list based on the complexity of the contract negotiation process.

Initially, in the first step, countries can be mapped according to our complexity scoring system to assist in deciding which countries should be included in the trial feasibility work.

Investigational sites in one single country, or several countries involved in a multinational and/or global projects can then be scored during the planning and feasibility data collection phase to map contract negotiation by complexity for decision-making, “i.e. should we or shouldn’t we involve this country given the impact of contract negotiation in expected timelines?” or to prioritize activities once the trial commences.

As described higher values obtained in the scoring system identify a more complex negotiation process, while lower values correspond to a less complex contract negotiation process.

12. Country-Specific Standard Templates

Historically the UK was the first country to introduce a harmonized contract standard agreed between the regulators, representatives of the pharmaceutical industry and of public institutions, the NIHR-ABPI template, revised in 2011. This is a very valuable initiative that simplifies and better regulates the contract negotiation process.

The same approach was recently implemented also in the Netherlands (published July 2013) and in Spain (to be fully implemented in late 2014), where a unique national template should be used for contract negotiation.

In Spain a target duration of the negotiation process has been proposed, being 60 days after Sponsor’s request.

\(^1\) Intended as Sponsor/CRO applicable legislation of the country of origin
However the actual added value of national standardized contract templates still depends on the conditions of use – i.e. that neither party seeks to make significant modifications to the standard template.

If nationally accepted/enforced limitations to modifications are not established, it is likely that there will be no difference with any other available contract template.


The scoring system proposed in Table 1 would rank countries and even each investigational site in the same country on the complexity of the negotiation process, based on the five factors proposed to be of key importance: type of negotiation, type of institution, type of contract, accepted legislation and language requirements. However, this alone does not propose a mitigation strategy to limit their impact.

The necessity to simplify the contract negotiation process has been largely addressed by some countries in Europe that recognized already the added value of simplification and introduced standard national templates.

Standard national templates however, are not available yet for all countries, so what can clinical research services providers do to improve the process? The answer may be that we should try to help each other!

As mentioned previously, Sponsors and CROs have had the tendency to propose long and complex clinical trial agreement templates, with plenty of complicated legal terminology, “change-proof” and which rarely mention compliance to the local legislation, applicable in the country of original of the investigational site.

This approach has the effect of:

- Requiring private practices/clinics to send contract outside for legal review;
- Requiring public institutions to apply substantial modifications to comply with local (i.e. national) requirements;
- Increase negotiation time due to an unpredictable increase of review and comments rounds.

To overcome this important issue and to mitigate the risk of long contract negotiation, over the last seven years we introduced country-specific templates for contract negotiation, extending the possibility to choose for the same country, templates applicable for private or public institutions, and for separate, combined or tripartite (with CRO, sponsor and institution) contracts.

The possibility to have the right tool available for the job has substantially reduced the time of negotiation (mainly related to the financial section) required for every study. Additionally,
very limited changes are now requested to the legal sections, which are already provided in language requiring compliance to the local law.

Every time a country is included for the first time in our projects, efforts are made to create a new template in compliance with the local requirements. This requires some additional resource, but once achieved, this is another tool to be easily used consistently in the future.

We established our set of financial templates applicable for all cases, an experience-based and shared (with sites) resolution.

When required by our Sponsor to work on their own contract template, our country-specific templates can still be used as a reference to implement changes and ensure higher compliance to local requirements.

14. Conclusions

The clinical trial start-up phase is one of the most important stages of any clinical research project. However, it is also one of the least predictable ones, due to the variety of elements impacting on its development: application processes, regulatory frame, regulatory and ethical review, contracting process.

Understanding the challenges of the start-up phase and proposing alternative scenarios to mitigate and simplify these processes, when possible, would increase chances for a successful start-up phase.

As we have seen, the contract negotiation process could potentially be the rate-limiting step of the start-up phase because even with full regulatory and ethical approval, investigational sites cannot be initiated and activated without a fully signed contract in place.

Contract negotiation is affected by a variety of factors, such as the type of negotiation, type of contract, accepted legislation and language requirements.

Based on these factors, which we assume are common to every negotiation process, we introduced a scoring system applicable to country, or to single investigational sites in that country, to rank the complexity of negotiation, and define priorities.

Finally we emphasized the tendency by Sponsors and CROs to propose just one contract template, which is always subject to extensive modifications to comply local and or site-specific requirements.

To simplify the contract negotiation process we decided to implement an approach to contract negotiation based on the creation of country-specific and, where necessary, institution-specific templates providing tailored solutions. This proved to be an optimal resolution that improved our performance metrics in contract management, reducing time to final contract and review rounds.
This is also positively perceived by the investigational sites, who appreciate the efforts made to simplify contract negotiation and respect local legislation and/or requirements.

15. About the Authors

Davide Garrisi, Client Services Development Director – Head of Feasibility Unit, CROMSOURCE

After gaining his degree in Pharmaceutical Chemistry and Technologies, in 2003 Davide started to work in the pharmaceutical industry, API manufacturing, focused on quality assurance and regulatory affairs. In 2005 he joined CROMSOURCE as a project manager in the International Clinical Trials Unit. He managed several international and global clinical trials in a variety of therapeutic areas and in 2011 became Director of the Project Management Department. In the meantime he also set the standards for the feasibility process in CROMSOURCE, one of the pillars of CROMSOURCE services under the FEASIBILITY PLUS® brand.

In September 2013 he started an Executive Master in Business and Administration, and while maintaining the responsibility for feasibility service in CROMSOURCE, he was appointed Director of Client Services Development, collaborating with CEO in developing and implementing the marketing strategy and providing leads to business opportunities. Davide can be contacted at davide.garrisi@cromsource.com.

Cinzia Bernini, Director of Project Management Department, CROMSOURCE

After gaining her degree in Biomedical Laboratory Techniques, Cinzia joined CROMSOURCE as a Clinical Research Coordinator in 2000. Since that time, Cinzia has held several roles of increasing seniority responsible for the operational aspects of project management and delivery. In 2013 Cinzia became the Director of the Project Management Department with responsibility for overseeing project management and delivery of all CROMSOURCE clinical projects. During her career Cinzia has gained experience in many therapy areas and in delivering trials across all European regions, and globally. Cinzia may be contacted at cinzia.bernini@cromsource.com.
16. References

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2. Centerwatch. Survey of Investigative Sites in the US. 2009


17. About CROMSOURCE

CROMSOURCE is a high quality ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

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CROMSOURCE North America Headquarters:  
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Phone +1 617 871 1128

European Headquarters:
Via Giorgio De Sandre, 3
37135 Verona - Italy
Phone +39 045 8222811

e-mail us at:
cromsource@cromsource.com

www.cromsource.com