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We Can Work It Out: Dos and Don'ts for Small Biotech and CRO NDA/BLA Submission Partnership

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ABSTRACT

Many pharmaceutical/biotech companies rely on outsourcing much of their biometric and regulatory work to CROs – even critical NDA or BLA submissions. At the start of 2020, as the reality of a global pandemic was setting in, a small biotech with only 2 statisticians and 5 programmers was able to file their company's first NDA with the support of a small CRO. The NDA was comprised of over 30 studies including 2 pivotal phase IIIs and additional phase III open label studies with back-to-back locks, as well as legacy and remediation work. As the sponsor programming manager and CRO programming lead, the authors of this paper will share our lessons learned from this multi-year successful collaboration that began as a single phase II outsourced study and ended in a big win for both companies.

INTRODUCTION

By the end of 2018, Rho, a small CRO, had successfully completed limited service biostatistics and programming work on the sponsor's phase II study and had begun the same scope of work on the phase III studies. At that time, Rho presented a strong case to the sponsor that they should be chosen as the CRO to undertake work on the full NDA should the phase III studies show success. Based on projected lock dates for the phase III double blind (DB) and open label (OL) studies, the sponsor had a clear timeline in mind and was able to share the projection with Rho along with their expectations for quality, cost, and desired working style. Key database locks would happen in early/mid 2020 and the NDA would be submitted at the end of 2020. Millions of data points, thousands of decisions, and hundreds of meetings later, this goal of a successful NDA submissions at the end of 2020 was accomplished. In this paper, we will outline the 7 keys to success for this amazing achievement and successful partnership.

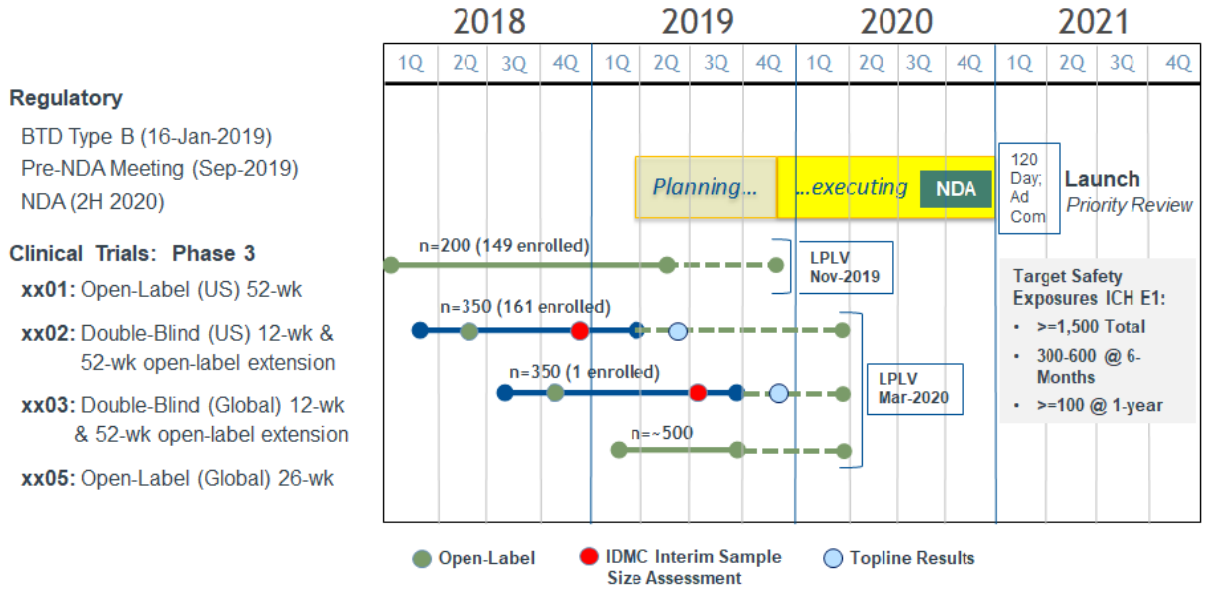


Figure 1. Key NDA Timeline expectations of the sponsor as presented and discussed in the late 2018 NDA Bid Defense Meeting with the CRO. Additional phase I, phase II, and legacy data packages are not pictured but were part of the scope of work.

THE SEVEN KEYS TO SUCCESS

Overview of the 7 keys to success in order of their chronological appearance in the process:

1. Vendor Selection and Strategy – Sponsor should aim to find the best match for each functional area.
2. Start the Work as Early as Possible – Because plans and analysis goals will change!
3. Make the Most of Meetings
4. Quality Execution of Work
5. Keep the Big Picture in Mind
6. Excellence in Staffing is Essential
7. Build Trust, Partnership, and Have Fun!

1. VENDOR SELECTION AND STRATEGY

Believe it or not, choosing a CRO partner/vendor to execute the work required for an NDA is surprisingly like a homeowner selecting a contractor for a kitchen remodel. Many of the steps for choosing a home improvement partner are similar to the steps outlined below for choosing a CRO/vendor to collaborate with for an integration project like a marketing application.

To being, the sponsor will need to have a clear understanding of their own internal attributes. Similarly, some homeowners might have architectural or labor skills to contribute to a remodel and others struggle to change a lightbulb. It is important to understand what kind of expertise and working style exists internally so that the group can determine their desired partnership style. Does the sponsor prefer a CRO that can fill in knowledge gaps or perhaps the sponsor prefers a vendor that will compliment or enhance the expertise that already exists in-house? Do they prefer a vendor that will follow sponsor specification or author the specifications themselves? Who will be steering the ship? The sponsor, like a homeowner, needs to be aware of what their anticipated contribution level is and what kind of partner match is desired.

Next, whether you a pharmaceutical company or a homeowner, you should have a clear understanding of your own expectations for the project scope, complexity, and desired timeline. These details are essential information for prospective vendors. The CROs will need as much information as possible to provide a detailed bid for the project.

Finally, the sponsor company should know where they land as an organization on the value triangle that consists of 1) Quality 2) Speed 3) Cost – also known as “Good, Fast, and Cheap”.

Figure 2. Sponsors should decide where they land on this spectrum. This is important not only for vendor selection but also for setting realistic goals so that all parties understand what "success" looks like for the project.

Sponsors, prospective vendors (and the industry as a whole) should work towards the goal of achieving quality, fast, inexpensive output – the "UNREALISTIC" center of the diagram. However, achieving 2 of these 3 should be considered a success provided what is achieved is in line with sponsor goals communicated internally and to vendors at the start of the project.

Once the sponsor is aligned internally on their current capabilities, needs, and values, the next step is to provide each vendor with an RFP (request for proposal). The RFP will need to contain a clearly defined anticipated scope of work along with focused questions for the potential partner CRO. Ensure that you ask all prospective vendors the same questions so you will be able to evenly compare answers. If possible, do not wait until the last minute to start the RFP process. You will want to allow sufficient time for vendor responses and perhaps a short clarification phone call if needed. We recommend asking the prospective CRO to include names of likely project staff. If discussions progress to the bid defense stage, ask that project governance and named staff members attend the bid defense.

All sponsor functional areas should begin the bid defense selection process with a clear set of questions and the expectation of having discussions with the bidding CRO around topics of interest. Below are a few examples of items related to the authors area of expertise (statistical programming) that are frequently of concern to sponsors in bid defense meetings:

- What is CRO's statistical programming QC process? Not all CROs utilize double independent programming. It's important that you don't assume this.
- Will there be a dedicated project manager? Who will organize meeting agenda/minutes/timelines?
- Who will attend routine meetings? For example, will programmers join the meeting as active participants that contribute to the technical discussions about the data?
- What do the CRO's dataset specifications include? If the sponsor has expectations about the contents and format of programming specifications, it's important to get clarification on what the vendor's process and output are.
- Will TLF delivery include supporting datasets? This may not be of value to some sponsors but for those that prefer to programmatically validate CRO output, supporting datasets will be necessary. Don't assume they are part of the standard delivery.
- What is the change order process? Could the CRO describe common change in scope charges that they encounter?

2. START THE WORK AS EARLY AS POSSIBLE – BECAUSE PLANS WILL CHANGE!

While it is important to have a clear timeline that is agreed upon by all parties (see Figure 1 above), make sure that the timeline does have some breathing room if possible. Scope tends to increase rather than decrease and unexpected events will always arise. Initiate work on your submission as early as possible– even if this means starting work at-risk before the phase III readouts are completed. One of the strategies that Rho and the sponsor decided to build in some flexibility with the timeline was to begin the legacy data and submission packages early. These were completed in 2019 prior to the phase III results, and completing this work made it possible to made it possible to complete required components of the project in advance of the critical path.

Many timeline stressors come from common external factors such as FDA feedback and other study vendors not meeting their timelines. In our NDA project, the FDA asked for an additional 10+ studies to be integrated as supplemental safety analysis. This work was not planned, and the project team had to act quickly to determine how best to execute this work while keeping the planned goal of a 2020 submission intact. Fortunately, Rho was the CRO responsible for all the phase III programming, biostatistics, and

CSR activities so the dreaded issue of the phase III CRO being late with their work and negatively impacting the NDA timeline did not occur. Because the target submission date was in 2020, the largest and most unforeseen external issue that impacted our work was a global pandemic - COVID. In March of 2020 most of us went home to work and most never returned to the office. Fortunately, both organizations had sufficient technological and personnel infrastructure in place to allow the work to continue without substantial setbacks because of the pandemic.

Other factors that commonly cause timeline instability might come within the study team. Hopefully, sponsors will ask about staff turnover rate during bid defense meetings, but a common source of negative timeline impacts is staff turnover – on the sponsor and CRO side. It's advisable to try to avoid partnering with CROs that have high turnover rates in their biometrics and regulatory departments. In addition to staff turnover, requests for updates from internal medical review or slow enrollment are other common pitfalls of timeline trouble that can come from within an organization.

To illustrate the need to plan for the unexpected, the following is something that we encountered in our NDA project: the sponsor discovered that they were required to include 3 Japanese studies that needed translation. Neither Rho nor the sponsor had translation services in-house. A translation company was hired but the company had no programming expertise. Rho and the sponsor developed a plan to translate the data, handle the Japanese non-ascii characters that aren't accepted in eSub deliverables to the FDA and programmatically and visually QCed the columns that did not need translation to verify that the data in those did not change in the process. Because Rho and the sponsor had agreed to complete the legacy work early, the inclusion of the Japanese study translation work did not derail the final timeline. Because we had planned and started early, we were able to absorb this additional work.

3. MAKE THE MOST OF MEETINGS

Meeting Content

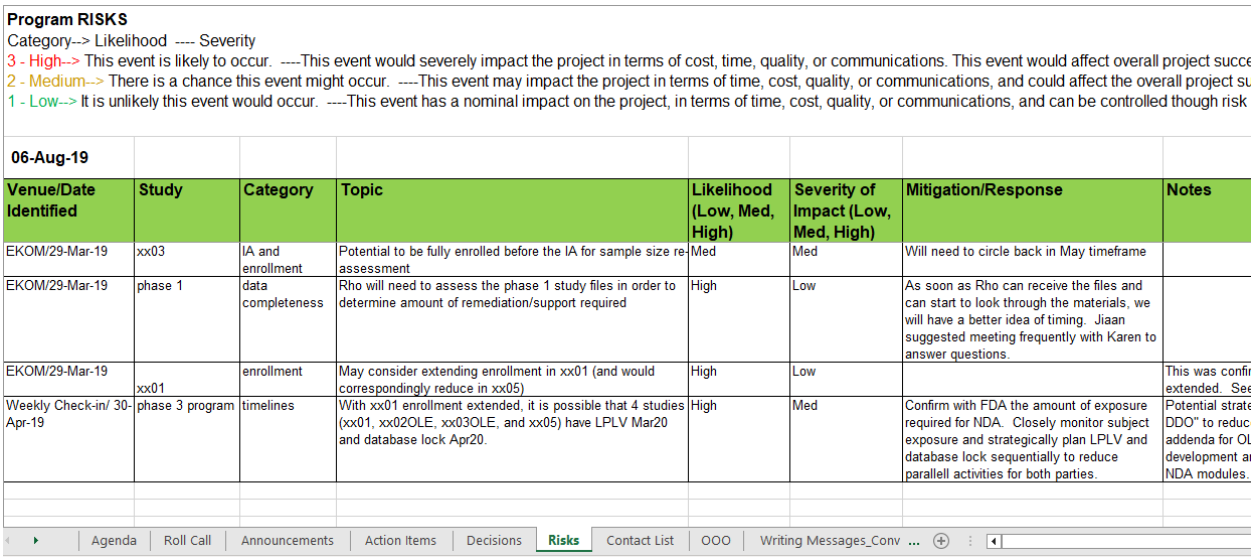
All of us have experienced meetings that routinely add little value. It is hard to resist the urge to multi-task, maybe it seems like the same people go on and on about the same topics, and decisions are never reached. Your team needs to be committed to having productive, engaging, goal-oriented meetings. Here's how.

To maximize meeting value, meetings must have:

1. A Proven Leader – We will discuss this individual more in the Staffing Section of this paper, but having a qualified leader that can keep the discussion moving and contributors on topic and focused is essential. For our NDA project, the meeting leader was our overall PL.
2. Reasonable Goals – Each meeting agenda should include a clear set of attainable items that outline what can be accomplished during the meeting. Typically, this is a rollcall, general announcements, timeline updates, and then specific updates or running agenda items for various functional areas. The closeout of the meeting is a good place to highlight ongoing high-level risks and mitigation strategies.
3. Risks/Considerations – One of the most valuable features of our NDA project meetings centered around awareness of risks, evaluation of risk severity, and mitigation strategies. All too often, teams are afraid to openly communicate about risk to their external partners. As a result, they end up watching a disaster unfold in front of their eyes as predicted. For our NDA project, all project risks were not updated at every meeting and if additional risks were identified, they were added to the "Risks" tab of our RAMM (see figure 2 below), and conversation about risks occurred regularly.
4. Timeline Updates – A brief summary of the project timeline is an essential part of each project meeting. Highlighting upcoming deliverables, shifts in timelines, and timeline risks help to keep everyone aligned in their work. Likewise, acknowledging deliverables that have been completed are a nice motivation. Everyone loves crossing things off their "to do" list!

Regular team meetings should have a clear, organized agenda and thorough minutes. Both the agenda and the minutes should be posted on a common site where both parties can have access and can add comments if desired. If possible, both sponsor and CRO should set the expectation that all team members should prepare for the upcoming meeting by reading the agenda and supporting documentation rather than starting to process the agenda topics in the meeting.

Rho uses the RAMM (running agenda and meeting minutes). We found the RAMM to be an essential organization and communication tool for our NDA project with the sponsor. The RAMM contained information past and present relating to the project and personnel as well as key meeting minutes. A snapshot of the RAMM is below. The format is XLS which makes it easily editable for all team members and it is organized topically by the tabs or sheets included.



Program RISKS

Category--> Likelihood ---- Severity

3 - High--> This event is likely to occur. ----This event would severely impact the project in terms of cost, time, quality, or communications. This event would affect overall project succe

2 - Medium--> There is a chance this event might occur. ----This event may impact the project in terms of time, cost, quality, or communications, and could affect the overall project su

1 - Low--> It is unlikely this event would occur. ----This event has a nominal impact on the project, in terms of time, cost, quality, or communications, and can be controlled though risk

06-Aug-19

Venue/Date Identified	Study	Category	Topic	Likelihood (Low, Med, High)	Severity of Impact (Low, Med, High)	Mitigation/Response	Notes
EKOM/29-Mar-19	xx03	IA and enrollment	Potential to be fully enrolled before the IA for sample size re-assessment	Med	Med	Will need to circle back in May timeframe	
EKOM/29-Mar-19	phase 1	data completeness	Rho will need to assess the phase 1 study files in order to determine amount of remediation/support required	High	Low	As soon as Rho can receive the files and can start to look through the materials, we will have a better idea of timing. Jiaan suggested meeting frequently with Karen to answer questions.	
EKOM/29-Mar-19	xx01	enrollment	May consider extending enrollment in xx01 (and would correspondingly reduce in xx05)	High	Low		This was confi extended. See
Weekly Check-in/ 30-Apr-19	phase 3 program	timelines	With xx01 enrollment extended, it is possible that 4 studies (xx01, xx02OLE, xx03OLE, and xx05) have LPLV Mar20 and database lock Apr20.	High	Med	Confirm with FDA the amount of exposure required for NDA. Closely monitor subject exposure and strategically plan LPLV and database lock sequentially to reduce parallell activities for both parties.	Potential strate DDO" to reduc addenda for OL development a NDA modules.

Agenda | Roll Call | Announcements | Action Items | Decisions | Risks | Contact List | OOO | Writing Messages_Conv ...

Figure 3. Snapshot of the RAMM Risks tab. Notice the Likelihood, Severity of Impact, and Mitigation columns. These categorizations help facilitate a purpose-driven discussion. Other common tabs such as roll call and contact list were present along with tabs for Action Items, Decisions, and team Out of Office information.

Adhering to the meeting agenda and goals are important to the success of the meeting. The meeting leader/project lead will occasionally need to remind people to stay on the agenda topics and refrain from talking in detail about new topics unless they are time-sensitive showstoppers. Of course, late breaking agenda items do happen, but often the best course of action is to have a smaller technical meeting with key personnel to discuss how best to proceed for items outside of the meeting agenda.

Meeting Timing and Purpose

Once the project has been awarded to the CRO or vendor, we recommend a lengthy kick off meeting. This meeting should include the study level functional area leads, the integration team leads, legacy and remediation personnel, as well as lead writers and regulatory decision-makers. The overall project lead for the vendor/CRO should own the meeting in conjunction with the sponsor side overall project lead if the sponsor will have a project oversight representative. The meeting should include many of the key elements outlined in the section above but with additional emphasis on risk. High level, key risks that could impact the overall timeline and quality goal should be identified during this initial KOM and revisited as the work builds.

We recommend weekly project meetings with the entire team. During crucial work times, additional assemblies might be necessary if the team feels alignment is needed or on the contrary, meetings may be cancelled to allow for focused work. Additional recommended formal meetings that worked well for us included an ISS SAP roundtable, an ISS TLF review, and periodic governance check-in meetings that include only key decision makers and stakeholders.

4. QUALITY EXECUTION OF WORK

Investing in quality will be difficult if the sponsor organization has opted for fast and inexpensive as their model for a successful NDA. Even in a fast and inexpensive working model there are still areas to be invested in to facilitate a quality end product. Quality should be present in the integration process and deliverables but investing in quality prior to integration is even more beneficial.

Our first suggestion for quality NDA deliverables is to make sure specifications and documentation are completed and maintained exceptionally well. For those who have programmed ADSL, you know that ADSL is often the first ADaM dataset to be created and the last ADaM dataset to be finalized. Our NDA ISS ADSL was no exception. While creating our NDA ADSL dataset (subject level analysis dataset for all integrated safety), we made sure to update the specifications each time a variable or algorithm needed to be changed. This was a burden for our team members that were often focused on rapid output, but the documentation of what was being done in ADSL for each variable for each contributing study was hugely important when fielding comments from medical colleagues, writers, and reviewers seeking to understand data values from ADSL during crucial review periods.

This detailed specification and documentation approach was also implemented on the individual contributing studies that Rho created for the ISS and ISE and was a big assist in the integration effort later on. We invested heavily in high quality consistent mapping and specification of the phase III studies in house at Rho. As a result, we had high quality stackable pivotal data that helped with the flow of the ISS and ISE downstream.

Another example of where quality documentation helps is investing in detailed annotation of TLF shells. Rather than just relying on “Chemistry tests for all visits”, taking the time to think through and list the tests and visits to be displayed can be a very useful to workflow and reduction of rework. For our phase III work, this extra bit of annotation was not in Rho’s original project scope of work with the sponsor, but it was a very useful not only to the TLF programmers but also to those that were doing ADaM specifications and programming.

We recommend ensuring that both the sponsor and CRO have skilled functional area expert counterparts. While we realize that it is not possible for all sponsor companies to implement this suggestion, it was a big benefit to our work on the NDA project. Expecting team members on either side of the partnership to provide reasonable and valuable comments or discussion outside of their area of expertise might be a drain on timelines and derail meaningful work. The ability to have knowledgeable and experienced team members on both sides will also help ensure that the most important aspects of the work are prioritized should competing tasks arise. These working personnel counterparts will be able to find reasonable, efficient, and often creative solutions to unforeseeable issues.

Finally, another factor that will help ensure quality work for the NDA is for the sponsor to commit to providing consolidated comments to the CRO when requesting changes. The term “consolidated comments” gets tossed around and often ignored, but to truly get expedited, consistent results from a CRO or vendor, consolidated comments are worth the investment.

5. KEEP THE BIG PICTURE IN MIND

Now for our Dos and Don’ts.

DO plan with the end in mind. Define success and work as a team towards success.

DON’T let timeline milestones slip.

DO look for risk, plan for mitigation of risks, and communicate risks throughout the process.

DON'T assume completely linear development of milestones. Staggering deliverables is more realistic and can help ensure a more fluid and stable workflow.

DO plan efficiencies from the start. Look for ways to repeat work rather than starting from scratch each time. We were able to produce very good SDTM and ADaM mapping for the first phase III study and use those specs and programming to map the other phase III and Open Label studies.

DON'T sweat the small stuff. Keep focused on a successful submission and don't get distracted by things that aren't of consequence.

6. EXCELLENCE IN STAFFING IS ESSENTIAL

Leadership Personnel

As mentioned previously, investing in a capable, experienced, CRO-based project manager will be immensely important. Our NDA project was led by a senior level Regulatory Strategy lead. She was fully dedicated to the project, owned the RAMM, maintained all timelines, and ensured that all large and small milestones were met. As mentioned in the "Quality Execution of Work" section above, we recommend that, when possible, each CRO functional area lead has a corresponding counterpart on the sponsor side. In the case of our submission project, the CRO Project Lead had two counterparts on the sponsor side who understood the importance of all milestones and had access to sponsor's upper management each step of the way as needed.

Prior to project kick off, identify key decision makers for the NDA project. It is suggested that there be one key decision maker for each functional area. These individuals will serve as points of escalation, if needed, and they will be responsible for final agreements and prioritize tasks as the need arises.

CRO Staffing Best Practices

There are several things that the CRO can do when staffing for a large NDA submission that will help ensure the success of the project. The first thing is to assign experts to do the work instead of just dropping in experts who will participate in end stage review. Building highly experienced workers into the workflow will help reduce costly re-work that can often result when a CRO assigns one senior worker and many low skilled staff. Having experienced staff, although at a higher bill rate, with their hands in the day-to-day work will result in better deliverables. The second thing that CROs could do to ensure high quality on large NDAs is to commit to providing a core staffing model across all the studies in the program if possible. Core staffing is a small, lean group of programmer and biostatisticians that initiate the work, and as the scope increases, additional team members are added to the core group. The alternative is a siloed approach of study-by-study staffing that often creates inconsistencies in content and quality for the different studies in a program. Using the core team approach allows the CRO to be the gatekeepers of quality even with the sponsor company has separate teams for each study.

7. BUILD TRUST, PARTNERSHIP, AND HAVE FUN!

Throughout all the stages of our partnership – from the first phase II study in mid-2016, to the award of the NDA integration work in early 2019, to the completion of the whole NDA in December of 2020 – our 2 teams truly worked as one in collaboration with a single common goal of having a high quality, successfully executed, on-time NDA submission. During that time, both the sponsor and Rho acquired mutual trust, respect, and even friendships – like the authors of this paper.

Accomplishments, trust, and respect are great, but what about fun? It wasn't all work and no play! As the NDA work started, our Rho project manager began each meeting with a fun "icebreaker" topic for roll call. It was 3 to 5 minutes of time well spent. The PM would ask a question and each team member would answer the question. Questions might be "What was the last dessert you ate?" or "Where would you like to go on vacation?". There were lots of laughs, some surprises, and we all learned a lot about each other.

One of the questions was “What is your favorite movie?”. Jiaan ended up watching “The Godfather” and the “Lord of the Rings” series many times since our collaboration.

CONCLUSION

As stated in the introduction, millions of data points, thousands of decisions, and hundreds of meetings after project initiation, the goal of a successful NDA submission at the end of 2020 was accomplished. Not only was the overall timeline achieved, but even the smaller timelines were met or exceeded. Best of all, we had no questions about data quality or eSub packages from the FDA: only a minor request 2 months after the submission was accepted that resulted in a few additional TLFs. It was an amazing journey!

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