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Tips and traps on how to efficiently accelerate clinical trials to successful submission, approval, and launch

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ABSTRACT

Scenario 1: your review division team has suggested that if your submission can be accelerated by 6 months, then your company will be at the advisory committee meeting along with your competition

Scenario 2: The preliminary results from your study have been presented at a clinical meeting and a health authority has contacted you indicating that this study could be the basis of a successful submission as it may provide effective treatment for patients who have none.

These represent actual historic situations demanding rapid development and submission. I present here some basic approaches that have been effective in the past in such accelerations. These require up front efforts, maturity, and discipline. As cultural change is involved, these practices are not standard nor even commonly encountered.

Some of the practices presented include developing a submission focus as opposed to being study centric, strong parsimony and control over the bulk of reporting, focusing on telling the story that is in the data, financial arrangements to avoid stopping the flow of work, and engaging cross functional teams with clear lines of communication.

While these practices are particularly important for key situations, they are also just plain good practice for each, and every trial.

INTRODUCTION

There are times when there is a clear need for speed in clinical trial development to aid public health, to meet unmet needs for patients who have limited or no treatment options. Furthermore, from a business perspective, getting a moderately successful intervention to market one month early often results in additional tens of millions of dollars of revenue.

There have been rare cases where effective acceleration of development programs was needed and was achieved. This paper intends to lay out some basic practices and processes that have proven effective in some of these instances.

A rough outline of the paper follows:

Avoid study centricity. The focus should be on submission readiness for each, and every study.

Develop and communicate a dynamic submission plan.

Develop a dynamic story line on the development program.

Create the list of critical variables which contribute to the key evidence from the trial.

Reduce content to the essential. Debulk the Tables of Contents of reports.

Focus the content on the evidence needed for the task at hand.

Refine the approach to dry runs.

Set up for *ad hoc* requests, rapid responses, unanticipated changes in plans.

LET'S GET STARTED

Avoid study centricity.

All studies should be conducted with the submission in mind. Data should be collected, analysed, and reported in as standard and consistent manner as possible to facilitate the eventual integrated summaries.

Run SDTM and ADaM validation checks for each, and every deliverable from the first to the last and continually address issues and mitigations.

Plan to provide full electronic submission packages for individual studies and integrated data pools.

For each study/pool provide:

Define.XML for both SDTM and ADaM

Data files (.XPT) for both SDTM and ADaM

Reviewer's Guides for both SDTM and ADaM

CDISC Validation/Compliance reports for SDTM and ADaM

Annotated CRFs

Make every effort to understand regulatory needs and preferences. Be sure to engage in technical detail discussions at the End of Phase 2 or PRE-NDA or other regulatory meetings.

Ask about the following:

Is a formal Technical Review expected?

Requested data formats and/or analyses

Requested analysis code

Other special requests, such as review aids or data visualization for Clinical Reviewers. Note that if your clinical team needs additional data views for study review and/or maintenance then these are likely useful to the health authority reviewers, as well.

Discuss if Subject-level Data Line Listings by Clinical Site, and a Summary-Level Clinical Site Dataset that are used for planning of BIMO inspections by the Center for Drug Evaluation and Research (CDER) are needed.

Develop and communicate a dynamic submission plan

A submission plan should be in place in advance of the first pivotal study beginning. The scope, scale, and schedule of regulatory submissions should be planned and charted out including overall submission goals, estimands, population and analysis definitions, and subset needs. The timelines and milestones should be communicated and progress should be actively tracked.

To most effectively collaborate, these plans should be communicated to the Biometrics CRO if one is engaged. There should be regular meetings to discuss timelines, milestones, and progress.

There should also be a mindset to continually assess where there are logjams, speed bumps, other impediments to study progress.

If there are lagging data and/or patients, these should be studied, and alternatives considered, in order to remove these drags on the timelines. The known last visit and follow-up dates for participants should be tracked. Efforts should be made to ensure that a few late participants are not holding up the entire study.

If data, such as a special lab assay, are rate limiting, explore with regulatory agencies if these results can be provided in a follow-up report and not slow down the main CSR.

Develop a dynamic story line

Develop, discuss, and maintain a story line, ideally including a wide participation of influencers such as patient advocates and marketing. This should be done as early in the development program as possible. This will aid determination of the critical body of evidence supporting whether the trial meets goals or not.

The story line should be expressed in terms of what label is expected upon approval. A 'Label as driver' approach if executed well can define what an optimum label would be like and what label would be so unattractive that it might be the walk away point for the development program. This discussion should be a guide to what evidence is needed to demonstrate efficacy, safety, ease of intervention, etc.

There is frequent push back on this when there are no effective treatment options as some will say we do no know what an effective therapy would look like. This is really no barrier to developing the story line, particularly if the 'bookend' scenarios of best and worst case are considered.

Develop the list of critical variables.

A critical variables list should be developed. Not all data are equally important in a trial. The critical variables are those designated in the protocol and statistical analysis plan as supporting the primary and key secondary effectiveness, safety, and tolerability of the intervention.

Furthermore, these critical data should be tabulated and tracked. At any point in the study lifecycle, one should be aware of the enrolment, cleanliness of data (patient by visit), expected denominators in key analysis sets, and other key aspects such as the expected number of participants who have response or who have lost response when that is germane to the study design and goals of the study. This table is not for the study report. It should be maintained and shared with clinical colleagues so all are on board with expectations.

Reduce content to the essential

The principal of parsimony is a real aid to moving with agility. Do not collect unnecessary data. Debulk the Tables of Contents of reports. Focus the content on the evidence needed for the task at hand.

Review the content with a mind to reduce. Consider the Top Line Results. Data are for decisions. Twelve to 24 TFL's should be sufficient to determine if the study was successful or not and should be sufficient to drive decisions on the development course. Primary safety and primary (and possibly, key secondary) efficacy endpoints should suffice for reporting.

The same applies to the reporting on the integrated data pools.

Bear in mind that reducing the health authorities review burden allows them to focus on the key critical evidence and actually allows them to easily find the same.

Most Tables of Contents for a CSR can easily be reduced by 25 to 30% by asking basic questions such as:

Is this request intended for the purpose of the CSR or does it fulfill expected downstream

purposes such as providing responses to expected regulatory requests.

Does this request enhance the message to regulators?

Does this request impact the timelines/cause re-work?

Other approaches to simplicity and parsimony can add value. Accept standard data displays wherever possible. Approximately 70% of the tables can and should be standardized. This includes demographics, exposure, concomitant treatments, adverse experiences, safety labs, ECG, etc. All the additional attention and focus should be on efficacy and special safety analysis and reporting.

Don't care about formatting. If you are talking about formatting, then you are not thinking about the dynamic storyline of the critical data.

Refine the approach to dry runs

A dry run is a draft production of the datasets, metadata, and outputs. One purpose is to finalize the analysis datasets and TLFs programming and gain confidence that submission-ready statistical outputs are being generated.

Consider the following approach to dry runs for a particular study. At a point in the study where enough data has been accumulated that the TFLs can be meaningfully populated (approximately 50% of the study information) ensure that a clean cohort of data is available. This would include all completers and those who prematurely discontinue the study. If appropriate for the study design, responders and/or those with loss of response are also identified and all data fully cleaned. Given this clean cohort, one is confident in the data quality and these data are used to determine that the TFL generating programs are correct as per specifications. At a later point, where nearly all data are complete these validated programs are run off of the accumulated cleaned data to assess if there are additional unanticipated issues in the data complicating analyses.

Dry runs provide a key finger on the pulse of how the team is doing with respect to the story line. The mock data are not informing decisions. If there are many changes and additions at the dry run, then the team does not yet have a concept of the storyline, has not done their work, and are not prepared. This is a key diagnostic for problems to solve. However, the diagnosis is made too late for effective actions to treat this problem.

Dry run reviews are a frequent source of expansion in the numbers of TFLs to be produced.

Any new requests should be challenged in a cost/benefit sense balancing enhancements to needed demonstration of efficacy and safety versus impacting timelines by increasing the volume of work. Additionally, error resilience can be impacted by having to address late changes.

And remember to do everything in your power to avoid hard coding.

Create a process to handle unanticipated *ad hoc* requests, rapid responses, changes in plans.

I recall a breakthrough moment in discussions on debulking CSR TOCs. The lead biostatistician said "I do not need these for the CSR. I am confident I will need them for rapid responses, EMA pricing and reimbursement discussions, in publications, etc." When queried why these were included in the CSR TOC, the reply was that the CRO programming team was in place for the study duration including analysis and reporting and the lead biostatistician wanted all TFLs at this time before the team was redistributed.

The response was to clearly identify what is needed for the CSR, integrated summaries, health

authority specific deliverables, *ad hoc* requests to prepare for rapid responses, pricing and re-imbursement discussions, promotional materials, etc.

Then a billing structure was created to avoid impediments or delays to work. Agreement was gained with the CRO to proceed with the work up to a pre-specified limit of cost over-run (tranche system). When one tranche was near to completed, discussions were held about activating the next one.

Another approach is to build the Parking Lot of prioritized list deliverables for tasks so that the programming staff can immediately work on these when the CSR TFLs are completed or whenever they encounter free time.

Another alternative is to have a time and materials budget for ad hoc requests and rapid responses that is not necessarily linked to individual study budgets but rather supports at the submission level.

It is also prudent to have a standard formal email template to gain rapid approval of unanticipated work guaranteeing future payment for urgently needed rapid responses. This allows the work to continue while the administrative tasks around cost overages and out of scope costs are completed.

SUMMARY

These tips and traps can be deployed to any study and any submission. They will not guarantee rapid review, approval and launch but each has been proven as useful tools to facilitate these goals. There is much more that could be discussed, in particular, the impact of Senior Leadership style on the ability to move with agility or not.

CONTACT INFORMATION

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