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A Systematic Review to Observe the Impact of Risk-Based Monitoring as Compared to Conventional On-Site Monitoring in Randomised Clinical Trials and Quality Management in Large Cohort Studies

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Abstract

International Council for Harmonisation, Good Clinical Practice R2 (ICH GCP R2) focuses on quality management as per risk-based methodology, and there has been a lot of focus on monitoring strategy, which is a mixed method of on-site and centralised monitoring. This systematic review was planned to search for the articles providing the evidence for the impact of risk-based monitoring methodology and monitoring standards for cohort studies. A literature search was performed on MEDLINE, COCHRANE, and WEB OF SCIENCE were as per the keyword's searches. All the publications were reviewed for the data that provides evidence risk-based monitoring for randomised clinical trials and its impact to ensure that data integrity, patient safety, and results obtained were reliable. The search resulted in four articles that were qualified that discussed about the comparison between monitoring techniques and the risk-based monitoring methodology in randomised control trials and other interventional trials. Two publications suggested that the SDV% can be <8% and range from 20-50%, respectively, depending on the assessed factors and risks. Although there is research being conducted to generate the evidence for risk-based monitoring and reduced SDV linked to data errors, further empirical quantitative research should happen to show the impact of risk-based methodology for clinical trials. There is a lack of systematic and empirical data for monitoring as part of quality management in cohort studies.

Keywords*: Cohort, monitoring, Quality management, Risk-based monitoring, Source data verification.*

Introduction

ICH-GCP E6 R2 guideline [1] for Good Clinical Practice (GCP) states that "the sponsor should implement a system to manage quality throughout all stages of the trial process. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results". The guidelines advise that the quality management system should use a risk-based approach. The guideline also defines monitoring 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), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)" and has further added that it is the responsibility of the sponsor to develop a systematic, prioritized, risk-based approach to monitoring clinical trials. It provides flexibility in the extent and nature of monitoring by providing the following approaches that improve the effectiveness and efficiency of monitoring, with appropriate explanation to the approach.

1. On-site monitoring.
2. A combination of on-site and centralized monitoring.

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3. Centralized monitoring only, where justified.

As one of the purposes of monitoring is to ensure that the reported trial data are accurate, complete, and verifiable from source documents, sponsors have relied on 100% source data verification (SDV) as a primary method of monitoring. However, this approach does not guarantee error-free data and reliable results. Historically, the 1988 FDA Guidance on Monitoring of Clinical Investigations stressed personal contact between the monitor and investigator. USFDA withdrew the same in 2010 as evidence grew for the need of a shift in monitoring approach. The 1996 ICH E6 (GCP Guideline) provided flexibility in how trials are monitored; centralized monitoring alone is appropriate only in exceptional circumstances. In 1998, USFDA issued a guidance document in which the agency suggested that monitoring can be flexible so far it is acceptable and provides data standards for studies with minimal on-site monitoring. In 2009 Clinical Trial Transformation Initiative (CTTI) was formed, and the mission was to identify practices that, through broad adoption, will increase the quality and efficiency of clinical trials. CTTI included 120 members from FDA, academia, industry, government, and patients and investigators. The project was to identify current monitoring practices and link it with Quality by Design (QbD [2] principles to clinical trials. During the period of 2009 and 2010, there were more FDA Warning Letters issued to Sponsors with findings of failure to adequately monitor clinical investigators. These findings included an improper selection of investigators who subsequently failed to meet GCP requirements, failure of monitors to find protocol compliance issues, and/or failure of sponsors to promptly take actions to correct deficiencies when identified through monitoring.

In 2011 two draft documents were issued from the FDA and the EMA to modify our monitoring practices. In 2013, the FDA and EMA each finalized their guidance documents. The landmark shift happened in 2014 when Trancelerate issued a position paper on Risk-based monitoring (RBM) methodology [3]. The paper that suggested to shift the monitoring processes from an excessive concentration on Source Data Verification to comprehensive risk driven monitoring. The impact of RBM was targeted to have earlier detection of issues, with a greater focus on resolution and prevention of issue recurrence, reduction in efforts expended on low-value activities through centralization and data analysis, cost reductions through more focused centralized monitoring activities, and targeted on-site monitoring, greater compliance with Good Clinical Practice (GCP), relevant regulatory requirements and a more collaborative cross-functional team approach – the coordination of monitors, data managers, statisticians, medical monitors, and site staff.

Since then, there have been research studies and systematic reviews in monitoring methodology for clinical trials to show that reduced % of SDV is non-inferior to 100% SDV [4]. However, the systematic review research has been limited to interventional randomised control trials where monitoring is conducted in routine settings [4]. Systematic review for clinical trials shows that one hundred percent SDV is not a rational method of ensuring data integrity and subject safety based on the high cost, and this literature review indicates that reduced SDV is a viable monitoring method [5]. There has been no work done in Cohort studies. However, it is important and significant to have the monitoring techniques defined as a standard practice in Cohort studies also, as the data collected need to be reliable as they feed into policy and give the pathway to translational research.

The data is critical, and safety is important as these are extra test beyond standard of care for collection of data. With Cohort studies, the monitoring is conducted with a different approach and has been an area, which lacks research. With the above background, the systematic review is aimed to identify, examine,

and investigate the available literature for the monitoring approaches executed in cohort studies.

Methods

There have been several clinical research systematic reviews, however, primarily for clinical settings and disease indication. A systematic review is an approach towards identifying the literature and analysing the literature data. This review provides the basis to identify, examine and investigate the available literature for the monitoring approaches in interventional clinical trials and cohort studies. We conducted a search by defining the protocol with primary objective to identify, examine and investigate the published papers for the monitoring approaches in clinical studies for randomised control trials (update systematic review for other interventional clinical studies) and cohort studies. We planned to extract data on different monitoring approaches, identify the factors that may be involved in the monitoring approaches. These other factors included risk levels for trial and participating sites, type of data management system, recruitment numbers, and critical data fields assessment. Additionally, it was planned to detail the components of risk monitoring: informed consent document, critical data fields, critical processes, on-site monitoring, central monitoring, and explore the proportion of Source Data Verification (SDV) undertaken. It was also intended to describe the use of a collaborative team approach for reducing the errors, clarify the evidence linking the percentage source data verification percentage with error rates and assess the impact of risk-based monitoring techniques on the subject safety, data integrity, and cost reductions. The Population, Intervention, Comparison, and Outcomes (PICO) criteria were used for including the studies in the review (Table 1). While developing the protocol for search, PRISMA guideline was followed. The search was conducted by using MEDLINE, COCHRANE, and WEB OF SCIENCE electronic search databases for the last 10 years; from 1 Jan 2009 – 25 Sep 2019 by the first reviewer and a second reviewer independently using free text to include all the available published papers. A detailed search strategy is provided on Table 2.

Table 1. The Population, Intervention, Comparison, and Outcomes (PICO) Criteria

Population, or participants and conditions of interest	For this search, the defined condition of interest is interventional clinical trials and Cohort studies (no restriction to disease and population).
Interventions or exposures	For this search, monitoring is considered as an intervention. Monitoring could be an internal quality improvement or external monitoring as part of sponsor responsibilities. Monitoring includes data monitoring, process monitoring, or safety monitoring as part of sponsor responsibilities.
Comparisons or control groups	This search is based on the comparison being 'No monitoring' is considered as the comparator for the cohort studies and 'risk-based monitoring' for randomised control trials and other interventional clinical trials.
Outcomes of interest	The outcomes of interest are error rates, subject safety, data integrity, and cost reductions

Table 2. Detailed Search Strategy

Search Database	[1] “quality management” OR “quality control” OR “quality assurance”	[2] “clinical trials as a topic [MeSH]” / “clinical trial*” OR “Clinical studies as topic [MeSH]” /” clinical stud*” OR “cohort stud*”	[3] “data monitoring” OR “clinical trials data monitoring committee*” OR “remote monitoring” OR ‘risk-based monitoring’ OR “risk adaptive monitoring” OR “central* monitoring’ OR “On-site monitoring” OR “process monitoring”	[4] “monitoring approach*” OR “monitoring technique*” OR “monitoring strateg*” OR “source data verification”
	(n)	(n)	(n)	(n)
	Exclusion: Articles which are beyond the last 10 years from the date of search (25 Sep 2019), any editorials, language other than English, articles which are not full text, study data which did not have any detailed data, articles which are not research on humans			
Medline	17619	1233548	1555	313
Cochrane	5035	79123	1519	155
Web of Science	75569	422792	11958	8363
	Search: [1] AND [2] AND [3] AND [4]			
	[N]			
Medline	5			
Cochrane	2			
Web of Science	17			

Results and Discussion

Our search strategy and keywords resulted in the 5 full-text articles as per MEDLINE [6-10], 2 full-text articles from COCHRANE [4, 11] search, and 17 full-text articles from Web of Science [6-9, 12-24]. The search resulted in a total of 19 publications from MEDLINE, COCHRANE, and WEB OF SCIENCE, after removing duplicates from the total of 24 articles as shown in Figure 1. 14 articles described methods for quality management, monitoring of clinical trial activities in varying levels of detail by the clinical team in clinical settings, data management process, central statistical monitoring, technology systems for central monitoring, these were not referring the monitoring techniques and approaches in clinical trials or cohort studies. These were also not describing the research conducted on monitoring techniques and comparison for quality management and therefore were excluded. 1 article was excluded as the full text was not available in English, though the title abstract was available in English. 4 articles were qualified based on the information available in abstracts and title to be included in the systematic review. These articles discussed about the comparison between monitoring techniques and the risk-based monitoring methodology in randomised control trials and other interventional trials. A summary of all the included publications is listed on table 4.0 with the limitations.

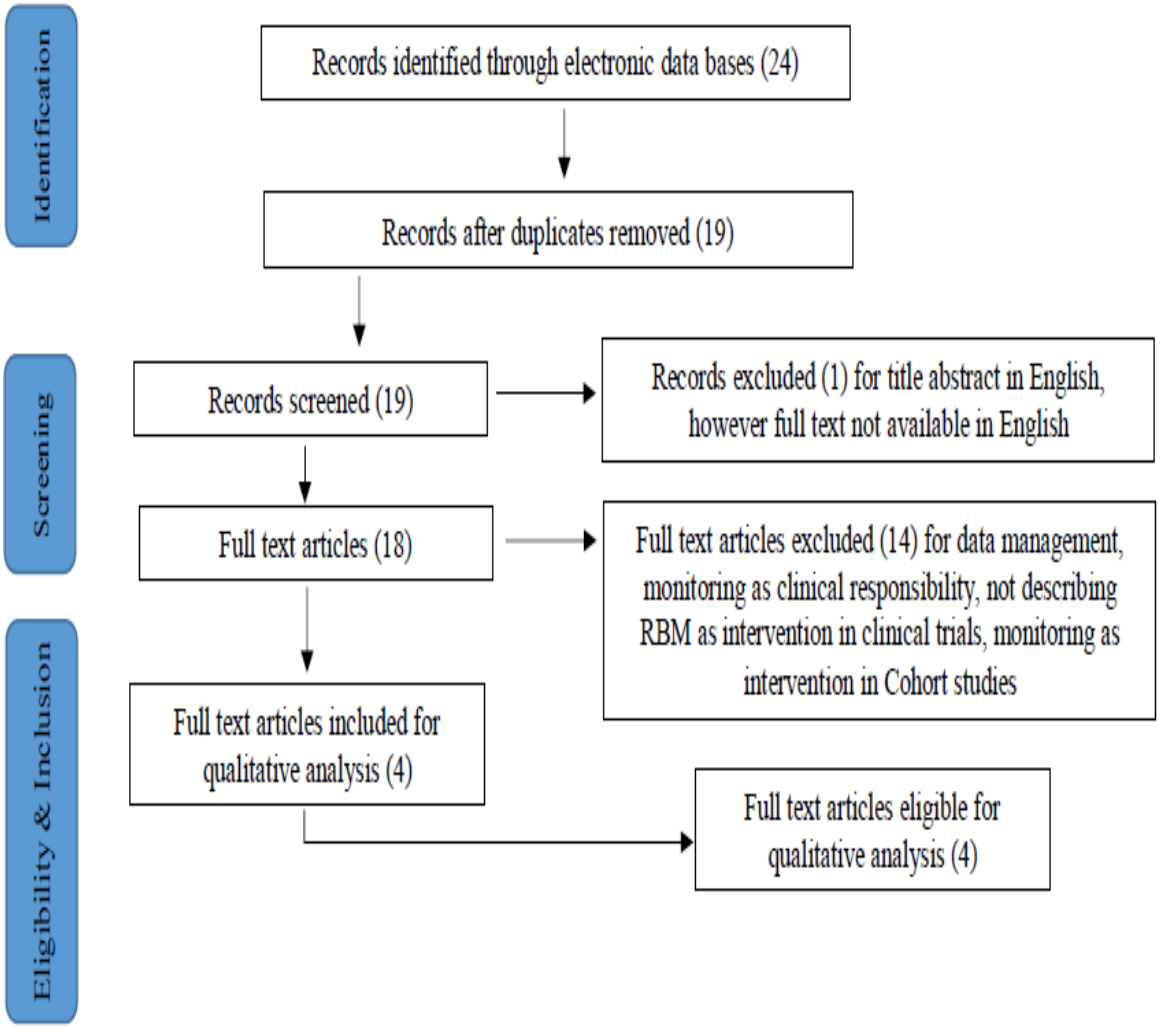

Figure 1. Literature Search Protocol Design and Results

Table 3. Summary of Publications Assessing the Impact of Risk-based Monitoring as Compared to Conventional On-site Monitoring in Randomised Clinical Trials and Quality Management in Large Cohort Studies

Publication Title	**Author**	**Research type**	**Type of studies researched**	**Type of Intervention**	**Description**
Generating evidence on a risk-based monitoring approach in the academic setting - lessons learned.	von Niederhausern B, Orleth A, Schadelin S, et al.[6]	Systematic	Interventional & Observational	Monitoring conducted as per sponsor responsibility	Paper describes the monitoring approaches and quantitative analysis in the academic research settings
Risk-Based Monitoring: A Closer Statistical Look at Source Document Verification, Queries, Study Size Effects, and Data Quality.	Tantsyura V, Dunn IM, Fendt K, et al.[21]	Systematic	Interventional	Monitoring conducted as per sponsor responsibility	Paper describes the published literature and evidence towards the effect of errors and error corrections with size of the study and suggests the average <8% SDV may be adequate
Triggered or routine site monitoring visits for randomised controlled trials: results of TEMPER, a prospective, matched-pair study.	Stenning SP, Cragg WJ, Joffe N, et al.[24]	Empirical	Interventional	Monitoring conducted as per sponsor responsibility	Paper describes the prospective study of the monitoring approaches and triggered visits concept (RBM) as intervention
Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomised study.	Brosteanu O, Schwarz G, Houben P, et al.[4]	Empirical	Interventional	Monitoring conducted as per sponsor responsibility	Paper provides evidence for risk adapted monitoring strategy as an intervention in randomised clinical trials

Monitoring Strategy and Factors Defining Monitoring Strategy

The challenge is to have the evidence for how much SDV is sufficient to meet the fundamental requirement of GCP as safety and well-being of participants and reliable results.

The evidence on the effects of errors from the literature published [21] for the period of 2011-2014 was studied. They suggested the operational considerations for minimising the impact of data error on the study conclusion by mitigating the factors that poses risk. These were (a) risk of error occurrence further categorising into data never queried / never changed, queries leading to no change, changes (non–key data), changes (key data points), and initially missing data that are added later without query (usually as a result of monitoring activities) (b) probability that error will not be detected and corrected and (c) error severity. They estimated the SDV effectiveness, SDV redundancy, study size effect, and error hierarchy by severity. It was recommended that SDV, rather than just focussing on the key primary efficacy and safety outcomes, focus on data clarification queries as highly discrepant (and the riskiest) data. They suggested that the monitoring strategy should take the study size effect into consideration, focusing SDV on ''high-value'' data points.

Risk ADApted MONitoring (ADAMON)[4] study was conducted to investigate whether a trial-specific, risk-adapted, reduced on-site monitoring strategy is as effective as an extensive, non-targeted on-site monitoring strategy in preventing major or critical violation of GCP objectives, as ascertained by independent audits at the end of the trial. ADAMON was designed to be a stratified, cluster-randomised non-inferiority study. Trial sites within participating clinical trials were randomised either to extensive or to risk adapted monitoring. Their results showed that the average number of monitoring visits and Time spent on-site was 2.1 and 2.7 times higher in on-site monitoring than in risk-adapted monitoring, respectively. The findings were identified in 18%–99% of the audited patients after monitoring. The study demonstrated that risk-adapted monitoring is non-inferior to extensive on-site monitoring. This benchmark study also showed that Risk-adapted monitoring in only a sample of patients is sufficient to identify systematic problems in the conduct of clinical trials. It was concluded that Risk-adapted monitoring has a part to play in quality control and should be part of a comprehensive quality management approach covering the entire trial lifecycle. Another critical aspect innovated during ADAMON study was a classification of trials based on risk identified. The criteria's used were standard to classify as K2, intermediate-risk, and K3, low-risk trials based on publication [20] describing the risk-adapted on-site monitoring in non-commercial trials.

Another literature article that focussed on the monitoring strategy was titled as Triggered or routine site monitoring visits for randomised controlled trials: the result of TEMPER, a prospective, matched-pair study [24]. The study was designed as a prospective study to assess the value of triggered monitoring in distinguishing sites with important protocol or GCP compliance issues which are not identified by central monitoring. The primary analysis showed that 88.1% of triggered monitoring visits had at least 1 new Major or Critical finding when compared to 81.0% of untriggered monitoring visits. Several re-consent issues were found during these visits; therefore, once reconsent findings were excluded, it resulted in 85.7% versus 59.5%. It was suggested that a triggered monitoring approach might be used but needs to be complimented and improved with an investigation of further central monitoring triggers.

Evidence Based Linking the Percentage Source Data Verification Percentage and Error Rates

It was concluded that the value of SDV is currently hugely overestimated, and for large

studies, SDV produces no detectable return on investment [21]. The research group estimated that manual SDV is approximately 15 times less effective than computerized data validation by deriving from data from [25] and TransCelerate [3], respectively. Their analysis demonstrated that the true effectiveness value of SDV (measured as a proportion of key data points modified because of SDV) is minimal (0.1%-1.4%), especially when the acceptability of error by industry is 5% alpha error. The important aspect that was shown is that overall, 97% of data in a typical study never change, and only 0.9% of key data that are typically modified after original entry and need possible attention. It was estimated that non-queried data is 0.22% and bears risk, if any, and therefore no intervention is required, including on-site SDV. Their analysis demonstrated minimal effects of errors and error corrections on study results and study conclusions, with diminishing effect as the study size increases. It was also suggested that, on average, <8% SDV is adequate to ensure data quality, with perhaps higher SDV rates for smaller studies and virtually 0% SDV for large studies. The limitation of the monitoring model described was that it was based on assumptions that the query generation process, including data validation and centralized monitoring, is comprehensive and focused on key data points; (2) that errors are distributed randomly across subjects and variables; and (3) that the 80% of prospective data changes are identified and captured as ‘‘queries”.

The evidence was generated on a risk-based monitoring approach in academic settings [6]. The mixed-method study was conducted at the Clinical trials unit of the University Hospital in Basel. The studies were selected according to the assessed base don ADAMON for a stipulated duration between 2012-2014. The study had quantitative retrospective analysis with the study level variables as study design, study type, study sponsor, study design, type of research, study phase (I-IV), and type of study population (e.g., the inclusion of vulnerable population). The variables further were specifically selected for site-level information as site location, ADAMON risk category, presence of electronic database, principal investigator, and whether he/she changed during conduct, staff experience, and a number of planned subjects at the site.

At the level of each monitoring visit, information collected was a type of visit (i.e., initiation, interim, close-out), the number of findings categorised by administrative, patient rights, patient safety, laboratory/biological specimen, data point confirmation, and endpoint related. The study also conducted prospective semi-structured interviews of the monitors involved on these studies. It was concluded that the risk-based approach majorly identified administrative findings contributing 46.2% of total findings and right subject findings contributed 49.1% of total findings. The interviews with monitors resulted in the conclusion that the monitors understand the positive aspects of a risk-based approach but fear missing systematic errors due to the low frequency of visits concluding that a risk-based on-site approach should further be complemented by centralized monitoring for trial data quality.

Monitoring in Cohort Studies

The search showed that there is literature available for the randomised control trials and other interventional trials. There is gap in literature for quality management and monitoring in cohort studies. Systematic and empirical research is required for research in data and process monitoring in the cohort studies.

Conclusion

Risk-based monitoring is imperative advancement in clinical trial monitoring methodology. Evidence shows that reduced on-site monitoring is a viable method of monitoring in randomised clinical trials. Evidence has been generated that a risk-based monitoring approach for clinical trials complimented with centralised

monitoring is the way forward for randomised clinical trials. However, there is no data is available for quality management and monitoring in the large cohort studies. As known, cohort studies come with their own specifications as these are large in sample size, longitudinal in design with several facets. These contribute largely to evidence generation for indication study at the population level, and therefore, the quality management for these studies should not be underestimated. In conclusion, cohort study has a large magnitude. The data generated from these cohort studies should be of utmost quality as these are the primary source for feeding the data for policy generation. As there is a gap in the literature for quality management in cohort studies, research needs to be conducted for standardising the quality management and monitoring methods for cohort studies.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

[1] Integrated Addendum to Ich E6(R1): Guideline for Good Clinical Practice E6(R2). Published online November 9, 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

[2] Quality by Design. Published online 2009. https://ctti-clinicaltrials.org/X.

[3] Position Paper: Risk-based Monitoring Methodology. In: TransCelerate; 2014. http://www.transceleratebiopharmainc.com/wp-content/uploads/2016/01/TransCelerate-RBM-Position-Paper-FINAL-30MAY2013.pdf.pdf.

[4] Brosteanu O, Schwarz G, Houben P, et al., 2017, Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomized study. *Clin Trials Lond Engl*., 14(6):584-596. doi:10.1177/1740774517724165.

[5] Hurley C, Shiely F, Power J, et al., 2016, Risk-based monitoring (RBM) tools for clinical trials: A systematic review. *Contemp Clin Trials*., 51:15-27. doi: 10.1016/j.cct.2016.09.003.

[6] Von Niederhausern B, Orleth A, Schadelin S, et al., 2017, Generating evidence on a risk-based monitoring approach in the academic setting - lessons learned. *Bmc Med Res Methodol*., 17:26. doi:10.1186/s12874-017-0308-6.

[7] Morrison BW, Cochran CJ, White JG, et al., 2011, Monitoring the quality of conduct of clinical trials: a survey of current practices. *Clin Trials*., 8(3):342-349. doi:10.1177/1740774511402703.

[8] Oba K., 2016, Statistical challenges for central monitoring in clinical trials: *a review. Int J Clin Oncol*., 21(1):28-37. doi:10.1007/s10147-015-0914-4.

[9] Timmermans C, Doffagne E, Venet D, et al.,2016, Statistical monitoring of data quality and consistency in the Stomach Cancer Adjuvant Multi-Institutional Trial Group Trial. Gastric Cancer., 19(1):24-30. doi:10.1007/s10120-015-0533-9.

[10] Tudur Smith C, Stocken DD, Dunn J, et al., 2012, The value of source data verification in a cancer clinical trial. *PloS One*., 7(12): e51623. doi: 10.1371/journal.pone.0051623.

[11] Klingberg S, Wittorf A, Meisner C, et al.,2010, Cognitive behavioural therapy versus supportive therapy for persistent positive symptoms in psychotic disorders: the POSITIVE Study, a multicenter, prospective, single-blind, randomised controlled clinical trial. Trials., 11:123. doi:10.1186/1745-6215-11-123.

[12] Wilson B, Provencher T, Gough J, et al., 2014, Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma's

Approach, Part 1. *Ther Innov Regul Sci*., 48(5):529-535. doi:10.1177/2168479014546335.

[13] Van den Bor RM, Oosterman BJ, Oostendorp MB, Grobbee DE, Roes KCB., 2016, Efficient Source Data Verification Using Statistical Acceptance Sampling: A Simulation Study. *Ther Innov Regul Sci*., 50(1):82-90. doi:10.1177/2168479015602042.

[14] Sheetz N, Wilson B, Benedict J, et al., 2014, Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials. *Ther Innov Regul Sci.*, 48(6):671-680. doi:10.1177/2168479014554400.

[15] Houston L, Probst Y, Yu P, Martin A., 2018, Exploring Data Quality Management within Clinical Trials. *Appl Clin Inform*., 9(1):72-81. doi:10.1055/s-0037-1621702.

[16] Hullsiek KH, Kagan JM, Engen N, et al., 2015, Investigating the Efficacy of Clinical Trial Monitoring Strategies: Design and Implementation of the Cluster Randomized START Monitoring Substudy. *Ther Innov Regul Sci*., 49(2):225-233. doi:10.1177/2168479014555912.

[17] Sudo T, Sato A., 2017, Investigation of the Factors Affecting Risk-Based Quality Management of Investigator-Initiated Investigational New-Drug Trials for Unapproved Anticancer Drugs in Japan. *Ther Innov Regul Sci*., 51(5):589-596. doi:10.1177/2168479017705155.

[18] Rosenberg MJ., 2014, Key Considerations in the Transition to Risk-Based Monitoring. *Ther Innov Regul Sci*., 48(4):428-435. doi:10.1177/2168479013519631.

[19] Cornu C, Binquet C, Thalamas C, et al., 2013, Public Clinical Trials: which Kind of Monitoring Should be Used? Therapie., 68(3):135-141. doi:10.2515/therapie/2013032.

[20] Brosteanu O, Houben P, Ihrig K, et al., 2009, Risk analysis and risk-adapted on-site monitoring in non-commercial clinical trials. *Clin Trials*., 6(6):585-596. doi:10.1177/1740774509347398.

[21] Tantsyura V, Dunn IM, Fendt K, Kim YJ, Waters J, Mitchel J., 2015, Risk-Based Monitoring: A Closer Statistical Look at Source Document Verification, Queries, Study Size Effects, and Data Quality. *Ther Innov Regul Sci*., 49(6):903-910. doi:10.1177/2168479015586001.

[22] Barnes S, Katta N, Sanford N, Staigers T, Verish T., 2014, Technology Considerations to Enable the Risk-Based Monitoring Methodology. *Ther Innov Regul Sci*., 48(5):536-545. doi:10.1177/2168479014546336.

[23] Smith CT, Stocken DD, Dunn J, et al., 2012, The Value of Source Data Verification in a Cancer Clinical Trial. *Plos One*., 7(12): e51623. doi: 10.1371/journal.pone.0051623.

[24] Stenning SP, Cragg WJ, Joffe N, et al., 2018, Triggered or routine site monitoring visits for randomised controlled trials: results of TEMPER, a prospective, matched-pair study. *Clin Trials*., 15(6):600-609. doi:10.1177/1740774518793379.

[25] Mtchel J, Cho T, Gittleman D., 2014, Time to change the clinical trial monitoring paradigm: results from multicenter clinical trial using quality by design methodology, risk-based monitoring, and real-time direct data entry. *Appl Clin Trials*. (Published online January 17).