Paper CM03

A Journey Through End to End Data Flow

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ABSTRACT

Many organizations pursue digitization and automatization of the data flow in the clinical trial process. The creation of a platform that would encompass the whole end-to-end process from study concept to Tables, Figures, and Listings is a challenging one. UCB – a mid-size biopharma company has embarked on just that journey. Building a platform with an initial focus on risk management and protocol complexity assessments, the system's core functionalities hold the foundation to a digital protocol including the schedule of assessments, and protocol risk information. In further stages, the system was expanded to include functionalities around Quality Tolerance Limits monitoring and vendor risk management. Through this functional and data growth, a repository of digitized protocol information was created. This foundation and growth have empowered further development that focuses on digital data flow. The paper presents the concept of the system and key challenges and learnings acquired by the company in the digitization journey so far.

INTRODUCTION

At UCB everything we do starts with a simple question: “How will this create value for people living with severe chronic diseases?”, this applies to technology as well. When evaluating embarking on a journey to create a platform that would encompass the end-to-end process this question still applies. How can End to End bring value to our patients'? The answer is time. Patients with severe diseases are looking for solutions to provide them a better quality of life. Any aspect that can help reduce the time it takes to provide them with those solutions is worth the time, effort, and investment.

UCB has embarked on just that journey. Building a platform with an initial focus on risk management and protocol complexity assessments; the systems core functionalities hold the foundation to a digital protocol including a schedule of assessments and protocol risk information. In further stages, the system has matured to include functionalities around Quality Tolerance Limits monitoring and vendor risk assessment and management. Through this functional and data growth, a repository of digitized protocol information has been created. This has empowered further development that focuses on the clinical data flow.

The number and complexity of activities leading from stating the scientific question in the study concept to answering it in the clinical study report and publication are significant. A

feasible strategy in working to build an end to end platform is both defining a maturity level model as well as dividing the identified work into stages. The combination of a maturity plan and incremental solution implementations ensure that every stage generates genuine business value but also contributes to the growth of an overarching ecosystem. Defining what "maturity" means from both a technology and process perspective helps to guide the timing and strategy for progressing towards a fully mature ecosystem.

This paper presents the core clinical data flow – i.e. the envisaged scope of the automation, the business processes that were first supported by the system and key challenges and learnings acquired by the company in the digitization journey so far.

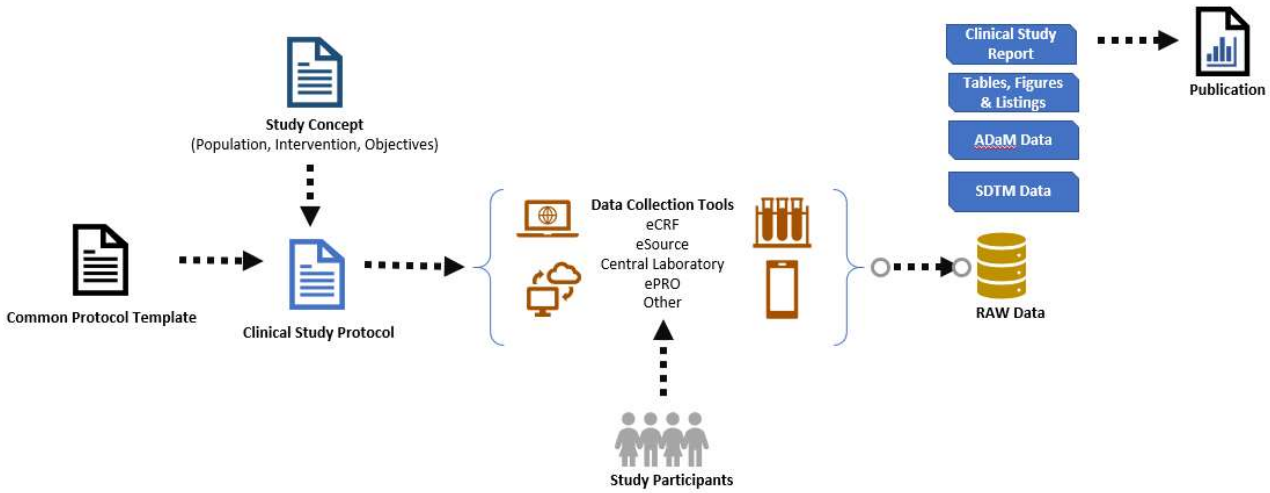
CORE DATA FLOW & SUPPORTING PROCESS

The ultimate goal of every clinical study is to answer a scientific question. Depending on the development phase, answers to these questions allow sponsors to decide on the continued development of assets, regulators on registration of medicinal products, payers on reimbursement, and finally patients and physicians on the usage of the registered medicines.

The scientific question is usually put forward in the form of a study concept that includes the population that will be studied, the intervention that will be used, and the objectives of the study. This study concept, usually after approval by the sponsor's governance bodies, is translated into a full clinical study protocol. This activity is essentially a process of merging the study-specific information included in the study concept with information standard for a study type or phase that is included in the protocol template. A document created becomes a core source of information that governs the study execution.

DRIVING NEED TO AUTOMATE

Figure 1 - Core Clinical Data Flow



Many industries have embarked on a journey towards automation. Some have been driven by the need to improve overall quality, some by the need to gain efficiencies in process, and more often it is a combination of multiple key factors. For the pharmaceutical industry, there are again multiple factors at play. Historically speaking the industry has had a tight-knit relationship with paper and the manual processes related to the collection, storage, and reporting of the information on that paper. From paper protocols to paper case report forms that collect data from participating patients, paper diaries for data entry, paper surveys all the way to submission reports and more. With paper comes some key pain points and prime

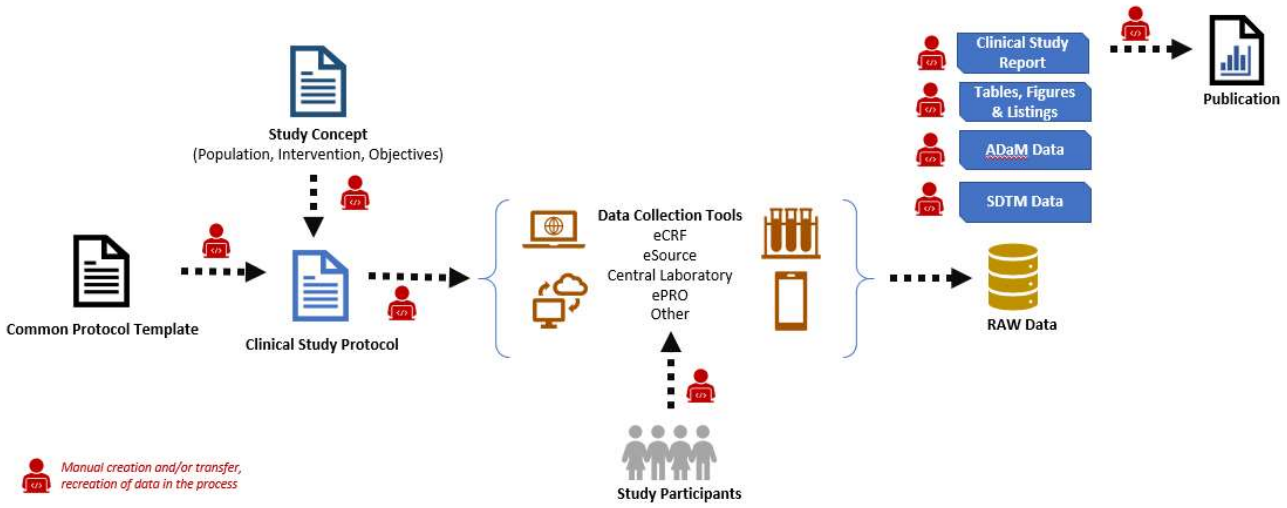
opportunities for transformation and automation. How can data only stored within the confines of a document facilitate process flow between two systems? Ask yourself why is paper still playing such a strong role. There are several key hurdles to overcome with paper. Paper in a process is time-consuming, allows for entry error, does not allow for a record of what, who, and when something changed. Paper extends the time it takes to complete a process that comes at a higher cost. Paper is not easily mined for historical analysis and data trends. Think of the last time you were asked to evaluate data that was only stored on a document. How much time and effort did it take to find and review all the paper versions of those documents to identify the answer to a simple question?

Another need to consider are the numerous technological solutions already in place in your existing architecture landscape. Each of us has our own unique infrastructure to consider. Do these existing solutions talk to each other, can they? If not, how do we evolve to an environment where they can and where fewer transitions from one platform to the next are needed but rather transformed into a seamless environment. Enabling the processes and users that are key elements to those processes to collaborate. In addition, allowing for efficiencies between those groups to be identified and implemented producing timeline gains, quality gains and enabling users to focus on more critical tasks at hand.

With pressure to shorten the time and costs it takes a compound to go through its development lifecycle the question becomes; How can we identify those processes and systems that could benefit from digital transformation and provide key connections within an end to end ecosystem.

While the industry has made great strides in adopting electronic data capture for such areas as case report forms and patient diaries, they are still struggling to transform other key aspects to a digital state. In addition, moving to electronic data capture for case report forms is still only part of the overall data flow in the bigger end to end process. What about electronic data capture further up and downstream? What and where should we be capturing data in a digital format that will facilitate data flow from as early in the overall process as possible. When asking these questions, most of the time, part of the answer that is discovered is not only are these processes disconnected but the groups responsible for each process are siloed. Silos in themselves create separation, create manual tasks to get one element from one silo to the next. This creates another key need for end to end automation. How can we break down these silos and create a seamless flow of digital information at key steps in the clinical development process? How can those handoffs be digitally managed, captured, and improved upon?

Figure 2: Identifying the Manual Elements



CURRENT TRENDS

When looking at the pharmaceutical industry that is not only heavy on process but regulated process it seems logical that end to end automation would be not only present but mature. It is, however, quite the opposite. Many struggle with identifying the right "digital" project.

The problem statement of how to create a value-add end to end ecosystem and utilize automation is being asked by many. UCB is not the only one looking to solve this riddle. There are several industry groups, technology vendors and more starting to scratch the surface of this conundrum. One group that is looking at this full picture is TransCelerate through their efforts in the Digital Data Flow workstream. While this workstream is initially focused on protocol to study startup, it too has identified the need to take a manual process to a fully automated one. Through their efforts, the workstream has identified the numerous manual gates and areas for potential automation through what could be an open-sourced, vendor-agnostic solution [6].

There are a variety of key aspects available in the world of automation. One aspect is the use of robotic process automation (RPA). At its core, RPA takes repetitive manual tasks that are clearly defined and automates them. RPA offers such benefits as efficiency, reduced costs, and consistent quality. When looking at the end to end process, a number of key repetitive manual steps can be identified for RPA implementation. One step that could be considered is as simple as transferring a file from one system to another. This would transform a manual task that not only takes time but creates white space in the end to fully automated tasks that are triggered upstream by an action in the end to end platform.

Another key tool to be considered in the end to end ecosystem is artificial intelligence (AI). Artificial intelligence comprises of varying degrees of intelligent technology from machine learning progressing to deep learning. How can these automated algorithms provide added value to the end to end goal of automating the core data flow? This can also be a strong tool to be applied in automation. In addition to considering the use of AI, there is also the powerful aspect of augmented intelligence where one can utilize the power, efficiency and improved performance provided by an algorithm and still have the human element in the defined process at smaller defined steps playing more of reviewer role. Having this integrated into the platform will help to speed up a manual process by providing suggestive content, actions,

and more. Through those intelligent suggestions, the end-user can make quick decisions that help to provide consistency and efficiencies throughout.

When considering all the technology, trends, and unknown future advancements it is important to evaluate each aspect not only independently but holistically to the overall end to end goal. Ensuring to not only look at the as-is but the potential future state that is constantly evolving with changing needs. When incrementally developing the SRAMPS platform, we have done just that. While starting at the core digital data capture functionality, this led to having the key data needed to embark on potential AI elements within the platform. As that core data set grew in both subject area and content, the ability to develop and apply the first core machine learning algorithms began. We will discuss further in the paper the aspect of predicting risk on a protocol design as well as the audits needed to ensure quality by design (Figure 6). Both added AI elements take on the augment AI approach, where the machine does the initial heavy computing and determination and the end-user accepts or decides another path. Even that decision by the end-user to decide a different path is captured and utilized in the future analysis of the algorithm for better future predictions. It is this full circle approach that grows and strengthens not only the algorithm but the overall platform itself.

RISK BASED MONITORING & QUALITY TOLERANCE LIMITS

Traditionally activities to assure the quality of clinical trials were based mainly on full source data verification (SDV) and frequent onsite visits. This approach was applied almost uniformly to almost all industry-sponsored clinical trials and generated significant cost estimated at around 30% of all trial costs. Despite the high cost, the approach was considered ineffective as demonstrated by the significant number of NDA submissions not resulting in drug approvals due to reasons not related to the efficacy of the drugs [1]. The first impulse to a more fit-for-purpose model of clinical trial monitoring came from regulators publishing their position papers in [2-3]. The industry responded by publishing TransCelerate model of Risk Based Monitoring (RBM) and piloting RBM in multiple trials [4]. Nowadays RBM is the dominant model of monitoring of trials required by ICH E6(R2) GCP.

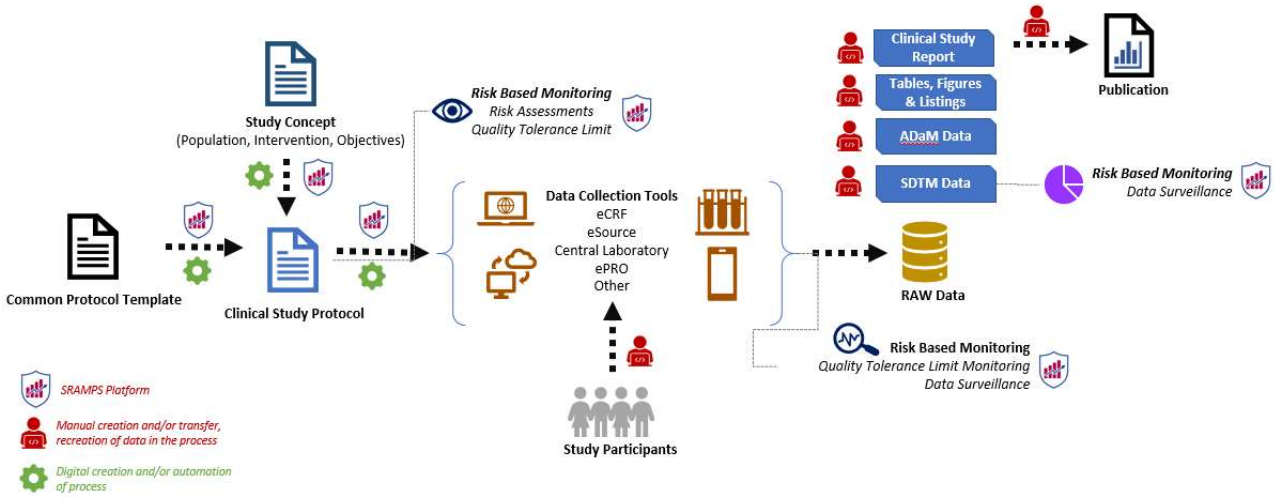
Risk Based Monitoring includes several components. Ahead of the study start critical data and processes are identified. Next, a risk assessment exercise is performed to identify risks related to critical data and processes. Based on those an overall study risk score may be calculated, and mitigations are defined. The mitigations are cross-functional but include an appropriate monitoring strategy. In the RBM model, the monitoring activities include central monitoring, remote monitoring, and onsite monitoring. The SDV is limited to the critical data where transcription errors are possible.

As part of this process, UCB's began with functionality in the platform that digitally captures those key elements needed to perform the assessment. The initial scope of UCB's SRAMPs system started with the evaluation of the process and aspects needed to support the Risk Based Monitoring processes. Through this evaluation key aspects of the protocol were identified for the initial aspect of digitization. The initial set of functionalities of the platform would digitally capture the core aspects that define the protocol such as study objectives, inclusion and exclusion criteria, data collection components, risk assessments for the purposes of Risk Based Monitoring, and protocol complexity assessments and was further expanded to Quality Tolerance Limits. Those assessments were more efficient through the digital capture of the protocol that allowed for quick and cross-functional review and risk

assessment. Within the risk assessment process, the risks and associated mitigations are captured for lifecycle management.

This was the start of the digital ecosystem, capturing what once was in paper format and now transforming that into a digital protocol. This transformation took what once was a word, excel, or even PDF file and created a machine readable format. Having this data at hand for assessment, management, and historical analysis and insights is a critical component of the platform. In addition, this initial focus set the foundation for key functionality that would be needed to grow the value and processes captured within SRAMPS.

Figure 3: The ecosystem starts to take shape within the core data flow process.



At UCB the RBM implementation included also the element of protocol complexity assessments. During this activity, all study procedures are classified according to their relation to study objectives to calculate complexity scores. Based on those scores recommendations on protocol simplifications are provided. By capturing those elements of the protocol digitally that create the protocol complexity, the platform enables a digital record of the assessment and the evolution that study design takes as it evolves from the recommended simplifications. That data can then be analyzed for future protocols design consideration. Questions such as, did the changes made to a protocol provide value? Should those be considered in the next protocol design in this compound's journey, are digitally available for analysis. Having a growing digital data protocol asset also allows for further historical analysis such as, where else has this inclusion criteria been used and were there any risks associated?

Quality Tolerance Limits was a new requirement introduced in ICH E6 R2. TransCelerate interpreted this requirement by proposing study-wide parameters that would be reflective of quality in a clinical trial and monitored throughout the study duration. According to the regulation, the deviation from the parameter should trigger the assessment for the presence of a systematic issue.

The platform has further evolved to digitally capture those defined Quality Tolerance Limits, application of those limits on a protocol, monitoring of those limits and issues and actions taken when deviations are identified. With this newly added functionality in the platform, key

value-added digital data continues to grow. With this growth, a holistic picture of a protocol, its overall risk, and quality is evolving. That evolution is growing the maturity level of the platform in both digital data being capture and the possibilities of the next step in its evolution. With a growing pool of digital data, the introduction of key machine learning can now be introduced.

The next step in SRAMPS maturity growth is to predict risks on a protocol. Implementing machine learning that looks at the historical data of the protocols and all the key associated data collected which allows for the early prediction of potential risks during future protocols design phases. Buy evaluating predicted risks during protocol design, teams are able to not only take those into consideration for the design of the protocol but allow for a proactive approach in mitigating those predicted risks.

CLINICAL STUDY QUALITY RISK ASSESSMENT & AUDIT PREDICTION

In a highly dynamic environment with more demanding compliance expectations and more complex study designs (in line with the advances of science and technology), the clinical quality role is changing.

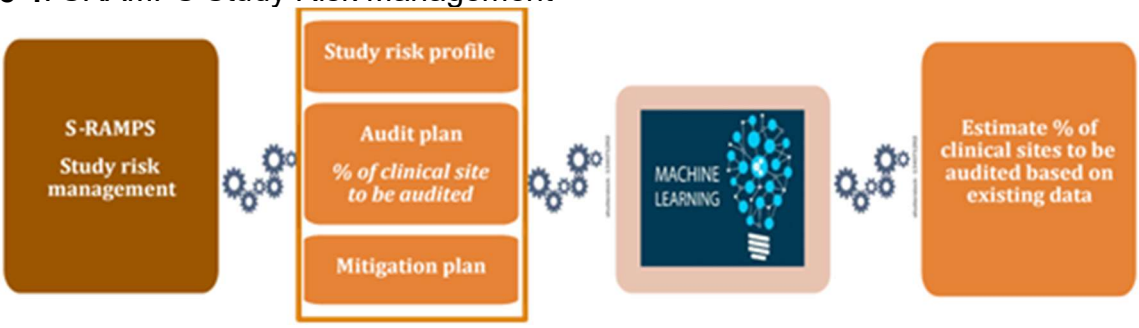
In a process where the opportunities for improvement are identified primarily as issues and formulated as '*Things that went wrong*', the role of Clinical Development Quality (CDQ) was often perceived as reactive.

The risk management framework, attempting to answer questions as '*What can go wrong?*' and '*How can it go wrong?*', change the perception to increasingly consider the CDQ role as a proactive enabler in preventing rather than remediating quality issues post audits or regulatory inspections.

Risk management should be an on-going part of the quality management process and the output/results of the risk management process should be reviewed to take into account new knowledge and experience. Proactive identification of risks, risk grading, and categorization managed in SRAMPS facilitate understanding, communication, reporting, management of risks and improves accountability in mitigation activities.

Being a key element of the Quality Management System, audits continue to be a significant component of the activities of a CDQ group. The risk management approach in SRAMPS is allowing the quality function to develop a risk-based audit approach by leveraging the study risks and their associated score for more targeted and effective audits.

Figure 4: SRAMPS Study Risk Management



In this risk management framework supported by additional in-process quality control

mechanisms (such as targeted use of metrics and key quality indicators), the quality function should foresee a monitoring, trending and analysis function. Ongoing review of quality dashboards, monitoring quality control elements, may be more cost-effective and preferred over traditional audits. The new platform enables the ability to capture the data historically empowering the teams to see a more complete picture of risks and their impact on a protocol. In addition, CDQ can now look back historically for key insights and understandings while evaluating current risk assessments.

As the CDQ function continues to gradually evolve from the implementation of Good Clinical Practices (GCP) and regulatory compliance to a broader role including a significant focus on quality risk management, the CDQ Study Risk Assessment & Management at UCB is a process to anticipate, prevent, and address protocol, regulatory, and/or GCP non-compliance issues, should they arise.

CLINICAL VENDOR QUALITY ASSESSMENT

After the implementation of the study risk management and risk-based audit plan approach, SRAMPS has continued to evolve and grow its value-add functionality. The Vendor Risk Assessment process is now captured digitally within the platform. This addition takes a prior paper-based process and transforms it digitally. With yet another risk element being captured within the platform, UCB continues to grow a holistic view of a clinical study's risk profile.

While Global Quality Assurance drives the due diligence assessments and the development of the quality agreement with third-party vendors, the quality organization will contribute to the audit and inspection section, including risk management, to ensure UCB is working in partnership with the vendors.

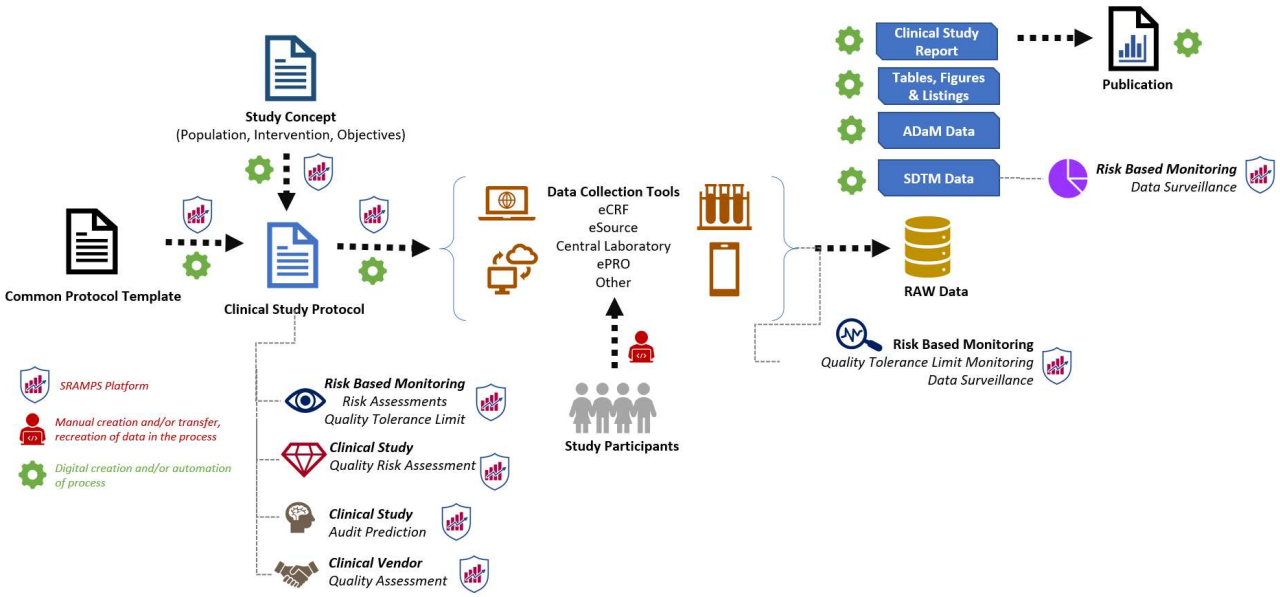
A vendor quality risk management plan (VQRM) should be completed for each vendor. The risks to be listed in the VQRM should include those which could compromise the overall quality of the services and data provided by the vendor and/or the potential impact to UCB. Risk categorization was developed to translate risk levels into GCP relevant terminology. This should allow the Vendor Quality Managers completing the Risk Assessments to make use of their judgment and audit experience to analyze identified risks in a consistent manner across vendors. Scoring of each category allows the risks to be identified and prioritized and to determine the subsequent mitigation actions to be taken for the areas of the highest risk. For each Risk Category, the Impact, and Likelihood of the risk being realized/actualized are assessed. The Management Control Effectiveness is also assessed – this determines the effectiveness of the management controls already in place for this vendor.

Connected to the SRAMPS database, a reporting environment delivers reports based on the predefined data requirements and a dashboard provides relevant information and metrics regarding the risk management framework. Approval & Filling complete the process.

Figure 5: High-Level Process Overview

Automating and replacing the manual process, the data digitally captured provides the ability to perform historical analysis gaining key insights into Study and Vendor risk trends and impact. The new release provides Clinical Development Quality with a fully integrated risk assessment and management system.

Figure 6: A Maturing End to End Clinical Data Flow



LESSONS LEARNED

Throughout this journey, UCB has learned several lessons none more critical than encouraging and growing the end user's ability to think past the "as is" and imagine that what could be. Many times, projects and change of this magnitude naturally bring out doubt and resistance. Change management is critical not only in the rollout of new functionality but more importantly at the early stages of defining and developing that new functionality. Ensuring all stakeholders and end-users are partners on the journey help to build and strengthen the collaboration and the transformative ideas. Change management for an evolution of this size and impact takes on a different meaning and embodiment. It is about culture, patience and encouraging growth and exploration. One never knows where the next idea may sprout. It is also about support from all levels of your organization.

Another key lesson learned that impacts not just the success, but the timing of impact is to take small pieces of the puzzle for implementation. When evaluating what element of end to end to develop, implement, and transform; focus on the value that element brings to the overall process and organization. Take incremental approaches that provide a return to the business in a variety of ways (financially, efficiencies, quality, and others). This positive impact and timely return will then provide additional support as well as a positive influence within the end-user community. With the growing positive impact, this helps to manage the first lesson learned on change management. Taking too long to deliver on functionality and value provide room for doubt, distraction, and disregard from stakeholders and end-users. It is critical to provide genuine business value to influential stakeholders to ensure continued support and funding to grow and move the vision forward.

As the journey continues overtime the organization must be honest in its continued evaluation of value-add functionality, this may mean that something delivered in early releases may no longer provide value, may not be needed as processes continue to evolve and it is important to look at this with an unbiased perspective. Sometimes, it might even be a “trial and error” approach, as with creating new functionalities, sometimes you can not predict which elements will prove to be useful in day-to-day practice, and which will not. This may mean decommissioning aspects of functionality to ensure the overall approach continues on a positive path. This may mean decommissioning aspects of functionality to ensure the overall approach continues on a positive path. UCB has made such choices along the way, during the evolution to bring Clinical Quality onboard synergies were identified between their risk assessments scoring process and the process within RBM. These synergies lead to the combined scoring approach and the decommissioning of the initial Risk Assessment Categorization Tool (RACT) assessment functionality within the system. This honest evaluation and change ensured the platform not only grew in the user base but ensure that functionality stays in line with the overall goals.

A key insight that was learned throughout this journey is that all things point back to the clinical study protocol. With each process that is evaluated for functionality and automation, the conversation always leads back to the core protocol elements driving downstream decisions, processes, system setups and more. Having that core protocol digitally captured to enable automation at the earliest point of the end to end journey is a critical aspect.

Another key lesson learned is the balance one must find when developing and managing a platform of this magnitude.

Balance the performance of the system to the complexity of the functionality being provided. End users want performance, it is a critical aspect to the user community embracing new technology and not only utilizing it but becoming a champion for it. But what is performance? Each group may define it differently, each technical aspect may have complexities that limit it.

Balance the control of the cross-functional list of values, code lists, and multi-use functionality. Standard values, code lists and the cross-functional use of functionalities is a key element to any platform. The management of those values can become complex when various user groups use the same list within various business processes. Too tight of control will limit the user-friendliness and flexibility of the platform. To lose control will create dirty

data. Establishing key users and governance for those elements that are standard and cross-functional from the start is critical. As the system evolves and those managed lists evolve, at times a collaborative cleaning effort may be needed to ensure the highest quality of data within the platform.

Balance user-friendliness and functionality. Often when a new platform is being developed teams will assume they know the best approach for user interfaces and functionality. Making that assumption is a mistake. You must ensure that your end users are true partners on the journey, contributing feedback and ideas on the user interface, functionality and overall interactions with the platform not solely during use but proactively during development requirements definition. Take the time at the start to include your end-users in the design thinking, screen mockups, beta testing and more to get real scenario feedback. Workshops, user groups sessions, open feedback forums and more help to establish a trust-based relationship that creates a balance between development and users. The time invested at the start will save more time later that would be spent on rebuilds. Your end-users are not "End" users but full stage partners and key collaborators in the design and definition. Who better to conceptualize ideas for functionality than the people most intimate with the process driving the functionality.

CONCLUSION

"In the middle of difficulty lies opportunities" (Albert Einstein)

In conclusion, UCB embarked on a journey to provide an application that enabled the Risk Based methodology and over time it evolved into the foundational platform that is now enabling end to end automation for the clinical data flow. Through that journey, UCB has kept an open and challenging mindset as to the "what" that could be. Through this mindset, we have not only built a platform internally but laid the foundation for our journey towards an end to end ecosystem. With the current platform capturing a digital protocol, risk assessment and management, RBM processes, Clinical Development QA, and initial implementations of augmented intelligence.

We now look to the next stage of maturity within our ecosystem and for the platform. Advancing our end to end data journey through an integrated Master Data Repository. Ensuring standards and key digital data throughout the clinical data generation lifecycle, from SDTM through clinical submission reporting and more. Growing the process and system integrations along the end to end journey and increasing the artificial intelligence impact within the platform. This growth can help to accelerate and analyze the increasing volume and complexity of clinical data allowing UCB to take meaningful timely actions. Through these timely actions and a true end to end ecosystem, we will be able to deliver impactful solutions that benefit patients' lives faster.

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RECOMMENDED READING

TransCelerate Digital Data Flow Initiative Overview.
http://www.transceleratebiopharmainc.com/wp-content/uploads/2018/12/Digital-Data-Flow_Initiative-Overview.pdf

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