medicinska revija
medical review

UDK: 616-071:658.562

COBISS.SR-ID 220641292

Nikolić N. et al. ■ MD-Medical Data 2015;7(4): 287-290

Aktuelne teme/
Current topics

HOW CLINICAL RESEARCH ASSOCIATE JOB UNDERGOES CHANGES IN THE AREA OF RISK-BASED MONITORING OF CLINICAL TRIALS?

KAKO SE MENJA POSAO MONITORA NA KLINIČKIM ISTRAŽIVANJIMA U OBLASTI MONITORINGA ZASNOVANOG NA PROCENJENOM RIZIKU (RBM)

Nataša Nikolić[1], Marko Simović[1], Tanja Dimitrijević[1], Marko Niketić[1]

[1] Centre for humanistic and medical studies, Belgrade, Serbia

Correspondence to:

Nataša Nikolić
Centre for humanistic and medical studies, Belgrade, Serbia
28th Skerlićeva Street, 11000 Belgrade, Serbia
Mobile: +381 64 1189892
Email: mail.natasa@gmail.com

Key words
Clinical Research Associate, risk-based monitoring, clinical trial monitoring

Ključne reči
Monitor na kliničkim istraživanjima, monitoring zasnovan na procenjenom riziku, monitoring kliničkog ispitivanja

Abstract

Both USA Food and Drug Administration (FDA) and European Medical Agency (EMA) had encouraged risk-based management (RBM) approach as the part of successful trial. The industry and regulatory bodies are going towards using risk-based management in clinical trials with a goal to decrease costs and improve study management. Many are already questioning the rationale of 100% SDV (Source Data Verification) suggesting that focus should be changed. This new IT (Informational Technology) technology will bring changes in everyday work of Clinical Research Associate (CRA). CRA is the main line of communication between Sponsor and the investigator/site with diversity of job tasks to perform. Will RBM decrease the need of CRA on and off-site? Or is industry at the beginning of understanding that CRA role will become more complex and important for the success of the trial. CRA with all previously desired skills will need to adapt and be trained (as well as the others in this business) to the whole new set of skills (deeper IT knowledge, risk and data management, patient safety, disease history and treatment etc.). This paper intends to explore how big the changes that CRA job will undergo are.

INTRODUCTION

If one decides to challenge him/herself in the field of clinical research as Clinical Research Associate (CRA, or more popularly as monitor), internet offers a lot of information. Non experienced individual just might be on a wrong track if provided information is just couple of years old. Various academic papers, experts in the field and relevant parties are for some time writing about challenging time of transformation of monitoring process, and therefore indefinitely CRA job description will be affected.

According to ICH GCP (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice), traditional monitoring is defined as: „The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).”[(1)] Even though, new draft version of ICH GCP from 11 June 2015 does include risk-based monitoring (5.18.3), it does not provide any significant changes in monitoring responsibilities (5.18.4 Monitor's Responsibilities).

With no doubt there will be significant changes in basic jobs – like CRA jobs. Will risk-based monitoring prolong the list of needed CRA skills? Or will a new job description be required?

Traditional CRA job

So what does traditionally the monitor do on a daily basis? For certain, not each day is the same, as monitoring itself does not occur each day. Most of monitors are allocated to more than one project; therefore preparation, monitoring and follow up activities can be more challenging and more time consuming than the other. Monitors usually do handle several projects at the same time and not rarely those projects are in different stages (some in startup, while the others begin with screening etc.).

Some of the core set of traditional monitor tasks include: excellent knowledge of study documentation (study protocol, IB etc.), knowledge of using different systems (like eCRF, IVRS/IWRS, CTMS etc.), coordinating with the ethics committees and other relevant regulatory bodies (and with it full understanding of ICH GCP and local regulations), liaising with clinical team in the hospital, monitoring the trial and site management (review accuracy and completeness of site records, handling investigational product, writing monitoring reports, following all adverse events etc.), closing down the sites etc.

Some monitors are assigned to the study from the very beginning, meaning they are actively involved and responsible for complete (or most of) study start up (feasibility, collecting essential documents, budget and budget negotiation, obtaining all regulatory approvals and licenses etc.). In some CROs (Contract Research Organization), monitors are as well responsible for archiving study documentation and correspondence in ISF (Investigator Site File) and TMF (Trial Master File).

What skills are required for someone wanting to enter the career of the monitor? Traditional wanted skills at job interview would definitely include: numeracy and an eye for details, ability to work under pressure, multi-tasking, ability to travel, good communication, organizational, IT (Informational Technology) and administrative skills. Background in nursing, life sciences or medical sciences is desirable due to nature of the business.

Even though working day isn't always the same, monitors obviously play multiple roles on daily basis. Monitor is a trainer (during investigator meetings, site initiations), salesperson (encouraging investigator to participate), planner (monitoring visit), negotiator (study budget), psychologist (dealing with different teams) and a detective (during site selection). (2)

Traditional CRA is facing with more and more of issues in his/her daily job. In the past few years there is an increasing inflow of clinical trial workload in almost all therapeutic areas. (3) This has posed phenomenal burden on the work-life of the field monitor. (3) As mentioned in this paper, CRA diversity of tasks is prolonging, the responsibility rises, while very few or none of the tasks have been allocated to other personnel. CRA is constantly performing multiple tasks simultaneously on a daily basis - from performing accountability (while trying to deliver key safety messages to PI (Principal Investigator)), cooperating with Study Coordinator (e.gon pending Ethics Approvals, query resolution), catching up with Study Nurse (e.g temperature excursions), analyzing inclusion-exclusion criteria with Sub-Investigators and finally performing 100% data verification. In between the on-site monitoring visits, CRA is constantly challenged with logistic (drug and lab kits delivery), technical (e.g assisting the site to access to various systems), administrative (e.g keeping TMF (Trial Master File) updated), regulatory (e.g. follow up of all regulatory approvals and notifications accurate and up-to-date) and management tasks (regular meetings within the project team, Client, Vendors).

About RMB - What risk-based monitoring (RBM) brings?

Both Food and Drug Administration (Guideline for Industry, Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, Aug 2013) and European Medical Agency (Reflection paper on risk based quality management in clinical trials, EMA/269011/2013) in their latest documents had encouraged risk-based management approach as the part of successful trial.

FDA believes „that risk-based monitoring could improve sponsor oversight of clinical investigations".(4) EMA defines RBM „as the process which should start at the time of protocol design so mitigation can be built into the protocol and other trial related documents (e.g. monitoring plan)."(4) EMA sees RBM as the way to „identify the risks on a continuous basis for risk-bearing activities throughout the design, conduct, evaluation and reporting of clinical trials." (4)

It's already been questioned many times in the past how really significant 100% SDV (Source Data Verification) is. One of the examples is partnership between Medidata and TransCelerate who will analyze the contribution of SDV to overall data quality through the use of software (analyze over 7000 clinical trials involving more than 120 sponsors). (5) Such an initiative can bring more valuable insight on this topic, as TransCelerateBioPharma Inc. as a non-profit organization now including 19 major pharmaceutical companies also working closely with regulatory bodies including the US FDA, EMA, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) with the goal to implement RBM approach in the clinical trials.(6)

One of the biggest CROs, Parexel had officially launched Data-Driven Monitoring tool in order to help sponsors develop risk-based monitoring strategies. (7)

New draft ICH GCP already included new approach to monitoring: „Centralized monitoring is a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner. Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring." (8)

RMB impact on CRO industry

Some believe that CRA role may even become obsolete or at least a much reduced role in a clinical trial. (9) On the other hand, looking at what risk-monitoring will bring, others are keener to believe that monitor job description will just need to adapt to new conditions and trends. How significant this adaptation will be? Are we on the path of a new hybrid monitor?

Advanced IT knowledge in daily work

So far, monitors were required to understand using different electronic systems and platforms like eCRF (electronic Case Report Form), IWRS/IVRS (Interactive Web/Voice Responsive System), eISF (electronic Investigator Site File) and CTMS (Clinical Trial Management systems). Per Oracle, these systems are usually linked but not really integrated (like cloud-based platform supporting RBM). (10)

This suggests that monitor will need deeper level of understanding of the systems rather than just being able to where to tick if query is resolved.

Ability to recognize, catch and prevent risks based on critical data and process indicators would require in the first place a whole set of trainings for present CRAs and definitely a new point to keep in mind when hiring. Experts, outsourced or employed in CRO, are going to be very needed, as many will need to learn - from Clinical Trial Assistants, Line Managers, Clinical Team Leaders to Human Resources Departments, Project Managers and Project Directors.

All would agree that CRA is a vivid job, full of tasks and events. Even an acronym for fun is explained as „Constantly Running Around". With new technology CRAs will be able to receive new information and triggers even more "run" in real time and decide to skip a planned visit or make an unplanned visit – all while on the road. [10] This increased mobility may just burst his/her productivity in helping the site to overcome numerous upcoming issues.

Influence on Human Resources (HR) department - Opening of new positions

If CRA will need to recognize and understand findings from remote data and review, this suggests more liaising between in-house CRAs and Data Managers (DM). Relatively recently, in-house CRA role is designated in order to work closely with CRA by providing centralized (off-site). He/she, assists with the preparation, organization and follow-up of CRA tasks and activities. These tasks include: communication with site staff for non-medical site questions, maintain of study trackers, keep an eye on TMF, assist CRA in study start up (collection of essential documents) and conduct phase (resolution of investigational data queries) etc. In-house CRA-DM could take over some DM responsibilities and duties while still actively assisting CRAs. This could be the birth of a new job description. HR department will need to be trained and refocused to different requirements when interviewing potential candidates.

Influence on Clinical operation department - Upgraded CRA

As monitors will be obviously less overloaded with SDV, the time spent on site can and should be used differently. Monitor might be finally able to analyze site performance, quality, compliance to the protocol and safety of the study participants more effectively.

EMA „Annual report of the GCP Inspectors working group" in the past several years has consistently shown persistence of a significant number of findings in fields/areas of monitoring that cannot be fully or partially captured with currently developed risk-based techniques, such as essential documents, presence and adherence to SOPs, trainings, and the quality of source documentation. [11][12] These represent critical indicators in determining sites and after all investigator product future success. These factors might have been overlooked when monitors were overloaded with SDV most of the time at their 4 to 8 weeks on-site visits.

Clinical Operation departments will need to change traditional monitoring plans. Per draft ICH GCP, „Outcomes of any centralized monitoring should also be reported". Independent consultant and trainer from the Institute of Clinical Research, Jane Tucker mentioned „the monitors also need to know how they can identify exactly what they are supposed to do on each site visit, and the processes they need to follow if they do find something is not working. They need to have a route to escalate risks that are not being managed backup to the team." [13] This calls for some level of management skills and higher responsibility in decision making process.

When she talked about CRA, in the same interview she explained that „specific background education in pharmaceutical risk management would certainly be beneficial". [13] This brings up a thought that CRA with bachelor's degree in nursing or a life sciences field, or a master's degree in medicine or pharmacy will be more desirable in the future. Having changed focus on the site's processes, Clinical Operational departments can allocate more adequate time for analyzing and follow up of adverse events, complex medical histories, concomitant medication and overall quality of data might work as advantage for employees with above mentioned background.

Therefore with the reduced „face time", strong site relationships based on ample training and clear communications are even more critical. [14] CRA becomes as a consultant, trainer and manager, who improves site performance and strengthens the relationship between sponsor and site. [15]

Influence on Regulatory Bodies

Moving away from CRA, risk-based management will influence Regulatory bodies as well. She also noted that we might expect changed focus in future inspections/audits: "Rather than inspectors looking for everything to be perfect, which isn't viable, they will be looking for evidence that a robust process was used to determine which risks required managing and what actions were taken to manage them." [13]

As stated by FDA: „A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations". [16] Maybe even on contrary, CROs will finally be able to make quality investment in protecting participants safety - through in the first place professionally trained monitor with upgraded focus both during off and on-site. The regulations are not specific about how sponsors are to conduct monitoring. This implicates that combination of traditional and new can be a winning solution at the moment and the safest way to a successful trial. FDA was clear in the same guideline stating: „Effective monitoring of clinical investigations by sponsors is critical to the protection of human subjects and the conduct of high-quality studies". [16]

EMA concluded in their reflection paper in 2013 „the current practice can however be expensive and there are too many trials in which avoidable quality problems arise. This is illustrated by the nature and extent of findings, identified by European GCP inspectors, during inspections. The combination of these findings and the high cost of the oversight of clinical trials strongly suggest that current approach to clinical quality management is in need of review and reorientation." [4]

Risk-based approach just might be a solution to „do more with less", as „limited resources can be used where

you're sure they will deliver the greatest benefit, whether it's to the study, the site, the drug development programme etc." (13)

CONCLUSION

CRA will, without a doubt stay the main line of communication between sponsor and the site/investigator, as defined in ICH GCP, no matter if Pharmaceutical companies and CROs should embrace risk-based approach entirely or not.

While the whole industries RBM knowledge and experience is still fragile and at its beginning, combination of well-established traditional on-site monitoring and RBM can be the win-win solution with one premise. CRA's focus needs to be shifted on higher-value tasks, which can make more significant contributions to the success of studies.

Therefore, CRA role will become more complex and demanding but as well more important for the success of the trial. New set of skill will be required and the whole industry will need to be trained and adapt quickly. CRAs with good multi-tasking, communication and detail orientated approach might just not be enough, but additional deeper IT, management and life-science knowledgemight be what the industry will be looking for.

Sažetak

Američka Agencija za hranu i lekove (FDA) i Evropska Agencija za lekove (EMA) su ohrabrili pristup „monitoring zasnovan na procenjenom riziku" (na engl. „risk-based management" (RBM)) kao deo uspešne kliničke studije. Industrija i regulatorna tela žele da korsite RBM u kliničkim ispitivanjima sa ciljem da se smanje troškovi i poboljša upravljenje studijom. Mnogi već dovode u pitanje opravdanost provere 100% izvornih podataka (na engl. SDV – source data verification) predlažući da se ovaj fokus promeni. Ova nova informaciona tehnologija doneće promene u svakodnevnom poslu monitora na kliničkom istraživanju. Monitor predstavlja glavnu liniju komunikacije između Sponzora i istraživača/bolnice sa raznovrsnim poslovima koje treba da obavi. Da li će RMB smanjiti potrebu za monitorima i kad su van bolnica? Ili industrija počinje da shvata da monitorska uloga postaje sve složenija i važnija za uspeh kliničke studije. Monitor sa svim prethodno traženim veštinama će morati da se prilagodi i edukuje (kao i svi ostali u ovoj industriji) na čitav spektar novih veština (naprednije znanje korišćenja informacionih tehnologija, upravljanje rizicima i podacima, bezbednost pacijenata, istorija bolesti i lečenje itd.). Ovaj rad ima za cilj da istraži koliko velike su promene kojim će monitor na kliničkim ispitivanjima biti podvrgnut.

REFERENCE

1. ICH Harmonized Tripartite Guideline for Good Clinical Practice E6 (R1). UK: The Institute of Clinical Research; 1996
2. Kunal Shah, A day in the life of a monitor! PerspectClin Res. 2010 Oct-Dec; 1(4): 134–138.
3. Kamala Rai. Integrated monitoring: Setting new standards for the next decade of clinical trial practice. PerspectClin Res. 2011 Jan-Mar; 2(1): 28–33.
4. Reflection paper on risk based quality management in clinical trials. European Medicines Agency. EMA/269011/2013. 18 November 201
5. Brennan Z, TransCelerate partners with Medidata to focus on risk-based monitoring, 22 May 2014
6. http://www.transceleratebiopharmainc.com/
7. Brennan Z, TransCelerate partners with Medidata to focus on risk-based monitoring, 22 May 2014
8. Brennan Z, Parexel hones in on risk-based monitoring with new tool, 21 May 2014
9. Integrated Addendum to ICH E6(R1): Guideline for good clinical practice E6(R2) Current Step 2 version, 11 June 2015
10. An Oracle White Paper, Beyond SDV: enabling holistic, strategic risk-based monitoring. CA: Oracle Health Sciences; 2014
11. Annual report of the Good Clinical Practice Inspectors Working Group 2012. European Medicines Agency. EMA/627138/2012. 28 May 2013
12. Simovic M, Nikolic N. Challenges of risk-based monitoring of clinical trials. Clin Res RegulAff. 2015; Vol.32, No.3: 85-89
13. Tucker J, Understanding Risk-Based Monitoring: An interview, http://www.icr-global.org/crfocus/2012/23-1/understanding-risk-based-monitoring
14. Artyomenko A, Medpace. Newpaper. http://www.medpace.com/Offers/RBM/ Risk-Based-Monitoring-Medpace-Whitepaper.pdf
15. Rosenberg M, Goldfarb N. The Site Monitor Reborn as Consultant, Trainer and Manager, J Clin Res Best Pract 2007; 3(3):3
16. FDA Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring - August 2013

■ The paper was received on 10.11.2015. / Accepted on 15.11.2015.