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Discussion Paper

The future of monitoring in clinical research – a holistic approach: Linking risk-based monitoring with quality management principles

Die Zukunft des Monitorings in der Klinischen Forschung – ganzheitlich gesehen: Die Abhängigkeiten zwischen Risiko-basiertem Monitoring und Qualitätsmanagement

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Abstract

Since several years risk-based monitoring is the new "magic bullet" for improvement in clinical research. Lots of authors in clinical research ranging from industry and academia to authorities are keen on demonstrating better monitoring-efficiency by reducing monitoring visits, monitoring time on site, monitoring costs and so on, always arguing with the use of risk-based monitoring principles. Mostly forgotten is the fact, that the use of risk-based monitoring is only adequate if all mandatory prerequisites at site and for the monitor and the sponsor are fulfilled.

Based on the relevant chapter in ICH GCP (International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice) this publication takes a holistic approach by identifying and describing the requirements for future monitoring and the use of risk-based monitoring. As the authors are operational managers as well as QA (Quality Assurance) experts, both aspects are represented to come up with efficient and qualitative ways of future monitoring according to ICH GCP.

Keywords: monitoring, risk-based monitoring, quality management

Zusammenfassung

Seit einigen Jahren wird von den verschiedensten Autoren – aus den industriellen, akademischen oder behördlichen Bereichen der Klinischen Forschung – das Risiko-basierte Monitoring fast wie eine Wunderformel beschworen und bewertet. Um die damit erzielten Verbesserungsmöglichkeiten nachzuweisen, werden generelle Effizienzsteigerungen und Kosteneinsparungen bei den unterschiedlichen Monitoringaktivitäten beschrieben: weniger Monitoringbesuche am Zentrum, reduzierte Dauer der Monitoringbesuche oder mehr technisch unterstütztes Monitoring.

Direkt oder indirekt enthalten die Publikationen oft auch Hinweise auf die notwendigen Voraussetzungen sowohl beim Zentrum als auch bei Monitor und Sponsor, um Risiko-basiertes Monitoring adequat einzusetzen; bei der Umsetzung werden diese Bedingungen gerne vergessen.

Durch den ganzheitlichen Ansatz in dieser Publikation soll Risiko-basiertes Monitoring unter Einhaltung dieser Voraussetzungen beschrieben werden. Die Autoren, darunter sowohl Operational Manager als auch QA-Experten, haben auf der Grundlage der relevanten ICH-GCP-Kapitel die Notwendigkeiten und vor allem die Möglichkeiten eines Risiko-basierten Monitorings identifiziert und definiert.

Schlüsselwörter: Monitoring, Risiko-basiertes Monitoring, Qualitätsmanagement

Introduction

Because clinical development costs for drugs are increasing steadily over the years [1], attempts have been made on all sides to lower these costs through more efficient study-management. Since monitoring accounts for a substantial proportion of the total study costs, many efforts targeted to show how savings in monitoring costs can be achieved through the technically assisted preanalysis of electronic Case Record Forms (eCRF) and a risk-based Source Data Verification (SDV). Savings of over 20% have been claimed through the use of "*modified site management ... source document verification be centralized, ... with minimal verification performed at local trial sites .... on-site monitoring might be limited to a selected set of records from those sites in which anomalies were detected*" [2]. Monitoring expenditure can be effectively controlled through so-called triggered or targeted monitoring, which refers to the practice of continuous evaluation of the patient data entered at the trial site by data management right from the beginning of the study. Various parameters are recorded in this approach to help the monitor in the decision when it would be appropriate to arrange a centre visit. Both the volume of patient data and certain parameters specified for the study beforehand, such as centre effects for primary variables or the reporting frequency of AE/SAE, are taken into consideration. This, together with an adapted SDV plan, with the stipulation of 100% SDV only for very important variables and with spot checks in all other cases, should reduce the expenditure for SDV.

Many of these proposed methods of targeted or triggered monitoring are useful, since they provide the monitor with valuable information about the quality standard of the trial site in preparation for the monitoring visit.

However, the problem with these proposals is that they almost always focus just on SDV and a reduction in the number of visits: "*...it may be possible to limit on-site monitoring to those sites where central monitoring suggests that there might be a problem*" [3], whereas many other tasks of the monitor, according to the ICH GCP Guideline, are neglected.

In addition, SDV often focuses exclusively on correcting mistakes that have already been made, whereas the primary goal of monitoring should be preventing mistakes. An up-to-date quality management strategy means implementing and optimizing the systems and processes in such a way that mistakes are prevented from occurring in the first place. In this way monitoring adopts a preventive approach.

Various initiatives and publications have tackled this subject. In June 2011 the result of the Clinical Trials Transformation Initiative (CTTI) on the subject of monitoring was published [4]. One of the key sentences of the publication reads: "*It is a widely accepted hypothesis ... that on-site clinical trial monitoring is a source of significant inefficiency in the conduct of clinical trials, and that current monitoring activities do not always lead to increased quality in clinical trials*". An article issued by the PhRMA BioResearch Monitoring Committee in July 2010 listed "Best Practices" and calls for the following: "*...the greater objective of any monitoring endeavour should be to detect procedural or systematic inadequacies at the site level that can potentially affect overall study results*" [5].

In addition to proposals from the front ranks of the pharmaceutical industry, comparable approaches have been presented in the academic field. A comprehensive review was published by the ADAMON (adapted monitoring) study group [6].

The Draft Guidance published by the FDA in August 2011 also focused very strongly on a risk-based monitoring approach [7]. In this paper the FDA presents a range of options for risk-based monitoring. At the same time, FDA points out that the correspondingly qualified monitor must ensure that the preconditions are satisfied at his/her centres. Consequently, the monitor is given much greater responsibility for ensuring quality and study management at the centre.

This conflicts with the experience accumulated from audits and inspections, identifying weak points in almost all areas of monitoring, often classified as major or critical findings (see the Annual Report of the Good Clinical Practice Inspectors Working Group 2009) [8].

The authors, some of them QA personnel since many years, acknowledge the progress made in managing clinical trials and monitoring clinical trial sites over the past 15 to 20 years. However, still today very often the approach is focused on detection and elimination of non-compliance. In consequence, the very same difficulties, problems, and non-compliances are repeating over time. Clinical teams and QA are too often too isolated to allow the QA experience to be fully integrated into planning and setting up new trials. Bridging these barriers would allow for avoiding problems in the first place. Some recent changes to a more proactive quality management approach by close and early cooperation of clinical teams with QA staff can be seen within the pharmaceutical industries. Unfortunately this seems not yet to be the case to the same extent for CROs.

We are convinced that only a holistic view of, and approach to, monitoring can provide the necessary improvement.

In order to illustrate this holistic approach, we have listed the **tasks of the monitor according to ICH GCP 5.18.4** (http://ichgcp.net/518-monitoring) and described how we see these in comparison with the current standard tasks. In each case we have taken into account the technical support options that should be utilized in the context of risk-based monitoring.

Monitor's tasks

Communication

(a) Acting as the main line of communication between the sponsor and the investigator.

Communication is the key. This very general statement is often neglected in practice. An intense information flow does not necessarily equate to good communication. More information is shared more rapidly thanks to new communication channels, but the monitor is responsible for ensuring that the right information is received at the right place and processed appropriately. In order to ensure proper communication, the monitor therefore plays the key role as the primary contact person.
Parallel to the monitor as main contact for the site, different sponsor contacts with site personnel, depending on the functions and/or systems involved, are often used; and in many cases the monitor is not sufficiently aware of these.
However, the monitor needs to have access to all information related to his/her centre in order to be able to proactively manage the centre.
Ideally a communication plan, communication rules or a manual for each trial should define the relevant communication lines, procedures and documentation thereof.

Site selection

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

At the start of the study, the monitor checks whether the selected trial centre and its participating staff possess the qualifications and resources required to conduct the study properly.
The monitor should operate this process in two directions: he should forward the information about the study to the centre in order to check whether the centre can participate. But he should also receive comments and proposals from the centre, particularly if the centre has considerable experience in conducting studies. Based on these information the team, designing the study can be alerted of any anticipated relevant problems at an early stage and might even redesign the study to keep it as simply as possible, particularly from an operational standpoint. This requires the monitor to see the study documents, e. g. protocol, SDV plan, etc., at an early stage providing an opportunity to make comments.
The monitor who will subsequently monitor the centre should, ideally, also be responsible for selecting the centre from the start. Of course, he must also be suitably qualified for making this selection. In addition, after selecting the centre, he also continues to be responsible for the performance of the centre, so that a different employee does not have to compensate for his poor selection at a later stage during the study. This means that the monitor retains a personal interest in making this selection very carefully. In our experience, the monitor will also apply more operational selection criteria in this situation, e. g. availability of files and internal processes (e. g. involvement of pharmacists, laboratories or smooth cooperation of the different departments etc.) and not just the availability of patients.
From the outset he should plan more selection visits/calls than the number of centres required for the study so that he has the option of not initiating those centres that do not prove to be suitable. Simply from the standpoint of efficiency it should be borne in mind that every centre that fails to enrol any patients has to be visited several times, which means that careful selection can save on visits. Every activated centre that fails to recruit patients incurs costs of tens of thousands of Euros.
An experienced monitor can anticipate possible problems and weak points at an early stage and then work with the centres to prepare preventive measures to keep these potential risks to a minimum during the course of the study.
The monitor is responsible for ensuring that the centre remains adequate during the course of the study, e. g. in the event of a staff change. If the centre is well trained, the monitor should immediately be informed by the centre staff of such a change and not have to wait until getting notice at his next visit. This is particularly important with a central/remote monitoring approach, since the time between individual visits can be very long.

Training/coaching

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

The monitor should prepare and train the centre staff right at the beginning of the study. The study protocol should be discussed and special attention should be directed to critical activities and processes which the monitor knows from his experience (e. g. inclusion, exclusion criteria, data recording by staff members, handling of IMPs and trial related materials etc.). The monitor should also review, together with the study team, "internal" site processes (e. g. cooperation with different depart-

ments, availability of staff for assessments) to ensure proper conduct of the trial at the site and its integration into daily routine. In addition, the monitor should support the site in analyzing the impact of the information and implementing appropriate measures, and he should share best practices as well as bad experience from other study sites to help the team to improve their performance/skills and to avoid mistakes. Such trial-specific training is a preventive measure. It should be prompt and comprehensive to ensure that the study team is adequately qualified and not only informed about the study procedures. The monitor must ensure that new team members joining at a later date also receive study specific training.

During the whole study period the monitor should verify on an ongoing basis that the processes are performed correctly to avoid protocol deviations. Consequently, spot checks will then be sufficient for verifying the results. In case of deviations from the protocol the monitor should analyze the reasons for the deviations to ensure that any systematic mistake is detected, and corrective/preventive action can be taken. The monitor should also help the site team analyze possibilities for process improvements, and ensure that preventive actions are implemented.

The monitor should ensure that the technical and electronic equipment at the site is adequate and fit for purpose (validated/qualified) before the enrolment of any subject.

During the ongoing trial the monitor must ensure that all new or updated information is given to the trial site in a timely manner, as well as proper training before implementation of new documents. He must also ensure that the processes are adapted accordingly.

The monitor must make certain that new staff members included in the team will be qualified and trained. The principal investigator is responsible for their training and qualification. The monitor will assist the training process. The monitor should confirm that documented training has been provided before a new team member undertakes his first action in the clinical study procedures.

The main objectives of the monitoring strategy around training and coaching should be risk reduction and the prevention of protocol violations or other major deficiencies.

Oversight/control

To ensure that the quality requirements are fulfilled, the monitor must be informed of any changes as soon as possible to maintain oversight and control of the study. Ideally, the monitor should play an active role, being informed about changes at an early stage and being actively involved in the study reorganization process.

Investigational product (IP)

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(ii) That the investigational product(s) is (are) supplied only to subjects who are eligible to receive it (them) and at the protocol specified dose(s).

(iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

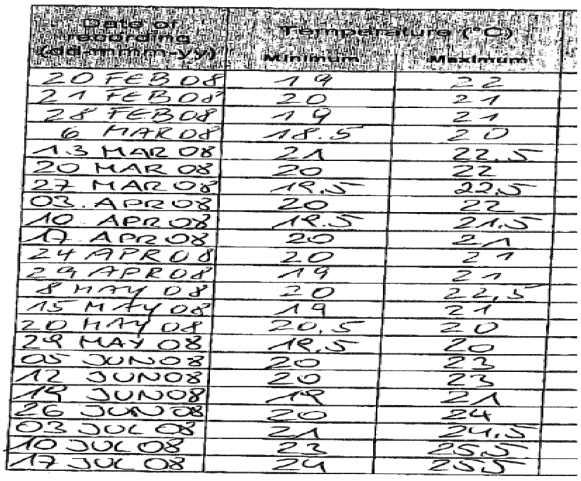
(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

In order to ensure that the IP is stored, used, documented and destroyed properly, routine checking is an important part of the monitoring process. Ideally, however, the monitor should take every opportunity to identify and prevent mistakes and erroneous developments at the trial site before they arise.

As an example, we would like to describe the correct procedure for checking the storage conditions.

Often the monitor only reacts when a result is “out of range” and informs the sponsor of this deviation. The ideal situation would be to detect a trend towards such a possible deviation, discuss this with the responsible person at the trial site and thus prevent the deviation from occurring.

A typical example is shown in Figure 1: The temperature log documented a gradually rising trend of the temperature towards the limit (25 °C), without any visible intervention to improve the storage condition before the limit was reached.



Date of storage (dd-mmm-yy)	Temperature (°C) Minimum	Maximum
20 FEB 08	19	22
21 FEB 08	20	21
28 FEB 08	19	21
6 MAR 08	18.5	20
13 MAR 08	21	22.5
20 MAR 08	20	22
27 MAR 08	19.5	22.5
03 APR 08	20	22
10 APR 08	19.5	21.5
17 APR 08	20	21
24 APR 08	20	21
29 APR 08	19	21
8 MAY 08	20	22.5
15 MAY 08	19	21
20 MAY 08	20.5	20
29 MAY 08	19.5	20
05 JUN 08	20	23
12 JUN 08	20	23
19 JUN 08	19	21
26 JUN 08	20	24
03 JUL 08	21	24.5
10 JUL 08	23	25.5
17 JUL 08	24	25.5

Figure 1: Typical example for a temperature log

Essential documents

(d) Verifying that the investigator follows the approved protocol and all approved amendments(s).

(e) Verifying that written informed consent was obtained before each subject’s participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

*(p) Determing whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial (*http://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial*).*

Together with the personnel responsible at the trial site, the monitor must ensure that the study documentation at the trial site is complete and up-to-date. It is not sufficient for the monitor to repeatedly report open items, he is expected to take active measures to ensure that the issue is solved and the appropriate documentation is completed.

The important and frequent problem of protocol deviations should serve as an example. The frequency and the handling of protocol deviations are important factors for data quality and thus the evaluability of the study. The monitor should regularly discuss and analyze with the trial site potential risk areas for protocol deviations and, where applicable, take appropriate measures at an early stage. Should any protocol deviations occur, it is important to have established a standard procedure for ensuring that these are forwarded in the appropriate way. Going beyond the individual case, the monitor should also ensure that no systematic cause is present at the centre concerned or other centres. Nowadays, this process should be assisted primarily through automatic checks (plausibility checks in the e-CRF) or other risk identification systems which compare information available in different systems (e. g. IXRS, Site Management System, PV database) so that the monitor can be alerted to risk areas as soon as possible and thus accelerate the causal analysis.

In addition to the protocol, the informed consent documents are particularly important. Although the Informed Consent Form (ICF) process has improved over the years, the lack of version control and the use of differing ICF versions within the same study are still common problems. It is not sufficient for the monitor to ensure that the corresponding documents are properly filed. The monitor must ensure that versions are correctly implemented throughout the trial site's entire system.

Source document verification

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRF and are consistent with the source documents.
(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
(iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRF.
(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRF.
(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRF.

Source documents must be kept accurate, complete and up-do-date at every trial site. To ensure this, the monitor must have accurately identified and located source documents already at the start of the study.

It is not sufficient to check a certain percentage of data for one patient during SDV, but to have an overall picture of the respective patient. The monitor therefore needs to scan the whole medical file, even if the SDV plan specifies just 20%. While much has been described and said about the extent of SDV, the crucial factor is the active identification of inconsistencies and not a mere comparison of the CRF against the source data. The monitor must consider the data for a patient as a whole in order to ensure that the presentation of the patient in the CRF is correct. This overall picture can, among others, prevent AE from being overlooked.

As already mentioned, in this task the monitor can and should be supported by the eCRF system with automatic plausibility checks or other risk identification systems.

Adverse events

(o) Determining whether all adverse events (AE) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

AE, and particularly SAE, are of high importance and need to be given special attention by the monitor in order to support the investigators in their reporting obligations. Additionally, an increased incidence of non-reported AE/SAE require further training measures and a more detailed analysis of the causes by the monitor, because major deviations can have serious consequences for the quality of the study. Again, a central review by data

management of AE reporting rates across centres could support the monitor with an important indicator.

Issue management

(j) Reporting the subject recruitment rate.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary) and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(q) Communications deviations from the protocol, SOP, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Querying the recruitment rate at the centre is no longer necessary, since these figures are reliably available at all times through the various electronic systems. Nevertheless, the monitor should regularly discuss this rate with the centre and compare it with the plan drawn up at the start so that any under-recruitment or unwanted over-recruitment can be detected at an early stage and countermeasures taken. Moreover, in a situation of under-recruitment, it often becomes apparent at an early stage that problems are occurring with inclusion and exclusion criteria or logistical and operational circumstances

As part of this preventive approach, the monitor should also systematically utilize the latest technical resources that have been available for some years (e. g. IVRS, eCRF and central lab data) in order to carry out early checks on the selection criteria and thus prevent unsuitable patients from being enrolled in the study. This continuous monitoring can be carried out independently of site visits. To make his job easier, this information should be made available to the monitor centrally.

Early checks of the processes at the centre and the CRF-data by the monitor and/or the data management can help in the detection and correction of systematic errors. It is important that any errors should subsequently be analyzed to see whether these are specific to the centre or study so that, if applicable, other centres can be informed accordingly and thus avoid the same mistake.

The monitor should not only focus on the correction of individual errors, but on the disclosure of systematic errors. This is often not achieved with 100% SDV, but only through the detailed discussion and analysis with the centre of the study processes, including the data entry and data reporting processes.

To this end, data management should provide the monitor at an early stage with listings and analyses that will help him in the detection of systematic errors.

Accordingly, an issue escalation process must be defined for each study so that the monitor knows how, and to whom, problems should be reported that he is unable to resolve himself. This process must also define how, and when, other functions or responsible persons should be informed.

Discussion

The purpose of monitoring as specified in ICH GCP clearly highlights the need to ensure the three following aspects: the safety and well-being of the patient, the quality of the data and compliance with regulatory requirements. However, the discussion in recent years about the further development of monitoring [9], [10], [11] and the changes noticed by ourselves, reveal a disproportionate degree of concentration on the retrospective checking of data that has already been entered (Source Data Verification). This strong focus on SDV, which can take up to 75% of the time available for monitoring, means that too little attention is paid to the processes at the centre, despite the growing volume of documentation and administration. There is a risk that the options offered by risk-based monitoring are used exclusively for reducing SDV – and thus the time spent by the monitor on site. But it is frequently forgotten that **all** of the preconditions for risk-based monitoring must be fulfilled both by the centre and the sponsor. Examples include risk assessments at study level in respect of patient safety and data validity, which also determine the extent of monitoring, but also the careful centre selection taking into account study experience and the technical and personnel-specific preconditions.

As part of the risk assessment and continuous improvement process at the trial site, the monitor must be able, together with the centre personnel, to critically scrutinize the processes required for the study in order to identify and eliminate potential weak points at an early stage. The ultimate goal is to avoid errors instead of just correcting or amending them retrospectively.

As a result this will also entail a reduction in the amount of work required during the course of the study, a lower query rate and fewer protocol violations, a lower number of audit and inspection findings, and a better overall study quality.

High priority needs to be given to this aspect of quality management during the training of monitors. We would suggest that the principles of quality and risk management should be taught after the basic training and initially accompanied centre visits, but **before** the monitor takes on actual responsibility for the centres.

After this initial period, constant training, supervision and co-monitoring should accompany the monitor's activities. It takes at least 2 years of professional experience to enable a monitor to fully master the various challenges of monitoring.

As requested in the ICH GCP Guideline, the monitor has a key function in the study. In order to fulfil this function, he must acquire the necessary skills to act as a centre coach that communicates all the study aspects to the

centre and helps with their implementation, rather than performing pure checking activities.

This discussion was prompted by the pressure to perform studies more efficiently and thus save on costs. We want to remind everybody of one of the simplest, but often forgotten and most effective methods for saving costs, namely not to open up centres that can be expected to show serious quality deficiencies or fail to recruit patients. However, what can be achieved at any rate through the application of the procedures outlined above are the early detection of such shortcomings and the immediate closure of these centres in order to avoid further expenses.

As shown, we do not agree with the view expressed in the simple wording "More SDV automatically means more quality".

Instead we hope that we could illustrate embracing ways for major improvements of quality in clinical trials. The key is prevention of non-compliance and this requires well trained and experienced CRAs. The importance of their work needs to be acknowledged as well as their expertise valued. Fulfilling the ICH GCP criteria for a proper monitoring requires the CRA being provided with decision making competence for their tasks.

As a perfect "one sentence summary" we completely agree with William Edwards Deming: "Eliminate the need for massive inspection by building quality into the product in the first place" [12].

Abbreviations

AE – Adverse Event
CRA – Clinical Research Associate
CRF – Case Record Form
CRO – Contract Research Organization
CTTI – Clinical Trials Transformation Initiative
eCRF – electronic Case Record Form
FDA – Food and Drug Administration
ICF – Informed Consent Form
ICH GCP – International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice
IEC – Independent Ethics Committee
IMP – Investigational Medicinal Product
IP – Investigational Product
IRB – Institutional Review Board
IVRS – Interactive Voice Response System
PhRMA – Pharmaceutical Research and Manufacturers of America
QA – Quality Assurance
SAE – Serious Adverse Event
SDV – Source Data Verification
SOP – Standard Operating Procedure

Notes

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Competing interests

The authors declare that they have no competing interests.

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