ORACLE

Oracle Health Sciences. For life.

Breathing Life Into SOPs With an Automated Workflow-Driven Process

WHITEPAPER

This white paper describes how automating SOPs for study startup - a notorious bottleneck[2] - can guide sponsors and CROs to compliance using workflows consistent with organizational standards and country-specific regulations.

Contents

Executive Summary

Standard Operating Procedures (SOPs) have long been fundamental to many industries, and the clinical trials sector is no exception. Yet, too often, after companies devote significant time and resources into creating SOPs, they may not be followed. They may be ignored or even avoided. Failure to keep accurate records and establish and maintain SOPs appear frequently in Form 483 violations and Warning Letters issued by the FDA.

With the advent of intelligent document routing technology, stakeholders have the ability to support country-specific document regulatory workflows. This functionality allows for better compliance with SOPs, which, in conjunction with regulatory pressures, help boost operation efficiencies of clinical trials and shorten cycle times in the study startup phase.

Adhere to SOPs and Streamline Study Startup

Standard Operating Procedures (SOPs) have long been fundamental to many industries, and the clinical trials sector is no exception. With the advent of the Good Clinical Practice Guideline in 1996 from the International Conference on Harmonisation (ICH-GCP), stakeholders have been motivated to develop SOPs, not only for regulatory compliance, but also as a routine business practice. SOPs are defined in the GCP Guideline as detailed, written instructions needed to achieve consistent performance for a specific function,[1] with a goal of instilling quality into clinical trial operations. Yet, too often, after companies devote significant time and resources into creating SOPs, they may not be followed. They may be ignored or even avoided.

This is where Oracle Health Sciences Activate Cloud Service, Oracle Health Sciences' purpose-built automated workflow solution, can help.

The smart study startup workflows contained in Activate facilitate and track document collection and handoffs across the globe, and provide version control, status reporting, and role-based assignments to ensure appropriate access. Also, alerts notify study team members when pre-requisite work is completed.

With these capabilities, Activate functions as a virtual assistant or a virtual team member, a business tactic that is growing in popularity.[3] A virtual team member, whether human or digital, plays a valued role in bringing greater efficiency to operations. With the help of built-in workflows, these virtual players are looking over the shoulder of stakeholders, and guiding them through the process of clinical trials as they unfold. This automated approach to SOP compliance makes it easier to prevent bottlenecks that typically occur throughout the start-up phase of clinical trials, allowing for better study quality and tighter adherence to timelines and budget.

> " With the advent of intelligent document routing technology, stakeholders have the ability to support country-specific document regulatory workflows."

SOPs and the Regulatory Environment

Conducting clinical trials is justifiably a highly regulated activity. Encouraging volunteers to participate in the testing of investigational products has inherent risks, so ethics dictate that carefully defined SOPs are fundamental to the substantial safeguards and protections needed to enhance patient safety.

What exactly are SOPs? They are living documents[4] meant to describe who does what, where, when, why, and how.[5] They serve as a formal written resource for ensuring that common processes and activities are conducted in a consistent manner across clinical trials. Research by Gough and Hamrell notes that if a company implements an SOP, it must be adhered to.[6] And importantly, over time, as procedures change, SOPs must change, too.[4]

Interestingly, the literature has comparatively little to say about how to structure an optimal SOP.[7] Furthermore, the Food and Drug Administration (FDA) regulations for drugs do not specifically mention SOPs as a requirement for sponsors, contract research organizations, or investigative sites, and there is virtually no guidance on SOP system design, whether for manufacturing or clinical research.[8,9] Yet, failure to comply with SOPs can result in violations during regulatory audits.

In Fiscal Year 2015, the FDA Office of Bioresearch Monitoring, which conducts onsite inspections and data audits of FDA-regulated research, issued 283 violations known as "483s,"[10] which are issued when inspectors notify management of objectionable conditions. Specifically, failure to follow written procedures, conduct clinical trials in accordance with signed documents or SOPs,[11] or failure to keep accurate records and establish and maintain SOPs appear frequently in Form 483 violations and Warning Letters issued by FDA. These findings reflect the fact that companies may not have procedures that support operational processes,[12] procedural changes may not have been formalized in the current version of the SOP,[4] employees do not understand their job responsibilities,[13] they lack access to the SOPs, or are not aware of them.[11]

To mitigate the risk of non-compliance, numerous suggestions for developing SOPs have emerged, typically including multiple steps, such as authoring, editing, training, implementing, revising, and archiving.[14] They need to be clearly written, and because of the level of detail involved, they may best be written by the lead individual performing the task in question.[4,14]

ICH-GCP SOP Guidelines

- **5.1.1 – Quality Assurance and Quality Control**
  The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)

- **5.18.4(q) – Monitor's Responsibilities**
  Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

- **5.20.1 - Noncompliance**
  Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/ institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

Chart 1

Source: International Conference on Harmonisation/ Good Clinical Practice 1996

SOPs are essential for conducting clinical practice in accordance with ICH-GCP guidelines. In particular, Section 5.1.1 of the ICH-GCP code states that the sponsor is responsible for using written SOPs to implement and maintain quality assurance, and to ensure that data are generated according to the protocol, GCP, and the applicable regulatory requirements.[15] Other referrals to SOPs in the ICH-GCP guidelines appear in Chart 1.

While SOPs are not named in FDA regulations for sponsors, CROs, or sites, the regulations do infer responsibilities associated with clinical research—and SOPs are needed to formalize how to comply with those responsibilities.[16] For example, some FDA regulations define responsibilities of the investigator.[17] In the regulations from the European Medicines Agency (EMA), SOPs are mentioned several times, mostly related to auditing and monitoring activities (Chart 2).[18]

The need for SOPs is expanding with the November 2016 release of an updated guideline from the ICH-GCP, known as E6(R2).[19] It is intended to replace the industry-standard R1 guideline. Significantly, it reflects the increasing complexity of clinical trials, and is designed to modernize approaches to clinical trials, as stakeholders embrace technology to facilitate clinical trial design, conduct, management, oversight, and now, study startup (Chart 3).

Section 5.0 of the new guideline is particularly noteworthy as it focuses on quality management, and the sponsor's responsibility for ensuring operational feasibility, avoidance of unnecessarily complex protocols, and efficient design of clinical trials. All of these factors play a role in improving study startup through systematic safeguards that use technology to ensure adherence to SOPs.

Activate Automates SOP Workflow

Stakeholders have long recognized the value of SOPs, but until recently, SOP manuals were renowned for their unwieldy size and length, and sometimes incomprehensible material. Activate, a cloud-based technology accessed through a user friendly dashboard, offers a dynamic alternative to the infamous SOP manual, which typically takes up a lot of space and may be relegated to a forgotten but secured closet visited occasionally, maybe in anticipation of an audit. Yet these SOPs are a company's first line of defense for any inspection and help ensure quality in clinical trials.[6]

To mitigate this situation, Activate automates workflows based on how a particular SOP is to be followed. It is a major improvement over traditional attempts at following often confusing SOPs, with deviations sometimes resulting in violations.[13]

SOPs Mentioned or Inferred

Food and Drug Administration (FDA):

- **312.53 – Responsibilities of investigators and monitors**
  A commitment by the investigator that he or she: (c)(6)(a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects

European Medicines Agency (EMA):

- **5.18.4(q) – Monitor's Responsibilities**
  Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Chart 2

Source: 21 Code of Federal Regulations Part 312; EMA ICH Topic E 6 (R1) Guideline for Good Clinical Practice

Technology in the ICH-GCP E6(R2) Guideline

Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. This guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity.

Chart 3

Source: ICH-GCP E6(R2)

For study startup, which includes country selection, site selection and initiation, regulatory document submission, contract and budget execution, and more, countless country requirements must be factored in, reflecting the global nature of clinical trials. An automated workflow is effective for complying with those varied requirements, particularly to manage the volume of document exchange inherent in study startup. Workflows function by integrating SOPs into Activate, an out-of-the-box tool that provides real-time study status and standardized processes.

The Value of SOPs

SOPs in clinical trials serve numerous essential functions. In addition to managing issues of compliance that align with company policies and regulatory guidelines, they also:

- Create operational efficiency by ensuring processes that have been examined, optimized and standardized amongst all studies.
- Reduce the learning curve and training of staff.
- Ensure business continuity: SOPs allow for continued operations in the event that a key staff member is unavailable. By referring to the SOP, someone can handle an urgent task and do it correctly the first time.
- Improve quality control by reducing errors or variations. They improve the quality of the data collected, thereby improving the science of the study.

These benefits provide a level of formal accountability for team members and deter noncompliance on a systemic level. But, they cannot help if they are not used. Some explanations as to why they are not followed consistently include difficulty in locating the total collection of SOPs, they are written in a foreign language, and more (see chart).

These findings are similar to those from a survey about using SOPs for clinical trials in which 18 German pharmaceutical companies participated. Results showed that a mere 19% of respondents were fully satisfied with the SOP system in their respective companies. The main complaint was the complexity and lack of clarity of individual documents, which made it difficult for users to rapidly locate the relevant sections of SOPs or instructions in the SOP manuals required for day-to-day work or in a specific on-site situation.

Reasons Why SOPs Are Not Followed

- The required SOP is difficult to locate in the total collection of SOPs.
- The SOP is written in a foreign language.
- The user has inadequate training.
- The SOP is confusing as it is written in language that is difficult to follow.
- The procedure is described in an unfamiliar way.
- The user believes he/she knows another or better method.

The standardization aspect of Activate is important as clinical trials become increasingly global. A report from the EMA notes that the number of investigative sites involved in pivotal trials submitted in marketing authorization applications to EMA changed dramatically over a six year period.[20] According to the report, in 2011, 71.9% of sites conducting those trials were located either in North America or the European Union. This is a big drop from the 2005 figure of 89.5%. As a result, technology needs to accommodate this trend, including how SOPs can be used to better manage global study conduct.

This entails addressing factors such as country-specific regulatory document flow among stakeholders, version control, status update, and ability to spot bottlenecks—a difficult task when SOPs for these factors remain paper-based or are not readily available.

Activate's smart workflows operate like a virtual assistant or team member who can shave hours from the study startup process by completing delegated tasks.[3] This involves configuring settings in real-time to accommodate changes in country specific regulations or organizational SOPs. Authorized team members, as defined in the SOP, can view and manage existing configurations, and then edit them to create the settings needed for tracking documents, submissions, and milestones. In addition, real-time alerts help decision makers intervene immediately, before a major setback has occurred, instead of after the fact.

" Activate's smart workflows operate like a virtual assistant or team member who can shave hours from the study startup process by completing delegated tasks." [3]

With the help of this system, a sponsor or CRO can identify sites, and continue identifying them until analytics indicate with 90% – 95% probability that they will meet the enrollment target. In the meantime, those sites that are ready to activate can do so. This creates an environment in which sites can compete to be selected and compete to reach enrollment targets.

Figure 1 shows a sample Activate workflow, one of over 70 standardized country workflows, which includes tracking site activation, protocol amendments, quality reviews, and expiring documents. These capabilities are critical, given the ongoing slowness in study startup, which is stubbornly clinging to a cycle time that sometimes takes as long as 14 months.[21]

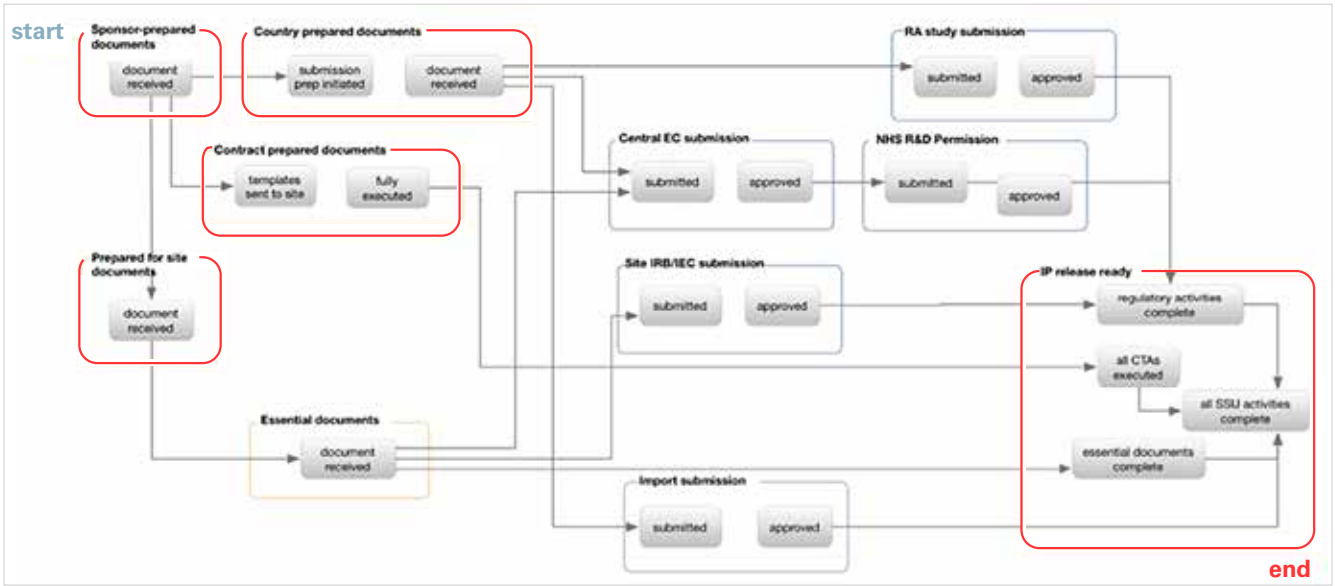

Figure 1

Figure 2 depicts a step-by-step automated workflow for documents needed to start a study in the United Kingdom.

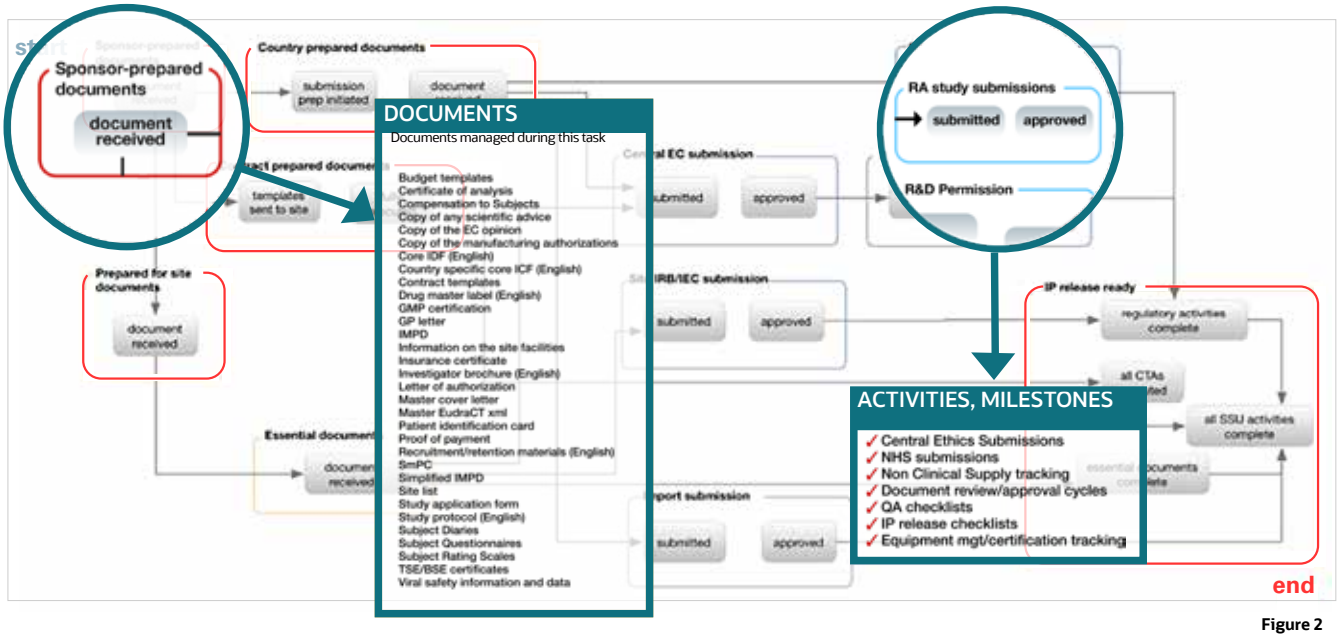

Figure 2

Better SOP Compliance…Better Quality

With the advent of intelligent document routing technology, stakeholders have the ability to support country-specific document regulatory workflows. This functionality allows for better compliance with SOPs, which, in conjunction with regulatory pressures, help boost operational efficiencies of clinical trials and shorten cycle times in the study startup phase. Historically, regulations have not provided specific guidance on the format or content of SOPs, allowing companies to design SOPs that best conform to their unique practices.[4] But the long history of SOPs being confusing, overly complex, or existing in paper format has led to their less than consistent use, even avoidance. Activate is a dynamic improvement with consistent processes that engage users with easy-to-follow smart workflows, breathing life into SOP compliance and adherence to clinical timelines and budgets, while improving quality.

References

1. ICH GCP, guidelines, 1.55. Available at: http://ichgcp.net/1-glossary. Accessed June 28, 2016.
2. Morgan, C. Study Startup: New Battleground in CRO Differentiation Strategy. Clinical Leader. Available: https://www.clinicalleader.com/doc/study-startup-new-battleground-in-cro-differentiation-strategy-0002
3. Dizik, A. 10 things to outsource to a virtual assistant. Entrepreneur. December 27, 2012 Available at: https://www.entrepreneur.com/slideshow/299695
4. Kumar M. SOPs: Least understood, most important tool to ensure regulatory compliance. Regulatory Focus. October 2011. Available at: https://www.amarexcro.com/articles/docs/RAPS_Focus_SOPs_Oct2011.pdf
5. Applied Clinical Trials Editors. SOPs: A must for sites. Applied Clinical Trials. March 1, 2010. Available at: http://www.appliedclinicaltrialsonline.com/sops-must-sites
6. Gough J, Hamrell, M. Standard Operating Procedures (SOPs): Why Companies Must Have Them, and Why they Need Them. Drug Information Journal. 2009; 43:69-74. Available at: https://journals.sagepub.com/doi/abs/10.1177/009286150904300112
7. Schmidt GB. SOPs in Clinical Research. Applied Clinical Trials. August 1, 2013. Available at: http://www.appliedclinicaltrialsonline.com/sops-clinical-research?pageID=1
8. Anderson C. FDA and EMA: Differences in Approach. SOP Writing. April 5, 2011. Available at: https://sopwriting.wordpress.com/2011/04/05/regulatory-requirements-differences-between-fda-and-ema/
9. Inspectional Observations. Food and Drug Administration. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations
10. Saxena A. SOP Writing for Clinical Trials: Staff Training Aspects. 2005. Available at: http://sopwriting.blogspot.com/
11. Pickett JM. Reading for a US FDA inspection. Expert Briefings. May 23, 2013. Available at: http://www.expertbriefings.com/tips/readying-for-a-us-fda-inspection/
12. Peterson DC. Assuring the Effective Use of Standard Operating Procedures (SOPs) In Today's Workforce. BioPharm International. Sept. 2, 2006. Available at: http://www.biopharminternational.com/assuring-effective-use-standard-operating-procedures-sops-todays-workforce?id=&sk=&date=&pageID=3
13. Vick M. SOP Writing for Clinical Research. Institute of Translational Health Sciences. University of Washington. March 2010. Available at: https://www.iths.org/wp-content/uploads/ITHS-SOPs-for-Clinical-Research-03-03-10.pdf
14. ICH GCP, guidelines, 5.1.1. Available at: http://ichgcp.net/5-sponsor
15. Sajdak R, Trembath LA, Thomas KS. The Importance of Standard Operating Procedures in Clinical Trials. Journal of Nuclear Medicine Technology. 2013;41(3):231-3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23853088
16. 21 Code of Federal Regulations Part 312. Investigational New Drug Application. US Government Publishing Office. Available at: http://www.ecfr.gov/cgi-bin/text-idx?SID=29bce88cdf8ce294019da4ab281ff014&mc=true&node=pt21.5.312&rgn=div5
17. ICH Topic E 6 (R1) Guideline for Good Clinical Practice. European Medicines Agency. July 2002. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf
18. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry. Food and Drug Administration. Available at: https://www.fda.gov/files/drugs/published/E6%28R2%29-Good-Clinical-Practice--Integrated-Addendum-to-ICH-E6%28R1%29.pdf
19. Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency. Overview of patient recruitment and the geographical location of investigator sites Containing data from 2005 to 2011. European Medicines Agency. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf
20. Miseta. E. Getz: Site activations hurt by commodity mentality. Clinical Leader. May 16, 2016. |ttp://www.clinicalleader.com/doc/getz-site-activations-hurt-by-commodity-mentality-0001

About Oracle Health Sciences

As a leader in Life Sciences cloud technology, Oracle Health Sciences' Clinical One and Safety One are trusted globally by professionals in both large and emerging companies engaged in clinical research and pharmacovigilance. With over 20 years' experience, Oracle Health Sciences is committed to supporting clinical development, delivering innovation to accelerate advancements, and empowering the Life Sciences industry to improve patient outcomes. *Oracle Health Sciences. For life.*

CONTACT

+1 800 633 0643

healthsciences_ww_grp@oracle.com

www.oracle.com/healthsciences

CONNECT

blogs.oracle.com/health-sciences

facebook.com/oraclehealthsciences

twitter.com/oraclehealthsci

linkedin.com/showcase/oracle-health-sciences