PharmaSUG 2015 - Paper MS06

Advantages and Disadvantages of Two Commonly Used CRO Resourcing Models in the Pharmaceutical SAS Programming Environment

Ying (Evelyn) Guo, Amgen, Thousand Oaks, CA
Mark Matthews, GCE Solutions, Indianapolis, IN

ABSTRACT

In the current pharmaceutical and biotech industry, outsourcing data services to a CRO continues to exist. In today's industry, two commonly used models, "Deliverable Based Model" and "Full-Time Equivalent (FTE) Time and Material Model" (also called as role based model), are widely used. Previously, one presentation at PharmaSUG (See PharmaSUG 2012 –Satyavarapu "A Comparison of Two Commonly Used CRO Resourcing Models for SAS/ Statistical Programmers") identified the differences of these two resourcing models and specifically discussed those models from a CRO point of view. Our paper will emphasize the advantages and disadvantages from a sponsor point of view and discuss how these variances affect the project work and collaboration. By discussing the comparison of these two models, this paper will provide valuable consideration points for sponsors to choose the CRO resourcing model that is of best fit and share ways to bridge the gaps that exist in the models.

The two authors have worked in the pharmaceutical environment for a total of 16 years and the CRO environment for 10 years. They have experienced individual contributor roles, team leadership and supervisory roles in statistical programming. They will share their experiences they have encountered while working with multiple pharmaceutical companies and CROs.

INTRODUCTION

The use of CROs that a sponsor company implements as part of their responsibility has become prevalent in the pharmaceutical industry today. The two models described above that are widely used bring forth some similarities and quite a bit of difference. A straightforward answer that describes the differences and similarities between the two can be as follows: In a deliverable based model, the CRO does clinical research for the sponsor company. In a role based model, the CRO does clinical research with the sponsor company. Choosing different models will result different effort and cost. However, in any of the two models, the clinical research that ultimately gets done has the common goal of bringing medicines to market. That is, one does the same work in either model. (See PharmaSUG 2012 –Satyavarapu[1]).

DELIVERABLE BASED MODEL: ADVANTAGES AND DISADVANTAGES

ADVANTAGES:

Timeline and cost

If properly planned and specified, the timeline and cost are predictable and reliable in general. The timelines and cost are predetermined and settled before the project starts. Usually there is not a timeline discussion after project start and it is easy to achieve the pre-set milestones with proper project management. Timelines and costs are impacted by changes in the requirements or scope increase or decrease of the project. It requires additional overhead administrative cost in order to agree on the change of scope and cost of the new project. From a sponsor company, it will be very important to fully address the knowledge of the entire scope of work. An example can be a sponsor company set up a contract to perform SDTM and ADaM programming with SAP creation and the development of all TFLs for a particular set of trials for a compound. However, halfway through the project kick off, there may be a question about who is to perform the annotated CRFs. The sponsor company may assume the CRO would perform this at the pre-determined cost, and the CRO did not even have it in the scope and cost because it was not specifically asked for. In the end for this example, a change order would be the obvious choice and the CRO would get rightfully compensated for the additional scope of service and ultimately adds additional and unplanned cost to the project. Thus, there are 2 key elements here to minimize any substantial scope of service. The sponsor company should look very closely at the detail of all tasks and costs associated around everything that needs to be complete. And secondly, the sponsor company should have a proactive relationship with the CRO to encourage the CRO to include all tasks based on their experiences of working with other sponsor companies. A good practice is for the sponsor leads at the time of the request for work to actively ask the CRO if they feel if there are any elements missing from the request. CROs are trained to ask the detailed questions because there is risk associated with unforeseen complexity in the project; the sponsor company should take advantage of that.

Training requirements

The sponsor company does not need to invest in time or cost training the CRO. The CRO takes full responsibility to ensure all personnel are trained to the company requirements including internal Standard Operating Procedures, GxP, etc. The CRO will take full responsibility for the whole project in scope which requires less communication and effort around training requirements. This is a substantial advantage to the sponsor in a deliverable based model that can go overlooked in terms of advantage. Although the CRO does recover cost in terms of ongoing training for its associates, it is not generally itemized as a cost, and it is our experience that training cost is not a substantial cost to list out. The real benefit is that the sponsor does not have to spend their time investing in training the CRO resources for regulatory compliance, project knowledge, industry standards knowledge, or compound knowledge. The expertise and experience should already be there at the CRO project team. It is when the sponsor requests a sponsor-specific requirement that the CRO may not be exposed that can incur time and cost. For example, a sponsor may have their own has their own company standard other than CDISC. In this case, the sponsor will need to use extra time to educate the CRO team on what exactly is needed, and spend effort following up to ensure they interpret the sponsor specific requirements correctly. It will be good practice for the sponsor recognize when sponsor-specific requirements are needed in order to educate the CRO team on unforeseen complexity that can impact project timelines, as well as quality and compliance concerns.

Consistency and quality

Usually, the CRO will setup their process and programs to follow the latest regulatory requirements. This process and programming environment will apply to their entire set of clients. In this case, this system can be reliable, since it was tested by multiple projects and sponsor companies. The quality and consistency of the project are reliable. In addition, it is also easy to repeat. The sponsor company should leverage the fact that the CRO generally experiences many best practices when working with sponsor companies and often times implements those best processes and even technology within their own environment to apply high quality and consistency within their own standards.

DISADVANTAGES:

Team Selection

Here, the resources that CRO allocates to the project are generally at the will of the CRO and not of the sponsor. We all enjoy selecting proper teams who are compatible and complement each other's capabilities, and the CRO will select the team in order to achieve the best harmony. The sponsor is generally hands-off in team selection, and as a result, the CRO will consider placing less costly, and thus, less experienced personnel on the project and still attempt to deliver it correctly. For example, the CRO may have a team with experienced personnel to deliver the SDTM and ADaM, but switch to another team with less experienced personnel for the TFLs. If the CRO is in the position to maximize profitability in this way, then they will. Also, there is no guarantee that the CRO will keep the same personnel on the same project and sponsor from beginning to end. The programming lead who is interacting with the sponsor may be the same, but the project team members can rotate to other projects that may not even be related to the same sponsor. It is recommended that the sponsor build a trusting and transparent relationship with the CRO so that the CRO will be more willing to be influenced on who they will assign to the project. This way it can be more likely the CRO will place their best associates on the project and keep them there from the beginning to the end of the project.

Team Stability

The budget, timeline, and scope of work are generally fixed at the time of project launch. And unless the sponsor offers a consistent queue of subsequent deliverable based projects, the CRO, in general, will reallocate their sub-teams from one project to another – and often times among different sponsors. When the team moves to other projects, it is hard to call them back, because they had already committed to another timeline. As described above, the CRO may use experienced team for ADaM and less experienced team for TFLs to lower their cost. In this case, the original team who delivered the ADaMs may have already moved to another project before TFLs are complete. If the sponsor changed their requirement which needs modification of ADaMs, it will create challenge for CRO to complete it on time. The CRO may decline the request due to lack of resources, or may use the unexperienced team, which may have the risk of reducing the quality.

Hands-off deliverable

In general, this scope of work is fully executed by the CRO. The sponsor may only be provided the outputs, but not the programs. Often times, the CRO will not release their programming macros and systems because they may argue that it is company asset information. If the sponsor would like to modify something after being released from the CRO, it may not be easy to repeat the original table if the requirement is not clear and if there is limited supporting information provided in the final deliverable. The sponsor may only have the final output without programs or even

the datasets. Simply summarized – a black box. Even if the CRO provided the analysis datasets, the data may not fit in the sponsor's company standard. In these cases, it would pose difficulties for the sponsor if they decided to change CROs, or move the project back in house.

In this model, there can be a lack of transparency to the sponsor's data and how their data is being processed. The sponsor should establish an agreement to be able to access the data at any time throughout the project. With web based technology in the current age, it becomes easier to request (controlled and secure) access to the CRO system in order access the sponsor's own data. And if this is not possible, the sponsor should request for the CRO to develop a final deliverable package that not only includes output/analysis, but the entire set of programming systems and supporting metadata and documentation.

OPTIONS/SUGGESTIONS

- In this model, the sponsor heavily depends on CRO expertise. Thus the evaluation of the CRO internal resources will be a key to success. In general, a bigger, established CRO may have more internal resources than smaller, new ones.
- The CRO brings their expertise, and use a lot of pre-setup processes and programs. On the other hand, the CRO will also use less experienced personnel to achieve the goal, since there are fewer requirements of experience levels in this setting. In this case, the sponsor will be better off to follow the CRO.
- This is not the model you train the CRO. The CRO may have a significant amount of more experience than the sponsor, and the sponsor should discuss with the CRO any added experience that the CRO can provide at a no-cost benefit. Keep in mind this is one size fits all; if the CRO provided you some table shells or standards, then it is better to take it, since that is what the CRO is good at. Try not to be individualized too much. Particularly, their model may be more suitable for industry standards. Also, it costs less, and is done faster with less mistakes, if they did it the same way for all their clients.
- Try not to use the sponsor's company standard in this model. Some sponsors have their own standard in their company in which they like to use their own standard to produce all the TFLs for example. In this case, the CRO cannot use their existing process and programs. Instead, the CRO will need to create another new set of programs/process for this specific sponsor. The sponsor will lose the benefit to use an existing and reliable system, and the CRO has to increase the cost in order to bring more experienced personnel and set-up costs to the projects. The sponsor should try to leverage the use of CRO standards when working in a deliverable based model.
- If the sponsor anticipates that they will modify the requirement mid-stream, or have new TFLs and analysis, then it is better to have interim analysis datasets, and programs if needed and pay for this additional cost. Or, they can separate the tasks using two models.
- It is best if the requirements are done in details, and not have any gray area for the CRO to guess at what the sponsor is trying to specify. Requirements can be done by the CRO, and the sponsor can do a simple or lengthy review as needed.
- Communicate with the CRO lead thoroughly before the project kick-off meeting. And when it starts, let it be; trust it.

FTE MODEL: ADVANTAGES AND DISADVANTAGES:

ADVANTAGES:

Flexibility

In this resourcing model, the statistical computing environment is generally in-house of the sponsor. The scope of work is usually governed by a lead sponsor programmer where they manage the day to day tasks of the CRO programmer. There is a level of "control" of owning the process, people and technology. For the scope of work and timelines, there is opportunity to demonstrate flexibility and influence to cross functional teams on when and what work is performed. It is easier to maintain internal programs, analysis data and procedures which provides opportunity for the sponsor to make changes without any future use of the CRO programmer. In this model, it is often that the CRO programmer operates in the sponsor's system and use the sponsor's hardware. The CRO programmer is frequently referred to as an "extension" of the sponsor company as if they were their own employee.

Quality of Resources

The CRO will usually provide the programmer who is the most experienced and capable of performing the tasks. A benefit of the CRO to do this is because it will require less management support on the CRO end since the programmer is managed day to day by the sponsor. And moreover, this is an opportunity for the CRO to demonstrate excellence in the services provided in hopes that the sponsor will be attracted to even more resources when the workload warrants. As a result of the CRO programmer performing developments inside the sponsor's environment,

the sponsor can maintain historical knowledge and documentation easier, especially when it is time for the CRO programmer to end the contract.

Choice of how things are done

Since the resources are used inside the sponsor's environment, the sponsor can follow their own standard in this model. In this case, it is easy to combine with other in house studies for future integrated analysis. A value here is that the data about the molecule can be more portable against other studies on the same compound but different indication. In addition, the sponsor has the freedom to create different styles of analysis datasets and TFLs to satisfy their needs. For example, sponsor can create different style of TFLs to fit in different journals for their publications. Since this model has the design in mind for the personalization and changes, there is lower risk of poor quality when implementing more novel and unique analysis, especially when multiple modifications of requirements are anticipated.

DISADVANTAGES:

Expensive

The FTE model usually costs more than the deliverable based model to perform the same task. The CRO will provide most experienced personal to this model, which may increase their budget to perform the same task. In addition, the scope and timeline are not fully determined at beginning, thus the sponsor may not be able to fully use the programmer's time during the project. Since the contract is usually setup by headcount, not by task, the sponsor can end up paying for their down time when no task is assigned. The cost considerations is not just the hourly or monthly rate, but the effort of the sponsor's internal resources to manage the workload of the CRO programmer to ensure they are fully utilized.

Loss of CRO expertise

Sponsor is fully responsible for the entire requirements of tasks, and the programmer will follow the sponsor's instruction. In this case, the sponsor cannot use the CRO's internal resources, process and expertise. Although the programmer may provide certain opinions and expertise on some tasks according to their own experiences, the sponsor still loses the benefit of taking advantage of CRO existing systems and best practices.

Quality depends on the individual

In a deliverable based model, the CRO may choose less experienced personnel where the quality is guarded by their reliable system and internal programs and procedures in place. However, on the other hand, in the FTE model, all tasks will be done by the individual programmer. The quality of work will be individualized due to different experience and skill level of each programmer. Sponsor may end up spending more time to communicate with the programmers and review their product to ensure the quality. Or conversely, have oversight as if the CRO programmer is a true extension of the sponsor. It ultimately comes down to the quality and character of the individual programmer.

Training and communication

Since the programmer may not be familiar with sponsor's system, the lead programmer in the sponsor company may spend substantial time and effort to train new programmers. This is on top of the usual standard operating procedures needed to be read, understood, and acknowledged when on-boarded. For example, the sponsor may have to spend time to show the CRO programmer how to use the sponsor's intranet for project communication. Also it is common for each initial task that the lead programmer or statistician in the sponsor company will explain the entire details to the CRO programmer and answer questions through the project. It can result in more oversight on the sponsor's end. This is generally not a hands-off model.

OPTIONS/SUGGESTIONS:

- In this model, the key is to properly and efficiently train the team. This is the model where the programmer needs to be trained as your own employee. The more you train them, the more efficient they are. The training may not be fully complete before task starts; it may also require training throughout the entire projects lifecycle.
- Since the programmer will work as one of sponsor's employees, it will be easier to provide as much information as possible to the programmer. In one hand, the programmers can manage their own pace to achieve the timeline. On the other hand, the programmers can provide valuable suggestions that are taken from what they may have experienced within their own CRO environment. For example, when sponsor encounters a new table or figure or analysis, the CRO programmers may provide a tip or trick they learned from their own company.
- Since the sponsor may put a lot of time and effort to train the programmers, it will benefit the sponsor if the

programmer is stable. In general, the FTE model is set as headcount and not specific personnel. The contract of FTE model usually renewed periodically, say yearly. That means the CRO can change personnel as needed, but still meet the headcount requirements of the contract. However, changing personnel may lose all the historical knowledge and trainings done by sponsor. The sponsor may need to negotiate with the CRO to keep the FTE member stable throughout the entire project. It is important for the sponsor to establish good relationship with programmer which can keep the member, and their knowledge on the same team for a longer duration as needed.

- Since sponsor may have to pay for the down time, it may benefit the sponsor company to fully use the resources by sharing the same personnel between two or three studies.

SUMMARY OF THE TWO MODELS

Table 1:

	Deliverable based model	**FTE model**
Advantage	• Reliable timeline and lower cost • Minimum training needed • Reliable consistency and quality	• Flexibility • Free choice of how the work gets done • Quality of resource
Disadvantage	• Little opportunity for team selection • Team may not be stable • Less flexibility • Potential 'black box' deliverables	• Expensive • More training and communication needed • Quality depends on individual • Loss of benefit to use CRO expertise

Table 1. Advantage and Disadvantage of these two models

PROJECT SCENARIOS:

SAFETY REPORTS

- This is well suited to use the deliverable based model. This reporting should be a change free and one size fits all deliverable. For example, the FDA requires periodic safety update reports for all existing studies and the entire industry should follow the same standard to submit their safety reports. In general, the CRO has existing programs to deliver these outputs for multiple sponsors. Using this model will fully use CRO expertise.
- Suggestions: In this task, the choice of CRO may be the key factor. Choosing a CRO having the expertise to deliver safety reports may result of high quality and less effort and cost.

PHASE 3 CSR TFLS

- This is a good example to use the deliverable based model, but with options and clear expectations. The majority of CSR TFLs are repeating tables and standard analysis, such as AE, demographics, vitals, and disposition. Those may not require much change. However, other tables such as efficacy and dose exposure, may vary among different studies, and also the decisions may change until the final data lock. So these sets of tables require more attention when using a deliverable based model.
- Suggestions:
    - To better use this model, and lower the risk of quality concerns, it will be easier to build the complicated variables in the analysis datasets. As described above, the dataset may be done by more experienced personnel, and TFLs may be done by more junior personnel. If the complicated steps are contained in analysis dataset building, TFLs are only one PROC away. This will increase quality and shorten work time. In addition, it will be easy for the sponsor to review. The sponsor can check important variables in analysis datasets, which is easier, programmatically, than checking from the TFL output. When modification is needed, try to make the modifications in analysis dataset, or add new variables in the analysis dataset instead of creating new TFLs with complex calculation. This will easier in the long run.
    - The sponsor can request detail annotated requirements from the CRO. This will be clearer on how the outputs are generated from analysis datasets. This will limit the black box and it will be easier to regenerate the same table and analysis in the future without the original program.
    - Since this project scenario will have anticipate changes mid-stream during the project, it is necessary to allow extra time during planning. In addition, try to limit the changes for this project, and leave modifications and additional analysis ad hoc, and implement that in the FTE model, or in-

house. If there are more certainty on certain sections of the project, the sponsor can separate this project into two pieces, and use both resourcing models to achieve all.

AD HOC ANALYSIS

- This is well suited for the FTE model, and also has potential to use in a deliverable based model. In general, ad hoc analyses are added along the way from team reviews and future data mining needs. So it is challenging to define a scope of one project. It is not suitable for the deliverable based model where the scope should be fully defined. However, most mock shells are still the same as the primary CSR analysis. And when the sponsor may have a substantial amount of TFLs required at one time, this may fit in the deliverable model.
- Suggestion: Separate tasks to fit in different models where it makes sense, or use the FTE model in this project.

PRE-CLINIC ANALYSIS AND PHASE I/II STUDIES.

- Same as Ad Hoc analysis above: In general, phase I/II studies have a lot of anticipated modification needs as well as the start and stop times are more rapid than phase III studies. Moreover, the mock shells and analysis datasets vary among different studies and sponsors. This may not fit in the CRO established system due to variability. However, sometimes, the sponsor may have a substantial amount of TFLs following the same mock shells and thus may fit well in the deliverable model.
- Suggestion: Separate tasks to fit in different models where it makes sense, or use the FTE model in this project.

PUBLICATIONS AND FDA RESPONSES

- These projects are challenging to fit in a deliverable based model. The scope and design of TFLs are different among journals and regulatory responses. In addition, the time and scope of modification is not predicable. In order to satisfy the fast changes and rapid response time, the existing programs and historical knowledge are critical, and this the FTE model is better suited in this case.
- Suggestions: Maintain the programming environment and historical knowledge of key personnel. Use the FTE resourcing model in this case.

CONCLUSION

Collaboration and partnership between a CRO and a sponsor is an ongoing event in order to accelerate medicines to the market for the patients in need. It is important to leverage this collaboration so that the use of CRO clinical services for the sponsor is conducted in the utmost efficiency so that quality, compliance, safety and cost are optimized. Selecting the correct resourcing model is a substantial factor that a sponsor should consider when outsourcing their programming tasks.

Fully understanding the advantages and limitations between the two models can be a factor of success when the sponsor chooses to outsource their statistical programming services. The FTE and Deliverable Based models presented are two common ways that a sponsor can leverage CRO services in order to achieve their drug development objectives.

REFERENCES

[1] Satyavarapu, R. Mouly (2012): “A Comparison of Two Commonly Used CRO Resourcing Models for SAS/ Statistical Programmers” http://www.pharmasug.org/proceedings/2012/MS/PharmaSUG-2012-MS11.pdf

CONTACT INFORMATION

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

Name:	Mark Matthews	Evelyn Guo
Enterprise:	GCE Solutions	Amgen
Address:	14078 Empire Dr,	One Amgen Center Drive
City, State ZIP:	Bloomington, IL 61701	Thousand Oaks, CA 91320
Work Phone:	309.826.0078	317.571.9736
E-mail:	mark.matthews@gcesolutions.com	yingg@amgen.com