Dynamic Process Management towards Sustained Compliance and Benefit in Clinical Research

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Summary

Beyond the countless Good Clinical Practice (GCP) regulations, successfully managing the complex processes in a clinical trial takes a multitude of skills and tools. One promising yet largely untapped set of tools for managing them appears to be dynamic process modeling and simulation. What could be its contribution to sustained compliance in clinical trials?

Taking a fresh perspective on clinical trials as dynamic processes addresses two important questions persistently arising in clinical research: How could trials be set up to generate intrinsically GCP compliant results? How could trials be managed to take no longer than planned?

This report describes a generic dynamic modeling approach for one essential section of a clinical trial, from finalized protocol to the complete Case Report Form (CRF) in house. To visualize and understand dynamic sources of non-compliance in clinical trial processes, model structures published under “strategic project management” and “quality improvement programs” in different industries have been adapted.

We hypothesize that such a model should also be a valuable tool for efficiently planning and managing clinical trials. Specifically, the model could be used as the virtual companion of a clinical trial, providing pro-active answers to “what-if”-questions before a risky try-out. The model would help establish those timely feedback loops necessary for firmly grounding process-oriented, cross-functional knowledge about GCP compliance with all people involved in a clinical trial.

Introduction

Clinical research is required to meet tough regulations. Since 1996, the International Conference on Harmonisation (ICH), together with national regulatory authorities and pharmaceutical industry associations, have successfully developed harmonized rules for globally conducting clinical trials to identical standards[1]. Although the ICH guidelines are the generally accepted "gold standard" in clinical research, slightly varying requirements can be found in national drug laws or guidance documents. [2]

To help meeting the standards, there are sophisticated packages of Standard Operating Procedures (SOPs) to be prepared exemplifying the pertinent Good Clinical Practice (GCP) rules and guidelines for each and every process step. During a clinical trial, experienced project managers, clinical monitors, investigators, and well-trained site personnel, assisted by independent auditors, work hard towards valid clinical data that is generated in compliance with the trial protocol and, following ethical principles, is free from bias and acceptable by regulatory authorities in a submission package to market a new drug.

Aside from significant irregularities, or just unforeseeable events that could cripple any planning, from a regulatory point of view the management of a clinical trial should have everything going for them. Usually one should expect clinical trials to provide compliant results right on time. However, it is still the rare event that a trial does not incur costly or even damaging delays.

Initiatives on many fronts are contributing to quality improvements in clinical trials, as for example by raising training standards, introducing advanced systems auditing techniques, or implementing comprehensive quality management systems.

Often, however, delays detrimental to a trial may be linked to the processes' dynamic behavior, which, in turn, emerges from underlying interdependencies not obvious to a local process improvement perspective.

In this paper, we suggest adopting dynamic modeling and simulation as a toolset to understand better and help managing more effectively the dynamics of clinical trial processes.

Concept for a clinical trial process model

Every clinical trial is for collecting data, which either confirm or refute hypotheses on the effects of the drug being tested. Clinical trials must be run as "one-shot-only" projects with no room for iterative improvement of the drug during a trial, and severe consequences to the project if quality did not conform to the strict regulations. Because drug development often means very substantial financial investments even before a clinical trial, schedule problems and budget overruns – being the norm rather than the exception during a trial – may seem a price worth to be paid. On the other hand, clinical trials show many of the characteristics that have been reported from the dynamics of complex development projects such as by Lyneis (2001), and Ford and Sterman (1998).

We have taken a system dynamics based approach towards improved compliance by modeling a clinical trial along the processes' natural backbone, which is the collection of data in the Case Report Form (CRF). By modeling a clinical trial as a dynamic process, we decided to take a strategic, integrative perspective on the management of a trial's processes. We hypothesize this integrated perspective to help uncover improvement potential, rather than viewing the drug developing company, the investigator site, the monitor, the external auditor, the Independent Ethics Committee (IEC), and the regulatory authorities as separate institutions working based on their own inner logic and independently from each other. Consequently, the model should be usable for exploring overall policies for both improved quality and reduced schedule problems throughout a trial.

The life of the CRF in a Clinical Trial as seen from a dynamic process point of view

The CRF plays an important part in a clinical trial as it documents for every trial participant/patient all trial-related examinations, medical history, concomitant medications and any medical events. The CRF must be unambiguously reflect the schedule of the trial protocol and must provide fields for every data point throughout the course of the clinical trial. The CRF must be designed, and handled so as to ensure maximum data quality. It is a supportive questionnaire to the investigator, a data receptacle to the investigator site personnel, and a reference memory of the data to the monitor and data management personnel. It moves through all of the process steps in a clinical trial while being transformed from a mere blank form conforming to the protocol into a precious document holding data critical to the success of the trial. When the clinical trial data is processed and statistically analyzed, the CRFs represent the source for these vital process steps towards the trial result. We therefore take the CRF for the centerpiece of a clinical trial's process model and use it for the physical quantity that flows through the process steps in the model.

When, after completion of the Drug Development Plan, the trial protocol has been developed, reviewed, and approved, the design and writing of the CRF is started. For mapping that process, we use a stock-and-flow approach. Figure 1 displays a chainlike cascading series of the process activities and the intermediate results from those activities.

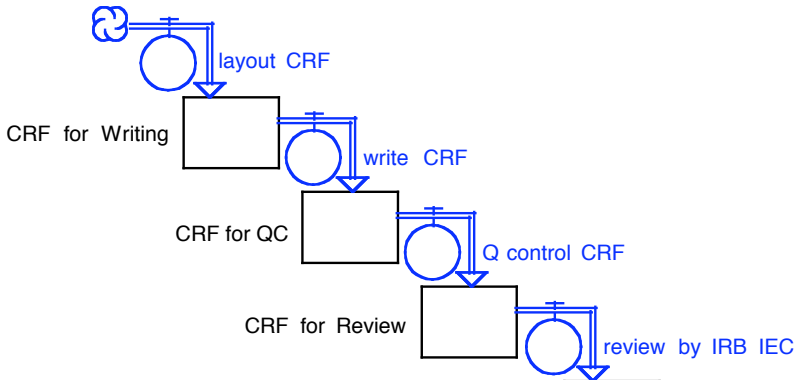

Fig. 1 Mapping of process activities and intermediate results from layout of the CRF (layout_CRF) to review of the CRF by IRB/IEC (CRF_for_Review and review_by_IRB_IEC)

In the mapping, activities are represented as flows, whereas the results from the activities are kept in stocks for the next activity to take place. After having laid out the CRF, the modules are waiting in "CRF for Writing" for the "write CRF" process activity. Next, the written CRF modules are waiting in another stock for "Q control CRF" to take place, and so on. After having passed quality control, the CRF is ready for being reviewed by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and so on.

The mapping in figure 1 depicts the overall physical flow only, without detailing interdependencies and feedback loops, which eventually make it show dynamic behavior. There are many potential causes for dynamics. The importance of understanding them might be illustrated by the following example. People writing CRFs often have to cope with two local difficulties:

- They cannot allocate most of their time to writing CRFs, and
- they are not very familiar with CRF design principles.

Both may slow down writing a bit anyway. More important though: there is likely to be a shift of the burden towards Quality Control (QC). QC now has to check quality *afterwards*, and part of the writing work probably enters a rework-loop with QC sending back to writing people work that didn't pass the standards.

On the other hand, for people performing quality control, the control of CRF writing makes up only a small part of their work because this task is added on top of their daily responsibilities. Therefore, QC people might tend to overlook some more subtle aspects of the feedback they are supposed to provide for the people writing the CRF.

Dedicated support from QC in how to achieve compliant quality in the first place would certainly improve quality, and most probably speed up processes as well, e.g. by avoiding much of the rework-cycle. Thus, among other policies, "putting your best people into QC"[3] could be key to achieving improvements for that part of the process. Through a model-based approach, thoroughly understanding the feedback dynamics of the cooperative effort of the people in writing CRF and those in QC would then become an essential prerequisite of sustained success, as has been emphasized for a different industry by Lyneis (2001).

Further downstream, some more interesting dynamics in the life of a CRF can be encountered during the clinical phase (Fig. 2). Once the initiating site visit has taken place, investigators will begin enrolling trial subjects, collect data, and fill it into the CRF. Investigators, personnel at the investigator site, and monitors are required to coordinate their respective activities according to the protocol. Often that turns out to be all but routine work, even for a single investigator site, and in the face of explicit rules and supportive guidelines. Even experienced clinical investigators are confronted with a new CRF layout and contents for each individual clinical trial.

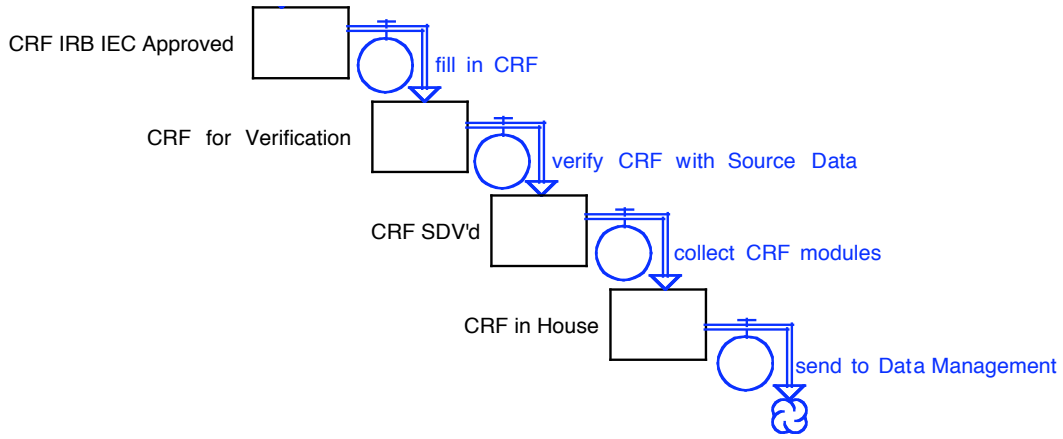

Fig. 2 Mapping of process activities further downstream (cont. from Fig. 1). The clinical phase, started by the initiating site visit, begins with filling in CRF (fill in CRF) and ends with the complete 'CRF in House' sent to Data Management

The monitor's role in a clinical trial is to support the investigator in conducting the trial, through review of trial documents and, most important, through Source Data Verification (SDV). SDV means a thorough comparison of CRF data fields with original medical records for each trial subject. The monitor has to decide when first, and with what frequency, to allocate time for CRF review on site. Opting for a later first visit at the site may give the investigator, and the site personnel, some time to collect experience with the new CRF. So the monitor's visit could be revealing more substantial information about data quality issues related to the conduct of the trial and CRF completion.
On the other hand, by choosing that option she/he may miss an opportunity for early feedback on significant questions. These typically come up during the early phases of subject enrollment and data collection. Also, quality problems and inconsistencies in the protocol and the CRF, gone unnoticed during the setup of the trial, might now call for additional explanation by the monitor to prevent mistakes early on. Besides, erroneous entries in the CRF having slipped the attention of the monitor may later prompt Data Management to cause rework on the CRF.
But early and frequent visits by the monitor increase her/his workload, potentially to the point of becoming ineffective. Source Data Verification (SDV) on site being just one of the monitor's

obligations, she/he must allocate resources wisely – and dynamically. A rigid schedule just may do for the textbook-conforming trial. Figure 3, referring to the mapping in Fig. 2, shows some of the feedback loops governing the dynamics of the interaction between the investigator, the site personnel, and the monitor during the clinical phase.

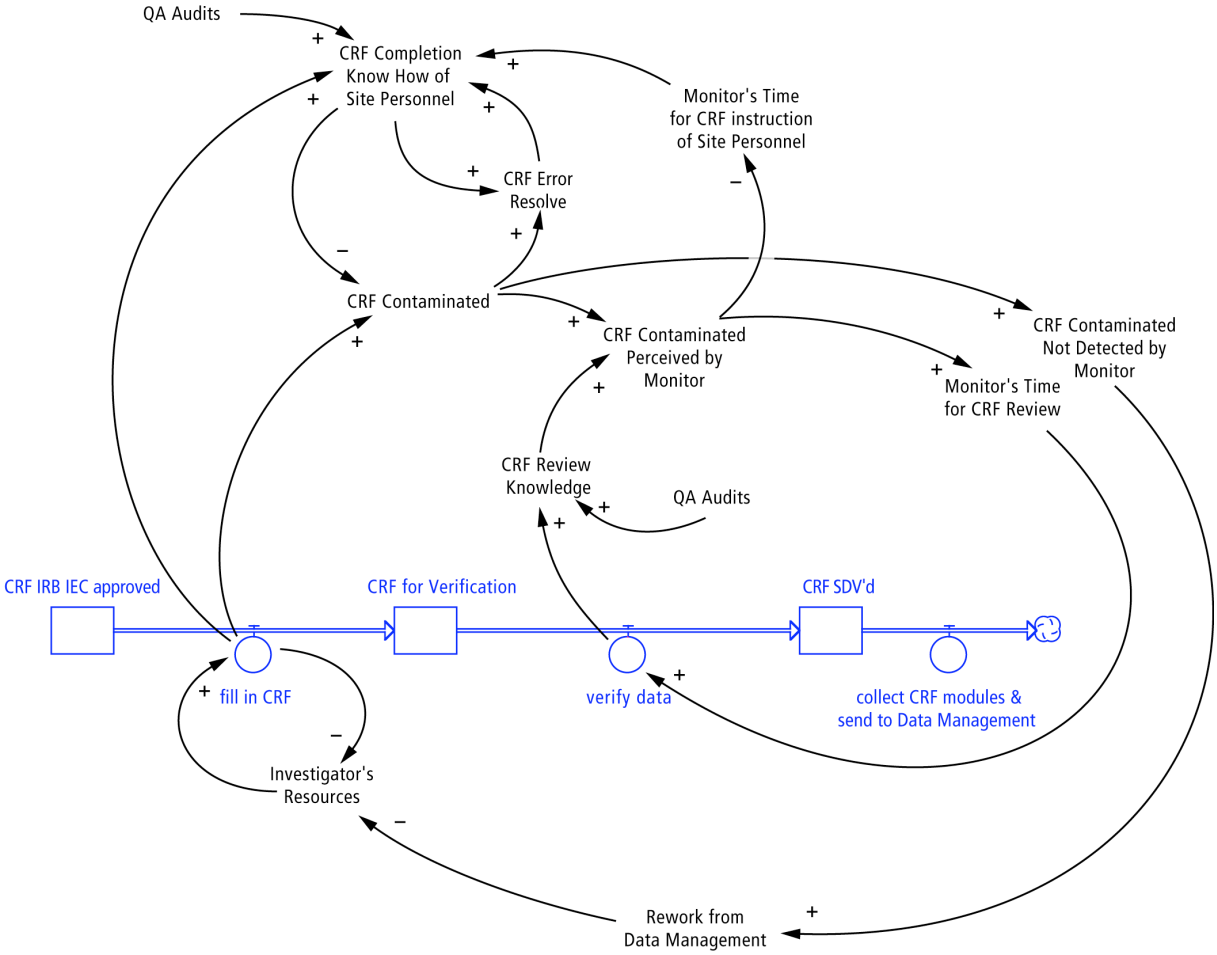

Fig. 3 Causal Loop Diagram for the clinical phase (cf. mapping in Fig. 2). Arrows indicate the direction of causality. A "+" sign means that, all else equal, by the cause increasing (decreasing) the effect increases above (decreases below) what it would have been otherwise. Likewise, a "–" sign means that, all else equal, by the cause increasing (decreasing) the effect decreases below (increases above) what it would have been otherwise.

General management tenets such as keeping good communication channels with everybody on the team, providing timely feedback on unclear issues and questionable items, and appropriately reallocating resources may help the monitor with managing the workload.
Beyond that, what could be done to avoid significant delays? How to reduce the risk of running into delayed, gradually unfolding setbacks, eventually threatening the successful progress of the clinical trial? What if there was an opportunity of playing various scenarios to see how it all worked out under given circumstances *before* choosing the best available option?

What could dynamic simulation contribute to managing a Clinical Trial

Dynamic simulation methodology has come of age in industries often less significant to the health of human beings than clinical research. It has been put to use in areas such as consumer electronics development, car manufacturing, defense project management, or in the financial services industry. It has proven successful in uprooting persistent dynamic problems in managing complex projects such as

implementing quality improvement programs or overcoming project performance problems as described by Sterman (1994), and Lyneis (2001).

Beyond being a highly effective tool for both analysis and design of complex processes, dynamic modeling and simulation has also become indispensable for learning to cope with the dynamics of complex systems. Flight simulators in the airtransport industry, based on serious dynamic models of an airplane, expose pilots to intricate situations they hopefully never encounter in reality. Without risk, that enables pilots to reflect confidently on their own deficiencies under pressure in 'Cockpit Resources Management', and develop their capabilities far beyond standard skills before facing any demanding situation in the real cockpit.

Likewise 'Management Flight Simulators' in a business environment help novices as well as seasoned managers share built-in collective experience from their fellow professionals and prepare themselves for the unexpected. More so, controlled simulations can provide them with insight into the causes of sometimes puzzling process dynamics. Why that? Many difficulties in handling complex dynamics stem from mental models characterized by poor understanding of delayed and interdependent feedback effects caused by own decisions[4].

Because the mental models underlying those decisions mostly remain untouched in day-to-day business, it takes either time-consuming, and at times embarrassing, learning the hard way, or a model-based approach directly addressing those underlying mental models. In a simulation-based learning environment, conditions in reality too few and far between can be presented in a condensed way, mental models can come uncovered, and future decisions be based on thorough understanding. This is key to intrinsic quality being managed proactively.

All of the above also holds for the clinical trial environment. However, beyond commercial consequences a drug developing company faces, there are the implications human subjects and patients have to endure. Every delay and each undetected quality problem in a clinical trial can, eventually, be translated into increased or extended risks enrolled subjects have to take, and into prolonged waiting times patients possibly have to suffer through before a drug finally can be approved by regulatory authorities, e.g. the Food and Drug Administration (FDA).

Simulating scenarios, answering what-if-questions

Drawing on extensive experience in Quality Assurance work for the clinical research industry, we have built a simulation model capable of reproducing some of the dynamics familiar from clinical trials. Currently, parameter values and nonlinear relationships used in the model have been roughly estimated from descriptive data.

A base case has been defined describing a fourty weeks long average clinical trial (Fig. 4). During nine regular one-day visits at the investigator site, the monitor reviews CRFs (SDV), every time communicating detected problems to the investigator and the site personnel, and giving recommendations for resolving the discrepancies. While completed CRFs accumulate steadily, verified CRFs are supposed to catch up with every site visit by the monitor. The accumulated number of errors found in completed CRFs usually rises during the early visits and gradually tapers off towards the end of the trial. There are various sources for errors in the CRF as for example unclear formulations of questions in the form leading to inconsistent answers, lack of experience with the new trial both with the investigator/site personnel and the monitor, and bad communication between the monitor and the site personnel. Errors that would prematurely terminate a clinical trial are exempted from the model, all others have been aggregated in 'contaminated' CRFs. Doing SDV follows a review policy typical for a monitor. Usually, for the first monitoring visit, all CRF will be reviewed and one hundred percent of data fields will be compared with source documents. For subsequent visits, in case no significant errors indicating systematic problems have been identified, only 75 percent, and then 50 percent, of the CRF are verified. Given fully dedicated attention by the monitor during a site

visit (‘monitor’s distraction’ zero), and assuming standard error rates and good communication between monitor and site personnel, no schedule problems arise and data quality stays within acceptable levels of non-significant errors.

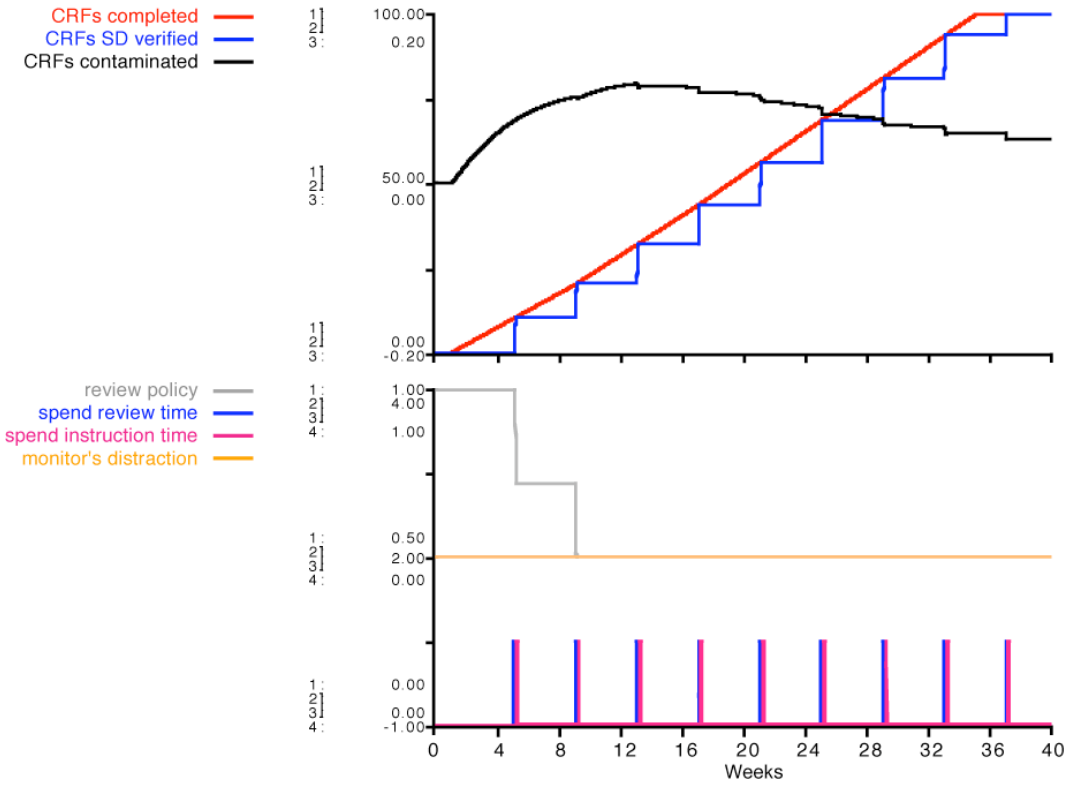

Fig. 4 Simulation of the base case. Regular visits, and undivided attention, by a skilled monitor lead to low error contamination and completed CRF in house on schedule towards the end of a trial’s time frame.

What if a monitor reduced the number of site visits for a specific trial (Fig. 5; on color representations of the following graphs: the base case remains visible in reduced opacity for easier comparison)? Monitors often are involved in more than one clinical trial at a time. A review policy commonly encountered in practice, monitors try to reduce workload by reducing the number of site visits. But the problem and error detection rates rarely depend only on the monitor’s speeding up his review work. Rather the effectivity of the communication between monitor and site personnel suffers, As corrective actions will be delayed and less effective, in the end, increased error contamination as well as schedule overrun will be the result.

Clinical investigators and site personnel usually conduct clinical trials in addition to their regular workload (Fig. 6). The time required to prepare the trial-related documentation and to complete the CRFs is often limited and, unfortunately, inadequate to produce high quality data. The lack of resources leads to fewer CRFs being completed so that massive schedule overruns are to be expected. Furthermore, following the standard monitoring and SDV policy, the monitor is confronted with increased workload as she/he is not able to provide sufficient feedback on the CRF data to the investigator. This leads to significantly higher levels of error contamination of CRF data, a fact that can not be corrected without adapting the review policy.

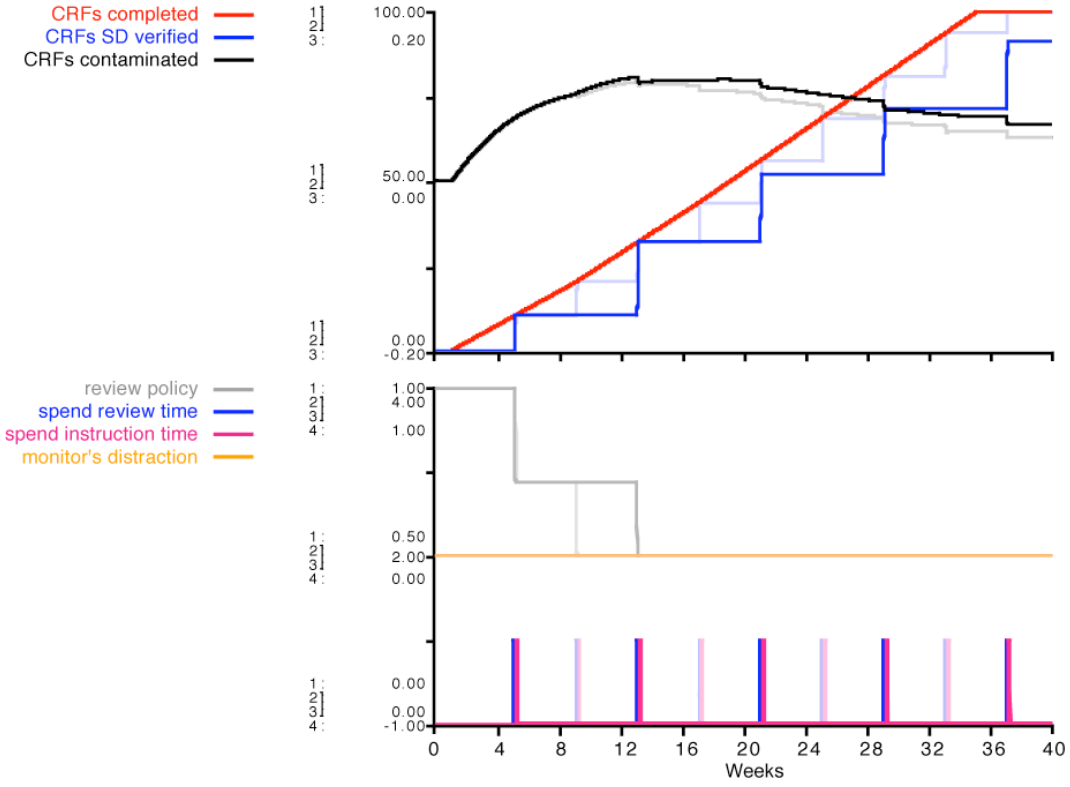

Fig. 5 The monitor reduces frequency of visits on site. The schedule would be overrun with error levels higher than normal (on color representation of the following graphs: base case remains visible in reduced opacity for easier comparison).

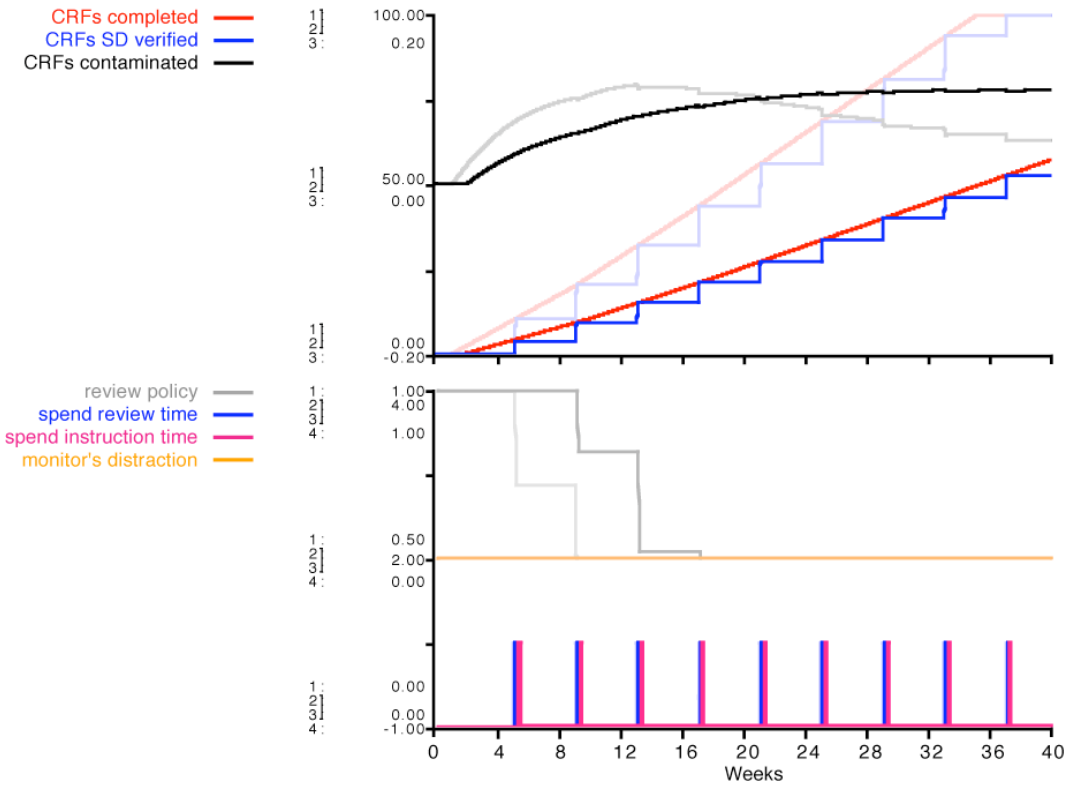

Fig. 6 The investigator lacks resources. Besides massive schedule overrun, inexperienced or overworked site personnel would likely lead to significantly higher levels of error contamination, and to increased workload of the monitor.

A QA audit in mid-term can make all of a difference (Fig. 7). QA auditors are completely independent of the departments and the personnel of the investigator, and the clinical monitor. Because they are not involved in any operational procedures related to clinical trials, they are in a position to assess compliance with the protocol and GCP regulations in an unbiased way. Therefore, the QA auditor's input typically boosts quality by raising awareness of potential sources of errors as well as improving process orientation with all people involved in the operations.

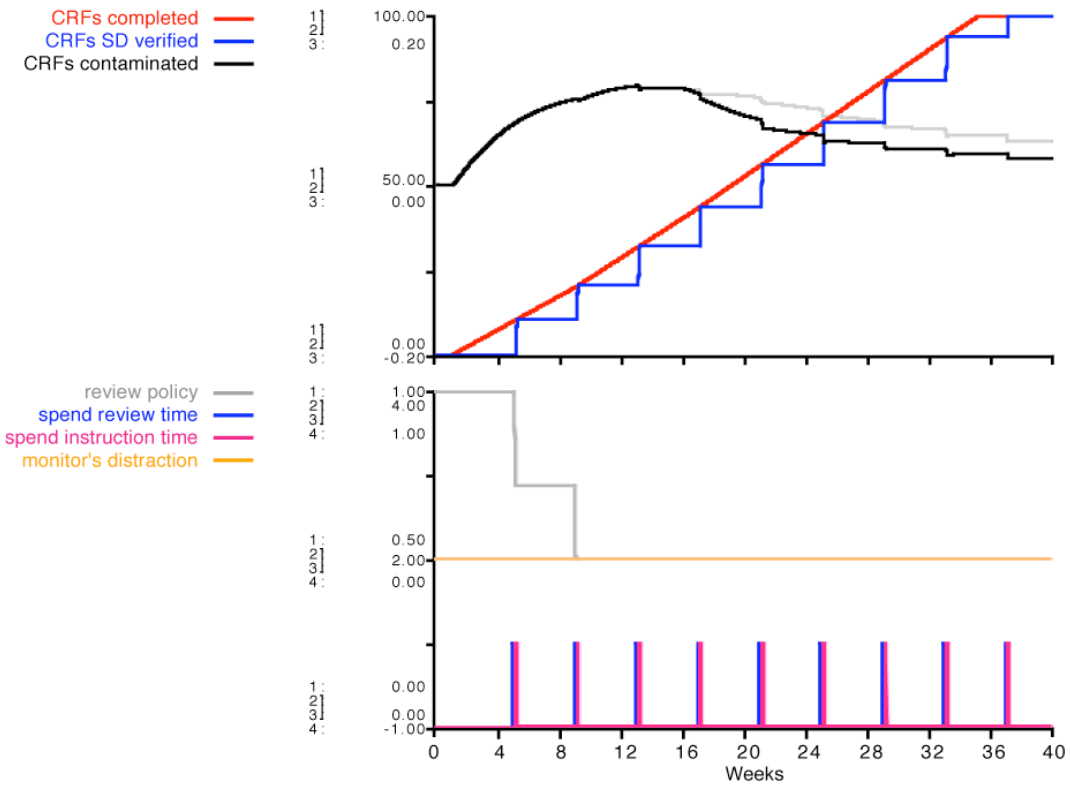

Fig. 7 Visualizing the effect of a QA audit. In mid-trial (week 16), an independent external QA auditor boosts quality. The trial likely ends with error levels significantly lower than normal, and on schedule.

Clinical monitors are confronted with a variety of responsibilities, SDV being only one of them. Organizational issues, communication with external providers as for example clinical laboratories or drug shipment facilities have to be handled as well. Therefore the available time for SDV might be significantly reduced, leading to substandard data quality and schedule overrun. Completed CRFs will pile up, and the monitor will have no chance of finishing CRF review on schedule unless the review policy is adapted.

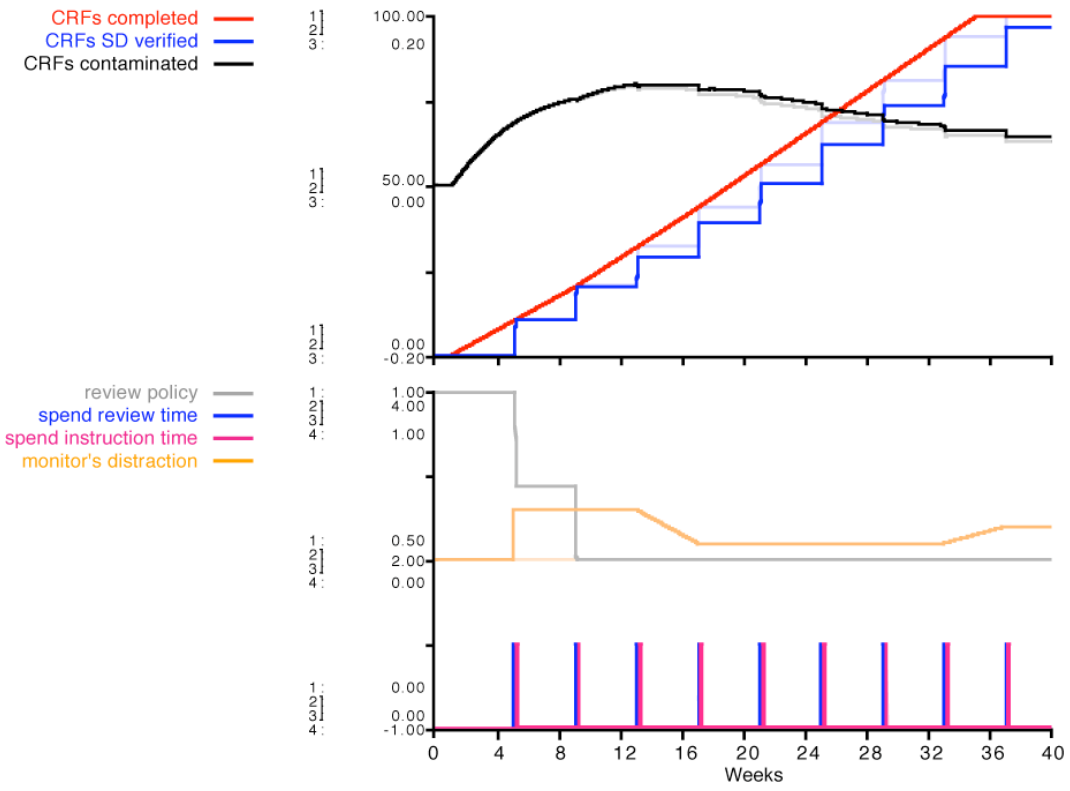

Fig. 8 Demonstrating the effect of a distracted monitor. For a distracted monitor, the likely result will be substandard data quality and schedule overrun.

Further Development

In the clinical research environment, simulation of how clinical data's availability and quality is impacted by various factors, such as lack of resources at the investigator site or the consequences of particular review policies, has helped gain a more refined process understanding. Although in an early stage of development, the model components described here have already provided interesting insight into scenarios that frequently occur in conducting clinical trials.

For further development of the model outlined in this report, the draft model will be broken down to empirically better testable modules. These modules will focus on particular problems as for example the delayed monitoring and CRF review. Some of the model structures already employed here are well known. For example, in general, Lyneis (2001), Sterman (2001) described structures such as the rework cycle and various feedback loops explaining the effects of schedule pressures on data quality. Other feedback effects more characteristic of the clinical trial environment may dominate the interdependencies of monitor, investigator, and investigator site personnel.

Together with additional modules, the model will cover dynamic problems along the entire process chain of clinical research. In particular, the data management and analysis phase as well as the impact of, by nature stochastic, subject recruitment rates on the quality and availability of CRF data will be included in the model. Furthermore, scalability of the model will have to be addressed carefully. As there are usually many investigator sites participating in a clinical trial, the monitors usually visit more than one investigator on a regular basis. By spreading their experience across different investigator sites, the monitors introduce some kind of crosstalk that will have to be modeled.

Conclusion

Already in this (fairly early) stage of our modeling project, the system dynamics approach has proven to provide new perspectives on common problems occurring in clinical research. The development of the model and the discussions on feedback loops and their specific consequences was very enlightening[5] [6]. For a professional in QA and GCP auditing, the modeling effort and the simulation model supported the move from reactively trying to mend problems towards proactively designing and supporting improved quality in clinical trials.

The process model is expected to become the basis for an innovative training tool for professionals involved in the conduct of clinical trials. It will help uncover and understand dynamic feedback effects linking process steps as well as different functional areas over space and time and, therefore, assist in increasing process awareness and quality in clinical research. Ultimately, the modeling project will help transform QA to become systemically integrated in clinical research.

Notes

[1] The Value and Benefit of ICH to Industry; *International Conference on Harmonization of the Technical Requirements for Registrations of Pharmaceuticals for Human Use*, January 2000, www.ich.org

[2] Ball, G.; Harmonised Best Practises, *Qual Assur J*, 2002; **6**: 68f

[3] Hattemer-Apostel, R.; GCP Non-Compliance – A critical reflection of the reasons and possible ways out of the dilemma, 37th DIA Annual Meeting, 9th July 2001, Denver, CO, USA

[4] Sterman JD. 2001. System Dynamics Modeling: Tools for Learning in a Complex World; *California Mgmt. Review*, **43**/4: 12

[5] Hattemer-Apostel, R.; Sustained Compliance through GCP²: Generating Compliant Processes means Good Clinical Practice; 38th DIA Annual Meeting, 19th June 2002, Chicago, IL, USA

[6] Simon, M.; Dynamic Simulation Methodology as a Tool for Enhancing Process Management; 38th DIA Annual Meeting, 19th June 2002, Chicago, IL, USA

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