
# STREAMLINING CLINICAL TRIAL START-UP WITH A KANBAN SYSTEM: A CASE STUDY TO IMPROVE EFFICIENCY AND REDUCE COSTS

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**Abstract:** This paper proposes the use of a Kanban system to improve the conduct of clinical trials for drugs and medical devices. The main goal is to shorten the lead times in clinical trial start-ups, resulting in faster access to new therapies and cost savings. Additionally, the proposed system aims to increase employee satisfaction through workload balancing and empowerment. The research is qualitative and can be further typified as a combination of case research and action research. To identify the causes of long lead times in clinical trial start-ups, two Contract Research Organizations (CROs) that conduct clinical trials for sponsors were analyzed. The proposed Kanban system was implemented in one of these companies to test its viability and results. According to initial estimates, the results show a possibility of achieving a lead time reduction of at least 7% per study. This translates to savings of about $680,000 per Phase III study of the trial and significant improvements in employee satisfaction.

## 1. Introduction

The clinical trials of drugs and medical devices have been an industry in constant expansion since its inception. According to market research published in June 2021, the global clinical trials market was worth $44.3 billion in 2020 (Grand View Research, 2021). According to the given research, a continuous growth of 5.7% is expected at the annual level until 2028, and the market is expected to be worth around $69.3 billion in 2028. Although there has been some slowdown in growth due to the COVID-19 virus pandemic, the future of the industry is bright, according to research, as the decentralization of clinical trials and the increased use of new technologies are expected to cause growth in the industry.

The goal of conducting clinical trials is to collect data that will prove the safety and effectiveness of the tested drug or medical device. Upon this evidence marketing license for the drug or medical device should be obtained. The average duration of Phase III clinical trial is about 700 days (Pharmaceutical Executive, 2008). According to estimates, the cost of

conducting a Phase III clinical trial ranges from $11.5 to $52.9 million (Applied Clinical Trials, 2018). Therefore, any extension of a clinical trial consequently leads to a delay in the release of a drug or medical device to the market. The aftereffect of this is both an increase in costs and a delay in the arrival of therapies to patients.

According to some estimates, 72% of clinical trials are more than a month behind schedule, with each additional day of delay costing clinical trial sponsors up to a whopping $8 million (Schimanski, 2013). Moreover, there are often several different drugs with similar characteristics that are in the race to the market, so a delay can mean a significantly worse starting position on the market and a potential loss in profits. It is difficult to quantify the impact of the delay of drugs and medical devices reaching patients, but it is safe to say that shortening the cycle of clinical trials and getting new therapies to patients faster can have an immeasurable impact on patient's lives.

Study start-ups are highly significant in clinical trials, as they play a crucial role in determining the success of a clinical trial, and the duration it takes to kickstart a trial may have an inverse correlation with the rate of participant enrollment (Huang et al., 2018; Cheng et al., 2010). Delaying the initiation of start-up procedures frequently leads to prolonging the overall timelines of a study, resulting in substantial additional expenses and posing a potential risk to the trial's feasibility (Atassi et al., 2013; Kantarjian et al., 2013; Kurzrock et al., 2009). The start-up phase often includes the utilization of a Contract Research Organization (CRO). The primary responsibility of the CRO is to strategically organize, synchronize, carry out, and oversee the various stages of clinical trial development. Acting as a crucial liaison between the sponsor and other key stakeholders in the trial, such as ethics committees, regulatory agencies, vendors, and hospitals, the CRO plays a pivotal role in planning, coordinating, executing, and supervising these processes. The role of CRO in clinical trial delays is somewhat controversial. For example, Krafcik et al. (2017) argue that the utilization of a CRO can either accelerate or delay the clinical trial start-up, depending on the specific aspect being considered. McClure et al. (2021) discuss common issues encountered during clinical trials and identify several connected to CROs that could delay the trial, e.g. unclear communication, inadequate staffing, and complex processes. Another issue might be the limited and/or unscalable capacity of the CRO, often as a consequence of sponsors not being fully aware of their requirements, which results in additional complexities and congestion (Tan et al., 2022; DeCorte, 2020).

Lean manufacturing has shown numerous benefits, primarily in shortening lead times, improving on-time delivery and increasing product quality (Gupta et al., 2016). It has been demonstrated that the application of lean manufacturing methods can shorten the cycle time by up to 90%. (Bhasin, 2015). One of the most recognizable elements of lean manufacturing is the pull system, a systematized way of managing material flows that has helped Toyota, as well as other companies around the world, to achieve success. The main task of the pull system is to control in-process inventory, and thereby influence the shortening and stabilization of production lead times. A typical way of implementing the pull system is through Kanban, which is one of the most frequently used tools of lean manufacturing (Tomašević et al., 2021). Although primarily used in manufacturing, Kanban is also utilized in other environments. A common area of its application is software development, as a part of an agile approach (Stalder, 2022). Some authors claim that the use of Kanban systems could bring benefits in the field of clinical trials as well (Stalder, 2022; Sampaio et al. 2021; Krishna & Ulmer, 2020). However, practical evidence of utilizing Kanban for streamlining clinical trial start-ups remains scarce.

This paper aims to investigate the organizational factors that cause long lead times and delays during clinical trial start-ups from the perspective of a CRO and to develop a Kanban system that could address these factors and streamline the process. The remainder of the paper is

organized as follows: Section 2 offers a theoretical background for the research; Section 3 describes a methodological approach used in the research; Section 4 presents the results of the research, and; Section 5 presents a discussion and the conclusion.

## 2. Theoretical background

### 2.1 Clinical trials of drugs and medical devices

A clinical trial can be defined as a prospective study comparing the effects and value of intervention(s) against a control in human beings (Friedman et al., 2015). For a certain medicine to be on the market, the medicine must go through several phases of clinical trials. According to data from the US Food and Drug Administration, the average duration from the start of clinical activities to the approval of the given agency is 8.2 years (Drug Development, 2020). It is important to note that the average of 8.2 years represents the period of clinical development, which is preceded by a period of preclinical development (molecule identification, computer simulations, laboratory testing and animal testing). Therefore, the entire cycle can last significantly longer, up to 15 years. Also, it should be taken into account that the period of 8.2 years of clinical development represents an average for all drugs, which means that for some more complex therapies, it can be significantly longer than that.

According to the guidelines of the International Conference on Harmonization, which presents the industry standard, the stages of a clinical trial could be summarized as follows (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 1997):

- Phase I - in Phase I, the drug under investigation is applied to humans for the first time. Depending on the characteristics of the drug, it can be applied either to healthy volunteers or to patients (drugs with predicted high toxicity, e.g. drugs for the treatment of carcinomas, are usually tested on patients). The goal of the study is a better understanding of the safety and tolerability of drugs, pharmacokinetics (how the drug is resorbed, metabolized and excreted from the body), pharmacodynamics (the effect of the drug depending on the dose) and the initial assessment of the therapeutic effects of the drug.
- Phase II - the main goal of Phase II is to evaluate the therapeutic effectiveness of the drug in patients. They are performed on a smaller number of patients with relatively narrow inclusion criteria (high level of similarity between patients) leading to a homogeneous population. In this phase, it is crucial to determine the doses and administration regimen that will be used for phase III.
- Phase III - the goal of Phase III studies is to demonstrate or confirm the therapeutic benefit of the drug. They are designed to confirm the data collected in Phase II. They include a larger number and greater heterogeneity of patients. Also, due to the increase in the number of patients, side effects that occur with less frequency are observed.
- Phase IV – Phase IV studies are conducted after the drug has been approved for marketing. They represent the monitoring of the use of the drug in the general population to better understand the safety of the drug and interactions with other drugs and the like.

CRO, which conducts clinical trials for clinical trial sponsors, primarily deals with Phases I, II, and III because they are necessary for a drug to receive marketing authorization (Choi et al.,

2015). From an operational aspect, a clinical trial, regardless of the phase to which it belongs, can be roughly divided into three stages:

1. Clinical trial start-up – it aims to bring the study sites to a state of readiness for the inclusion of subjects. This stage is known as a start-up or site activation, however, the meaning of the terms can vary from company to company. Some of the activities included in this part are the identification of study sites, the selection of study sites, the collection of the necessary approvals from ethical committees and regulatory bodies, and the conclusion of the necessary contracts with study sites.
2. Active implementation of a clinical trial – the essential stage from the aspect of drug development. In this part, patients are included in the clinical trial and are followed in detail to collect all the necessary data. It represents the most complex part with a large number of activities.
3. Closing of the clinical trial – the stage where the clinical trial is closed. All patients have finished participating in the trial, data processing is ongoing and it is necessary to carry out activities related to the closure of study sites, return or destruction of excess trial drugs and medical devices, and notification to the relevant authorities on the completion of the trial.

If these stages were to be observed from the highest level of decomposition, it can be concluded that the clinical trial start-up is a non-value-added stage, albeit necessary to conduct the clinical trial, while on the other hand, the next two stages create value for the stakeholders. Because of this, the aim of this paper is to consider how to shorten the clinical trial start-up time and, consequently, shorten the duration of a clinical trial in total, as delays during the start-up lead to delays in the inclusion of subjects, which later, in most cases, leads to the extension of the entire trial (Lai et al., 2021). A reduction in clinical trial lead time results in a cost reduction, a faster return on investment for sponsors of clinical trials, greater availability of new therapies to patients, and potentially lower prices of therapies due to lower development costs.

## 2.2 Delays in clinical trials start-up

Attasi et al. (2013) investigated predictors of trial start-up times and concluded that the main factor causing extended trial initiation periods is the delay in Institutional Review Board (IRB) review (which can last up to 125 days), and sites with seasoned personnel experience quicker timelines. Goyal et al. (2021) analyzed data from 9 clinical trials and found the median duration from study protocol delivery to the enrollment of the first participant was 255 days. Notably, this start-up time showed a significant improvement, decreasing from 267 days for trials conducted between 2004 and 2007 to 237 days for trials conducted between 2008 and 2012. Sites that employed a central regulatory process exhibited a significantly shorter start-up time of 199 days compared to sites using a local regulatory process, which had a longer start-up time of 287 days. Consequently, the authors suggest the use of local IRBs to shorten this time. On the other hand, Krafcik et al. (2017) argue that the use of centralized IRB decreased total clinical trial start-up time. In addition, the authors investigated other factors contributing to delays and found that total start-up time was shorter in device trials, studies that did not use a CRO, studies with a less experienced project manager, studies utilizing fewer ancillary services, and in interventional versus observational studies (Krafcik et al., 2017). Furthermore, the authors did a cause-effect analysis (in the form of an Ishikawa diagram) of reasons for start-up delays and grouped them into four categories (research personnel, access to study population, study logistics including collaboration with CROs, drug/device services, administrative issues, and delayed regulatory approvals) but don't go beyond the identification of potential causes for delays.

Lai et al. (2021) reviewed the available literature to identify any factors that might lead to delays in clinical trials start-up. The factors are systematized into 8 categories: contract negotiation, regulatory activities, logistical issues and organization of service providers, administrative activities, insurance-related activities, site identification and selection, clinical supplies, and site activation. In response to the mentioned risk factors, the authors suggest the use of a work-defined checklist as well as the hiring of experienced workers but do not go into a more detailed consideration of how to act on the variability factors that lead to delays. The authors provide several more general recommendations for preventing delays in the clinical trials start-up, such as information flow mapping, more detailed planning, greater use of technologies, etc., without explaining in detail how these recommendations could be operationalized.

### 2.3 The role of CROs in clinical trial start-up delays

Pharmaceutical organizations have begun outsourcing clinical development activities to CROs as a means of lowering drug discovery and development expenses (Wadman, 2006). However, engaging a CRO in a clinical trial can lead to delays due to an increased need for coordination, additional administrative work, and transfer of responsibilities to CROs. Krafcik et al. (2017) argue that the utilization of a CRO can either accelerate or delay the clinical trial start-up, depending on the specific aspect being considered. For example, using a CRO can decrease the time needed for administrative phases of clinical trial start-ups. On the other hand, using a CRO increases the complexity of communication, as it introduces more lines of communication and handoffs, which can contribute to delays. Schimanski (2013) suggests that both clinical trial sponsors and CROs should pursue simplification to streamline the process of monitoring and managing tasks in clinical trials start-up for multiple study sites. The author suggests that using new technologies, such as digital document management, can further increase the efficiency of the process, as well as the visibility of both information and material flows between CROs and sponsors. McClure et al. (2023) claim that some of the issues can be contributed to frequent staffing changes that are causing breaks in communication, and argue that information consolidation through centralized shared locations could address these issues.

Given the complexity of operations involving many different actors, as is the case with clinical trials, effective project management becomes crucial. CROs are often working with a network of sites, which stresses the importance of good project management and coordination within CROs' operations as well (Lamberti et al., 2013). This can be mitigated by using highly experienced project managers (Krafcik et al., 2017), or by using contemporary approaches to project management, such as agile (Stalder, 2022; Di Fiori et al., 2019). The other issue that comes with complexity is insufficient capacity, the inability to precisely track the progress for certain phases of clinical trials, and consequently inadequate resource allocation. One of the reasons for limited capacity, which can lead to delays in clinical trials, is poor communication between trial sponsors and CROs, where sponsors can't articulate their needs clearly and understandably (Tan et al., 2022; DeCorte, 2020). Consequently, this situation might require capacity adjustments later on, which are not always possible or may require more subcontracting, which requires even more coordination, or some prioritization is needed, where limited resources are allocated to projects based on some criteria, that are often not agreed upon between sponsors and CROs. The other reason is the poor management of clinical trial start-up processes by CROs. Several authors have suggested streamlining the clinical trial process, especially in the start-up phase, aimed at introducing simplicity and improving visibility, which will ultimately result in a shorter lead time (Perez-Gracia et al., 2023; Abu-Shaheen et al., 2020; Schimanski 2013).

## 3. Research methodology

The research was conducted with two main goals in mind. The first goal was to investigate some of the organizational factors that cause long lead times and delays during clinical trials start-up from the perspective of a CRO. For this part, a case study method was chosen to understand the current way of conducting clinical trials start-up. The case study was chosen because it enables the study of phenomena in the natural environment and the generation of relevant theory based on the understanding derived from the observation of real practice (Yin, 2017), which is particularly significant for this research. After all, to the best of the authors' knowledge, the application of Kanban systems has not been studied in the context of clinical trials start-up. Also, the case study allows us to answer the questions of why, what and how with a complete understanding of the nature and complexity of the phenomenon (Voss et al., 2002). The information was gathered through structured data collection methods (e.g. semi-structured interviews with the employees) and archival data.

The second goal was to propose a Kanban system that could address organizational factors that cause delays and streamline the process. For this part, action research was deemed appropriate, as it involved a series of unfolding actions over time within a specific group (Coughlan & Coghlan 2002). Action research was chosen for several reasons. Firstly, it necessitated active involvement of the research team with the practitioners to facilitate the implementation of proposed actions and enable continuous and reflective evaluation of their outcomes (Westbrook 1995; Reason & Bradbury 2001; Coughlan & Coghlan 2002). Secondly, it was expected that group members would comprehend how and why their actions could enhance the functioning of the system (Coughlan & Coghlan 2002). Lastly, the project was considered significant, with the expectation of generating sustainable changes as a result (Reason & Bradbury 2001). Action research involves cycles of diagnosis, planning, action, and evaluation of the results (Coughlan & Coghlan 2002). The diagnosis was done in the first part of the research (case study nested in the action research cycle); this was followed by planning a new Kanban system; the action of implementation was partially completed, due to time constraints; the evaluation was done partly based on the data collected by the time the manuscript was completed, and later completed through estimates of potential benefits.

Due to the limited number of available companies, two CRO companies were selected for this research. They are labelled as Company X and Company Y (real names obscured for confidentiality reasons). The smaller number of cases allows for a more detailed consideration of each case, but it must be noted that this is also a limitation of the work, (Voss et al., 2002). Both companies were used for diagnosis, while the action was implemented in Company Y.

## 4. Overview of research steps

### 4.1 Diagnosis of current organizational issues in Companies X and Y

Because the clinical trials industry is highly regulated, there are defined standard operating procedures for all activities that are performed. Standard operating procedures define what should be done and when, who should do the task, how it should be documented and the process map. It is important to note that standard operating procedures vary from company to company, companies that are at a higher organizational level have more refined procedures that contain all the elements above, while those that are at a lower organizational level may have procedures that are more descriptive than instructive. From the current point of view, companies generally

have a problem ensuring compliance with procedures, that is, following all the steps defined by the procedures. In line with this, it is questionable how much a more detailed job specification would lead to rapid improvements. Although in the long term, more detailed job specifications are necessary for a higher level of standardization, in the current situation, more detailed procedures would be introduced to the already low level of compliance, which would probably lead to great employee resistance and even less compliance.

Due to intrinsically long lead times of clinical trials start-up, which involve a lot of waiting, to achieve high staff utilization, each employee in the local team is assigned to several studies. Due to parallel activities on a large number of projects, multitasking is encouraged, which leads to a large amount of work in progress (WIP). According to Little's law (Little, 1961), a greater amount of WIP results in longer lead times. This alone shows that by encouraging multitasking, contract research companies are condemning themselves to longer lead times. From this, the basic premise is that if there is a desire to shorten flow times, the WIP should be limited. In addition, excessive amounts of WIP lead to various types of losses:

- Excessive waiting – a large part of the total lead time is waiting, where a particular resource is waiting for feedback from another resource. Due to the excessive amount of work in progress on both resources, the exchange of information is slow, which increases the overall lead time.
- Errors – there are reports that an increase in flow time leads to a decrease in quality and therefore more frequent errors occur, which in turn leads to a further increase in flow time, caused by the next type of loss, additional processing.
- Additional processing – due to the necessity for post-processing, the amount of work in progress increases and this in turn makes all other types of losses worse.
- Inefficient use of resources – due to all of the previous losses, it can be concluded that human resources are not used in the best possible way because they spend their time on either waiting, post-processing and debugging and not on creating value.

Another issue is the lack of adequate visual control over the course of the process. Due to the growth of CROs, there is an increase in specialization in local teams, so what used to be done by one person is now done by two or three specialized people. With increasing specialization, problems often arise with the distribution of responsibilities for borderline activities. Due to the lack of visual control of the process, it often happens that a couple of weeks can pass before it has been realized that a certain task is not attended to by anyone or that someone started working on it but is currently waiting for a document/information from another person while the other person is not aware that they should provide information or a document. Due to the late detection of these issues, and to avoid problems with the client, great attention is focused on expediting these tasks, which then has a negative impact on the other tasks that were in progress and now have to be postponed, which may lead to a situation where that the other tasks will also be delayed and require expedition.

As a consequence of the issues stated above, there is a high staff turnover due to employee dissatisfaction, which hurts performance and makes it difficult to achieve promotion. High staff turnover leads to various types of losses, such as reduced productivity because it takes a certain amount of time for a new person to get used to the system and procedures. The risk of losing relevant information is also present, which then results in either errors or additional work to reconstruct the relevant information. This all leads to an increase in work and creates a vicious cycle that continuously leads to even longer lead times and high staff workload.

Therefore, based on the analysis of the current way of clinical trials start-up, the conclusion is that the long lead times are mainly caused by the high amount of work in progress, the absence

of visual control and the high staff turnover. Accordingly, it is necessary to design a model that would address all of the identified organizational factors.

### 4.2 Planning of the new Kanban system in Company Y

After identifying the factors that contribute to long lead times in the previous section, the tools that can be used to act on these factors appropriately were discussed between the researchers and Company Y employees. To prevent excessive WIP, the Toyota production system uses the Kanban system, a simple solution in the form of cards that ensures withdrawal, i.e. that the upstream workstation should not produce until the downstream machine sends a signal. Based on certain parallels between software development and clinical trials, as well as the factors identified in the previous section, the Kanban system was chosen as a starting point for constructing a model for clinical trials start-up. Moreover, one of the main reasons why the Kanban system was chosen as a starting point is that the model for implementation does not require a significant change in current processes, but controls the flow of the processes in its present state. Therefore, the expected employees' resistance to changes is not expected to be significant (Anderson, 2010). Kanban cards represent tasks that need to be done, and moving the cards to the right frees the capacity, which is calculated by subtracting the number of active cards from the WIP limit for a given step (Anderson, 2010). The goal of applying a Kanban system is to equalize demand and delivery to establish a standard rhythm of work. Once the rhythm is there, all problems that might disrupt that rhythm become more visible and helps teams to focus on their resolution. By establishing a standard rhythm, the system becomes more predictable and reliable. Also, as the need for more work to enter the system increases, teams are motivated to move cards to the right as soon as possible, so there is a greater focus on communication, both internal and external, to unblock tasks (Anderson, 2010).

As noted in the previous section, increased specialization requires more coordination, which is perceived as a cost by the sponsors. In addition, decision-making becomes more centralized, which lengthens the decision-making path. Consequently, CROs should aim at reducing coordination, but also at increasing decentralization and autonomy by empowering employees at lower levels to make decisions.

All 12 steps of Anderson's (2010) model were used with some suggested adaptations. Step 6 concerning demand analysis is separated into two steps in the proposed model for clinical trials, i.e. setting the WIP limit is considered to be a separate step. Steps 8 and 9 of the original model are merged into one step because the authors' view is that due to the characteristics of the clinical trial industry, only an electronic Kanban board should be used. The content of the other steps remained unchanged, and for each step, a recommendation was given on how to implement it in the context of clinical trials. The adapted model is shown in Figure 1. The plan was to introduce the Kanban system at the level of local teams.

### 4.3 Application of the Kanban system in the Company Y

As already mentioned, the goal is to create value for clinical trial sponsors and patients by reducing lead times in clinical trial start-ups. Besides that, it is important to increase employee satisfaction by limiting the WIP, introducing visual control of work and enable employee empowerment.

A generic representation of the standard process of starting clinical trials is given in Figure 2. The process shown is an approximation of the real situation, as some details are purposely left out due to confidentiality reasons. Besides that, the process may vary depending on the country

in which the trial is conducted and the approach to clinical trials by the sponsor and CRO. With Company Y, the selection may continue even after the initiation of the sites because they gradually select the sites. Sometimes the contracts must be finalized before the approval of the study because they are necessary documents to get the approval. However, one of the defining characteristics of the Kanban system is simple adaptation, so creating a solution to every situation should not be a demanding process.

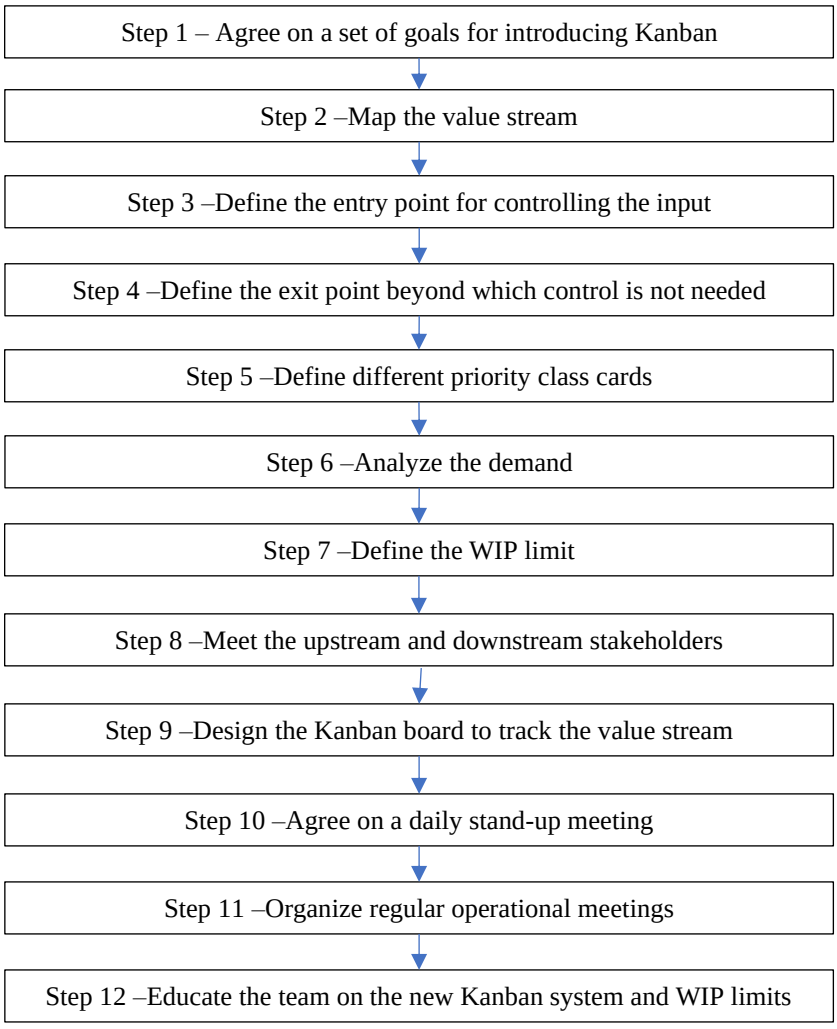


Figure 1. Steps for Kanban system introduction (adapted from Anderson, 2010)

The entry point from which control begins is the feasibility assessment. Although according to the process above it can be noted that the identification of study sites is the first step, this is usually not the responsibility of the local team. The Kanban system can also be applied to the central system, using the same principles used for the local team, but since the focus of the proposed Kanban system model is the work of the local team, the identification of the study sites will not be presented in this research. The exit point is the initiation and activation of the study site. From that point on, the study site is ready to enrol subjects and is no longer considered to be in the start-up phase.

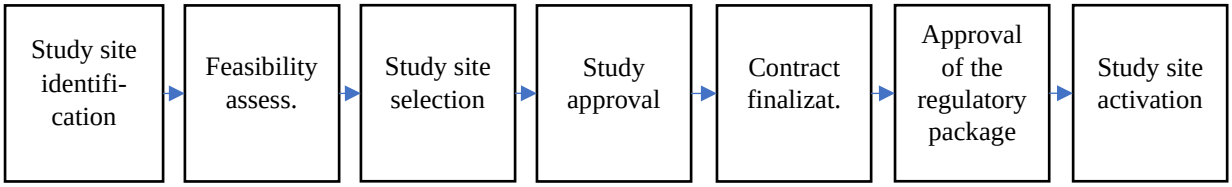

Figure 2. Generic value stream for clinical trial start-up

The original model of the Kanban system suggests four types of cards: expedite; fixed delivery date; standard class; intangible class. During the adaptation of the model for Company Y, it was decided to use just fixed delivery date cards. Due to the high focus on deadlines within the industry, the introduction of additional cards would increase the complexity of the system. The deadline is defined either based on a standard cycle time for the study start-up or based on projected due dates given to the client. However, the need for the jobs to be expedited might still emerge, and different colours of the card were introduced to signalize how much time is left before the date is due:

- Red colour – Less than 20% of the standard cycle time remaining or less than 3 business days until the deadline.
- Yellow colour – 20% to 80% of the standard cycle time has passed or less than 10 business days and more than 3 business days until the deadline.
- Green colour – More than 80% of the standard cycle time or more than 10 working days left until the deadline.

The percentages are arbitrary, and it was up to each team to adjust them to their preferences. The idea of having two criteria (percentages and fixed days) is an attempt to cover the large variability in the cycles of different tasks.

As a first step in demand analysis, the total number of hours spent on project activities listed in Figure 2 was determined. Afterwards, the monthly number of completed items for each of the activities in Figure 2 was verified. This was done to determine the average time spent completing different types of activities as well as the monthly frequency of each activity. Based on the frequency, their proportional ratio is determined, and based on the average time per activity, the number of activities that can be completed was calculated. These calculations are the basis for defining the WIP limit. As a second step, employees' time sheets were analyzed to estimate the number of overtime hours. The third analysis was done through a survey of employees regarding their perception of workload. The purpose of this and the previous analysis is to determine if the values calculated earlier need to be corrected, e.g. if the team has been overloaded in the last 12 months, those values cannot be used as a standard.

Although it is stated that it is better to define WIP limits with stakeholders from previous and subsequent processes (Anderson, 2010), the suggested adaptation is that it is more appropriate for the local team to define WIP limits. Due to the large number of local teams, it would be inappropriate to go over the WIP limits every time with the Project Management representatives, as each local team will have their own WIP limits due to their country specificities.

Although Anderson (2010) suggests that WIP limits should be defined in coordination with upstream and downstream stakeholders, It is considered crucial not to delay limit setting for WIP. After the analysis in step 6, the maximum number of cards for each of the columns on the Kanban board should be defined. It was decided to start with more relaxed limits and empirically monitor the results, to mitigate fluctuations that may arise due to changes in the structure of services. The plan was to tighten the WIP limit over time, as the entire team gets used to the Kanban system. While in software development it is not unusual for the work-in-progress limit to be 1 or even 1 per two people (Anderson, 2010), this limit needs to be greater in clinical trials due to the simpler nature of the tasks. The purpose of setting tighter limits is to prevent multitasking and context switching (Anderson, 2010), but considering the current distribution of work in Company Y, setting too strict limits would hurt the way work is done.

It is important to discuss the new Kanban system with the upstream stakeholders, which would be the Project Management sector, while the downstream stakeholders were only to be informed about the planned completion dates. The following items were discussed:

- The introduction of WIP limits and the effects that are expected.
- The ways of prioritizing clinical trials projects – when several projects compete for the capacity of the local team, the project management sector has to define priorities per the interests of Company Y. Starting a new project even though there is currently no free capacity will be possible only in cases where instructions are received from the Project Management sector which of the WIP projects can be suspended for a while, as an increase in the overall amount of WIP is not acceptable because of its negative impact on lead times of all other projects. Getting the green light from the Project Management sector for the new prioritization scheme was crucial in this step. Once consent is obtained and documented, it is the basis for the local team to reject a request to start working on a new project when there is insufficient capacity. It is also inevitable that the introduction of the Kanban system will sometimes lead to difficult but necessary discussions with the Project Management sector, i.e. the question of how to increase the productivity of local teams will be raised. But since now it will be visible how much each addition of a new WIP unit will lead to an increase in lead time, conversations will move in the direction of how to organize work in a better way and not expect workers to work more.
- Since all clinical trial start-up activities have pre-defined planned dates, the queue is formed based on deadlines. Since each activity has a planned due date, it is to be forwarded to a local team when some of the capacity is freed. In case requests arrive with similar start dates and the system does not have sufficient capacity, the local team manager escalates the situation to the project management department to prioritize the projects following the previous point.

Figures 3 and 4 give a generic overview of Kanban tables used in Company Y. The flowing factors were taken into account during the design of the Kanban table:

1. Columns for the client (sponsor), study site, ethics committee and regulatory body do not have a defined WIP limit, because it is not possible to impose a limit on external stakeholders. That is why each of these columns has columns Pr. (processing, meaning that the given stakeholder is working on a task) and Re. (ready, which means that the result of the work has reached the CRO). The next process activity draws a card from Re. column when it has available capacity.
2. As a rule, the cards go from left to right. Only in the Resolving columns, there is an option to move the card to the left. For example, if during the preparation of the documentation the client has comments, the card goes to the Resolving column, and after all the comments have been resolved the card is returned to the client until approved to continue with the next step.
3. There are certain cases where Feasibility assessment and Study site selection overlap. In those cases, cards from the Row column go directly to the Ready column in the Study site selection.
4. After the approval of the ethics committee, the documentation is submitted to the regulatory body: Central ethics committee (if applicable) – one card is created for all study sites covered by the given submission of documentation; Local ethics committee – a card is created for each study site that has its own ethics committee; Regulatory body – one card is created that includes all study sites or that covers a specific study site if the documentation is submitted before all approvals arrive; There are separate

columns on the Kanban board for ethics committees and regulatory bodies. It is not recommended to create parallel queues for individual ethics committees.

5. Two cards are made per contract - one for the budget part and one for the legal part because they are often considered by two different people at the study site, so they can have different speeds of movement.
6. To introduce additional quality into the process and greater compliance with standard operating procedures, it is recommended that the content of the task to be performed includes the following items:
    a. The name of the activity that needs to be done. For example, preparing an informed consent form;
    b. List of accompanying documentation to be generated according to the standard operating procedure. For example, a signed list of criteria for the correctness of the prepared informed consent form;
    c. Monitoring and filing activities to be done. For example, the informed consent form and the signed criteria list should be archived, and the version of the informed consent form should be entered into the system.

    Only after the worker confirms that all items are in place, the card can be moved to the order step. In case it is not possible to fill in any of the items, the reason is recorded before the card is moved. The benefits of this approach are numerous. First of all, it ensures that the card is withdrawn only after all the activities that need to be done have been completed. Additionally, it leads to a reduction in coordination costs, because the project group would track if filing activities have been completed just by looking at the board.
7. Kanban board includes a special row for expediting (framed with red lines in Figures 3 and 4). It is suggested that the WIP limit for this row should be set to 1, to avoid abuse of this row.

The structure of the Kanban card is as follows:

1. Clinical trial number and study site number (if applicable) – enables identification of a card on a board containing multiple different projects and study sites.
2. Description of the task to be completed – as previously stated, it is recommended that the card should also list the accompanying documents that should be completed while performing the task, as well as which monitoring and archiving activities should be performed.
3. The name of the employee the task has been assigned to.
4. When was the last change in the status of the card – based on this data and the data on the standard time for performing the tasks, it is easy to know which cards are at risk.
5. Standard time for completing the task – based on historical data.
6. Task due date.
7. Mark that the card should be escalated – if the due date is to be missed, the card is automatically escalated to a higher hierarchical level, which could influence the expedition of the task.
8. Mark that the card is blocked – a mark that shows that there is a certain problem that needs to be solved to be able to complete the task.

Short, morning meetings were introduced using a virtual meeting tool. The goal is to review only the most important items, without a detailed consideration of each project. Issues such as planned vs. done, escalated and blocked cards, risks of not completing all tasks, and newly discovered problems were discussed at the meetings. Monthly meetings were also organized to

discuss successes and challenges within the last month. Besides that, WIP limits, average lead times, and the trends of blocked/escalated cards were also reviewed every month.

| Row | Feasibility assessment | | | | | | | | | | | | | Study site selection | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Confidentiality contract | | | | | Questionnaire | | | | | | | | | | | | | |
| | Preparation (limit) | Study site | | Resolution (limit) | Ready (limit) | Preparation (limit) | Study site | | Resolution (limit) | Client | | Ready (limit) | | Appointment (limit) | Visit (limit) | Report (limit) | Client | | Ready (limit) |
| | | Pr. | Re. | | | | Pr. | Re. | | Pr. | Re. | | | | | | Pr. | Re. | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |

Figure 3. The configuration of the proposed Kanban board

| Study approval | | | | | | | | | | Regulatory package | | | | Study site initiation | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Preparation (limit) | Client | | Resolution (limit) | EO | | Resolution (limit) | Regulatory body | | Resolution (limit) | Complete | Ready (limit) | Preparation (limit) | Client | | Ready (limit) | Appointment (limit) | Initiation (limit) | Активација центра, (лимит) |
| | Pr. | Re. | | Pr. | Re. | | Pr. | Re. | | | | | Pr. | Re. | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| Contracts | | | | | | | | | | | | | | | | | | |
| Preparation (limit) | Client | | Resolution (limit) | Client | | Finalization (limit) | Signature (limit) | | Complete | | | | | | | | | |
| | Pr. | Re. | | Pr. | Re. | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| Documentation for regulatory package | | | | | | | | | | | | | | | | | | |
| Preparation (limit) | Study site | | Resolution (limit) | Complete | | | | | | | | | | | | | | |
| | Pr. | Re. | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |

Figure 4. The configuration of the proposed Kanban board (continued)

Finally, team members were constantly educated about the Kanban system in general and the benefits it could bring to the company. In the beginning, it was important to explain to the people that performance will be tracked continually and that a small drop in performance is to be expected until everyone gets acquainted with the system and the way it operates. It was also noted that some team members are experiencing periods of under-utilization. It was important to stress that these periods do not represent free time, but rather an opportunity to work on improving the system, and the process in general.

### 4.4 Evaluation of the results

Early results showed that it is possible to reduce the lead time for Company Y by 30%. Currently, there are no estimates of what portion of a total clinical trial start-up lead time is accounted for by CRO. The average total lead time for a clinical trial start-up is 36.4 weeks. A conservative (arbitrary) estimate is that 25% of that time is accounted for by CRO. Given the fact that an additional day in clinical trial start-up costs up to $36000 (Pharmaceutical Executive, 2008), 2.7 weeks lead time represents a savings of about $680,000 per study. It is important to note that the estimate is cautious, and that since the Kanban system is in use in Company Y for a relatively short time, possible lead time reduction could be greater once the system reaches its full stability, which means that potential savings could be even greater.

A quantitative assessment of the effects of the model on employee satisfaction is not possible because there are still no results of employee satisfaction surveys in Company Y. However, it is expected that there would be a reduction in capacity overloads and increased empowerment of local teams. Periods of under-utilization can be used for system improvement and personal development. A lower level of workload, fewer fluctuations in the amount of work, empowerment of employees and the emergence of “free time” to work on improvements should increase employee satisfaction, which should result in a decrease in staff turnover.

## 5. Discussion and conclusion

The results of applying a Kanban system or simply limiting the WIP in software development are encouraging, and in some studies, a reduction in flow time of up to 90% has been achieved (Anderson, 2010). On the other hand, there is currently no research in the field of clinical trials that practically test the hypothesis that limiting the amount of WIP with visual control of the process would lead to a shortening of the total flow time. Abu-Shaheen et al. (2020) report a lead time reduction of 45.6% as a consequence of changes in the way start-up activities are performed. While the improvement is greater than the one achieved in this research, it is important to note two things. Firstly, significant changes in the way activities are performed can lead to resistance to change among employees, as the old ways of work are being dropped. Moreover, as the process varies depending on the country in which the trial is conducted (e.g. local policies, regulatory bodies, and CRO itself), there is a possibility that suggested changes are not universally applicable. And secondly, the Kanban system in Company Y is still in its infancy, and greater results could be expected once it reaches full maturity. In addition, the proposed Kanban system is fairly simple to implement and does not require significant changes in the way activities are performed. The Kanban system utilizes several recommendations and principles for sponsors and CROs proposed by Perez-Gracia et al. (2023), as the system is simple, it avoids including unnecessary information, it uses user-friendly and intuitive electronic resources (electronic Kanban board), it increases the possibility for delegating tasks and enabling decision-making at lower organizational levels, and although it requires additional training it keeps it at a minimum required level. The system also supports the

recommendations made by Schimanski (2013), who claims that strategies in the area of clinical trials increasingly emphasize the importance of workflow management and the use of process improvement techniques such as Lean and Six Sigma, with the ultimate goal to improve visibility of the workflow and foster better communication and understanding regarding issues that might arise (e.g. blocked cards and the need for expediting) (Krafcik et al., 2017). Several authors stress the employee issue as an important factor for clinical trials start-up delays, identifying high turnover and a general lack of staff as primary issues (Abu-Shaheen et al., 2020; Krafcik et al., 2017). Although only anecdotal evidence was collected from this study, the proposed Kanban system should introduce several things that could impact the work environment in a way that could reduce turnover, namely decreased overload and consequently fewer overtime hours, increased accountability, better communication among team members, and even distribution of the workload. Finally, the system introduces several KPIs (e.g. average lead time, number of blocked/expedited cards, etc.) and promotes performance tracking through daily and monthly meetings, which are also identified as important factors for preventing delays in clinical trial start-ups (Abu-Shaheen et al., 2020; Krafcik et al., 2017).

This research primarily has implications for the practice. It proposes a framework that could easily be followed to introduce the Kanban system to any CRO, regardless of the specificities of its processes. The effects of the implementation of the Kanban system open opportunities for a CRO to pursue continuous improvement strategies that could affect other aspects of the business. The results of the study show that the improvements do not require significant changes in the way activities in the processes are performed and that significant results could be obtained through better utilization of resources that are at hand. The final implication comes from the empirical setting of the research, as the results are obtained in a real-life environment.

The research has several limitations. First, the results of the Kanban system implementation were not tracked for a sufficient amount of time, and it is still to be seen what the results would be like once the system reaches its maturity. Second, the evidence of the effects the system has on employee satisfaction is anecdotal, and more rigorous measurements are needed to support the estimates presented in this paper. And third, the focus on a single company presents a significant deficiency of the study, and more similar studies are needed for the benefit of the generalizability of the results.

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