Clean Clinical Research

Real RBM: Synergy of People, Processes, and Tools

Cyntegrity's and Synergy's Position Paper

Applying RBM analytics to improve patient safety and preventive care

November 2017

Table of Contents

Introduction

Nowadays many companies claim that they apply Risk-based Monitoring (RBM), however in reality it is usually only some elements of a holistic RBM implementation approach. E.g., company does centralized statistical monitoring but ignores issue management or implements Key Risk Indicators (KRIs) but is reluctant to implement risk assessment.

Two RBM consortium partners - Cyntegrity and Synergy have started a truly holistic fully-fledged RBM implementation, incorporating people, processes and tools.

The main goal of the project is to reduce clinical trial time and increase predictability of trial success.

> *"RBM is common sense and we are going to prove it", says CEO of Synergy Igor Stefanov.*

Holistic RBM, what steps does it include?

A holistic RBM process as established by the RBM Consortium[1] covers a number of vital steps following the GCP E6 R2 addendum [1]:

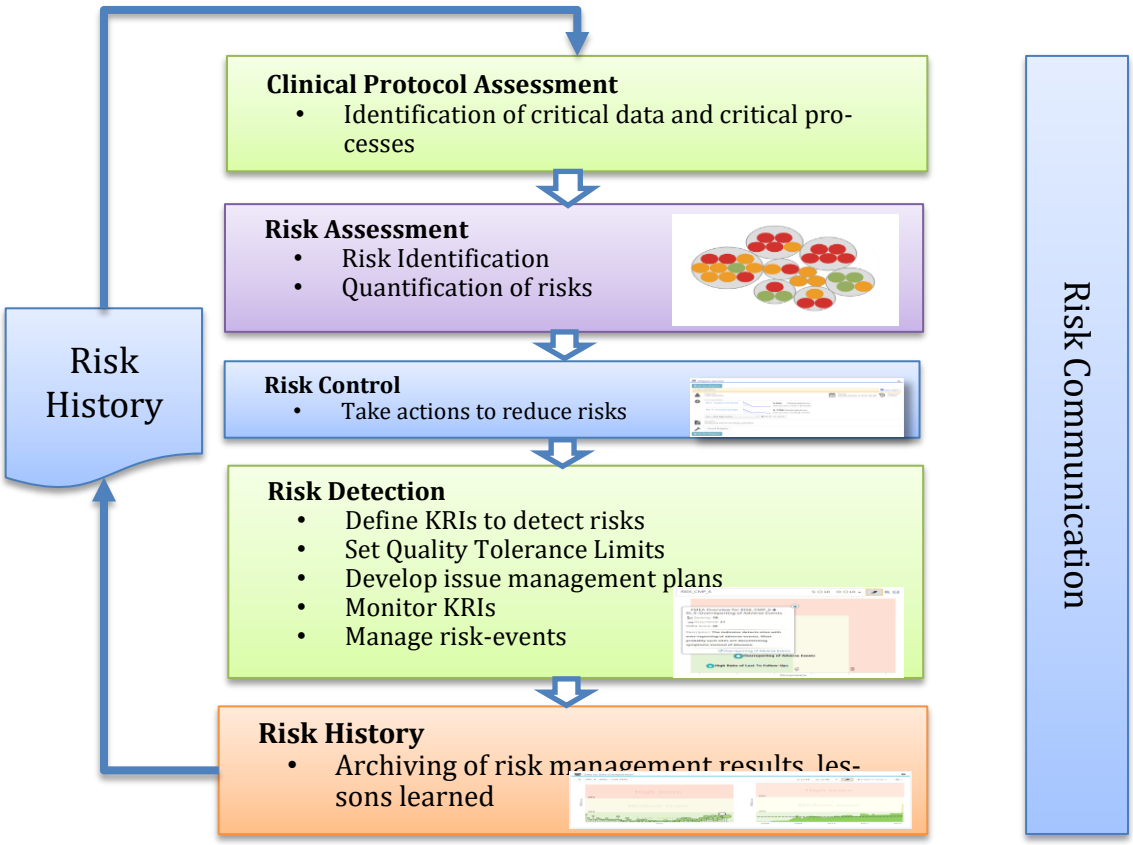

Figure 1. Holistic RBM Process according to ICH E6 (R2)

The RBM Consortium concludes in its whitepaper [2] that:

> *"Currently there's no trustworthy evidence that any RBM approach has saved a substantial amount of money, however, some companies claim petty savings. We are convinced that the implementation of a risk-based approach to manage clinical trials… will lead to clinical trials actually completing on time and on budget."*

[1] RBM Consortium – an international alliance of experts from the quality risk management industry, such as Cyntegrity and Synergy CRO.

On time and on budget – the true goal of RBM

As we all know, currently roughly 30% of an average clinical study's budget is consumed by monitoring (i.e. physical visits). It is not a rocket science that by reducing the number of visits you lower the costs. Here is where common sense kicks-in. The basics of RBM center around the idea that you only need to monitor what really needs to be monitored. The better the site, the less close monitoring you need. The better the site, the fewer the visits.

In reality surprises happen, as we all know. In theory, theory and practice are the same. In practice, they are "two different things". However, even when making our budgets with an RBM mind-set, in the end we usually have only one budget, which typically corresponds to the best scenario. Nevertheless, events rarely develop according to the most favorable plot – not only in pharma industry, but in general. Such is life.

Real-life teaches us that during the project unforeseen circumstances are expected to arise resulting in a change of course. A repetitive cycle starts of re-coordination, discussions, and negotiations, causing the trial to stall or even stop for a while. At this point in time the project begins to fall behind schedule.

Cost of risk

A far better approach is to do a reality check and conduct a preliminary assessment of all possible risks. Simple technology – evaluate risks, set triggers and plan risk mitigation tactics.

Today, a fully developed methodology [3] and affordable RBM "cloud" instruments [4] are available.

The problem is that we don't know how much it will cost to extinguish possible fires and how much money we need to reserve in the annual budget "just in case". Nevertheless, what we do know is that the costs increase exponentially in

situations where risks materialize and more and more time goes by after this event:

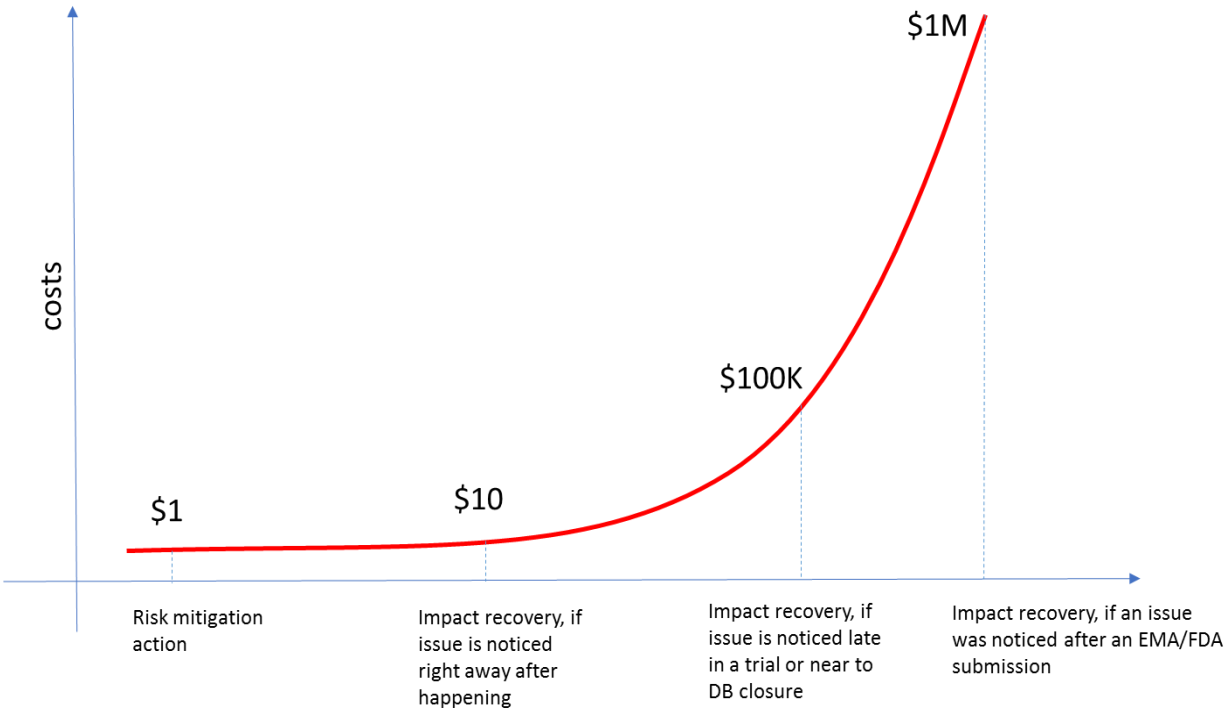

Figure 2. Cost model of pharmaceutical R&D

If risks materialize and are recognized late, you will fall behind the project schedule and require a huge "fire-fighting" budget.

In case of holistic RBM there is no need to reschedule a trial if a risk-event occurs, as we do not want to waste a second. Like in movies, there is a short call to a sponsor; "We have a situation here". In reply; "Act on plan B". And all involved know exactly what to do and how to act. As a result of this, the drug is registered on time!

The synergy of Process, People, and Tools:

The prerequisite of the above-discussed risk-intelligent behavior is the synergy of people, processes, and tools.

RBM is part of the risk management of a trial, part of quality by design, moving the emphasis from a reactive approach to a proactive approach.

The classic goal of clinical research monitoring is to be able to guarantee that the participants' rights are protected and the trial data are correct. Additionally, monitors look for protocol compliance, amendment compliance, GCP and legal compliance.

Data-driven RBM encompasses these activities: it controls data integrity, patient safety and all types of compliance. This happens remotely, rapidly and continuously.

RBM allows the monitor to focus on what really matters, providing a specialized graph for each area: insufficient recruitment, safety issues, serious protocol deviations, poorly performing sites and worthless data.

RBM system EarlyBird® does not make monitoring visits redundant, but optimize the time spent on site.

Turning RBM into a competitive advantage

By centralizing the location where all risk data are saved, managed, monitored, and reported, Synergy CRO gained the following competitive advantages:

- → Clinical projects run safely and more predictably
- → The dangers of study delays are easy to see on the dashboard, before an issue occurs
- → Data quality is increased through the elimination of systematic data noise sources
- → Clinical sites get more engaged as they receive earlier feedback

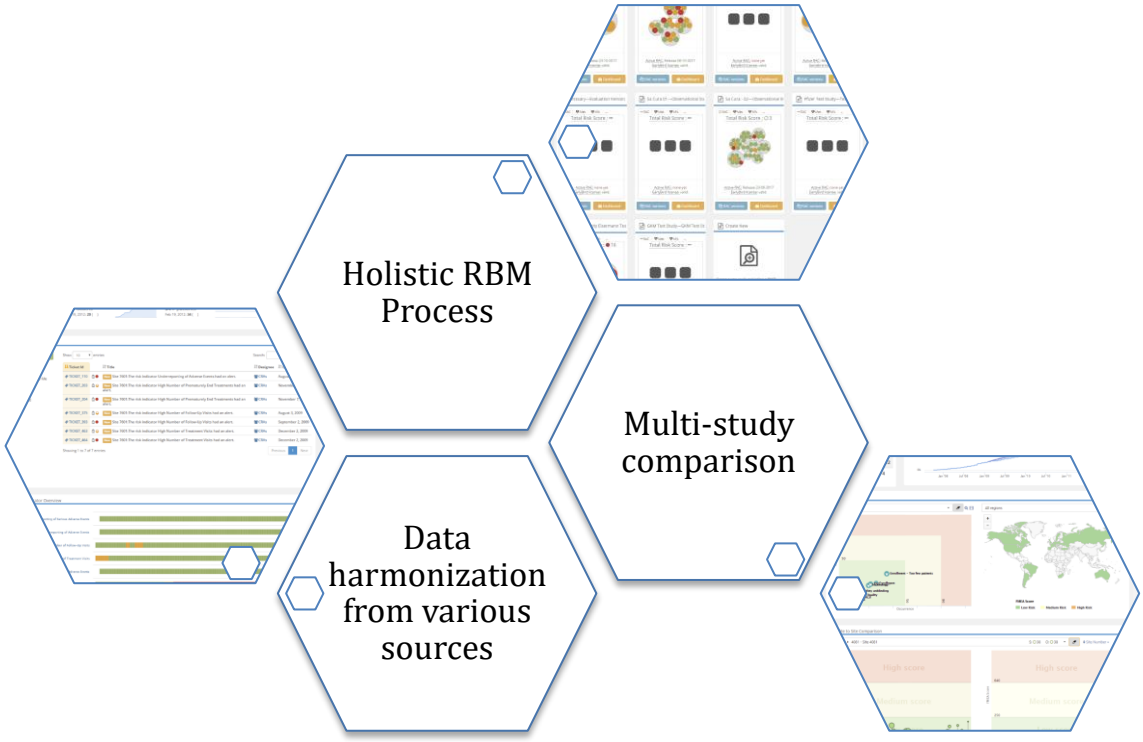

Figure 3. RBM System EarlyBird® from Cyntegrity

RBM, with its high-quality analytics capabilities has the ability to integrate knowledge from previous trials with contextual real-world data, improving patient-risk, and patient care.

It is beneficial both CROs and sponsors to take a step back and look at the current processes in order to make them more efficient, to build a sustainable, practical and efficient model. RBM offers a good opportunity for this change.

Conclusion

To do things right, it is advisable to involve external expertise for the proof-of-concept and pilot projects, because with poor implementation RBM can introduce its own risks. Align all processes, gain needed experience and lessons learned, leverage the processes with technology.

Technology plays a critical role in effective RBM. However, monitoring team remains more important. An RBM pilot trial demands well-trained monitors.

However, RBM is not a "formula" to configure and forget. It demands a structured, holistic approach. Only then, it can be used as a powerful tool to gain business, win strategic partnerships and grow further as a truly risk-intelligent pharma company or CRO.

Bibliography

[1] Artem Andrianov PhD; Beat Widler PhD; Maria Proupín-Pérez PhD, "ICH GCP Goes Risk Based," *Applied Clinical Trials*, Oct. 2015.

[2] M. Alsumidaie, M. Proupín-Pérez, A. Andrianov, B. Widler, P. Schiemann, and J. Schenk, "RbM Guidance Document: Ten Burning Questions about Risk-Based Study Management." [Online]. Available: http://www.appliedclinicaltrialsonline.com/rbm-guidance-document-ten-burning-questions-about-risk-based-study-management. [Accessed: 26-Jan-2015].

[3] TransCelerate BioPharma Inc., "Position Paper: Risk-Based Monitoring Methodology." 30-May-2013.

[4] Artem Andrianov, Ph.D., "Holistic RBM Platform for Monitoring Experts | Cyntegrity." Available: https://cyntegrity.com/products/clinical-trials-with-earlybird/. [Accessed: 10-Jan-2015].

About Us

Cyntegrity is an innovative company, which offers a specialized service with proprietary software for the efficient Risk-based Monitoring (RBM) of a clinical trial. Cyntegrity's mission is to offer high quality analytics that are more predictive than retrospective, which have the ability to integrate the knowledge from previous trials with contextual, real-world data to reduce patient risk and to optimize preventive care.

Cyntegrity offers expertise, technology and experience to make the transition to data-driven RBM fast and comfortable. We are happy to work closely together with our customers through this transformation.

Synergy Research Group is a full-service Contract Research Organization (CRO) founded in 2002 that delivers its Troika Promise of Speed, Cost and Quality to clients. The company provides transparency, access and control to sponsors during the entire project through its cloud-based monitoring system. Synergy has locations in Moscow, Saint-Petersburg, Novosibirsk, Yekaterinburg, Perm, Krasnodar, Almaty and Astana (Kazakhstan) and Kyiv (Ukraine). The company's headquarters are in Moscow.

Contact Details

Cyntegrity Germany GmbH
Altenhöferallee 3
60438 Frankfurt am Main

Tel: +49 6192 - 470 - 113 - 50
Fax: +49 6192 - 470 - 113 - 59

Artem Andrianov, PhD
Managing Director

Email: post@cyntegrity.com
Web: www.cyntegrity.com