› INSIGHT BRIEF

VERISTAT

Successful Preparation Strategies for NDA/MAA Marketing Applications

No two new drug applications (NDAs) or marketing authorization applications (MAAs) are the same. With each submission come special constraints, unique partnership dynamics, and a complex web of challenges due to timing of data analysis, medical writing, project management, and interaction with regulatory agencies. By utilizing key strategies, you can propel even the most complex submissions to successful regulatory conclusions.

In this brief, learn how to…

- **Manage common operational complexities**
- **Overcome data analysis challenges**
- **Optimize the medical writing process**

Optimize Your Approaches for Preparing a Marketing Application

Operational Complexities of Submissions

While all marketing applications are unique, there is no doubt they share common threads. Understanding each individual project's complexities in advance can help teams create effective approaches for planning, mid-stream adaptation, and final submission.

Solid strategies for virtually all submission projects include:

1	**Establish the baseline fundamentals** There are certain essential details that need to be in place regardless of project size, timing, or complexity.
2	**Create the submission timeline** The timeline serves as the project roadmap for teams and is the most critical working document.
3	**Be flexible when the timeline shifts** It's not a matter of *whether* a timeline will change, but how to adapt when it does.

Establish the Baseline Fundamentals Early

There are core concepts that need to be addressed prior to any submission's project launch. These involve building an organized and effective team and optimizing communication. When these key fundamentals are in place, the rest of the submission process can proceed more smoothly.

Build a truly integrated team

Regardless of the number of vendors involved in a submission, it is critical to have a fully integrated team. All members need to be seen as partners. By keeping everyone informed and involved in decision-making as early in the process as possible, the team can function cohesively and collaboratively. Successful integration can prevent common missteps related to unintentional silos and miscommunication, which often end up being costly distractions in terms of time and budget.

Overcommunicate

Rather than assuming certain members of the team do not need to be involved or informed, err on the side of overcommunication. This is an approach that is especially important in submissions projects, and includes a few basic strategies:

- Establish a fail-proof way to include the entire team, such as email distribution lists. *See Case Study #1.*
- Utilize a venue for evolving discussions, such as secure web-based chat services, to track group discussions
- Don't shy away from discussing pain points or difficult decisions; the sooner a potential issue is addressed, the better
- Encourage all team members to get involved in the discussion by establishing rapport and requesting input repeatedly if needed

CASE STUDY #1: *Overcoming Inefficient Communication*

SCENARIO:
During a recent submission project, one member from the client team and one member from a vendor team communicated exclusively with each other. Unfortunately, the decisions and action required from their discussions were not consistently shared with all team members.

SOLUTION:
Veristat created an email distribution list that encompassed all team members. It became a requirement to use the list when discussing project-related matters. Once it was implemented, communications were uniformly shared with all team members, allowing everyone to remain informed and raise concerns if any decisions had potential downstream effects.

It is critical for all team members to feel comfortable sharing concerns and working together as partners to create the right solution.

Utilize effective systems

Email communication is the general standard for sharing information, but it is not always the best tool for document transfer. Many submission files are large, creating challenges for downloads, email send/receipt restrictions, storage limits and more. A central repository – a common location for files and shared documents to be posted and accessible to everyone – can remove this technical challenge while simultaneously improving security, access, and chain of custody. Once an item is posted, an email is sent to the relevant team distribution list to make them aware and provide related details, including review deadlines.

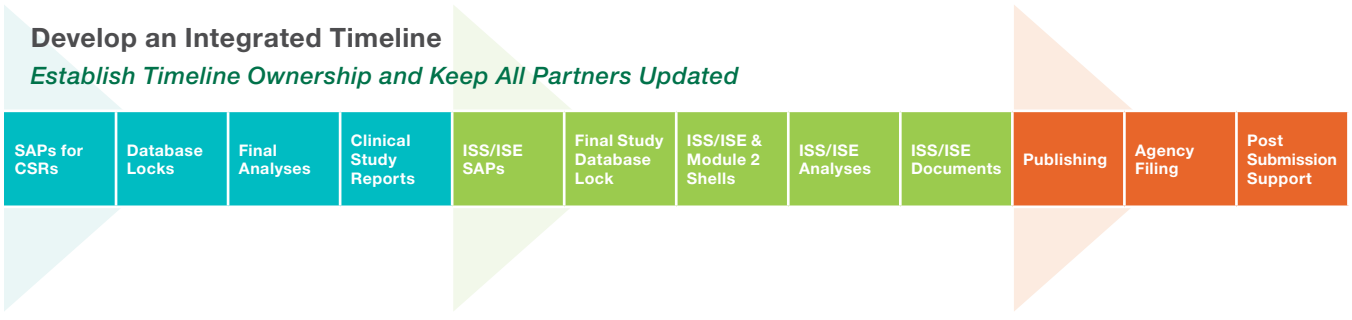
Think of Timelines as a Critical Operational Document

Other than the actual submission files, timelines are the most crucial document for any submission. They serve as a roadmap and organizational tool for every aspect of the process. Several practical strategies for timeline management can boost its effectiveness and accuracy:

1. **Designate a gatekeeper** to be the owner and manager of the key timeline document for the duration of the project
2. **Work backwards from the filing date**, taking publishing time into account
3. **Ensure that the timeline encompasses all elements of the submission and other competing team deliverables**, including post-submission expectations, advisory committee meetings, safety updates, agency rapid responses, and planned attendance at key conferences
4. **Budget time** for key milestones, including statistical analysis plans (SAPs), database locks, production of statistical outputs, document writing and publishing, document upload, and final electronic common technical document (eCTD) compliance checks
5. **Include a roundtable discussion with all key stakeholders** during document development to encourage live, proactive problem-solving and to avoid omitting key requirements during the initial draft
6. **Think outside the box about shaving time** from processes if your initial plan requires longer than the allocated time based on target filing dates. This may enable parallel work when feasible, rather than sequential steps.
7. **Share the integrated timeline document early and often** with all partners to make sure everyone is aware of all activities and can communicate if changes in one area will affect timelines in others

TIP: ***Plan proactively for post-submission requirements***

Be prepared for agency rapid responses, advisory committee meetings, 60-, 90- or 120-day safety updates, and any other possible additions to the timeline or post-submission expectations.



Creativity and Flexibility Are Essential When Timelines Shift

In all submissions, expect the timeline to shift at some point during the process. Adapt intelligently by prioritizing how you maximize efficiency:

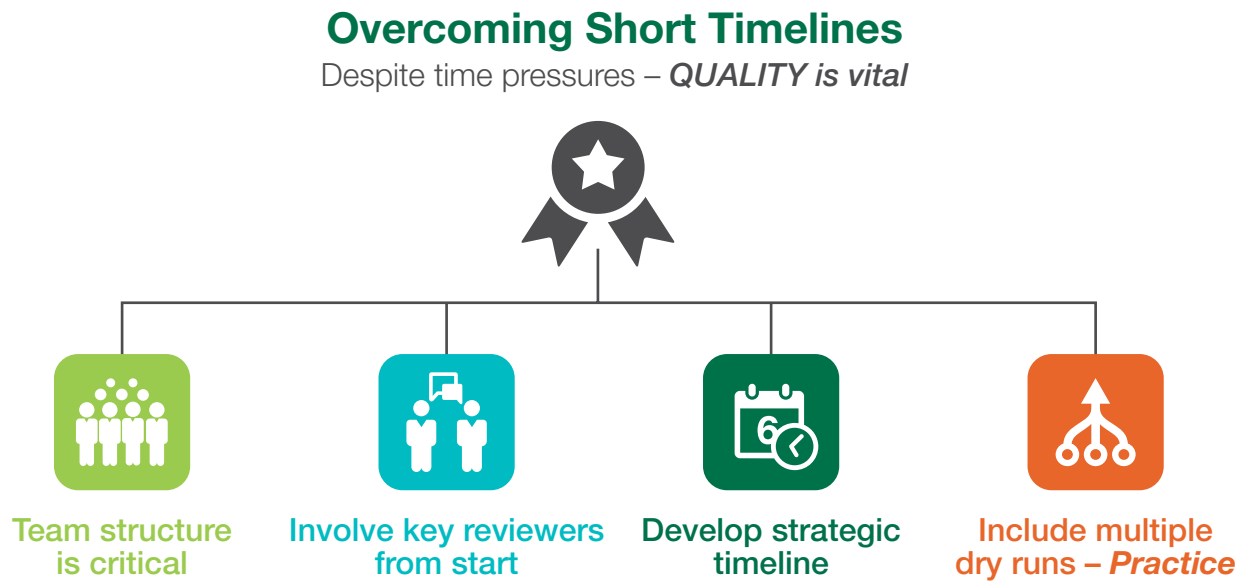
- **Collaborate with a single vendor** to make operational management smoother. Allow, for example, data management, program management, biostatistics, and medical writing teams to work together more efficiently and minimize downstream impact.
- **Function as an integrated team** by encouraging data management, biostatistics and programming, and medical writing team members to work closely together. This type of close collaboration runs most smoothly if you are working with a single contract research organization (CRO) for these services.
- **Involve** all key decision-makers in the discussion of timeline shifts likely to have a major impact on the overall schedule
- **Protect quality review time at all costs.** Work creatively to maximize efficiency in other steps, for example, consider parallel processing. It is ill-advised to shorten the review times for any quality control steps in order to shorten the overall timeline.

Overcoming Data Analysis Hurdles

With moving deadlines and potential delays in data receipt, the challenges surrounding database locks, unblinding and how best to prioritize the data conversion and analysis efforts, the biostatistical programming portion of submissions can be a key opportunity for strategic management to improve project productivity and timeliness without sacrificing quality.

Coping with Tight Submission Timelines

Strategies for overcoming short timelines are crucial, since submission projects frequently encounter delays. Consider some of the concepts below to head off time concerns, but never confuse flexibility and creativity in approach with a lack of quality — in the end, shortcuts on quality result in further delays and revisions.



Team structure is critical	In order to drive toward the same goal, the submission team should be considered one cohesive group, with no division of sponsor vs. vendor, between vendors, or among departments within the same company. The biostatistics leads need to be able to put on managerial hats to assist with creative, flexible thinking while managing their support teams. From a resource standpoint, there may need to be multiple technical teams, such as when clinical study report (CSR) analyses are needed simultaneously with integrated summary of safety (ISS) and/or integrated summary of efficacy (ISE) analyses. This requires cooperative leadership and cross-team communication to ensure consistency of messaging.
Develop a strategic timeline	From a biostatistics perspective, the Statistical Analysis Plan (SAP) is one of the main timeline drivers. It dictates the pooling approach and allows the planning team to work backwards to develop the optimal data conversion and analysis plan (e.g., approach to prioritization of study data tabulation model (SDTM), analysis data model (ADaM), tables, listings, and figures (TLFs)), in order to facilitate the medical writing and regulatory needs for submission.
Involve key reviewers from the start	This key strategy for overall submission management is also crucial during development of the SAP and TLF outputs. Consider a pre-SAP meeting — a strategic discussion among not only biostatistics, but medical writing, regulatory, medical, and any other key stakeholders — to identify key messages and determine pooling decisions. This helps minimize the potential for changes later, and sets the entire team on an aligned path early on.
Include multiple dry runs	Statistical teams are like sports teams: they need practice. Dry runs enable the team to work more efficiently when the data are ready, minimizing the chance of issues and delays at critical time points.

Addressing Database Lock Delays

There are several strategies for mitigating the impact on the timeline when there is a delay in database lock.

1. **Perform proactive risk mitigation and scenario building**
   These do not have to be formal, as long as participants proactively think through what issues may occur and can consider solutions in advance. Later, when issues do arise, similar scenarios discussed during this planning phase may already present a solution. Options include workshops, internal meetings, and planned discussions.

2. **Utilize an independent unblinding team for blinded studies**
   With appropriate firewalls in place, involve an independent team to ensure proper implementation of randomization codes to avoid data issues post-data lock. Having an independent data team review and incorporate any unblinded data in the programming (of course, without the blinded team's access) allows the main data team to move forward seamlessly once unblinding occurs.

3. **Automate as much as possible**
   This includes electronic quality checks and proactive, ongoing statistical checks

4. **Perform a dry run with a close-to-final data cut**
   The closer a dry run is done to the final data cut, the better chance of minimizing late-breaking data questions or issues. *See Case Study #2*.

5. **Provide rolling deliveries to medical writing**
   Consider a rolling delivery of tables, listings, and figures (TLFs) to medical writing to allow them to begin document preparation as early as possible. However, develop tight internal processes to rerun or subsequently update outputs as needed with the complete data package. Clear procedures and communication are critical to the success of this creative approach.

6. **Use the Word Compare technique**
   This function provides an actual comparison in Word documents to identify specific items changed by updated data and tracks these changes for medical writing to determine if updates are required in their documents. This allows a streamlined replacement process when needed.

CASE STUDY #2: *Adapting Timelines to Complex Restrictions*

SCENARIO:
Veristat was engaged for data migration work for 18 legacy studies and two ongoing studies. Sequential study migration would have delayed ISS and ISE development until completion of the final study, which was not practical for the submission timeline.

SOLUTION:
The Veristat statistics and programming team batched the data by domain and provided preliminary rolling data outputs to medical writing. Processing by domain allowed analysis of categories of data in parallel across all studies before moving onto other domains, giving useful output for certain sections of the submission documents prior to total migration for even a single study. Even though the database lock was delayed by two months, the submission timeline was met. This demonstrated a strategic timeline adaptation driven by key SAP elements.

Effective Integrated and CSR Analysis Management

Integrated analyses are often an amalgamation of various CSR analyses. This makes quality and consistency crucial. The statistical team should familiarize themselves with the individual CSRs to understand which analyses have been conducted, or are planned to be conducted, to align these with the integrated analysis.

To ensure quality in the development of integrated analyses, consider these tips:

- The integrated SAP development process should involve statistical review of each CSR to inform decisions about differences in data definitions and pooling
- Ensure that all statistical teams understand the analyses conducted for each CSR
- Overlap communication among the separate statistical teams so they can move in parallel with appropriate cross-team consistency
- Include medical/clinical and medical writing team members in the review of analysis plans
- Develop and execute statistical review checks early on. Statistical review checks are typically higher-level global review checks across ADaMs and TLFs that go above and beyond the programmatic quality control on each individual output. Define and execute these checks before all data are final. This makes the final review faster given the process is in place while also limiting the findings to the new data that has come in with the final lock.

Ensure Quality Outcomes Through Integrated Analysis and CSR Analysis

Medical Writing Keys to Success

Careful planning and an optimized timeline can reduce the time required to produce effective, consistent submission documents. A simple approach to minimize redundancy and the chance for significant revisions makes the most of medical writers' time, while also enabling efficient coordination with other critical teams.

Improve Efficiency via Clever Resource Planning

Thoughtful, detailed planning of medical writing assignments is critical in managing the timeline and message consistency to be carried throughout the submission. To plan effectively, it is important to understand how various modules of submission are derived and how they complement each other.

- CSRs form the basis from which the clinical modules for submission are derived. Using the final results of these studies, a writer can begin developing the clinical summaries, modules 2.7.1 through 2.7.4.
- If the submission includes integrated summaries, e.g. ISE or ISS, best practice is to develop them prior to the clinical summary 2.7 modules, as the integrated summaries are more comprehensive and contain the greatest level of detail. After the ISE and ISS are complete, the writer can easily distill that information into the individual clinical summaries, saving significant time.
- Module 2.5, the clinical overview, can be developed last, as it is the highest-level overarching summary of the clinical data

This planning model assists in assigning medical writers to each section. Consider assigning one or two writers to the module 2.7.1 and 2.7.2 biopharmaceutics and clinical pharmacology summaries; one writer to module 2.7.3 (efficacy); and one to module 2.7.4 (safety). In this set-up, a single writer is responsible for production of the ISS and then module 2.7.4, for example, to minimize duplication of efforts and inconsistency. If the timeline permits, the efficacy or safety writer could also be assigned to pivotal CSR sections to further leverage their knowledge of the data and strengthen the quality of writing in the summaries. Finally, one lead writer (typically the module 2.7.3 efficacy writer) can coordinate the production of module 2.5, the clinical overview.

TIP: ***Collaboration among writers is essential***

Ongoing, open communication is critical for strategic thinking among assigned writers. When a document is in review, unoccupied writers can step in and offer support to writers on other sections.

Establish Document Review Governance

A responsibility assignment (Responsible, Accountable, Consulted, and Informed, or RACI) matrix is important for document creation and review. Establish who will function as a reviewer and key decision-maker for each document as it progresses through development.

Include all stakeholders early on in strategic planning to define and agree on key messaging to be carried through all submission documents. Once the key messages are defined, try to refrain from continually evolving the messaging. A champion assigned for each document can help avoid changes in key messaging and timeline delays by taking responsibility for resolution of conflicting feedback, and ensuring queries are resolved quickly.

Have all reviewers commit to reviewing the document at each stage of development, starting with the first draft. This early engagement, along with the document champion, can ensure consistency of messaging and decrease the potential for rework.

Establish a Document Review Governance

Strategies for expediting document review include:

1. **Incorporate schedule blocking to review key data/documents in a timely manner**
   Work with the project manager or document champion to block review time on reviewers' calendars. In addition, consider blocking off sections of a document that have already undergone review (via highlighting or graying out text) to avoid repeat reviews of previously approved text.

2. **Consider roundtable live editing**
   This eliminates multiple cycles of revision and conflicting feedback. All stakeholders and the document champion should be in attendance so consensus can be achieved quickly on outstanding items.

3. **Develop a submission-specific style guide**
   This should capture key messages, as well as any special nomenclature and stylistic preferences for the brand or product. A guide ensures consistency among multiple documents and serves as a valuable tool for writers and the quality control team.

Be Strategic in Scheduling Pre-Submission Meetings with Regulatory Agencies

Timing your pre-submission agency meeting prior to finalizing pivotal CSRs can have a huge impact on the scope of work and attainable filing date. *See Case Study #3.*

Holding the agency meeting after finalization of CSRs and closer to submission creates the potential for agency requests for additional analyses that have a cascading impact on CSRs, integrated summaries, and module 2 clinical summaries. This can result in delays in filing. Regardless of timing, however, the medical writing team should remain nimble and prepared to adjust quickly to late-breaking agency requests.

CASE STUDY #3: *Simultaneous Submissions with Accelerated Timelines*

SCENARIO:
A mid-size pharmaceutical company engaged Veristat to complete an MAA, NDA, and New Drug Submission (NDS) with similar submission dates. The pre-NDA meeting was scheduled just two months prior to target NDA filing date. The FDA requested multiple additional analyses, affecting five finalized CSRs, modules 2.5 and 2.7 clinical summaries, and the ISS.

SOLUTION:
Veristat's project manager and medical writing team developed a collaborative plan to bring in more resources. Each amended submission document had a single champion to resolve conflicting feedback and facilitate communication and consistency. Document authoring and eCTD-compliant electronic publishing at Veristat streamlined the completion process, resulting in a final delay of only one month for the NDA and NDS submissions and on-time MAA submission, all submitted within a six-week timeframe.

Conclusion

As no two NDAs or MAAs are the same, following these best practices will help mitigate issues:

- **Truly integrated teams optimize the entire process** by working together efficiently. It can be easiest to achieve this by using a single partner to conduct project management, data conversion and analysis, and medical writing.
- **Quality is paramount.** Protect it at all costs — even with condensed timelines — by avoiding under-communication and fragmented, siloed teams.
- **Embrace creativity and flexibility** in developing solutions to maintain quality, mitigate risk, and avoid and overcome delays.

REFERENCES

Content originally developed as "Different Approaches for Preparing a Marketing Application: A Review of Successful NDA/MAA Preparation Strategies," an Xtalks webinar presentation delivered June 13, 2018.

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To learn more about Veristat or how we can assist you with your clinical trial design, execution and regulatory submissions, reach out to us today.

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