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RESEARCH

Agile Strategies in the Rigid Regulatory Environment

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ABSTRACT

This article will discuss the real-world application of agile project strategies to expedite the development of high-quality deliverables that satisfy the structure and rigor of the regulatory environment. The coronavirus disease 2019 (COVID-19) pandemic challenged regulatory writers not just to rethink the structure of their workdays and the nature of their interactions with their colleagues but to leverage technology and adopt strategic project thinking to help their teams meet aggressive timelines while working in the virtual workspace. Scenarios will include the application of agile project strategies to working on COVID-19 programs or programs heavily impacted by COVID-19, from expedited submission processes to rapid responses to regulatory authority requests for information. This assessment will include what strategies worked well, what strategies did not, and what an agile project should look like within the regulatory writing space.

Across industries, different methodologies for project management are used. The most popular include the waterfall, Kanban, adaptive project framework, lean, and critical path methodologies.[1] The reason for the variety in project management styles is simple—optimal delivery of a product in any industry requires processing of multiple intrinsic and extrinsic variables. In our experience in the biotech and pharmaceutical space, most regulatory writing deliverables have been planned by using the waterfall methodology; but the current space has become more dynamic, influenced almost daily by decisions made by regulators, research committees, health care professionals, venture capitalists, and—most importantly—the scientific method itself. Delivering quality regulatory documents in the current space requires methodology adaptation to an evolving landscape. As the discipline of project management in other industries has evolved to account for ever-increasing change, with project lifecycles now ranging from the very plan-driven to the iterative to the highly adaptive,[1] the authors considered whether non-waterfall methodologies could be adapted to regulatory writing.

This article briefly describes the *waterfall approach* historically used in medical writing and discusses the application of alternative project management methodologies to achieve quick, adaptive, and controlled regulatory document development.

THE WATERFALL APPROACH AND ITS PITFALLS

Regulatory writing project management typically has followed the waterfall method, which aligns with document development in an environment requiring sponsors to implement and maintain quality systems. The standard operating procedures (SOPs) that underpin these systems are often prescriptive, delineating steps that can be documented, thereby demonstrating compliance. Project timelines tend to mirror these SOPs in their fixed, stepwise progression toward controlled content creation. Project management software uses predecessor/successor inputs to capture this progression and can leverage this information to generate understandable outputs for coauthors and non–medical writing stakeholders. The benefits of the methodology include ample time for both the regulatory writer and coauthors to think, research, and then write and align reviewer comments and changes across the document before the next iteration.

This project management methodology is ideal for projects with a predictable path.[1] The format and content of nonpivotal clinical study reports (CSRs), annual investigator brochure updates, or developmental safety update reports (DSURs) are well described in the regulations, generally limiting stakeholder impact on document structure, and the timelines may be defined by regulation (eg, DSURs) or may be driven by fewer extrinsic factors (eg, a competitive landscape).

Whereas the waterfall methodology relies on predictability, the regulatory writing environment has changed dramatically since the pandemic began. Regulations regarding coronavirus disease 2019 (COVID-19) and non–COVID-19 studies, contract research organization (CRO) and site procedures, and sponsor priorities shifted to enable accel-

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erated clinical evaluation of diagnostic, therapeutic, and preventive products to address the pandemic. Regulatory writing projects have been initiated without an assessment of requirements (eg, initiation of a full protocol without identified study endpoints due to an evolving understanding of the clinical course of the disease), well-vetted concepts, or access to real-time investigator clinical observations.[2] Consequently, regulatory writers have been asked to coauthor in real time in a manner significantly divergent from the stepwise collaboration afforded by the traditional waterfall methodology.

ALTERNATIVE PROJECT MANAGEMENT STRATEGIES

During the first half of 2021, our operational and executive teams reviewed opportunities for continuous improvement. We focused on several COVID-19–related regulatory writing projects because of a recent uptick in requests for supporting projects with accelerated timelines and imperfectly defined parameters similar to what we had observed with COVID-19–related projects, leading us to wonder if a linear way of working might become a relic and if we might need to adapt all or part of our business model. The scenarios we selected for review included the following elements:

- Required multiple resources within the company (eg, regulatory writer and operations support).
- Required >50% resource utilization for the regulatory writer for a discrete period.
- Timelines did not follow a sequential pattern (ie, one or more authoring steps were concurrent), so the writer was unavailable for other projects.
- Coauthoring with the client was done by using collaborative technology.

The selected projects had a timeline that was prospectively created and/or maintained by the regulatory writer and that was available for resourcing manager review.

Scenario 1

At the time of project initiation, just shortly before the pandemic was declared, one could count on both hands the number of COVID-19–related studies in clinicaltrials.gov. The regulatory writer used relevant software and searches of clinicaltrials.gov for recruiting COVID-19 treatment studies to collect clinical intelligence and develop a protocol synopsis, which was then used to facilitate regulatory agency, CRO, and site interactions (Table 1). After receipt of Food and Drug Administration (FDA) feedback on the pre–investigational new drug application (IND) package and about 2 weeks before IND submission, the FDA issued guidance on COVID-19–related study conduct.[3-5] Given that the protocol was nearly finalized, the team had to quickly interpret the guidance, implement any changes addressing conflicts with prior clinical intelligence and an evolving standard of care, and confirm those changes with internal and external stakeholders (eg, confirm that the FDA's oxygenation cutoff for disease severity matched the site's cutoff).

Traditional stepwise project management methodologies were recognized as being too rigid for this dynamic environment, so the team incorporated strategies used in more adaptive methodologies. Change was rapidly communicated through a phone tree and scheduled check-ins every other day, with ad hoc meetings called for specific topics or live edits. The core authoring team was limited to the regulatory writer, clinician, and clinical trial manager,

Table 1. Scenario 1: Medium-Sized Pharmaceutical Company Filing an IND in a COVID-19–Related Indication

Type of Product	Treatment (COVID-19)
Requirements	File IND
Systems	Teams, PleaseReview (sponsor owned)
Regulatory Writing Resources	External consultants (no established MW department)
Timelines	Pre-IND meeting request package 3 weeks IND (2 weeks from pre-IND feedback)
Stakeholders	US regulators; later in the process, global regulators IRB/IEC Internal team Internal management Study sites External philanthropy groups (funding) CRO
Regulatory Landscape	Guidance still being drafted, no guidance available on endpoints and objectives yet; heavy cross-referencing to an existing IND in another indication
Risks	Proceeded with protocol and informed consent form writing at risk ahead of pre-IND feedback to meet timelines; defer many of the details on testing and analysis to ancillary documents (eg, Pharmacy Manual) because details not available yet (EUA for diagnostics had occurred only a few weeks previously[2])
Project Management Strategies	Communication phone tree Stand-up meetings every other day between work sprints Resource layering for ancillary writing tasks Small core team Cloud-based authoring and review

COVID-19, coronavirus disease 2019; CRO, contract research organization; EUA, emergency use authorization; IEC, independent ethics committee; IND, investigational new drug application; IRB, institutional review board; MW, medical writing.

with supplemental members reviewing specific language in the protocol, which enabled efficient and focused authoring during short work sprints. All authoring was done in Teams, with access managed by a dedicated information technology (IT) professional who was part of the phone tree. A regulatory writing operations associate supported the writer by formatting, locating references, and managing citations. The document underwent a single round of management review in PleaseReview, during which most of the reviewers used the software's commenting feature to provide substantive feedback. The team vetted management comments together, and the core authors discussed any outstanding issues with their line management outside of the review and reported back the results of the conversation. Roundtables attended by all core and supplemental authors as well as the management reviewers were used to efficiently align on resolution of any pending comments.

Structured communication and cloud-based tools were leveraged by the small core team, enabling them to efficiently respond to shifts in the regulatory landscape while also permitting team members to author, consult with management and subject matter experts, and achieve consensus. The team successfully provided a quality deliverable during an uncertain time in drug development and advanced an important potential treatment for COVID-19.

Scenario 2

This project proceeded in the context of hyper-compressed timelines and the need to look at not only new interim data but also cumulative data (Table 2).

While the CRO was pulling the marketing application documents together and facilitating the various reviews, full-time employees (FTEs) and consultants provided oversight and management of timelines and risks and facilitated interactions with multiple internal and external stakeholders. Because of the time constraints on the project, live data reviews were employed, during which the CRO regulatory writer engaged directly with stakeholders early in the drafting process, allowing for real-time drafting, consensus building, and a reduction in draft cycles. The success of this approach was contingent upon the availability of the correct attendees and their endorsement of this adaptation over more traditional iterative authoring and review processes.

Although Scenario 1 used a small core team with targeted reviewers to achieve consensus, this scenario used a larger review team, which included team members and management, to increase functional alignment at approval, which worked in large part because of the team trust at all levels. In this scenario, the use of PleaseReview followed highly prescriptive SOPs that did not enable the internal regulatory writers and the consultants (who only had reviewer licenses) to review live copies of fundamentally relevant documents (eg, parallel review of in-development CSRs or summary modules and in-development clinical overview). The system was used for a stepwise review, comment reconciliation, and closeout workflow. Although PleaseReview allows for the attachment of reference documents to the review, those documents were changing concurrently, rendering this option ineffective. Ultimately, a system was needed to facilitate document finalization with the key subject matter experts after team review. An initial attempt to use SharePoint for this activity failed because of a lack of prospective access management as well as restrictions on the use of guest accounts (for external consultants and regulatory writers) for internal SharePoint sites; the writer and subject matter expert resolved outstanding issues via email.

Table 2. Scenario 2: Medium-Sized Pharmaceutical Company Filing a Marketing Application in a COVID-19–Related Indication

Type of Product	Preventive (COVID-19)
Requirements	File a marketing application
Systems	Teams, PleaseReview (CRO owned), Veeva
Regulatory Writing Resources	CRO writers Internal FTE External consultants functioning as embedded FSP (established MW department)
Timelines	12 weeks (changed to 8 weeks)—critical/ASAP
Stakeholders	Global regulators, including multiple US bodies IRB/IEC Internal team Internal management Study sites CRO
Regulatory Landscape	Rapidly evolving; constant feedback from multiple agencies and the need to resolve divergent feedback; prior EUA and global conditional approvals
Risks	Competitive landscape is a significant concern Multiple overlapping documents to meet timeline Sponsor exponential growth in a short timeframe
Project Management Strategies	Communication phone tree Stand-up meetings every other day between work sprints Resource layering for ancillary writing tasks Small core team Cloud-based authoring and review

ASAP, as soon as possible; COVID-19, coronavirus disease 2019; CRO, contract research organization; EUA, emergency use authorization; FSP, full-service provider; FTE, full-time employee; IEC, independent ethics committee; IRB, institutional review board; MW, medical writing; SME, subject matter expert.

As a lesson learned from other submissions on the same program and aligned with sprint-style project management methodologies, the regulatory writing team attended specific key meetings, communicating about the submission and permitting the team more time to complete action items. The sponsor's Head of Medical Writing attended general meetings and CRO meetings, and the external consultants divided up CRO meetings and other internal meetings; all external consultants and CRO writers attended most document roundtables and stand-up meetings. Those who did not attend could access meeting information via a Teams chat, email, or a OneNote summary.

Overall, although there were observations for future process improvement, the regulatory and quality requirements of this dynamic submission were met, and a submission was filed on time for approval of a groundbreaking regulatory document.

Scenario 3

The work for this early-phase protocol began as sites across the United States began restricting access because of infectious disease procedures.[2] The protocol for this critical disease had been finalized around the same time the first COVID-19 cases were reported in the United States, and the study was in start-up (Table 3). As COVID-19 cases began to rise globally, the sponsor's concerns mounted regarding the likely impact on study enrollment as well as the ability to ensure proper safety follow-up if patients were enrolled. A protocol amendment was planned to allow for alternate assessments and to reduce the overall travel burden and the chance for COVID-19 exposure for the patient, with the amendment including home collection of samples, select phone visits, alternative media for patient-reported outcomes and informed consent, and home nursing for safety assessments and drug accountability and dispensation (as a last resort due to high cost). Guidance from the FDA on the conduct of studies during COVID-19 was issued several weeks into protocol development and informed several key mitigations that were planned[6]; however, at the time the guidance was issued, the pandemic was evolving, and the agency determined that prior public participation for the guidance was not feasible or appropriate, so early guidance was open to some interpretation.[7]

The core authoring team was limited to the regulatory writer, regulatory writing operations associate, clinician, clinical trial manager, regulatory strategist, program manager, and drug supply/ Chemistry, Manufacturing, and Controls manager. Involvement of each function in this group assured that the protocol was updated efficiently and accurately as conversations progressed with the CRO and other vendors in daily, 1-hour, focused working meetings. Authoring was done in Teams, with access managed by an FTE on the core authoring team. The document underwent a single round of management review using the sponsor-owned PleaseReview platform, with the regulatory writer initiating and managing the review. Similar to reviewers in Scenario 1, reviewers in this scenario mostly utilized the commenting feature. The team vetted management comments together, and the core authors gained alignment with their line management outside of the review. All authors as well as the management reviewers attended the roundtables.

By limiting the team to line-function representatives, employing regular meetings, and using authoring and review tools that promote transparency, the team effectively

Table 3. Scenario 3: Medium-Sized Pharmaceutical Company Amending a Protocol in a Non–COVID-19 Indication During the COVID-19 Pandemic

Type of Product	Treatment (non–COVID-19)
Requirements	Team was tasked with finding a way to add necessary flexibility to the study due to the evolving COVID-19 closures in H1 2020
Systems	Teams, PleaseReview (sponsor owned)
Regulatory Writing Resources	External consultants (no established MW department)
Timelines	2 weeks
Stakeholders	Global regulators, including multiple US bodies IRB/IEC Internal team Internal management Study sites CRO
Regulatory Landscape	Guidance on the conduct of studies during COVID-19 newly issued; IND had been open for some time, with one other completed early-phase study
Risks	Q&A on FDA guidance on the conduct of studies during COVID-19 issued and updated during amendment authoring; implementation required active discussion with CRO partners and subcontracted vendors to ensure proper description and execution; mitigations might not be successful and came with a high price tag; small company with limited resources
Project Management Strategies	Resource layering for ancillary writing tasks Core authoring team representing each function Cloud-based authoring and review

COVID-19, coronavirus disease 2019; CRO, contract research organization; FDA, Food and Drug Administration; H, half (of the year); IEC, independent ethics committee; IND, investigational new drug application; IRB, institutional review board; MW, medical writing; Q&A, Questions & Answers.

used multiple minor draft sprints to implement information and gain consensus as it became available in between meetings with stakeholders and partners. The project aligned with emerging regulatory guidance while mitigating the impact of COVID-19 on enrollment, study feasibility, and participant safety.

DISCUSSION

Each regulatory writing project has a unique budget and unique collaborators, timelines, risks, and gaps. The regulatory writer and regulatory project manager must discuss the linkages of a project with department and company goals and determine the project management principles to apply; gathering the project requirements should be a deliberate process even in the face of urgent issues or tight timelines.

In consideration of the scenarios described in this article, we determined that the strategies that best balanced a controlled process with adaptability were derived from the agile project management method (Figure 1), particularly the scrum framework. This method, often used in software development, is employed when the "requirements," or specifications the software needs to meet, change over time as a result of competitive intelligence or other factors; this method uses continuous planning to rapidly identify and implement change.[8] In all 3 of our scenarios, microdrafts were produced in short bursts, or "sprints," in between other milestones (eg, internal meetings, stakeholder meetings), continuously delivering a work product informed by feedback at all stages (Figure 2). Early and frequent delivery of microdrafts maintains project momentum and reduces the overall amount of work being done later in the process as well as the potential that late-breaking information could jeopardize quality or

Figure 1. Principles of agile project management.
Source: Rigby et al.[8]

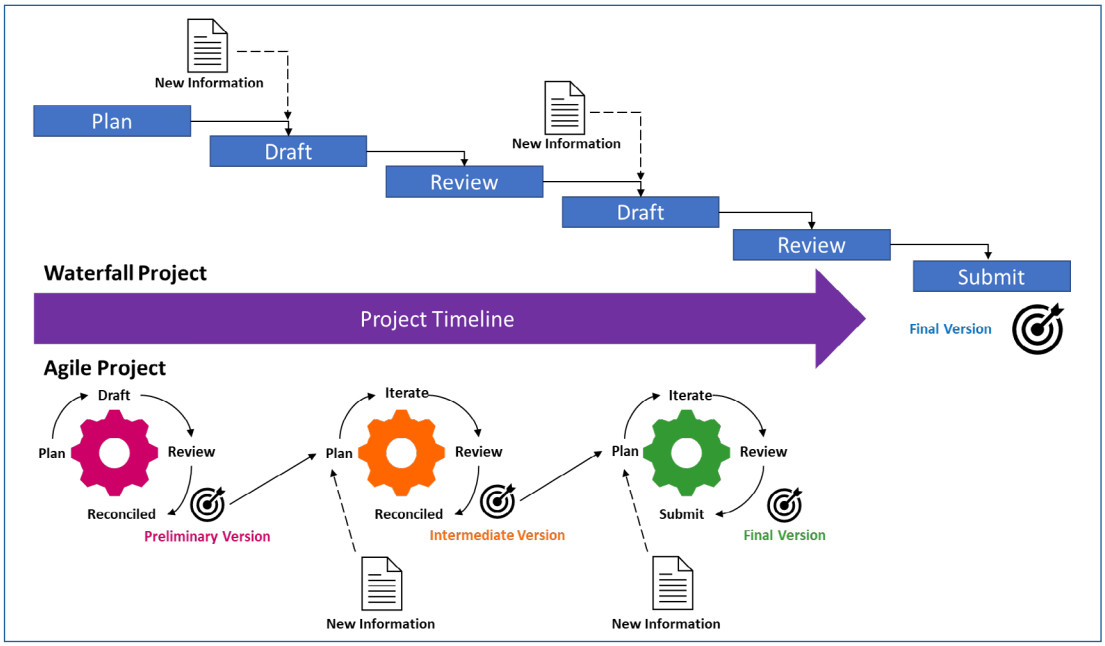

Figure 2. Waterfall compared with Agile methodology for document production. Adapted with permission from Kissflow.[10]

on-time delivery. Regulatory writers often leverage relationships to deliver quality documents on time, but the commitment in these scenarios to produce high-quality microdrafts required the authoring team to be in regular contact to self-regulate and agree on the tasks to be completed, check on progress, and course correct as needed. The focus on optimal technical quality and design in this method is inherently aligned with the rigor required for regulatory documentation as well as the need to position regulatory documentation for the intended audience, and the method's approach to simplicity is also aligned with the latest "lean authoring" trends in regulatory writing.[9]

Any methodology must be paired with the best tools, systems, and practices. Setting expectations for how the team will work together and outlining roles and responsibilities, as well as scheduling regular checkpoints, were critical success factors in each scenario. In addition, proactively managing systems access and education as well as the availability of a dedicated IT business partner to triage technical issues led to a more efficient authoring experience in some of the scenarios, even in a remote environment. It is also worth noting that no system is perfect; informing reviewers of any system limitations may help avoid pitfalls (eg, sponsor's SharePoint is only set up to retain a certain number of versions, or contractors may not have compatible versions of Microsoft Office for coauthoring). Lastly, archiving comments and decisions produced within any system requires regulatory writer discipline and should follow best practices and sponsor procedures to ensure that the rigor of regulatory documentation is met.

Project management software was critical to the success of each of these projects, but we also concluded that certain software features not often used by regulatory writers have become critical in assessing the available resource pool. For example, we had underutilized the project utilization feature to show the exact number of hours that a writer would be dedicated to a project within the start and stop dates for a task.[11,12] As the pandemic progressed and project complexity increased, we implemented the software's enterprise resourcing function, thereby enabling automatic initial notifications of project plan updates in between regular checkpoints.

As a result of our analysis, we also invested in Power BI business intelligence software to visualize data from multiple enterprise applications, including project management and customer relationship management software. Implementation of this analytical tool empowered our leadership team to efficiently track resource allocation and other details, including funds remaining on work orders at both the client and contractor level.[13]

Communication was paramount in the completion of each document in the scenarios. Although the teams came to different conclusions about meetings, they each decided proactively how often and how to interact. Setting such expectations up front in a project both increases the odds of the project's technical success and manages the potential for over-accessibility and burnout. If the team cannot pull away from these digital tools because of an inundation of competing requests, they cannot get the work done. In one of these scenarios, the sponsor acknowledged that they historically had this exact issue and successfully addressed the feedback by dividing and conquering meeting attendance. Thus, several of the principles within the agile method, including the preference for face-to-face interaction, maintaining a sustainable pace, and permitting the team to produce the deliverable, need to be balanced.

The limitations of this review are that the assessments were retrospective (as necessitated by the level of engagement required during the pandemic to complete the above projects) and that the number of projects sampled was small. The types of projects sampled met specific criteria, and any projects that meet some but not all criteria (eg, COVID-19 impact assessment for a CSR) may require a combination of strategies depending on the context. In addition, in Scenario 2, we were engaged as a resource late in the project planning phase and may have been able to influence the project management approach had we been involved earlier.

As we further consider implementation of agile methodology in whole or in part, we acknowledge that the agile method of project management assumes that the workers' time is retained, mostly available, and free of other distractions to be able to pivot. Within regulatory writing departments, resources often cover multiple deliverables over multiple programs, so a shift to properly resource agile projects may lead to a higher overall departmental budget. The ability to potentially get to market sooner, however, may outweigh this burden. This concept also may not be representative of the way that all regulatory writers want to work and in fact will work best when the team wants to rapidly innovate in a unique way[8]; commoditization of this way of working could increase the risk for burnout and cause workers to lose faith in the principles of prioritization, trust, teamwork, and problem-solving that are core to this project management method. Furthermore, this method may require writers with a requisite level of experience to be able to pivot as needed. Considering that experienced writers represent a finite portion of the workforce and given that the demand for this style of working may increase, this could

leave a large gap in the available resource pool that needs to be urgently addressed by leadership in the regulatory writing field.

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