

Review Article

Future of risk based monitoring in clinical trials

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ABSTRACT

Drug development is a complex and resource intensive endeavor. The average cost of developing a new drug, has been estimated to be \$2 to \$3 billion. However, the success rate of clinical trials is very low around and is estimated to be between 3-5%. The common reasons for failure of clinical trials include failure to demonstrate efficacy or safety, budgeting and financing, failure of subjects meeting protocol eligibility criteria, poor investigator site selection, patient withdrawals and dropouts. Considering the growing demands to get better and affordable treatment options, there needs to be fundamental shift required in drug development and specifically the clinical trials oversight processes to mitigate risks and reduce failures. The International Council for Harmonisation in the E6 R2 addendum has now provided guidelines for adaptation of risk based approach to trial conduct and monitoring to implement mitigation strategies for potential risks which might derail the conduct of the trial. The industry is steadily gearing up to put together the required processes, systems and teams to align to the new ways of working. However with the changing landscape of drug development which includes novel therapies like gene therapy, remote/decentralized trials, growing use of wearable technologies, eSource, electronic health record/electronic medical records interoperability, implementation of artificial intelligence and machine learning algorithms, the future of risk based approach towards managing clinical trials is going to be very different from what we see now. This paper explores the impact of these new developments on the future of risk based monitoring in clinical trials.

Keywords: Risk based monitoring, Centralised monitoring, ICH E6 R2, Key risk indicators, eSource, AI/ML

INTRODUCTION

Risk is an uncertain event or a condition which if occurs may adversely impact outcome of an expected event. In terms of clinical trials a risk may adversely impact achievement of its intended objectives which could include timeliness, costs and quality of submissions. Risks may result from variety of factors some of which include changes in scope, unavailability of skilled team/resources, failure to meet compliance requirements, lack of required infrastructure/ funding etc.

Drug development is a complex and resource intensive endeavor. The average total cost of developing a new drug, has been estimated to be \$2 to \$3 billion. Based on analysis of around 400,000 trials conducted between

2000 till 2015 for over 21,000 compounds, the success rate of clinical trials is around 5% (oncology has a 3.4%).¹ The patent period once the Pharma Company applies for new molecule is 20 years of which 10-12 years may go in clinical trials conduct and receiving marketing approval. Pricing regulations are in place post marketing approval to ensure patient rights and access to medicines are protected. Once the patent expires, generic companies have the rights to manufacture the product, significantly bringing the costs of the product down.

The common causes of clinical trial failures include following.

Failure to demonstrate efficacy or safety: Off the 640 phase 3 trials with novel therapeutics and found that 54%

failed in clinical development, with 57% of those failing due to inadequate efficacy.²

Budgeting and financing: 22% of the failed phase 3 studies they examined failed due to lack of funding.²

Eligibility criteria: Across 3400 clinical trials, more than 40% had amended protocols prior to the first subject visit, delaying trials by 4 months.³

Patient burden: 35% of delay in studies are due to delays in patient recruitment⁴. Also average 30% subjects enrolled in clinical trials drop out.⁵

Ineffective site selection: 1/5th Investigators do not enroll any subjects; 1/3rd enroll only 5% of evaluable subjects.⁵

Considering the growing demands to get better and affordable treatment options, there needs to be fundamental shift required in drug development and specifically the clinical trials oversight processes to mitigate risks and reduce failures. This include strategies and mitigation plans to manage controllable risks and adapt to handle uncontrollable risks.

OVERSIGHT OF CLINICAL INVESTIGATORS: TRADITIONAL APPROACH

Of the top 5 costs related to conduct in late phase studies, clinical monitoring of investigator sites can contribute around 15% of overall study costs.⁶ The clinical monitoring costs typically include scope of site selection, site training, onsite visits by clinical research associate (CRA) to review source data, perform source data verification (SDV) to ensure that the site personnel has accurately transcribed the source data captured by the investigator site team in medical records into electronic data capture (EDC) systems, perform review of drug accountability, lab data review, eligibility related data amongst other activities.

The sponsor organization typically outsources clinical monitoring scope to Contract Research Organizations (CROs) who specialize in site management activities. A Clinical Project Manager (CPM) is typically assigned to the study who controls project execution and acts as a single point of contact to the sponsor Pharma organization. The clinical monitoring plans is documented in the clinical operations plan which outline the schedule, scope and type of monitoring required for the study.

Once the site is initiated the CRA is expected to visit the site every month with additional booster visits required in situations where there are interim locks and toward final study lock. The CRA typically spends 4-5 hours per site for preparation, travels to the sites from the home location, and spends about 8 hours onsite for monitoring and then another 4-6 hours for preparation of site monitoring reports.

The CRA typically spends 40-50% of the time onsite per site visit for SDV. There are numerous studies which show that this practice does not yield adequate returns in terms of improvement in data quality, or detection of issues which may impact subject safety or eligibility. An empirical post hoc analysis of three phase 3 randomized clinical trials to assess impact of SDV on data quality showed that 100% SDV yielded an error rate of 0.27%.⁷ This study included data from a total of 2566 subjects including more than 3 million data fields were 100% source data verified post hoc.

The role of the CRA is to ensure compliance of site related to protocol specified parameters, ensure high quality data, imparting of training to site staff, monitoring and assisting subject recruitment. Since the current process of SDV takes away most of the time spend by the CRA at the site, the required focus on other key activities is not given making the current approach of site monitoring inefficient.

REGULATORY GUIDANCE ON RISK BASED APPROACH TOWARDS MONITORING

The industry has been implementing many approaches to driving efficiencies in the monitoring process with one key approach being adaptive monitoring. Many companies have tried implementing alternate models where remote monitoring of the site study data is performed by the CRA by accessing source systems like EDC, lab and interactive voice response system. With the advent of e Source and evolution of technology with secure access to source systems remotely, the CRA can review the site data remotely and can perform “remote visits” between the regular planned onsite visits. Although these may not be as effective as onsite visits, this approach does bring in efficiencies in the onsite visit since the CRA is already equipped with key site performance parameters which the CRA can focus on before the onsite visit is planned so that more focus on the required corrective and preventive action can be discussed with site staff making the onsite visit more productive.

However, the implementation of this approach has been elective. In August 2013 the USFDA released a guidance on risk based monitoring.⁸ The guideline laid the foundation for implementation of adaptive monitoring through a risk based approach challenging the traditional monitoring approach. This guideline emphasized the greater use of technology and use centralized monitoring tools and processes to drive oversight of clinical sites participating in trials.

Adaptation of risk assessment and mitigation planning although a standard practice in drug development and management of clinical trials, the need for a formal and structured implementation was mandated by the International Council for Harmonisation (ICH) in the E6 R2 addendum.⁹ Section 5 of the guidance document

describes that the sponsor of the clinical trial 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.⁹

Quality management includes the design of efficient clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making. The quality management system should use a risk-based approach as critical process and data identification, risk identification, risk evaluation, risk control, risk communication, risk review, risk reporting.

SOLUTION APPROACH: INDUSTRY BEST PRACTICES

Failure mode and effects analysis (FMEA) is a structured approach to discovering potential failures that may exist within the design of a product or process. It's one of many tools used to discover failure at its earliest possible point in product or process design. Historically procedure for conducting FMEA were used by the U.S. National Aeronautics and Space Administration (NASA) for a large number of their space exploration programs.¹⁰ Since space exploration programs are resource intensive and may pose risks to life in case of failures, its primary benefit is the early identification of all critical a system failures so they can be eliminated or minimized through design modification at the earliest point in the development effort.

The idea of application of tools like FMEA is to proactively look at risks which might derail the process and design of the product or process and put mitigation plans in place before these risks arise. Risks are identified and rated based on probability of occurrence, impact/severity of risk on the product/ process and detectability. Based on the probability, impact and detectability every anticipated risk is then categorized and ranked with a risk priority number (RPN). These risks based on the RPN can be classified as critical high or low categories and mitigation plans put in place to address these risks. Plans are developed and monitoring process put in place to address the risks based on their criticality and periodically evaluated based on their effectiveness. The risk based approached towards monitoring adapts a similar approach towards identification of key risks which may derail the study, implement mitigation plans to address these risks and use monitoring strategies to track and report performance of participating sites.

IMPLEMENTATION SO FAR: SUCCESS AND CHALLENGES

At the point when a risk-based monitoring system involves the centralized approach, real-time tracking of data with well-planned risk and mitigation strategies. This approach has really helped the overall industry

approach in developing the most effective tools which will be effective in managing clinical trials, proactive approaches incorporated in the framework; identifies issues early so that it can be acted upon quickly, safeguarding the patients and maintaining the trustworthiness of the study; improves the effectiveness of CRAs, as they focus on the sites that need assistance and helps the capable sites to work without any hindrance.

This approach has shown drastic improvement in the data reliability and verifiability keeping away the amazements or surprises during regulatory audits. Even though the risk-based monitoring approach is relatively new and immature to the industry, however based on the few preliminary data it has shown that it's equal or superior to the traditional monitoring approach of 100% SDV. It has been noticed that many pharmaceutical companies have already started shifting towards the more effective risk-based model approach on small and large clinical studies and the result was effective with noticeable improvement.

Even the regulatory authorities like US-FDA “encourages the centralized monitoring approach than the more traditional approach of 100% SDV model, with less emphasis on the on-site monitoring”. It has given the clear signal to the industry and many have started to take full advantage of the technology to the run the risk-based model approach. With the advent of various system which aids in the centralized monitoring of the clinical study, various challenges of managing the study protocol is effectively executed which in turn has helped in taking care and safeguarding the patient along with results, eventually it has shown noticeable reduction in the overall clinical trial costs.

The data collected by the Transcelerate Biopharma participant member from 2013-2017 on clinical trials implementing risk-based monitoring (RBM) showed >50% contribution towards improvement in all collected metrics. The implementation of RBM appears to improve the quality, timeliness and efficiency of clinical trials as shown in all metrics.¹¹

This assessment is based on the following set of key risk indicators (KRIs).

Table 1: Key risk indicators used for risk based monitoring.

Commonly used KRIs/ KPIs	Rarely used
1. Audit findings	1. Overall monitoring costs (rare)
2. Major PDs	2. Onsite visit intervals (rare)
3. Issue open to close	3. SAE reporting (rare)
4. eCRF entry	
5. Query open to close	

KPIs: key performance indicators; SAE: serious adverse event. PD: protocol deviations.

The assessment report also lists 28 novel KPIs based on inputs from members companies.¹⁰

Table 2: KPI/ KRI effectiveness measure: transclerate report.

Rank	KPIs/ KRIs
Extremely useful	1. Time from data "cut" to Action
	2. Ratio of on-site to off-site monitoring visits
	3. SDR & SDV backlog
	4. % queries resolved in 7 days
	5. % pages submitted in 7 days
	6. Important protocol deviation Incidence
	7. Missed assessments
	8. Dosing deviation incidence
Somewhat useful	9. Reports for centralized monitoring-user statistics to indicate frequency and duration of use
	10. Ratio of data correction XX days after initial data entry
	11. RBM user satisfaction survey
	12. Query rates
	13. Query rate (per 1000 data points)
	14. Qualitative interviews with HQ trial teams
	15. Survey for use and usefulness of site risk indicator report
	16. TMF compliance
	17. SAE/AE rates
Neutral	18. Action item aging
	19. External data review status
	20. CAPAs close on time (site)\
	21. CAPA # overall
	22. eTMF status
	23. Ratio of number of AE emerging per subject
	24. Query aging
	25. Ratio of number of AE emerging per subject
Not very useful	26. On-site vs. remote visit ratio: ratio calculated as number on-site to remote visits
	27. Ratio of missing data for the primary endpoint
	28. Ratio of missing data for the primary endpoint

KPIs: key performance indicators; SAE: serious adverse event; CAPAs: Corrective and preventive actions. SDR: source data review. TMF: trial master file.

However with the changing landscape of drug development which includes novel therapies like gene therapy, remote/decentralized trials, growing use of wearable technologies, esource, electronic health record (EHR)/electronic medical record (EMR) interoperability interoperability, implementation of artificial intelligence

(AI) and machine learning (ML) algorithms, the future of risk based approach towards managing clinical trials is going to be very different including some of the metrics used, process and technology for centralized monitoring.

FUTURE OF RISK BASED MONITORING

When done right, risk based approach have the potential to transforms clinical trials, enable lesser time to reach in the market and improve the focus on quality and integrity of clinical study. It would be unfeasible though for regulatory agencies, to mandate a one-size-fits-all methodology for the execution of a risk based monitoring approach. Also, as the landscape of drug development keep changing at a rapid pace, which includes the type of investigational products, growing use of technology like eSource/EHR/wearables, availability of AI/ML, the conventional model of site and centralized monitoring methods will also need to adapt.

Impact of eSource

US FDA regulations define an electronic record as any combination of text, graphics, data, audio, pictorial, or other information represented in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.¹² This includes eCRF, electronic health records captured by healthcare providers and institutions, electronic laboratory reports, digital medical images from devices, and electronic diaries (ePRO/ eCOA) completed by study subjects.

The dawn of eSource saw the use of paper CRFs manually fed into the eCRF through a centralized data management function with use of double date entry and QC checks to ensure data integrity. The eCRF has now become the norm with digital solutions offered on cloud to allow investigator sites a single platform to enter data directly into the EDC system. However, with growing use of eSource, the clinical trials of the future will see growing proportion of data entered directly from participating subjects with ePRO/ eCOA. Also growing use of wearables will soon overtake the proportion of data generated from patients.

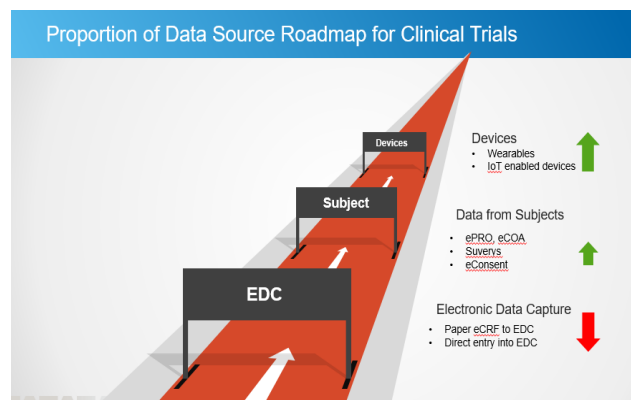


Figure 1: Projected proportion of sources of data captured for clinical trials

Figure 1 shows increase in proportion of data from devices/ subjects/ sites.

To successfully monitor trials with a larger proportion of data directly captured from patients or from devices, it will be important to revisit the conventional KRIs and factor KRIs which may include the following:

Table 3: Indicative list of KRIs for monitoring sites with eSource.

eSource KRIs/ KPIs
<ul style="list-style-type: none"> Percentage of sites/ subjects completing ePRO within timelines of protocol specified visits Sites with missing ePRO data % sites/ subjects visits with device data transmitted % Sites/ Subjects pending eConsent signs off (including amended versions)

Interoperability of EHR with EDC

The EDC system has been traditionally used to capture subject data for clinical trials and is specifically configured based on the study specific protocol. The investigator site team typically employs a study coordinator who manually transcribes the subject data into the EDC system based on the source notes which includes electronic health records, subject files and notes captured by the investigator, laboratory/ radiology reports, pharmacy notes amongst others. With the time/resource constraint faced by the investigator site team, this leads to significant delays in entering the data into the EDC system which creates a major hurdle to deploy centralized / remote monitoring of data. This results in most of the studies deploying KRIs to monitor site performance (missing pages and time taken for data entry).

Since the process of transcribing data from source records is a manual process, this does result in errors in data entry either due to data entry errors or errors due to interpretation of source notes. The clinical monitoring oversight process deploys a CRA who visits the site deploys a process of SDV and SDR, the former process requires a field level comparison of what is entered in EDC with source notes and SDR which requires a more cognitive effort on behalf of the CRA to assess the quality of data entered in EDC is in line with protocol and the protocol defined critical data and process.

The clinical data management also runs edit checks on the data entered in EDC to identify data entry/ quality issues which require the site to review and respond. The CRA at the site visit needs to ensure all queries are responded, answered and closed in the EDC system. This results in following KRIs tracked for site performance monitoring i.e. pages for SDV; % queries responded by sites within defined limits; total queries.

The USFDA released a guideline for industry for use of electronic health record data in clinical investigations in July 2018 which encourages sponsors and clinical investigators to work with entities that control EHR systems, such as health care organizations, to use EHR and EDC systems that are interoperable or fully integrated.¹³

The EHR systems mapped to specific elements defined for EDC specific requirements can potentially eliminate the need for data entry and related transcription errors with no need the perform SDV. Pilot studies for EHR integration have used the CDISC operational data model (ODM) and the health level seven (HL7) standards for the exchange of clinical information.

This will also ensure no lag in terms of data availability for centralized data monitoring. Many of the pilot studies have shown about 75% of study data elements available in EHR and rapid access to data in EDC from EHR systems with significant reduction in data entry timelines at screening and follow-up visits.^{14,15}

Table 4: Indicative list of KRIs for monitoring sites using EHR/ EMR data.

Traditional KRIs/ KPIs	New KRIs/ KPIs
<ul style="list-style-type: none"> Missing pages Time taken for data entry Pages for SDV % queries responded by sites within defined limits Total queries 	<ul style="list-style-type: none"> Average time for data availability in EDC after subject visit/ site Data accuracy: missing data from EHR to EDC, fields failing edit checks as defined for data collection / site

Wearables and IoT enabled devices

Currently, about 10% to 15% of trials are incorporating wearable devices, primarily to collect data as exploratory endpoints and it is estimated that by 2025, 70% of clinical trials will incorporate wearable technology which will include sensors.¹⁶ Some of the wearables and sensors include actigraphy utilized for studies on movement disorders, dermatology, sleep pattern analysis, epilepsy studies; wrist worn/ patch ECG devices to monitor HR, arrhythmia, SPO2; smart blisters, bottles, inhalers which automatically update the investigational product intake; motion sensors for gait analysis Parkinsons; IOT enabled devices like continuous glucose monitors, Spirometers, ECG, Holters, ABPMs, data loggers for tracking cold chain temperature excursions.

Use of wearables coupled with eSource will significantly increase the proportion of data collected directly from participating subjects and along with EHR integration will reduce the proportion if manual data entry into the EDC system to a very small component. Automated IP accountability will eliminate the need for CRAs to perform manual pill count and managing paper logs including drug destruction reports. Automated IP

adherence data from smart pills can be integrated into the EDC eliminating the need to enter these details in the EDC.¹⁷ For tracking site performance, the following KRIs can be considered linked to critical data and processes.

Table 5: Indicative list of KRIs for monitoring sites using wearables/ IoT enabled devices on participating subjects.

New KRIs/ KPIs
<ul style="list-style-type: none"> • % compliance of sites/ patients outside of IP adherence window as defined by study protocol • % sites with temp excursions outside of defined QTL • Rate of AE of special interest (linked to device related data for eg subjects with prolonged QTcF, hypoglycemia events on CGM) • Rate of sites with device malfunctions/ errors in data transmissions

Role of predictive analytics and AI/ ML

Predictive analytics and use of AI/ ML has gained a lot of interest in Life Sciences and clinical development. In Life and Medical Science the most common implementation so far have been around physiological parameter monitoring which includes data collected devices including wearables, followed by Imaging, Genetics /Genomics amongst others like Neurosciences, Public Health, Drug Discovery and Bioinformatics.¹⁸

Predictive analytics encompasses a variety of techniques from data mining, predictive modelling, and machine learning, that analyze current and historical facts to make predictions about future or otherwise unknown events.¹⁹ Machine learning tools help in predictive analytics by use of models (viz neural networks, decision trees, regression, support vector machine) used on sample training data to make predictions or decisions without being explicitly programmed to perform the task and include methods to train the model based on new data to make the predictions more accurate and precise.

Predictive analytics using AI/ML based methods can be used in centralized/risk based monitoring to assess investigator site performance and predict their performance based on how they have performed in the past and use deep learning techniques to fine tune the model based on new data as obtained from ongoing studies. This analysis can be used to implement adaptive site monitoring practice where site monitoring frequency and related resources can be increased for sites which show a high risk.

Deep learning methods, such as recurrent neural nets, long short-term memory, offers a lot of promise for Time Series forecasting, such as the automatic learning of temporal dependence and the automatic handling of temporal structures like trends and seasonality which can be used to train the model and provide more accurate prediction on site risk and resource planning. This approach may eventually replace the conventional and

more subjective approach of site tiers which are used for benchmarking sites for selection and creating the site monitoring frequency schemas.

Table 6: Indicative attributes for predictive analytics using AI based algorithms.

Predictive analytics
<ul style="list-style-type: none"> • Prediction of site which will not meet enrolment targets (based on screening rates, screen failure rate, early termination rates) • Prediction of sites for protocol deviation

Integrated risk assessment and mitigation planning

The risk assessment and categorization tool (RACT) tool from Transcelerate was created to share best practices in terms of identification of risks which could affect patient safety, data integrity or regulatory compliance.²⁰ The template provide a framework with 60+ questions across 13 categories which can be used to categorize anticipated risks for a planned program or study. The study team is encouraged to collaboratively work and develop mitigation plans which can be documented in respective functional plans as a part of the integrated quality and risk management plan and promote the use of quality by design. Once the assessment is complete the template provide a risk score for the study (high/ medium/low) based on the weightage provided to each of these categories. Mitigation plans documented in functional plans determine the monitoring strategies including site monitoring frequency and SDV/ SDR approach. The mitigation strategy includes reduction of risk before occurrence or contingency planning which may include a fall back plan after risk occurs. Others include avoid (remove source), transfer (another experience party through outsourcing). The critical data and processes obtained from this exercise is used to develop and finalize key risk indicators (KRIs) which are used for site performance monitoring.

A closer assessment of the RACT shows that the template include 20+ questions to assess medical (subject safety, subject population, investigation product, endpoints blinding) and around 40+ questions for operational risks (study complexity, technology, data collection, supply chain) for the study. Of these questions around 11 can be potentially linked to operational KPIs and KRIs which can be collected during the course of the study for the respective sites. The rest are either single time response questions (viz is the compound marketed product, is this pivotal trial etc) or may require subjective review from study team.

Hence a review of RACT during the course of the study would potentially require a combination of KRIs scores for each sites for the respective categories and a subjective assessment of questions/ mitigation plans based on issues/ reports shared by the study/ country teams. The RACT scoring and template can potentially be split into static assessments which will not change

during the course of the study and dynamic assessment which may change during the study and may require a review and effectiveness of mitigation plans implemented. The RACT re review process can then focus on dynamic assessment areas where study team can focus on data driven decisions based on the KRIs and KPIs scores to retire ineffective or redundant mitigation plans, add/ modify mitigation plans, change QTL of measures (KRI/ KPIs), retire or add new KRIs. Instead of a manual review and assessment the centralized monitoring systems which capture these KRIs can directly feed into risk assessment score to facilitate a more focused and effective risk review process. Historical records and data can be used to link mitigation plans which have been more effective than others and this library can be used for similar studies. Templates can be created with thresholds based on past data for Risk assessment a RACT score of below a particular threshold value may not need mitigation plans or may need a finite number of mitigation plans.

Table 7: Mapping RACT categories to KPIs/ KRIs.

Category number	Category	KPI measure
1.1	Safety	AE/ SAE rate
1.3	Safety	AE/ SAE rate
1.4	Safety	AE of interest
1.6	Safety	AE of interest
4.1	Subject population	SAE rate/ AE of interest
6.1	Data collection, CRF source	Query rate, query response time
6.2	Data collection, CRF source	Time taken for data entry
7.2	Endpoints	Early termination, withdrawals
10.2	IP logistics / supply chain	Excursion/ PDs
13.3	Geography	Site scores/ country scores
13.7	Geography	EC/ HA approval timelines

Table 8: RACT outcomes, risk review and effectiveness measures.

Risk review and mitigation planning KPIs
<ul style="list-style-type: none"> • Impact analysis of mitigation plans categorized as high/ medium/low based on their effectiveness on overall study score • Occurrence of risk estimated vs actual • Impact analysis of KRIs and related thresholds/ QTLs based on their ability to detect true issues • Threshold limits for study risk scores which can be used to link mitigation plans • # of uncontrollable risks which may include undetected, unanticipated risks and risks where existing mitigation plans failed

CONCLUSION

Implementing a risk based approach for clinical trial monitoring is now a regulatory imperative as driven through the ICH E6 R2 addendum. Data from the implementation of RBM across studies have shown to improve the quality, timeliness and efficiency of clinical trials across many metrics. However the changing landscape of drug development which includes remote/decentralized trials, growing use of wearable technologies, esource, EHR/EMR interoperability, implementation of AI and machine learning algorithms warrants a relook at the process, KPIs and systems used for implementation of RBM.

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