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Importance of Niche Provider for Successful NDA Submission: Rescue Case Study

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ABSTRACT

Of the several outsourcing models, a Functional Service Provider (FSP) model has become most successful and significant especially in data management, statistical programming and biostatistics service areas of clinical drug development. Most Sponsors prefer to have a single, full-service contract research organization (CRO) offering end-to-end services for an entire study including data submission components. However, with the stringent requirements for the CDISC compliant datasets by the regulatory agencies, the Sponsors are at a higher risk of getting a refuse to file (RTF) due to compliance issues with the submitted data. The full-service CRO may not have an all-round expertise in each of the service areas which will lead to poor quality of the submission deliverables and delays. An FSP model is a perfect fit to these services as it gives the Sponsor an ability to access the optimal functional expertise, in addition to the quality and operational needs, to meet their expedited submission timelines. In this paper, we will discuss a case study where we, as a niche provider, worked with a Sponsor towards their final NDA submission packet, even though the Sponsor had outsourced these services to a global full-service CRO. We will outline significant gaps identified in the deliverables provided by the full-service CRO, services we offered, and how we rescued this Sponsor to be able to meet the quality expectations and submission timeline. In addition, we will summarize lessons learnt during our engagement with this particular Sponsor.

INTRODUCTION – SHIFT IN INDUSTRY TOWARDS FSP MODEL

Sponsors of clinical trials outsource all or some of the tasks in an effort to accelerate drug development, lower overall costs, and have operational flexibility and access to the right functional expertise and resources. The process of outsourcing started as the Sponsor companies lacked in-house research and development resources, which therefore led to the development of a Full-service CRO offering end-to-end clinical trial services for an entire study [1]. Outsourcing all services to a CRO is commonly referred to as “one-stop shop,” a widely used model, where the Sponsors buy a range of services for a fixed price. These services include but are not limited to – Investigator site recruitment and monitoring, clinical operations, data management, biostatistics, statistical programming and medical writing [2].

Figure 1 below indicates how a Full-Service model functions. In the example, a Sponsor outsources an entire clinical Trial – A, B, or C to a full-service CRO (CRO 1, CRO 2, or CRO 3). Each CRO offers the following list of end-to-end services that flows horizontally in the direction of the arrow and where each project is handled independently

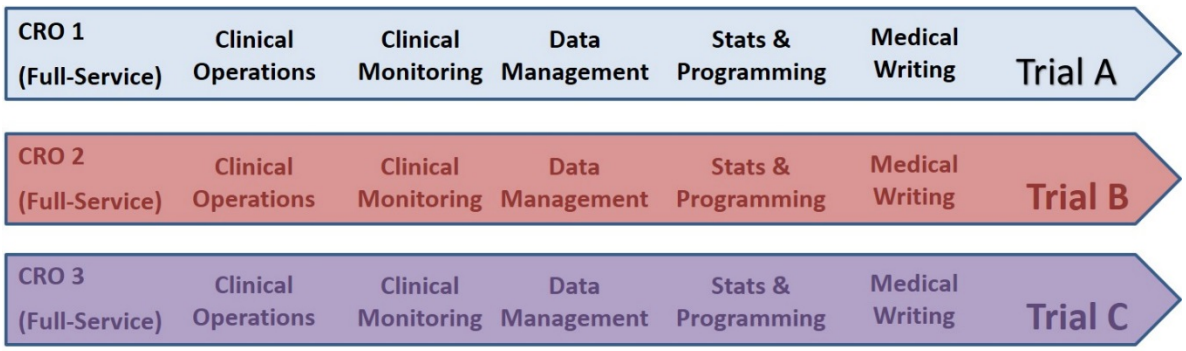

Figure 1. Full-Service CRO Model

There are however some disadvantages working with full-service CROs offering end-to-end services, such as lack of access to an all-round expertise in each of the service areas which will lead to poor quality of the submission deliverables and delays, lack of transparency and communication due to different companies working under a large/global firm that leads to poorly defined timelines and deliverables, limited flexibility and continuity of resources to name a few. For this reason, Sponsors (small to large sized) have lately started utilizing a functional outsourcing

approach (FSP model) where they contract a single vendor/CRO to deliver a particular service, resource or infrastructure across a single or multiple projects. This model not only allows the Sponsor to meet the expedited timelines of a New Drug Application (NDA) submission but also meet the Sponsor's defined budget goals.

In a Functional Service Provider (FSP) model, subject matter experts (SMEs) lead a team of efficient and talented individuals who can work independently with minimal interaction with the Sponsor. FSP model is now being employed in significant and specific areas of clinical drug development like biostatistics and statistical programming – CDISC submission deliverables, ad-hoc analysis, and more. In addition, the Sponsors can reduce the risks and costs of hiring, training and maintaining a continuity of staff for these services. Therefore, the FSP model has been most successful in the recent times in providing timely resources – **People, Processes and Systems** – vertically within a single functional service across wide therapeutic areas and multiple projects simultaneously, as shown in Figure 2 below.

Figure 2 depicts the role of a Functional Service Provider. In the same example below, an FSP offers a single functional service, such as Clinical Operations, Clinical Monitoring, Data Management, Stats and Programming, or Medical Writing, vertically across single or multiple projects simultaneously. This model maintains an operational consistency from a resource, processes and systems perspective and therefore reduces the overall costs of the deliverables.

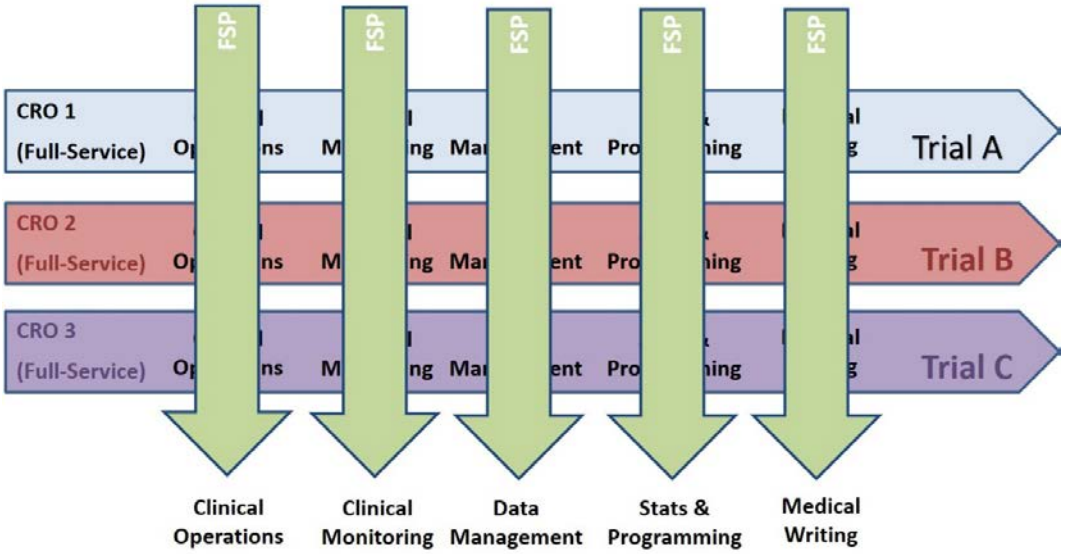

Figure 2. Functional Service Provider Model

Sponsor Advantages in a FSP Model

FSP model (niche providers) offer several benefits to a Sponsor:

- "Best-in-Breed" functional services allowing the Sponsors to leverage their own systems/processes.
- Timely availability and continuity of Resources – People, Processes and Systems.
- Access to optimal functional expertise for single/multiple projects simultaneously.
- Well-defined Scope, services and deliverables to maintain transparency.
- Meet expedited Timelines.
- Overall reduction in Budget and costs.
- Flexibility of resources with reduced training requirements.
- High Streamlined communication and immediate/quicker response.
- High Quality and efficient outcomes

Sponsor Challenges in a FSP Model

- Sponsor's (small or large sized) ability to understand the application of FSP Model.

- Understand requirements within Sponsor organization about what to outsource, especially with Sponsor's involved in drug registration, submission, and approval requirements.
- Identifying a Niche provider.
- Methods used to identify a functional service provider (Vendor/CRO).
- Ability to understand provider's best functional services.
- Experienced Resources to manage multiple providers/contracts throughout project

Irrespective of the outsourcing method used, it is essential for the Sponsors of any size to understand their responsibility for submission of clinical data. They are at a higher risk of getting a refuse to file (RTF) due to compliance issues with the submitted data if the Sponsor does not have an understanding of the Clinical datasets requirements for NDA submission, what goes into a clinical study report (CSR) or the preparation of a submission package for a Regulatory Agency review. Therefore, the combination of a full-service and a niche service provider clearly has several advantages in order to meet the accelerated timelines and stringent requirements for the CDISC compliant datasets by the regulatory agencies.

As a niche provider, Vita Data Sciences has handled several Sponsor rescue case studies since our inception. We will provide a list of items that Sponsors should request from your service providers for each deliverable to ensure you receive each component from them upfront rather than towards the end. It is even better if the clearly defined deliverables are built into your contract so they know what your expectations are in regards to these deliverables.

In this paper, we will discuss a case study where we, as a niche provider, worked with a Sponsor towards their final NDA submission packet, even though the Sponsor had outsourced these services to a global full-service CRO. We will provide a brief background and outline significant gaps identified in the deliverables, services we offered, and summarize lessons learned during our engagement with this particular Sponsor. Through a FSP collaboration, we were successful in accomplishing all the required submission components within a submission timeline of 10 weeks and provided the Sponsor tremendous benefits in the overall costs, quality, and timeline.

RESCUE CASE STUDY

BACKGROUND

A mid-size pharmaceutical company (Sponsor) was submitting their first ever NDA application to the FDA. As per their discussion at the pre-NDA meeting with the review division at the FDA, the Sponsor's commitment was to submit clinical datasets in addition to the ISS and BIMO datasets for six studies – three Phase I, one Phase II and two Phase III:

- Tabulation datasets in CDISC SDTM format for all studies.
- Phase II and Phase III analysis datasets in CDISC ADaM format.
- Integrated Summary of Safety (ISS) in CDISC ADaM format.
- Summary Level Clinical Site (BIMO) dataset and Site Level Subject Data Listings.
- All datasets should be submitted as per the standards defined under Study Data Technical Conformance Guide.

Table 1 provides a summary of the six studies to be included in the NDA submission along with the information about the format of tabulation and analysis datasets. Also included is the list of vendors that were originally involved and responsible for putting together submission-ready dataset package for each study.

Study List	Phase	Study Completion Year	Tabulation Dataset Format	Analysis Dataset Format	Outsourced Vendor
Study 1*	I	2007	SDTM (converted from Legacy)	Legacy	CRO 1
Study 2*	I	2009	SDTM (converted from Legacy)	Legacy	CRO 1
Study 3*	I	2009	SDTM (converted from Legacy)	Legacy	CRO 1
Study 4	II	2012	SDTM	ADaM	CRO 2

Study List	Phase	Study Completion Year	Tabulation Dataset Format	Analysis Dataset Format	Outsourced Vendor
Study 5	III	2015	SDTM	ADaM	CRO 3
Study 6	III	2015	SDTM	ADaM	CRO 3
ISS**	N/A	N/A	N/A	ADaM	CRO 3

Table 1. Information on the Studies to be included in the NDA Submission

*These studies were in legacy format for both tabulation and analysis datasets. These studies were outsourced to another vendor not referenced here who conducted their Phase I trials and generated legacy datasets and TLFs.

**ISS includes data from Phase III studies only.

The tabulation datasets of all three Phase I studies (Studies 1, 2 and 3) were in legacy format. The Sponsor had contracted a large full-service CRO (CRO 1/vendor), for the conversion of the legacy data to SDTM. This CRO 1 was also asked to put together a complete CRT package for all 6 studies including publishing of complete NDA. The Phase II and III studies, however, were in CDISC SDTM and ADaM formats that were outsourced to two different global full-service CROs (CRO 2 and CRO 3). CRO 3 was still finishing up with the generation of dataset supporting documents (define.xml, blankcrf.pdf, and reviewer's guide), though these studies were completed and the CSR TLFs were finalized.

The goal of the Sponsor was to submit their NDA by the end of September 2015. As of early June'15, the Sponsor realized there were multiple deliverables pending and that their vendor would not be able to meet the target NDA submission timeline. Additionally, they had also received comments from the FDA's eData team on their test submission and communication from the FDA's review division to ensure all supporting documents, such as define.xml and reviewer's guide, should be included in the original NDA submission. The review division also instructed them to ensure that the Sponsor clearly specifies in the reviewers guide as to which analysis datasets/parameters to use towards the study key primary and secondary efficacy end-points. They also requested them to include SAS codes (in ASCII format) for the reviewers to re-create their analysis datasets, and key efficacy end-point tables.

After receiving feedback from the FDA, the vendor (CRO 1) provided them with a revised target which was pushing the NDA timeline to end of November 2015. In addition, there were concerns over the change order this CRO 1 was generating for the tasks (e.g. blankcrf.pdf, reviewer's guide) which they were originally contracted out to perform. At this point, the Sponsor decided to reach out to us and requested our group to perform a gap assessment and provide them details on the remediation steps that would be required to make their NDA submission possible by September 2015 and also incorporate feedback they received from the FDA eData team and the review division.

GAP ASSESSMENT

The Table 2 below summarizes some of the key/significant observations we found in each study divided by tabulations datasets, analysis datasets, and miscellaneous items.

Study	Vendor	Key Gaps Identified in SDTM Datasets	Key Gaps Identified in Analysis Datasets (Legacy/ ADaM)	Miscellaneous
Study 1 Study 2 Study 3	CRO 1	• Lots of OpenCDISC validation compliance issues (errors and warnings) that were either not addressed in the datasets or justified (e.g. Epoch variables were missing, treatment emergent flag was missing, length of variables were not adjusted to actual stored data, data issues). • SDTM annotated CRF (blankcrf.pdf) was not in place for all 3 studies. • Define.xml was not yet generated. • No traceability report or assessment done upon legacy mapping to SDTM against the existing analysis datasets.	• No define document was generated for the legacy Phase I studies. • The analysis dataset from the legacy study (Study 1) were not Study Data Specifications (SDS) compliant (variable label were longer than 40 characters, same variable names were used across different datasets with differing attributes). • The analysis dataset specification document for Study 1 had lots of missing components.	• SAS® Programs from their legacy studies were not available. • Study 1 CRF was in word format. • OpenCDISC version 1.4 was used when the Phase III studies had used OpenCDISC v2.0.

Study	Vendor	Key Gaps Identified in SDTM Datasets	Key Gaps Identified in Analysis Datasets (Legacy/ ADaM)	Miscellaneous
Study 4	CRO 2	• Define.xml and reviewer's guide were not available for this study. • The SDTM mapping specifications which is key to generate define.xml and other submission components were incomplete (e.g. controlled terminology, CRF page reference, change log, origin, and role of the variables). • SDTM annotated CRF (blankcrf.pdf) was not in place. • FDA expected variables and recommendations per SDS v2.0 was not implemented (e.g. Epoch variable were missing, treatment emergent flag was missing, and length of variables were not adjusted to actual stored data). • Trial design domains were not available.	• Define.xml and reviewers guide were not available for this study. • The SDTM mapping specification was incomplete and didn't have all necessary components.	• SAS codes were not provided to the Sponsor.
Study 5 Study 6	CRO 3	• Missing define.pdf when define version 1.0 was used for xml version. • Hyperlinks within define.xml were not functioning well. There were few broken components. • Define.xml was not validated through OpenCDISC and it was not utilized to check against the SDTM datasets. • SDTM aCRF (blankcrf.pdf) was not annotated per instruction provided in the Metadata Submission Guidelines (MSG) and bookmarks were missing. • Reviewer's guide was not generated using the most current template of the SDRG available at that time. It only had compliance summary with no clear justifications of the pending issues.	• Missing define.pdf when define version 1.0 was used for xml version. • Hyperlinks within define.xml were not functioning well. There were few broken components. • Define.xml was not validated through OpenCDISC and it was not utilized to check against the SDTM datasets. • Reviewer's guide was not generated using the most current template of the SDRG available at that time. It only had compliance summary with no clear justifications of the pending issues. • No details were provided in the reviewer's guide as to where one would find key efficacy end-points information.	• SAS codes were not provided to the Sponsor to include in their submission per FDA request.
ISS	CRO 3	N/A	• Missing define.pdf when define version 1.0 was used for xml version. • Define.xml was not validated through OpenCDISC and it was not utilized to check against the ADaM datasets. • Reviewer's guide was not generated using the most current template of the SDRG available at that time. It only had compliance summary with no clear justifications of the pending issues.	• SAS codes were not provided to the Sponsor. • BIMO datasets and site level subject data listings were not programmed yet.

Table 2. Summary of key gaps identified in Sponsor's existing dataset package for all 6 studies and ISS

SERVICES OFFERED

After we did the above gap assessment, the Sponsor asked us to confirm whether we will be able to take on the task to meet their submission timeline. Based on our experience and taking an inventory of all the study documentations, we thought our team would be able to remediate and fix all the gaps and have the complete dataset package ready

within 10 weeks. Upon our confirmation, the Sponsor made the decision for us to step in and rescue them from the current situation.

Study List	Phase	Summary of Services Offered
Study 1 Study 2 Study 3	I	Our team was assigned to work with CRO 1 to review and provide feedback on the SDTM domains and any compliance issues. We were responsible to put together submission documents that were not in place yet (SDTM aCRF, Reviewer's Guide, and define.xml). Also we were tasked to put together define files (define.pdf) for the analysis datasets for all 3 studies. Provided traceability report to the Sponsor between mapped SDTM and existing analysis dataset.
Study 4	II	Generate define.xml, SDTM aCRF, and reviewer's guide for both SDTM and ADaM datasets. Add FDA expected variables to the SDTM domains (EPOCH, TRTEMFL) and adjust length of each variables to actual stored data. Generated Trial Design Domains. Work with CRO 2 to get access to the SAS codes for the study.
Study 5	III	Work with CRO 3 to provide feedback on the define.xml and have them fix any issues pertaining to datasets and define files. We were asked to take over generation of SDTM aCRF and Reviewer's Guide for both Phase 3 studies. We also had to get access to the study SAS codes and prepare the files for submission per request from the FDA review division. We were also contracted to put together BIMO datasets and site level subject data listings.
Study 6	III	
ISS	N/A	

Table 3. Summary of Services Offered

PROJECT TEAM

After the contract was signed, we put together a project team assigned specifically to this Sponsor. The kick-off meeting with the Sponsor was towards the end of June 2015. The team had 10 weeks to finish all the task and provide a complete CRT package for all 6 studies, ISS, and BIMO datasets to their eCTD publishing vendor. The team comprised of roles listed below.

Role	Responsibility
Project Manager	• Ensure project deliverables are on track in terms of timelines and within scope. • Serve as a point of contact for issue escalation. • Organize cross organizational meetings. • Manage change control and financial tracking.
Data Standards and Submission – Subject Mater Expert (SME)	• Develop data submission and programming plan, strategy, and specifications. • Provide direction and delegation of deliverables to statistical programmers. • Lead contact with Biostatistics representatives. • Attend and participate in study meetings.
Principal and Senior Level Statistical Programmers (n=4)	• Programming lead towards generation of the dataset submission documents (define.xml, define.pdf, SDTM aCRF) and reviewer's guide. • Review and QC all trial deliverables and trial documentation. • Program SAS code to generate relevant outputs. • Produce final deliverables and documentation. • Provide ad-hoc support for any submission needs.
Document Specialist	• Review and develop bookmarks and set PDF document properties per FDA requirements. • Review all PDF documents for proper hyperlinks functionality.
Sr. Biostatistician	• Review Study Data Reviewer's Guide for accuracy against the dataset, especially anything surrounding key efficacy/safety end-points. • Work with the Sponsor for any Statistical support. • Address any protocol/SAP level questions.

Table 4. Project Team

REMEDIATION PERFORMED

The following provides details on the remediation performed for each study and deliverables to meet the submission deadline:

Phase I (Studies 1, 2, and 3):

- Generated SDTM aCRF (blankcrf.pdf) for all 3 studies per the Metadata Submission Guideline (MSG), fully bookmarked by visit and by domain.
- SDTM define.xml version 2.0 for all 3 studies.
- Worked with the CRO 1 to fix any SDTM mapping and compliance issues.
- Ensure traceability across mapped SDTM domains and existing analysis datasets.
- Study Data Reviewers Guide (SDRG) using most current template from the FDA/PhUSE and documented any data anomalies and compliance issues with complete justifications.
- Define.pdf for legacy analysis datasets for all 3 Phase I studies.
- All PDF documents bookmarked and properties set as per expectations from the FDA/publishing group.

Phase II (Study 4):

- Generated SDTM aCRF (blankcrf.pdf) per the MSG, fully bookmarked by visit and by domain.
- Developed and QC trial design domains.
- Updated SDTM datasets to include FDA expected variables ensuring no changes were made to the existing data to avoid impacting existing CSR TLFs.
- Generated SDTM and ADaM define.xml version 2.0.
- Checked compliance of the SDTM and ADaM datasets using OpenCDISC and provided justification for each error and warning. Also checked datasets against the define.xml to ensure both are consistent.
- Developed SDTM and ADaM reviewers guide and added information about dataset structure, primary and secondary end points, and OpenCDISC compliance issues.

Phase III (Studies 5 and 6) and ISS:

- Worked with the CRO 3 to provide feedback on define.xml for Phase 3 and ISS.
- Generated SDTM aCRF (blankcrf.pdf) per the MSG, fully bookmarked by visit and by domain.
- Updated SDTM datasets to include FDA expected variables ensuring no changes were made to the existing data to avoid impacting existing CSR TLFs.
- Developed SDTM and ADaM SDRGs and added information about dataset structure, primary and secondary end points, and OpenCDISC compliance issues.
- Took inventory of all SAS codes, select key primary and secondary efficacy end-points programs and run in our environment to ensure FDA will be able to run it in their system with no or limited changes to the submitted codes.

BIMO Dataset and Site Level Subject Data Listings:

- Generate BIMO dataset (clinsite.xpt) per the FDA guidance and specification, including expectations set by the Office of Scientific Investigations (OSI) team for site inspection purpose.
- Developed define.pdf for the BIMO dataset.

PROJECT SUMMARY

The team was successfully able to generate all deliverables and a complete CRT package (…m5/datasets) towards this NDA by mid-September, 2015. Our project team took about 10 weeks to complete task at hand. During this engagement, the team worked very closely with the Sponsor and other vendors (CRO 1 and CRO 3) to meet the submission goal. The Sponsor was successfully able to submit their NDA as planned towards the end of September, 2015! The drug is currently under review by the FDA. The Sponsor has continued to work with our group after the submission and we also helped them address questions coming from the FDA review division.

With this incredible experience and the engagement which was very successful, we have provided a brief list of lessons learned:

- The contract with your vendor should clearly define the Sponsor expectations of each deliverable, including the timeline. The Sponsor should make a list of all submission components such as generation of define.xml, SDTM aCRF, SDRG, SAS codes, and other documents required towards submission and append that to the signed contract. The idea should be to have '**submission-ready**' datasets along with all submission documents from your vendor at the end of the study.
- OpenCDISC compliance issues should be addressed during the development of the SDTM datasets and not at the end when ADaM and TLFs are already generated [3]. Each issues should be addressed or justification should be provided if issue can't be resolved. This will ensure datasets are 'submission-ready'.
- Define.xml and SDTM aCRF should be developed early in the SDTM development life cycle. This should not be left at the end after the SDTM datasets are finalized [4].
- If multiple studies are outsourced to a CRO, ensure there is consistency used across these studies.
- Clinical datasets submission strategy should be discussed at the time of pre-NDA meeting with the FDA. We highly recommend Sponsors to have a test dataset submission to the FDA eData team. The Sponsor should work with their review division to ensure any expectations on the efficacy analysis datasets supporting their pivotal studies are met.
- Work with a vendor who fully understand FDA dataset submission requirements, are thought leaders in the space, and have worked on multiple submissions in the past.
- Prior to signing contract with a vendor, you should consider interviewing people who are going to be working on your project. You should ask them to share project team resumes and go through their submission experience. It is utmost important to have Data Standards and Submission SME as a part of this team.

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