How-To Guide

Despite having a bad reputation, incorporating automated SOPs into study start-ups is almost guaranteed to have a positive impact on budgets, timelines and clinical trial efficiency in general – so why are SOPs still not being utilised?

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Standard operating procedures (SOP) rarely grab the spotlight like transformational technologies or newer strategies, such as risk-based monitoring or Quality by Design. But SOPs deserve some love. With their coveted goal of improving operational efficiency, they have long been fundamental to many industries, and the clinical trials sector is no exception.

Sponsors are motivated to develop SOPs, not only as a standard business practice, but also in support of regulatory compliance. For example, Good Clinical Practice (GCP) guidelines state that audits generally involve a systematic review of trial-related activities and documents, including SOPs (1). However, just because a company has invested significant time and resources in creating SOPs does not mean they are always being followed. They may even be avoided. But this is where technology can help.

This article describes how automating SOPs for a key element of clinical trial conduct – study start-up (SSU) – can guide sponsors and CROs to comply with organisational standards and country-specific regulatory workflows. Other automated SSU features include facilitating document collection and handoffs across the globe, version control and status reporting. Using this approach, bottlenecks that typically occur throughout the start-up phase of clinical trials are reduced, bringing greater efficiency to the critical path and tighter adherence to timeline and budget.

Box 1: Regulatory guidelines

ICH-GCP:

5.1.1 – 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).

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.

EMA:

Regulation (EU) Article 41 – The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently. The sponsor shall keep detailed records of all adverse events reported to it by the investigator.

Source: ICH-GCP FDA, EMA

Clinical Research

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 to be utilised – along with intense safeguards and protection – to enhance patient safety. These include an array of regulations from the ICH (ICH-GCP) (2), the FDA (3), the EMA (4) (see Box 1) and other regulatory bodies across the globe. Collectively, they carefully detail how clinical trials are to take place, ranging from the responsibilities of investigators to how and when serious adverse events are to be reported.

On the manufacturing side, regulations note that SOPs must be supplied in writing and distributed to employees in a timely manner (5); furthermore, it is a requirement to set up and maintain quality control systems supported by written SOPs (2). Interestingly, there is virtually no guidance on SOP system design, whether for manufacturing or clinical research (6,7). Failure to comply with them, however, can result in violations during regulatory audits.

In 2015, the FDA Office of Bioresearch Monitoring issued 283 violations known as '483s', which are delivered when inspectors notify management of objectionable conditions (8). Specifically, failure to follow written procedures, conduct clinical trials in accordance with signed documents or SOPs (9), or failure to keep accurate records and establish and maintain SOPs appear frequently in Form 483 violations and warning letters issued by the FDA. These findings reflect the fact that companies may not have procedures that support operational processes (10), employees do not understand their job responsibilities (5), they lack access to the SOPs, or are not aware of them (9).

Definition of SOPs

What exactly are SOPs? According to the ICH-GCP, they are defined as detailed written instructions meant to achieve uniformity of performance of a specific function (2). They

Box 2: Reasons why SOPs are not used

- The required SOP is difficult to locate in the total collection of SOPs
- The SOP is written in a foreign language
- 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 a different, or better, method

Source: A Saxena 2005

describe who does what, where, when, why and how (11). Literature suggests that an SOP document should be created by the lead employee responsible for the task being described, and should include sufficient details. Diagrams and flowcharts are helpful to define the sequence of steps (12).

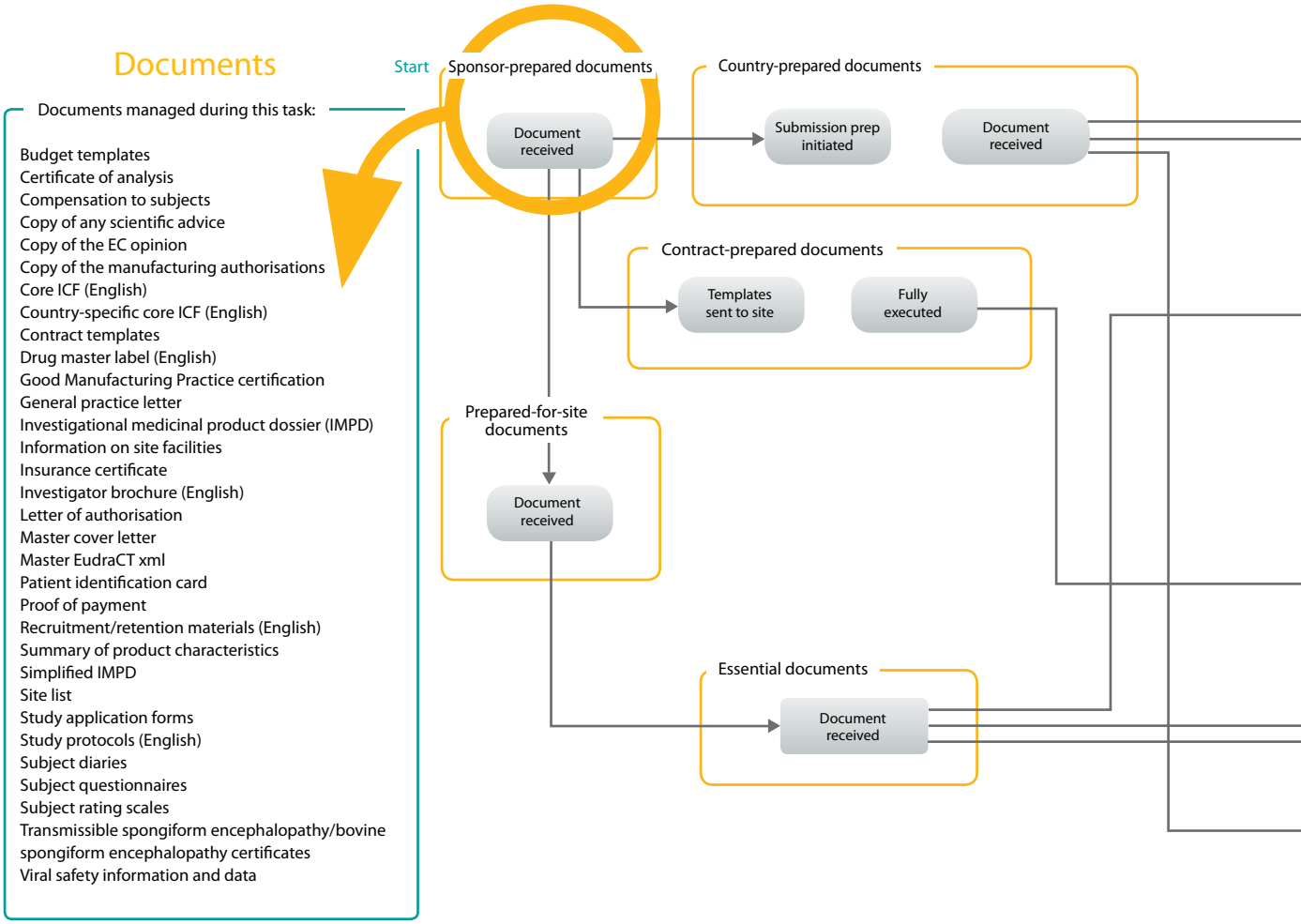
SOPs are also living documents meant to evolve with time and experience (12). In addition, for new as well as experienced employees, they serve as a resource for conducting clinical trials in a consistent manner. In simple terms, SOPs entail writing down what is to be done, and doing what is written down. They are an effective catalyst to drive performance improvement and organisational results.

The importance of SOPs in clinical trials cannot be overstated (12). Specifically, they:

- Manage compliance obligations in accordance with regulatory guidelines and institutional policies
- Create operational efficiency by ensuring processes that have been examined, optimised and standardised 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 enhance 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 they prevent non-compliance on a systemic level. But they cannot help if they are not used. Some explanations as to why they are not used consistently include difficulty in locating the total collection of SOPs, being written

Figure 1: Step-by-step automated workflow for starting a study in the UK



in a foreign language, and more (see Box 2) (9). These findings are similar to those from a survey about SOPs for clinical trials, in which 18 German pharmaceutical companies participated (6). Results showed that only 19% of respondents were fully satisfied with the SOP system in their respective companies, and that the main complaint was the complexity, length, and lack of clarity of individual documents, which made it difficult for users to rapidly locate the relevant sections of SOPs or instructions required for day-to-day work or in a specific onsite situation.

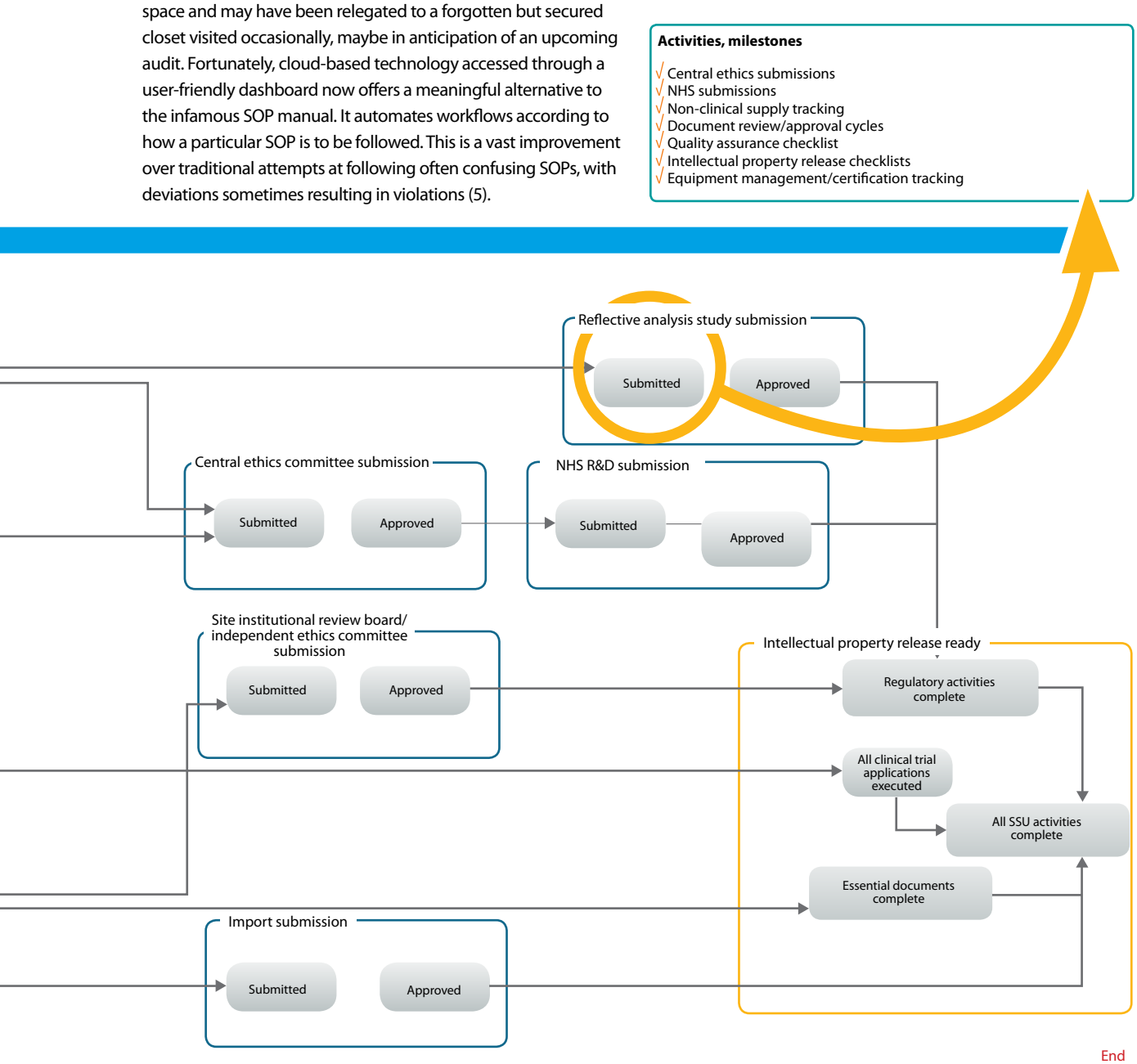
SOP Workflow

As suggested in the German survey, stakeholders have long recognised the value of SOPs – but until recently, SOP manuals were only renowned for their unwieldy size and length, and sometimes incomprehensible material. They took up lots of space and may have been relegated to a forgotten but secured closet visited occasionally, maybe in anticipation of an upcoming audit. Fortunately, cloud-based technology accessed through a user-friendly dashboard now offers a meaningful alternative to the infamous SOP manual. It automates workflows according to how a particular SOP is to be followed. This is a vast improvement over traditional attempts at following often confusing SOPs, with deviations sometimes resulting in violations (5).

For SSU – including 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 conforming to those varied requirements, particularly related to the volume of document exchange inherent in SSU: a frequent bottleneck. This works by integrating SOPs into an out-of-the-box solution that provides real time study status and standardised processes.

Becoming Global

The standardisation aspect is of growing importance as clinical trials are increasingly global. A report from the EMA notes that the number of investigative sites involved



in pivotal trials submitted in marketing authorisation applications to the EMA changed dramatically over a six year period (13). According to the report, in 2011, 71.9% of sites conducting those trials were located either in North America or the EU. This is a big drop from the 2005 figure of 89.5%. As a result, technology needs to accommodate this continuing trend, including how SOPs can be used to better manage global study conduct. They need to address 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 not readily available.

Jeff Kasher, President of Patients Can't Wait, and formerly Vice President of Clinical Innovation and Implementation at Eli Lilly and Company, comments: "With globalisation expanding its footprint, improved study start-up is essential for building speed into the clinical development process. Conducting clinical trials in places with unfamiliar regulatory pathways and limited infrastructure is highlighting the value of study start-up technology that allows for better SOP and regulatory compliance."

The automated workflow operates by configuring settings in real time to accommodate changes in country-specific regulations or organisational SOPs. Authorised 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. Figure 1 (page 41-42) shows a step-by-step automated workflow for documents needed to start a study in the UK.

SOP Compliance

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 guidelines, help improve the operational efficiency of clinical trials, particularly in the SSU 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 (12). But the long history of them being confusing, overly complex, or existing in paper format has led to their less than consistent use or even avoidance. Fortunately, there is now a more sustainable method that walks users through an easy-to-follow workflow, enhancing SOP compliance and adherence to clinical timelines and budgets.

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About the author

Craig Morgan is a technology and life sciences management professional with more than 15 years of experience in the application of informatics and bioinformatics to drug discovery. He currently heads up the Marketing and Brand Development functions at goBalto, working with sponsors, CROs and sites to reduce cycle times and improve collaboration and oversight in clinical trials.

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