

Orchestrating Clinical Sequels with a Strategic Wand - Challenges of introducing Rolling CSRs in a Master Protocol

Neharika Sharma, GlaxoSmithKline, Collegeville, PA, USA

ABSTRACT

The requirement of fast paced drug development is often leading to heightened intricacies in trial designs and an upsurge of multifaceted questions to be answered from the same study. This further induces pivotal questions like how to maximize the existing resources to intensify the overall compound strategy, how to be submission ready etc. We had a similar situation on a First Time in Human Trial, a master protocol with an adaptive design, for a gamechanger tried out in multiple cancer indications at different dosages. Introducing the concept of Rolling CSRs for the very first time, as the programming lead, I drove the locking down of the ready cohorts based on a frequent scrutiny of the ongoing subjects versus the targeted powered sample size, upgraded at regular intervals through futility analysis. In this paper, I would highlight the various challenges involved e.g. database soft lock/partial unblinding, driving cross functional agreement on the cohort selection and minimal outputs supporting the objective, automated tool to generate the reusable sections of CSR body etc. The strategic involvement of my role further expanded when a combination drug from another pharmaceutical company was introduced, demanding constant negotiations over decisions and safety reporting along with mitigating the unforeseen impacts of Covid-19 on the trial. I would also like to share the success story of striking a balance not only between supporting publications versus future readiness but also between the existing technology (SAS) versus new technology (R) especially when you have majority of the team (including FSPs) untrained on R.

INTRODUCTION

In the past, as drug development was still evolving, clinical trials dealt with basic study designs and had simple objectives to be obtained through lucid strategies. As clinical research is picking up pace, primarily to focus and deliver to the ever-changing landscape of unmet medical needs and expediting novel patenting, various downstream percolations are being witnessed. Let's talk about the impact on overall trial strategy and conduct. There is a heightened intricacy of the study designs with complex and advanced modelling to answer multifaceted and ambitious objectives under the framework of the same trial. This, in turn, is coupled with an aim of intensifying compound level strategies through maximizing the use/reuse of existing resources and meta-analyzing data through exploratory agendas. With the purpose of accelerating study pipelines, another trending organizational goal seen across the pharmaceutical industry is the need for speed to deliver results, and this is becoming a matter of essence much more than ever. This shift in paradigm directly impacts biostatistics and clinical programming with an increasing emphasis on shortening the analysis timelines, also keeping in mind the end goal of submission readiness all along.

The focus of this paper would be to share the experience of handling the transformative journey of a unique clinical trial, enlist the challenges faced by a project/study lead programmer that stem from the exposition set above, and highlight potential mitigation plans while dynamically endorsing recent paradigm shift and upsurging organizational objectives. Embracing the constant morphosis in the role of a data scientist, through this tale, I believe, I would also be able to bring in a perspective of the gaps one can bridge in the strategic schema of decision making and enhance cross-functional contribution in the grand picture of drug development with the power of data in hand.

THE TRIAL BACKGROUND

Having set the context, the need for complex study designs is not new to Oncology therapeutic area. But it is interesting to study how the traditional designs of 3+3 or Continual Reassessment Method (CRM) are advancing to designs like master protocol. The FDA defines a master protocol as "a protocol designed with multiple sub-studies which may have different objectives and involves coordinated efforts to evaluate

one or more investigational drugs in one or more disease subtypes within the overall trial structure.” Based on the combinations, this could be Platform, Basket or Umbrella. The trial under discussion is a First Time in Human (FTiH) trial following the design of a master protocol that is too complex to be put under either of the sub-categories. This trial had <800 patients recruited in 38 cohorts involving a GSK game-changing drug in multiple cancer indications like Head and neck squamous cell carcinoma (HNSCC), Cervical cancer, Non-Small-Cell Lung Cancer (NSCLC), Bladder etc.; at different dose levels; and with varying combinations of drugs. It is also of utmost importance to understand that not all the cohorts were randomized, and some of the cohorts involving combination drugs were blinded. The impact of this contrasting setup is explained in detail later in the paper. The Overall study design was a blend of parallel group and cross-over and was conducted in two parts: Monotherapy and Combination, both having dose escalation and dose expansion phases. As the trial followed adaptive study design, the recruitment of the various cohorts was updated on regular basis through futility analysis. Staying within the scope of this paper and not deep diving into futility analysis, it might suffice to state that within each cohort, the powered sample size was upgraded based on regular assessment of unconfirmed Objective Response Rate (ORR is defined as the proportion of patients with a complete response or partial response to treatment according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)).

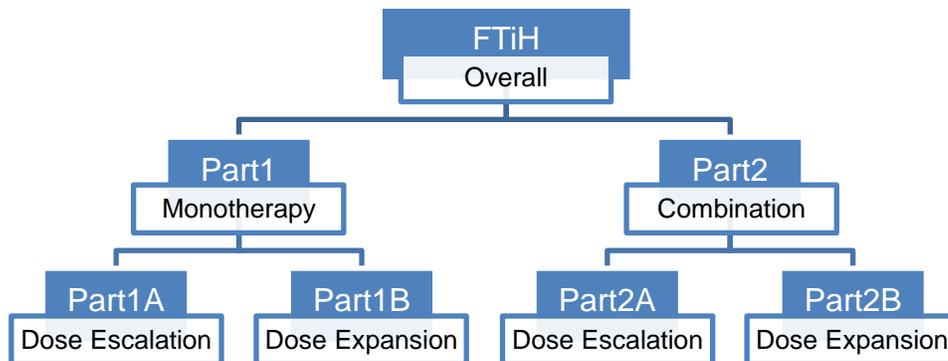


Figure 1. Study Design Schema

Need not say that trials with such a high level of complexity added to the study designs to answer some pivotal and challenging objectives are not always easy to work on. And when we refer to the role of the study lead programmer for such master protocols, it is almost a transition to a compound programmer as these sub-studies could be as demanding as individual trials, and the primary interest remains to keep these studies consistent.

To categorize these challenges and the strategic opportunities faced while working on this FTiH trial, the rest of the paper will cover the details in following buckets:

- Introduction to the concept of Rolling CSRs
- Conduct inspired by Agile Methodology
- Implementation of R in a mixed in-house/out-sourced setup
- Reduction in number of Outputs and static listings
- Overall impact of Covid-19
- Combination Drug with another Pharmaceutical company

INTRODUCTION TO THE CONCEPT OF ROLLING CSRS

As we discussed the study design in previous sections, this master protocol was conducted in 38 cohorts. Within these cohorts, the recruitment was paced differently based on the incidence rate of specific indication (e.g., the recruitment in HNSCC or NSCLC cohorts were faster than certain biomarker cohorts), availability of dose of combination drugs, and also the fact that certain sites recruited actively than others due to covid-19 restrictions explained later in this paper. Also, based on the efficacy of the drug seen in certain groups, Objective Response Rate varied between the cohorts showing different proportions of complete and partial responders based on RECIST 1.1. Consequently, some cohorts were ready to be closed faster than others, where the sample size was increased due to futility analysis.

While the team was anticipating the maturity of data for specific cohorts earlier than others, not only there was an interest to study results sooner than later, there was also a joint focus of being submission-ready from various functions in Clinical Trial Team (CTT). Soon after realizing the already huge overall size of the database, the risk of facing challenges at the later stage, from cleaning to reporting were undeniable. In no time, the team agreed to approach this in a staggered manner, and hence the concept of Rolling CSRs was introduced. As per this concept, the team decided to look at matured cohorts in cycles and report accordingly. The CSR was conceptualized as a book prefaced with standard sections talking about the overall trial strategy, and the locked cohorts in each cycle were treated as chapters.

USING VISUALIZATION TOOLS TO SELECT COHORTS

Various tools and techniques were used to support the decision of selecting ready cohorts for locking in each cycle.

1. **Microsoft Excel/CSV:** has always been the most common tool to monitor progress mainly due to its easy interpretability and exchange of information. For regular communication on data progress and maturity of the cohorts, an excel/csv template was generated using SAS. It was shared on a monthly basis reflecting details of scrutiny of the ongoing subjects against the targeted sample size.

The figure consists of three screenshots of an Excel spreadsheet used for tracking clinical trial cohorts and subjects.

Screenshot 1: Cohort Summary

	A	C	D	E	F	G	H
	Study cohort code	Number of Subjects	Number of Subjects Crossed Over?	Number of Subjects Died	Number of Subjects Discontinued IP	Number of Subjects Discontinued/ Completed Study	Number of Subjects Ongoing
1	x1	18	0	9	15	11	3
2	x2	23	0	16	23	19	0
3	x3	33	0	26	33	29	0
4	x4	64	0	42	57	45	7

Screenshot 2: Site Level Summary

	A	B	D	E	F	G	H	I
	Centre ID	Study cohort code	Number of Subjects	Number of Subjects Crossed Over	Number of Subjects Died	Number of Subjects Discontinued IP	Number of Subjects Discontinued/ Completed Study	Number of Subjects Ongoing
1	xxx	Overall	58	0	42	53	42	5
2	xxx	x1	26	0	18	24	18	2
3	xxx	x2	12	0	7	10	7	2

Screenshot 3: Subject Level Data

	A	C	E	F	H	I	J	K	L	M	N	O	P	Q	R	S	T
	Study cohort code	Centre ID	Subj ID	Primary tumor type	Subject Crossed Over?	Subject Died?	Did the Subject Discontinue IP?	Did the Subj Discontinued/ Completed Study?	Is the Subject Ongoing	Subj's Last visit date	Subj's Last First dose date	Subj's Last dose date	Cross over start date	Date of death	Date of Discontinuation	Date of disposition	
1	xxx	x1		Colon/Rectum	Y	Y	Y			WEEK 61	#####	#####		#####	#####	#####	
2	xxx	x2		Non-Small Cell Lung	Y	Y	Y			WEEK 19	#####	#####		#####	#####	#####	
3	xxx	x3		Bladder	Y	Y	Y			SURVIVAL	#####	#####		#####	#####	#####	

Figure 2. Screenshots of the tracker

The intended audience for this tracker was the entire CTT. The Clinical Scientist usually used the first tab to get an overall picture of the cohorts with no ongoing subjects. The Data Management team used this tracker to track center wise data progress for targeted database cleaning. Another key recipient was the team of site monitors, investigators and country contacts who used this information for the ongoing follow-up with the sites. This did help other functions like Study Delivery Leads, Safety team and biomarkers team for their due diligence.

- SPOTFIRE:** Another essential tool that comes in handy for data monitoring is Tibco Spotfire. This had been used abundantly for the mentioned study for regular monitoring of data cleaning of targeted cohorts, safety profiling and quality assurance. There were specific templates created to handle data exclusive to this study, taking care of the overall by cohort setup. The same tool was also used on a less regular basis for across compound combined safety monitoring.



Figure 3. Screenshots of the SPOTFIRE for data readiness by open query count

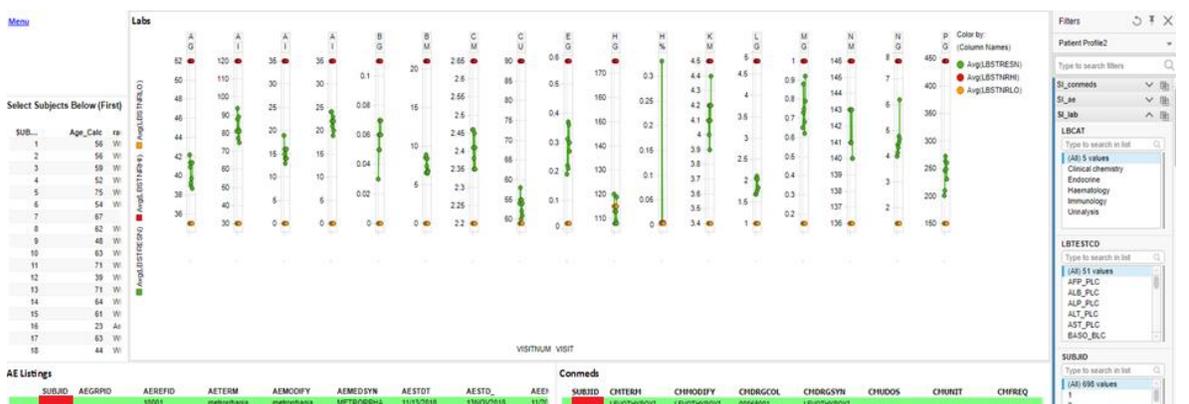


Figure 4. Screenshots of the SPOTFIRE for Safety profiling

- COCKPIT:** This is a new tool for the purpose of data visualization intended for safety and risk monitoring and data cleaning activities. This has an added advantage of reading raw data and allowing real time status check.

CHALLENGES/STRATEGIES IN TERMS OF IMPLEMENTATION

The journey from conceptualization to fruition is often a very demanding phase for any novel idea. Though the CTT was prepared for the challenges that might come along while implementing the concept of Rolling CSRs, it called for the greatest level of cross-functional collaboration. This is where clinical programming, with the access to data and the capacity to visualize/ manipulate the same effectively and promptly, provided an invaluable impetus to the entire team in coordinating various activities.

Following are the key highlights of the experience during the implementation phase:

1. **Handling Database:** Here lies the biggest challenge and difference of having a master protocol compared to individual studies - with multiple studies, unlike master protocol, because the databases are separate, we have the flexibility to release/freeze the data as per our schedule. With these 38 cohorts, the data was collected in a single database, which restricted us from having the standard hard lock process for Database Release (DBR) / Database Freeze (DBF). This situation was dealt with by introducing a soft lock in every cycle by signing off CRF pages by sites pertaining to only selected cohorts. Although this did take care of freezing only the data of interest, the implication was that between the sign off to release dates, the live database wasn't available for any data cleaning or extraction activities at the site as well as at the data management end. With the added complexity of only specific cohorts being blinded, the unblinding was also performed in cycles releasing a subsetted container list with every round. For the ease of the process and to cater to different schedules of CRF and vendor data, there were two different DBRs for each while SDTM release date remained common.
2. **Standardization of the process:** In order to streamline the series of activities that follow data release, it was of the essence to establish a process with the first round of Rolling CSR, which could seamlessly be adopted for the subsequent cycles. A frequent question asked in this direction is at what level did we subset the data to cohorts of interest (SDTMs/ADaMs/TLFs). The approach we followed here was that we did not limit SDTMs and ADaMs, and the reason is to get ready for submission (to be explained in the next point) and having more robust programs to be able to cater for any future cohorts following suit. Cutting the data at the display level, gave us an advantage of doing initial checks on the next set of cohorts (for the next cycle) and raising any potential data issues or algorithm issues much in advance.
3. **Being Submission Ready:** The most critical aspect of working on a promising drug is submission readiness. There is always a keen interest in quicker turnaround time while filling priority studies to regulatory authorities. We took care of some critical submission bits alongside CSR writing and publications. With each cycle, as we had SDTMs and ADaMs with all available data, Pinnacle21 was run each time to ensure CDISC compliance and any potentially accepted fallouts were maintained in Reviewers Guides (SDRG and ADRG). The labels and derivations across datasets and variables were checked for consistency to be CRT package ready. Potential efforts were made toward Real Time Oncology Review (RTOR) planning and implementation.
4. **Medical Writing Tool based on Visual Basic:** To save the time and effort for each CSR chapter from every round of Rolling CSRs, a Tool was developed from a joint effort between Medical Writing and Clinical Programming using Visual Basic. This tool took a mapping document (list of matching table numbers to their Rich Text Format (RTFs)) as input and populated some common and consistent sections from each round of CSR outputs. Though a thorough validation was done for the CSR document, this helped the team fast track the CSR generation soon after the outputs were made available. The generation of narratives was also automated.

All these situations provided excellent opportunities to drive some core clinical trial activities and be at the heart of the process. And this can be considered a perfect illustration of the increasing engagement of a clinical programmer in drug development. FTiH being the first study to implement this model, guidance was provided to the inspired studies across the organization.

CONDUCT INSPIRED BY AGILE METHODOLOGY

Originally Agile methodology was designed for product-based projects. Of late, with the increasing popularity of tenets of Agile, it is fascinating to witness the versatile dimensions of its application. Having a commonality with Rolling CSRs in terms of iterative cycles and the requirement to deliver at a fast pace, it encouraged enough to experiment in this direction. Although not 100% identical to Agile Methodology yet inspired by it, the following strategies were executed during the planning and conduct of the study.

- **Iterative Cycles:** The first cycle of Rolling CSR gave us an opportunity to think out of the box, implement and experiment and set up a process through learnings. As these cycles were fast and at some point in time, more than one cycle was running, we could define the flow of the events and the common triggers for each step. Each cycle was planned in such a way that we could target to deliver the maximum given the capacity of the team. This means that when deciding the number of cohorts to be included in each cycle, a striking balance was maintained between the cohorts that could be cleaned by the sites and the data management team in the target timeframe and the reports that Statistics and Programming (S&P) could handle at a time.
- **Early feedback:** Before each cycle starts, once the cohorts are selected, instead of generating the whole set of reports, we used to generate an optimum set for review and agreement. This set was decided during the first cycle and included a table, a listing and a graph for each category (Study population, safety, efficacy and PK). This was reviewed and agreed on the basic structure in terms of expectation from the Clinical team and usability for the medical writing team. This early feedback proved to be very effective in matching the clinical expectations and avoiding any surprises for medical writing team later once the outputs were delivered.
- **Planning the Sprints:** With the set process of delivering the minimum outputs first, the next sprints were divided by complexity and timing of the data availability. Batches were committed to be delivered as study population plus safety (usually the priority for this FTiH trial) going first and then efficacy set (being more complicated and requiring more time to program and validate). The last one was PK and Patient Report Outcome (PRO) because often this data being vendor-provided, used to get ready later than CRF data due to time taken in resolution of the queries.

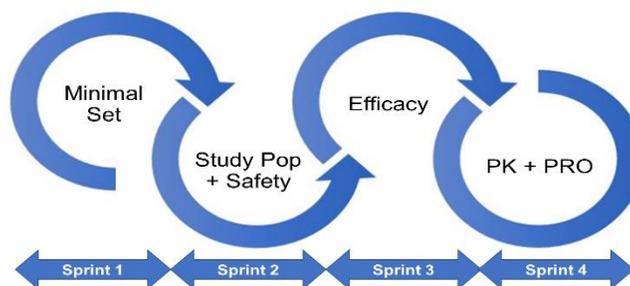


Figure 5. Flow of Sprints

- **Scrum and Focused Meetings:** The team used to meet weekly where common decisions and status were shared. This was the platform to discuss any potential issues and hurdles across the board. To keep these meetings crisp and to the point, separate focus meetings with limited participants were arranged where specific issues that might have digressed the scrum meeting were discussed. Usually, PK and PRO data had different complications and very specific questions, so these were discussed in focused meetings with just the relevant programmers working on it.
- **After Action Review:** Once a cycle is over, the team met to retrospect using a whiteboard exercise, jotting down what went well and learnings from each cycle. These were improved in the next cycle.

BALANCING BETWEEN PUBLICATIONS AND ROLLING CSRS

As with any oncology trial, there is an equal interest in publications at the various oncology conferences like American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), Japanese Society of Medical Oncology (JSMO) along with other required and regular reportings like Investigator's Brochure (IB) and Development Safety Update Report (DSUR). Usually, the challenge with such reporting is that the time required to convert them into CDISC compliant datasets is not always there; hence these reportings continued to be in the GSK native format of data collection. It was definitely a challenging task to share programmers between the two reporting verticals (publications and CSRs) and ensure no overlap between the two timelines. This not only required aggressive planning but also adhering to the plan. Some of the learnings from Agile came in handy in achieving this successfully.

IMPLEMENTATION OF R IN A MIXED IN-HOUSE/OUT-SOURCED SETUP

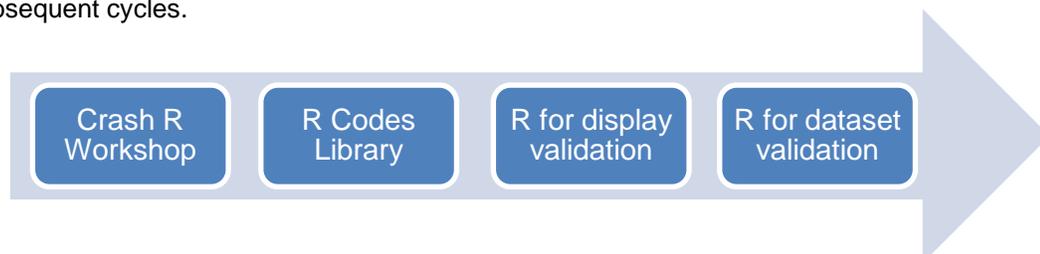
As the industry-wide interest in using open-source languages is increasing, many organizations are investing in growing the usage of R in clinical programming by training the existing staff and hiring R trained programmers. With this trend, it felt appropriate to scope out the challenges as a study lead programmer towards implementing R in this paper and share success stories that might encourage other leads across the industry towards attempting to increase the R usage. During the early days, GSK as an organization initiated this effort by first promoting the use of R for validation while the uncertainties in the regulatory acceptance were still explored. As a study lead, the following major challenges were faced, and the strategies implemented are enlisted:

Challenges:

- The FTiH team was huge, and the majority of the team was untrained in R. While there was ample trainings available for self-study for permanent staff, there were still challenges like taking out time from ongoing study activities.
- Another layer of complexity was added with the fact that more than half of the team consisting of consultants or Functional Service Providers (FSPs) were not directly trained by the organization.
- As study leads, we often ponder where to draw the line between implementing this risk-free approach and experimenting the trends.

Strategies:

- **Crash hands-on workshop during team meetings:** Beyond the available material for R training, separate hands-on virtual workshops were arranged. A team of three trained R users were invited to a few well-spread meetings. The scope of these workshops was not to teach the basics of R but the implementation of the concepts. In the first session as a team, we validated a simple frequency table using R. Offline one-on-one support was provided in case of errors or queries. The second session involved validation of a summary statistics table in a similar kind of setup. These two sessions brought in a comfort level to the programmers to try the language.
- **Reusing R codes from libraries and other studies:** Another jump-start in the implementation of R was reusability. A local repository was created by storing R codes from other studies and libraries to refer to for the programmers.
- **Setting the benchmark for each cycle:** Rolling CSR as a concept gave an opportunity to set a benchmark of the percentage of outputs to be validated in R and keep increasing with each cycle. For the first cycle, 20% of the reports were validated in R, and the number kept growing in the subsequent cycles.



REDUCTION IN NUMBER OF OUTPUTS AND STATIC LISTINGS

As discussed in the introduction, with the intention of expediting study channels, the Biostatistics and Clinical programming teams are focusing on shortening the analysis timelines. In this context, an objective gaining limelight across the industry is decreasing the time between Database Freeze (DBF) to Statistical Analysis Complete (SAC). In order to facilitate this, the first and most evident step is to optimize the number of outputs alluding to the study objectives.

A similar approach was taken in FTiH to cater to the need for delivering the results fast. This required a high level of coordination between the different groups and yet again presented clinical programming with an opportunity to facilitate a cross-functional agreement. An initial list/table of content (TOC) was proposed as a collaborative effort of statistics and programming. This list was presented to all the relevant functions like the Clinical Scientific team, Safety representatives, medical writing, Biomarker and Pharmacokinetics teams to gain their agreement and ensure the requirements were met. After each cycle, the list was again scrutinised against the outputs used in the CSR, and the requirements were recalibrated. This elaborate and arduous exercise resulted in reducing the number of outputs from >450 in the first cycle of CSR to <250 in the second round and limited to around 100 per set from thereon. This not only saved time in generation/validation but also for all the subsequent steps of reviewing and embedding into CSRs and thereby fast-tracked the entire reporting.

As there is a minor contribution of the static listings generated (which in most cases is a data dump), there is a separate organization-level effort initiated focusing on reducing the number of static listings to be produced after using an in-house data visualization tool. A list is prepared after consulting the requirements from major regulatory bodies like Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA), China regulatory or FDA's Bioresearch Monitoring (BIMO) program requirements, which will soon be implemented across GSK.

OVERALL IMPACT OF COVID-19

With the unforeseen hit of the pandemic, along with the other significant impacts of Covid-19, our industry has also witnessed its share of consequences.

To outline some of the direct impacts seen on the trial:

- Slow recruitment and enrolment of the subjects resulting in delaying some cohorts.
- The database experienced massive data entry and query backlogs due to the inability of site monitoring from travel bans, and investigators struggled to keep the data up to date.
- The missed visits and assessments also impacted the key analysis. This not only warranted algorithm adjustments to take care of these anomalies but also changed a few results, e.g. confirmation of responses.
- Due to delays in dose availability and sample shipment, we lost some samples and drugs due to expiry.
- It was challenging to implement any new protocol amendments and the new eCRFs to collect Covid-19 related data.
- Speaking about analysis of Covid-19, during the cycles when the guidelines of this data weren't available, it became extremely challenging to generate datasets and templates for analysis effectively.

As a team, we maintained a risk register to capture these risks in time and discuss the potential impact and mitigation plans. This setup and related meetings helped to keep the team aware of the ongoing situations and take decisions on the go. In terms of analysis, based on the first-hand experience of this trial, we effectively contributed to the industry collaborated Covid-19 guidelines documents.

COMBINATION DRUG WITH ANOTHER PHARMACEUTICAL COMPANY

As a constant endeavor to cater to the unmet medical needs and increase the accessibility of highly efficacious drugs, a praiseworthy patient-focused effort is witnessed through combinational drugs. Such an attempt from GSK, along with a big pharmaceutical company, was demonstrated through this trial. As mentioned earlier in the combination part of the study, in some of the cohorts, subjects were exposed to a combination of GSK and an already marketed drug. Due to the physiology of action of this drug, the trial was designed to test efficacy in monotherapy setup versus the catalytical effect produced in combination. Though it is a highly advanced and progressive step in the clinical industry, this also warrants some actions to maintain transparency in the collaboration and ensure the utmost ethical practices.

To stay within the scope of this paper and highlight the actions and opportunities experienced as a study lead programmer in this direction:

- A monthly safety report was shared with the other pharmaceutical representatives based on the patients exposed to combination drugs for their safety monitoring.
- With the introduction of new cohorts, the objectives and endpoints were discussed up front. Though different companies can analyze and report data differently, frequent discussions ensured that the standards were maintained.

CONCLUSION

Today's fast-paced drug development process and dynamic clinical industry demands constant upsurging technology, redefining our ways of working and zenith of cross-functional synergy. To embrace this transformation in its true sense, adaptability to the change and innovative mindset are some of the tools that would help one transcend the boundaries of the defined roles. In the horizon of a study lead programmer, with the power of data in hand, one can bridge the gap between the needed ends and the means to the ends and thereby enhance the scientific contribution to the overall strategic schema of trial.

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CONTACT INFORMATION

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

Neharika Sharma
GlaxoSmithKline
1250 S. Collegeville Road,
Collegeville, Pennsylvania, US, 19426-0989
Email: neharika.x.sharma@gsk.com; neharikaa.sharma@gmail.com

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