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Acceleration through Collaboration

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ABSTRACT

There is an increasing amount of pressure on pharmaceutical and biotech companies to find innovative ways to accelerate clinical development and to deliver the statistical results of their trials more efficiently. Traditionally, Contract Research Organisations (CRO's) have been used to produce the results as directed by the sponsor company. Recently, however, CRO's and sponsors have been working more closely together on the development of strategies which enable the rapid delivery of study results.

This paper will explore some of the ways that a CRO can collaborate with a sponsor company to produce results and report studies within a shorter time frame. Recent initiatives at Quintiles, including new resourcing models, methods designed to lower the number of patients required and our Standard Programming and Reporting Catalog (SPARC) will be discussed. These can be used to reduce not only the time required to report a study but the associated cost.

INTRODUCTION

The purpose of this paper is to explore ways in which sponsor companies and CRO's can work together more effectively to ensure that study results are generated as efficiently as possible. This paper covers 3 main topics; resourcing, building effective relationships and some recent initiatives at Quintiles.

RESOURCING MODELS

There are many different ways in which a CRO can provide the staff to run a study and produce results for a sponsor. More often than not, there are no discussions between the sponsor and the CRO about the most appropriate way to resource their studies. There are times where it is useful to resource a study in a traditional manner – to assign a set number of programmers and statisticians from one office to a study and have them work on that deliverable until the work is complete. However, there are times where it is advisable to think about whether it would be more efficient and more effective to resource in a different way. Below are 4 alternatives models.

SPONSOR SPECIFIC POOL OF RESOURCE

If a sponsor is outsourcing a large number of studies to a CRO they may want to discuss the possibility of having a pool of resource which can be used across all the studies instead of having a separate team resourced to each individual study. This is beneficial for sponsors as it not only increases consistency across studies but if one study suddenly becomes priority or if there are a large number of changes required, there are already people familiar with their standards that are able to carry out the work. There would also be less of a delay in finding additional resource as the sponsor is in a position to select which of the studies their pool of resource should be working on. This method of resourcing works well for CRO's as well as a set number of people can be assigned to a sponsor team and when changes to requirements occur they do not need to find additional resource but can discuss priorities within the drug program with their sponsor. This method of resourcing requires close communication between the sponsor and the CRO lead and requires the CRO staff to be flexible to changing priorities. The main challenge for the CRO when using this method of resourcing is keeping track of the scope of work when priorities change.

FEE FOR SERVICE

Fee for Service (FFS) models are a way of helping to guarantee the sponsor the resource for a study whilst they only have to pay for the hours actually worked, rather than agreeing a price at the start of the work. An agreement is put in place stating the number of staff who will be available if needed; this is usually agreed at least 3 months in advance. These staff are free to work on other projects if there are no requirements on the FFS study. There are many benefits to this for both the CRO and the sponsor. The CRO is able to bill retrospectively for the amount of hours spent on work thereby saving lots of time which would otherwise be spent managing the scope. As well as saving time for the

CRO staff (which can then be used to work on the study) this model means they can be confident that the cost of work will be covered by the sponsor so there will be no financial loss. This type of model is particularly useful where there are a large number of ad hoc request expected for the study – this could be additional exploratory work for an ongoing study, providing support to help put together a submission or any study where the scope of work is unclear.

WHOLE STUDY OUTSOURCING

This model is where the entire study is resourced by the CRO without project-level equivalent counterparts at the sponsor company - all project staff are provided by the CRO and they make the decisions on the requirements of the study.

The sponsor is likely to set up an overall oversight team i.e. a single team across all outsourced projects, possibly including representatives from the CRO. This team acts as a go-between between the sponsor and the CRO. The CRO meet with this intermediary team and there is a discussion based around what the project team wants to achieve with their trial. It is then up to the CRO to run the trial as they see fit in order to meet the objectives of the sponsor.

This approach is beneficial to the sponsor as they are free to progress with other work whilst these trials are led by the CRO. There is the additional benefit of having already selected a CRO so the work can be outsourced without having to go through the process of selecting who to work with and the only involvement for the sponsor will be agreeing the budget and setting the aims. It is also beneficial to the CRO to not have to go through the proposal and bid-defense stage of winning work, instead putting together a budget based upon an agreed costing model. The other main benefit for the CRO team is that they are given more responsibility than usual and they have the freedom to make their own decisions – both of these are extremely motivating.

GLOBAL WORKSHARING (GWS)

Sharing Biostatistics and programming resource across geographic locations is becoming increasingly commonplace. Of the studies which are currently active within the Quintiles UK biostats department, over half have some element of global work sharing – either shared programming responsibility or providing an unblinded site for DSMBs and/ or interim analyses. GWS means there can be a completely separate office used for unblinded intermediate deliverables which would prevent the accidental unblinding of the project team. GWS also has the benefit of being able to provide sponsors with programming and statistical staff from low-cost countries and therefore reducing the price, whilst still using staff who follow global working practices and use the same IT infrastructure. The benefit of being a work-share rather that solely running a study from a low-cost country is that there can be a lead in an office where there is more experience of reporting trials or from the same country as the sponsor. The lead sites often have in-depth knowledge of working with specific sponsors. Work-sharing also provides the opportunity for 24 hour production of deliverables as staff in different time zones can work around the clock.

GWS also enables a sponsor to have a much larger pool of resource available.

BUILDING EFFECTIVE PARTNERSHIPS

One of the easiest to achieve and most important ways of accelerating the development of a compound in a CRO-sponsor setting is ensuring that the partnership is working successfully for all parties involved. If there is a breakdown in the relationship for any reason this can impact on the ability to report studies in an easy and stress-free manner. Below are four simple ways to help build an effective partnership.

JOINT GOALS

We have found it extremely beneficial to establish high-level joint goals between the Sponsor and the CRO. Indeed, such goals may even be formalized objectives for key team members in both organizations.

DETAILED START-UP MEETINGS

It is advisable to have a detailed start up meeting covering all aspects of the study and for this to be face-to-face, if possible so that the team can get to know each other. It is much easier to build a relationship with someone if you have the opportunity to meet them in person. As well as an introduction to the study, this meeting should cover any possible issues which either party are aware of which need addressing i.e. an internal requirement for the sponsor to have top-line results in-house 2 days post DBL or a particularly busy time for a CRO where there may be some need to discuss availability of resource. An important discussion topic is the process for producing and reviewing the deliverables within each company. The CRO should make sure they understand the review and sign-off procedure at the sponsor company and the discussions should include how many rounds of review are required, who carries out these reviews, the importance of consolidated comments and the implications for the study if there are delays in the

reviews. Differences in the way that the sponsor and the CRO work are not always apparent to begin with and this can lead to problems at the time of delivery when the whole team are very busy and under pressure. The start-up meeting should also include a discussion about the purpose for each deliverable i.e., a safety review, an early look at the data, a format review only or a regulatory submission. As part of this discussion the sponsor and the CRO should discuss the importance of these deliverables and how flexible the timings are. It is a good idea to discuss the expectations of both the teams with regard to timelines, resource and communication.

AGREE LINES OF COMMUNICATION

It is possible for small misunderstandings to have a big impact on reporting so it is advisable to discuss the preferred method of communication. Some sponsors prefer to discuss all queries on the telephone so that views can be exchanged and a solution can be found that way. Other sponsors prefer all questions to be sent via email so they can think about the answers before responding. There is no right or wrong method of communication but it is a good idea to discuss which is going to work best for the study. For example, it may not be possible to always use telephone communication if the questions need to be addressed by more than one person or where the team are based in different time zones. Conversely, if a question is likely to lead to a lot of emails going back and forward then it may make more sense to discuss in a teleconference. Where conversations are held one-on-one on the phone or during a teleconference it is vital for someone to document the final decision via email or meeting minutes to ensure there are no misunderstandings later on.

We often use the Quintiles Question and Answer tracker to capture communications. This is useful as all decisions are captured in one document and will not get lost amongst other emails. A number of sponsors have told us this is their preferred method of communication. Please see below for an example page of the Q&A tracker.

Questions and Responses Tracker (Specs, Shells, CRF and SAP Issues)

(Most Recent at the top, in general red text = subject of question, black text=question details, blue text=response)

02. LAB – normal ranges for Bilirubin	
Carrie Eason (12SEP2006)	Could you please, confirm that the normal ranges you specified in your comments for Bilirubin (see email sent on 25/04/2006) are correct.
Joe Bloggs (12SEP2006)	We had doubts about the normal limits ourselves and rechecked them with the lab. They confirmed that these were the limits that should be used.

01. AE Questions – Table 14-10.4	
Carrie Eason (23Aug2006)	In the AE table 14-10.4 , the denominator calculations are not clear to me. In other AE tables each patient is only represented once in the table (so a patient having multiple serious AEs will only be counted once as per interim) but for this particular table (which was not present in the interim) the top line indicates a number of patients (always with a percentage of 100?), but the subsequent rows show numbers of events. If the percentage calculations for numbers of events are based on number of patients – the percentages could easily add up to over 100% where a few patients have multiple events. Could you clarify the way you would expect percentages to be calculated in these tables – or if percentages should be presented at all? Thanks
Jo Bloggs (25Aug2006)	On reflection it will be best to just quote the Ns for this table but also (if possible) to include an extra 2 lines in the table: to summarise the number of nausea events reported and the number of vomiting events reported. **Let me know if this is straight-forward to do.**

BE FLEXIBLE

Flexibility is vital to ensure an effective partnership and the flexibility has to be from both the CRO and the sponsor company. It is important that sponsors are able to understand that a CRO biostats department will have a large number of studies ongoing at any one point and that they may not always be able to drop what they are doing to action a new request for a study. It is important for the sponsor to keep the CRO up to date with changes to the study, especially with regard to timelines.

However, it is crucial to the relationship that the CRO understands that there are occasions where something different or additional to the planned work is required and their sponsor may not have been in a position to anticipate this need. It is a good idea to discuss any changes in detail and for everyone involved to get a good understanding of the importance and urgency of the requests. CRO's should remember that they are not the only ones under pressure at times and that their counterparts are likely to be getting internal pressures which the CRO are not aware of.

All 3 of these suggestions can be easily implemented and can be initiated by either the CRO or the sponsor. It is worth remembering that both you and your counterpart have the same aim – to successfully deliver a high quality study on time; working well together will make this more likely.

RECENT INITIATIVES AT QUINTILES

Many recent initiatives at Quintiles are designed to reduce the time required to report a study and to decrease the associated costs. This has obvious benefits for the sponsor but these are also important initiatives for CRO's to ensure that they remain viable in a very competitive market.

CSDD

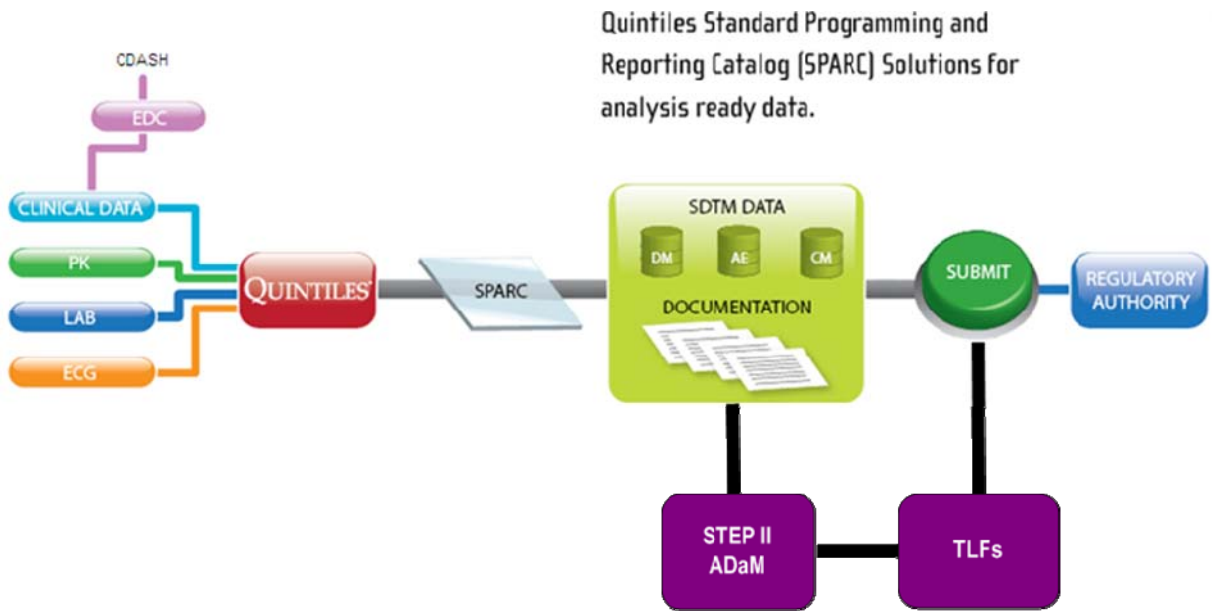
Quintiles has a group called the Center for Statistics in Drug Development (CSDD) which is made up of 8 Quintiles statisticians plus 2 external consultant members. One of the main aims of the group is to lead statistical development for sponsors by providing statistical consulting throughout drug development. In the last year in particular, the CSDD group has been working with sponsors to look at the number of patients required for their studies to investigate if adjustments can be made to the study designs to make the studies more efficient. Below is an example of a piece of work the CSDD group has recently carried out.

The CSDD group collaborated with a sponsor on the development of a Phase III strategy and program. The CSDD were able to re-evaluate the original study designs to meet a shorter timeline, use fewer patients and still meet the requirements for the efficacy analysis and the size of the safety database. The CSDD group worked closely with the sponsor and supported them at the end of the Phase II meeting with the FDA where the redefined plan was accepted. This successful collaboration and new approach resulted in savings of $8 million for the sponsor.

SPARC

One of the major initiatives currently running across Data Management and Biostatistics is the introduction of the Quintiles Standard Programming and Reporting Catalogue (SPARC). This is a tool which will be used on an EDC platform to collect, clean, transfer and transform data into an analyzable format using CDISC standards. The first stage of this initiative was to create CDASH-compliant eCRF's and for the data to be transferred into SDTM. This stage of the initiative was completed in April 2009 and training for data management and biostatistics staff is almost complete. The next phase of the SPARC initiative is to use ADaM guidelines to create analysis datasets and statistical outputs; this will be completed by Q4 2009 before roll-out to sponsors in Q2 2010.

A diagram of the SPARC workflow can be seen below:



The electronic CRF data plus any additional external data such as PK, ECG etc are collected by Quintiles. These data are loaded into SPARC where STDM data, ADaM data and the required outputs are produced. Once a study has been through this process it will be ready to submit to the regulatory authority.

There are many reasons why developing tools (such as SPARC) and standard practices are beneficial.

- There is an increase in quality as the tools can be validated.
- There is an increase in efficiency as programs are reusable and this saves time leading to a reduction in cost.
- SPARC SDTM datasets can be produced quickly and on an ongoing basis throughout the study.
- This also means ADaM datasets can be produced earlier using the SDTM data rather than at the end of the study.

There are additional benefits for both the sponsor and the CRO.

- The CRO are able to provide a cost effective solution for SDTM work on EDC studies.
- They will be more efficient through using global standards on these EDC projects and this style of working will also increase the project teams' familiarity with CDISC standards.
- The sponsor company is able to have their data collected, stored and presented to CDISC standards, in compliance with regulatory guidelines.
- As the CRO is becoming more efficient, the sponsor will benefit from a reduced price for their work.

This initiative is aimed mainly at small to medium size sponsor companies who have no or few biostatistics staff. However, in the future, this idea could be used in collaboration with a large sponsor company to produce a system specific for their needs.

CONCLUSION

There are many ways in which CRO's and sponsor companies can make changes to ensure that they are as effective and efficient as possible. These can be small changes such as building more effective partnerships or larger changes such as using some of the new options available such as SPARC. It is also important for both sponsors and CRO's to consider taking new approaches to working together, communicating and resourcing. It is often too easy to automatically adopt the approach taken on a previous study rather than looking at lessons learnt and trying new approaches. As sponsors continue to work alongside CRO's more and more it is imperative that successful collaborations take place so that the joint goal of accelerating drug development can be achieved.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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