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# A Precision-strike Approach to Submission Readiness: How to Prepare Your Filing Teams for Consistent Excellence

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## ABSTRACT

Getting an electronic submission through the door at FDA used to be a Fantastic Journey of Discovery for individual programming and biostatistics teams within our company. We faced the following challenges:

- Lack of a consistent process for handling electronic filing deliverables across products
- Varying levels of filing experience between teams, causing painful re-learning for each filing
- Beneficial best practices and lessons are kept within each filing team, not shared with others
- Variable understanding and engagement by other functions of programming-related filing deliverables

To address these issues, we established a small Submission Consultancy Group (SCG) consisting of 2-3 experienced filing lead programmers. The remit of SCG is to:

- Define standards around submission deliverable preparation to be referenced by all filing teams
- Proactively advise filing teams on planning and assembling all statistical programming filing deliverables, and review status and content of these deliverables to help optimize package reviewability at FDA
- Work with data standards groups to prospectively plan standards adoption for each filing
- Continually take best practices and lessons from each filing team and share those with other teams
- Communicate in a higher-level capacity with other functions such as Clinical and Regulatory to clarify stat-programming roles and contributions in filings to promote cross-functional understanding

Importantly, SCG only advises; decision-making itself remains squarely within each filing team. Our approach has proven to be highly successful over the years. Here, we will share what worked well and what did not!

## INTRODUCTION

Preparing the programming strategy and, where applicable, electronic data package in support of a marketing application to any regulatory body, especially for the initial filing on a compound that will be new to market, is often a multi-year endurance race. The U.S. Food and Drug Administration (FDA) encourages sponsors to start thinking of their submission data standards strategy as early as the Investigational New Drug (IND) application stage and is prolific in its guidance with regard to detailed preferred and expected data-related standards and bilateral communications along the way. Other agencies such as Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and China's FDA (CFDA) are gradually beginning to extend similar guidance, which often varies from FDA's in its nuances.

In addition to heeding this plethora of detailed regulatory guidance, sponsors also face the daunting task of implementing data standards based on implementation guides from external organizations like the Clinical Data Interchange Standards Consortium (CDISC), which provides detailed specifications for modeling submission data in the Study Data Tabulation Model (SDTM) and the Analysis Data Model (ADaM), among others. Sponsors can sense-check how closely their implementation follows basic modeling rules for such standards by using tools like Pinnacle 21 Community for SDTM, ADaM, and related Controlled Terminologies. Similarly, CDISC and other organizations have put out templates and guidelines for metadata to accompany standardized submission datasets such as define.xml files and Reviewer's Guides, along with suggested templates for regulatory communication vehicles such as the Study Data Standardization Plan (SDSP). As the whipped cream atop this deliciously convoluted data submission preparation cake, these documents and tools will change up to several times each year with minor point releases, major new versions, or even complete replacements of what went before.

Putting all of the above together into a coherent, compliant, yet still meaningful and reviewable submission package is a mighty fine accomplishment in and of itself. Toss into the mix how it often takes at least several years to collect and analyze all trial data going into a single submission while frantically keeping track of all these moving parts - adjusting strategies on the fly when requirements and insights change - and you end up with a wavy-windy Odyssey that would bring even ancient Homer himself to the edge of giving up.

Many organizations rely on their individual product teams to figure out the best way to fulfill this Odyssey and successfully deliver a quality electronic filing package in the end. This approach brings several challenges:

- Lack of a consistent process for handling electronic filing deliverables across products
- Varying levels of filing experience between teams, causing painful re-learning for each filing
- Beneficial best practices and lessons are kept within each filing team, not shared with other teams
- Variable understanding and engagement by other functions of programming-related filing deliverables

To counter these many challenges, we established a small, nimble Submission Consultancy Group (SCG) with a primary focus on statistical programming, which proactively gives direct, one-on-one assistance to filing teams. Let's talk a bit more in depth about what this group looks like and how it works its magic!

## ENTER THE SUBMISSION CONSULTANCY GROUP

### WHAT DOES SCG LOOK LIKE?

The number of staff rostered into a submission consultancy group will be tailored to the size of your department, the number of filings your company intends to conduct in the future, and the extent to which existing documentation and data standards are in place to help your teams get ready for submissions.

In our case, SCG consists of 4 current and former compound lead programmers with significant hands-on filing experience, along with a seasoned member from our cross-functional ADaM Consultancy Group. As needed, we can also reach out to pre-identified SMEs in other departments such as Biostatistics or Regulatory Affairs.

SCG participation is not a full-time job! All members are active product or project leads outside of SCG and contribute only between 5 and 15% of their time each month to SCG activities and meetings.

### TELL ME MORE - WHAT EXACTLY DOES THIS SMALL GROUP DO?

SCG is chartered for the following, described in further detail in smaller sections below:

- Define standards for submission preparation to be referenced by all filing teams
- Proactively work one-on-one with individual filing teams
- Work with data standards groups to plan standards adoption for each filing
- Proactively share best practices and lessons from each filing team with all other teams
- Promote understanding of and engagement in programming submission planning

## Define standards for submission preparation to be referenced by all filing teams

To ensure high-quality, easy-to-review programming deliverables by every filing team that are fully aligned with current regulatory requirements as well as anticipated future standards support start and end dates listed in, for example, the FDA Data Standards Catalog, SCG defines and maintains standard processes, templates, and tracking tools for preparing, producing, and delivering statistical programming deliverables for regulatory filings.

## Proactively work with individual filing teams by providing consultancy and review

For product teams with limited biostatistical and programming filing experience, which may include those working towards a first-time marketing application on a new product or those headed by a new product lead programmer, SCG provides ongoing consultancy on submission planning and preparation. To help minimize the risk of submitting a non-compliant filing or one that is hard to review by the agency. SCG also reviews general progress against best-practice timelines and standards accumulated from prior filings across all products. SCG further performs spot check data sets and metadata in mock and real submissions prior to hand-off, at least on the pivotal trials within a filing.

SCG will also, where feasible, review programming-specific content in briefing books and meeting minutes for pre and post-filing sponsor meetings with FDA and others, to sense-check appropriateness, completeness, and applicability to other filing teams or process updates.

## Work with data standards groups to prospectively plan standards adoption for each filing

SCG provides advice into the company's data standards groups on developing and maintaining company-tuned templates such as those for SDSPs and reviewer's guides, as well as promoting standard utility development for assisting filing package preparation such as a define.xml generator.

## Proactively share best practices and lessons from each filing team with all other teams

Without intervention from an entity like SCG, beneficial filing best practices and experiences remain siloed within each filing team and are not usually shared with others. To promote these best practices and to prevent familiar challenges from re-occurring in the next team gearing up for submission, SCG proactively takes lessons learned from individual filing teams and translates those into updates to straightforward guidance documents, internal web portals, and filing checklists, along with e-mail blasts and intranet news postings for teams barreling towards a filing.

## Promote understanding of and engagement in programming-related submission planning

Where needed, SCG communicates with higher-level management in other functions such as Clinical and Regulatory Affairs to clarify and emphasize programming roles and contributions for filings in general.

This ensures programming as a function is engaged in planning and preparation for the filing. SCG members also often represent Statistical Programming in cross-functional efficiency initiatives that focus on optimizing the quality and timeliness of submission preparation, delivery, and review.

### Communicate with FDA about general Agency submission needs and preferences

SCG will proactively communicate about general data package-related questions with FDA's CDER eData group via their e-mail inbox and share resulting insights with all filing teams per the processes described above. A recent example includes clarifying FDA's preference on how to present Analysis Results Metadata in any electronic filing package. It's important to note that SCG will not seek FDA advice about filing-specific reviewer content such as study endpoints or detailed integration plans; those types of questions will instead be raised and addressed directly between product teams and their respective review divisions.

## CALL ME, MAYBE? HOW SCG WORKS WITH INDIVIDUAL FILING TEAMS


Rather than conducting periodic large-group meetings with all statistical and programming filing leads in the same gathering, SCG instead will meet periodically and individually with the lead statistician and programmer on each filing team. In these meetings, SCG provides targeted advice based on our own insights gained along the way or based on best practices and lessons learned from other filing teams, conferences, or regulatory interactions. The next section in this paper provides a bit more detail on how we structure such meetings.

While SCG owns and governs content and revisions of all filing-related functional general guidelines and best practice documents, a key foundation of our operations is that SCG **does not make decisions on any aspect of individual filings**. Instead, our input is considered advice and will always include a risk assessment in terms of how the filing might be impacted if the product team decides to go another route with the issue at hand. This advice and risk assessment enables the filing team to make a well-informed decision based on their much deeper understanding of the product, analyses, resources available, and filing strategy. In rare cases where a filing team chooses to act counter to SCG advice, SCG accepts that the filing team made their decision based on careful assessment of all information available to them, and SCG will not challenge or question it.

It's fair to say that writing this conscious SCG design decision into our charter right from the start played a huge role in SCG's success. Too often, centralized bodies like ours and many others may be chartered to have decision rights about what product teams should and should not do. The assumption there is that the central entity knows best and product teams are merely advisors into the decision process. While this certainly has its benefits, we've also seen a juicy pile of disadvantages of entities operating in that way:

- they become bottlenecks where decisions are made too late if members also have a "day job"
- they sweat the small stuff, such as endless discussions about small and rather irrelevant details
- they may require many forms, detailed meeting minutes, and other more formal artifacts of internal and external communications and decision-making which take away from focusing on simply getting the "real work" done
- their decisions may be made with an eye towards consistency across products, even when that is not necessary to guarantee a successful submission and review – or even runs counter to that!
- they may be perceived by individual teams as an inefficient entity to be avoided rather than engaged
- as an outflow of the above, individual filing teams may resist such central decisions on their filing, or engage in numerous iterations and arguments to clarify with the entity or overturn its decision

In our model, we turned that frown upside down by de-centralizing the decision making. SCG is an advisor into each individual product team's filing decisions by providing insights that allow these teams to strategize for, develop, and deliver on their myriad deliverables and responsibilities with minimal or absent rework, errors, and delays.

The responsibilities of product filing teams remain the same with and without SCG, in that they retain the ultimate accountability for all timelines, quality, completeness, compliance, and reviewability of all aspects of their filing packages. This setup…

- successfully avoided all pitfalls of centralized decision making
- kept SCG operations lean and nimble with minimal internal overhead
- enabled extremely rapid decision making tailored to each filing team
- avoided red tape and any kind of an "us vs. them" mentality between filing teams and SCG, making filing teams interested in reaching out to us due to a pleasant, informal interaction that gives them exactly what they need!

## WHAT DO SCG MEETINGS WITH FILING TEAMS LOOK LIKE?

### Our initial approach was okay in concept, but not so much in reality

At first, SCG conducted a few large-group meetings with all active biostatistical and programming filing team leads together at the same time. This was less effective as it was tough to give specific filing advice to leads this way:

- Discussing details around 1 filing team was mostly a waste of time for the other filing leads
- Leads were hesitant to ask questions as they worried other leads would not have time for theirs
- Leads for which the current discussion was less relevant would multi-task or zone out
- Educating filings leads on a topic was of less interest to some, depending on that team's filing stage

### Formula for Success: Our Makeover

We therefore quickly moved away from this type of setup in favor of precision-strike 1-1 meetings with individual filing teams, which dedicates the entire meeting time to topics fully relevant to that one team and yields an immensely more productive and outspoken discussion with these teams. As the typical meeting frequency is once or twice every two months, it also still does not add much burden on SCG members – a win-win for all!

Once a product team begins planning for a filing, SCG will proactively schedule an introductory meeting with the product lead programmer and statistician on the compound. Using a new copy of our standard SCG questionnaire and tracker specifically for this filing team, in this meeting SCG will:

- obtain basic information on the filing such as indication, timeline, and studies involved
- canvass the data standards and metadata versions planned by the team for each ongoing or future study in support of the ultimate filing
- give the product leads an opportunity for questions
- settle on a meeting frequency and schedule moving forward

Subsequent 1-1 meetings between SCG and this filing team will usually occur once or twice every few months for an hour to an hour and a half each, depending on preference from the product team, and are owned and operated by the product lead programmer rather than by SCG. About a week prior to such a meeting, SCG will remind the product lead programmer to update the filing questionnaire and tracker with any updates or changes since last meeting, and to come to the meeting prepared with any specific questions they may have for SCG.

In the meeting itself, SCG and the filing leads will jointly review any indicated updates in filing strategy and data standards versioning as well as progress on open action items from the last meeting; here, SCG will also share or remind the team of pertinent new lessons learned from other teams or revised regulatory guidance. In the second half of the meeting, the filing team leads will ask SCG advice on their filing-specific questions.

The product lead programmer or designee will update the tracker "live" during the meeting, and send a meeting recap and action items to all involved after the meeting. This paves the way for the next meeting a few weeks or months later, and the cycle repeats.

## A GLIMPSE INTO THE FUTURE OF SCG

Building on the success story SCG has been to date, we recently began expanding the SCG remit. For one, we're gradually becoming stronger about ensuring that product teams are engaged with SCG along their submission preparations. As an example, while the initial meeting between a new filing team and SCG was optional, we recently made it required for all teams to have at least one initial meeting with SCG.


In addition, SCG advisory responsibilities are in the process of being expanded beyond immediate filing consultancy to also proactively guide and advise product lead programmers on long-term submission data standards version planning even for early-stage products that don't have a concrete submission planned for many years to come. This not only contributes SCG knowledge about future data standard version requirements expected to be set by regulators, but also significantly reduces the needless standards upversioning and all associated inefficiencies that often took place even between studies on the same compound. Here, too, the decision-making remains with the product lead programmer with SCG functioning only as an advisory body.

In spite of these additional responsibilities, SCG's informal lean design with decentralized decision making allows the group to remain at its current small size with only part-time contributions from across our function.

## CONCLUSION

Our implementation of the Submission Consultancy Group has provided many filing teams over the past several years with written guidance and tailored advice on smooth filing preparation, delivery, and review. We firmly believe that a team as small as SCG was able to pack such a punch based on two key guiding principles:

- we are advisors only; product teams make their own decisions, leveraging our advice as needed
- we conduct only direct, one-on-one meetings with each individual filing team to *really* focus on them

Based on the positive results delivered by our efforts, several other crossfunctional centers of expertise are similarly beginning to design or re-charter their own operations along similar lines, a further testimony to the benefits of keeping efforts like these simple, lean, formal, and de-centralized!

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## CONTACT INFORMATION

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

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