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Use of Failure Modes and Effects Analysis (FMEA) as a tool to map the risks involved in a clinical study

Uso da Análise dos Modos de Falha e seus Efeitos (FMEA) como ferramenta para mapear os riscos em um estudo clínico

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ABSTRACT

Introduction: This study describes the application of the Failure Modes and Effects Analysis (FMEA) as a tool for risk management during a clinical research to establish the treatment of patients simultaneously infected with HIV and tuberculosis. **Objective:** To demonstrate the importance of risk analysis associated with clinical trial protocols in safeguarding the participant and study data, as well as the study's quality standard. **Method:** Procedures demanded by the clinical protocol were detailed and then associated with failure modes based on the programmed visits of the participant to the study center. The failure modes were rated between 1 and 10 according to: Severity, Occurrence and Detectability, and the Risk Priority Number (RPN) was calculated by multiplying the three values. **Results:** In a panel of 25 procedures and 60 failure modes, 50% resulted in RPN > 120; six of which contained more than five failure modes. The highest risks were associated with the DOT strategy (RPN 294), blood collection (RPN 288), the Informed Consent Term (RPN 270) and participant data collection (RPN 240). **Conclusions:** The results demonstrate the importance of FMEA as a tool to assess risks in clinical studies, in line with the recommendations of international standardization organizations.

KEYWORDS: Clinical Research; Risk Management; FMEA

RESUMO

Introdução: O presente estudo descreve a aplicação da ferramenta de gerenciamento de riscos Análise de Modo e Efeito de Falha (*Failure Modes and Effects Analysis* – FMEA) a uma pesquisa clínica que estabelecerá um tratamento de indivíduos simultaneamente infectados por HIV e tuberculose. **Objetivo:** Demonstrar a importância da análise de riscos associada aos protocolos de estudos clínicos na salvaguarda do participante e dos dados do estudo, e como padrão de qualidade do estudo. **Método:** Os procedimentos demandados na execução do protocolo clínico e os potenciais modos de falha a eles associados foram estipulados com base na programação de visitas do participante ao centro do estudo. Os modos de falha foram valorados entre 1 e 10 de acordo com: Gravidade, Ocorrência e Detectabilidade, calculando-se o Número de Prioridade de Risco (NPR) pela multiplicação dos três valores. **Resultados:** Num painel de 25 procedimentos e 60 modos de falha, 50% resultaram em NPR > 120; seis deles contendo mais de cinco modos de falha. Os maiores riscos foram associados à estratégia DOT (NPR 294), à coleta de sangue (NPR 288), ao Termo de Consentimento Livre e Esclarecido (NPR 270) e a coletas de dados do participante (NPR 240). **Conclusões:** Os resultados demonstraram a importância da FMEA como instrumento de avaliação de riscos em estudos clínicos, alinhando-se com recomendações de órgãos normalizadores internacionais.

PALAVRAS-CHAVE: Pesquisa Clínica; Gerenciamento de Risco; FMEA

INTRODUCTION

Clinical studies are the foundation of evidence-based medicine[1]. To successfully conduct a clinical trial, it takes to assembly a multidisciplinary team composed of duly skilled professionals given with well-established duties and obligations. This team must include physicians, pharmacists, nurses and administrative staff, which are key elements for the proper conduction of a clinical study[2,3], according to the international guidelines of the IV Pan American Conference for Harmonization of Health[4]. The goals of the study must be integrated and coordinated to converge to the main objective represented by the establishment of the new therapy, combined with the addition of market value to the product or treatment[5], without neglecting ethical aspects related to the participation of volunteers and to the research project.

On being established as a practice in Brazil, clinical trials have complied with the recommendations of the International Conference on Harmonization of Good Clinical Practices[6] and the Document of the Americas[7], also adopting their periodic updates. The technical nature of clinical research projects is evaluated by the Brazilian National Agency of Sanitary Surveillance (Anvisa)[8,9].

According to the regulations currently in force in Brazil, (Resolution 466 of December 12/2012 of the National Health Council of the Ministry of Health and complementary documents), clinical studies involving human beings should be evaluated by the Committees of Ethics in Research – National Commission for Ethics in Research (CEP-CONEP) system. In this system, the initial evaluations are done by the institutional CEPs and, as applicable, by CONEP. Thus, the ethical conduct is ensured by the prior approval of the protocols by ethics authorities[10] that, when considering the involvement of human beings, have the function of protecting the research participants' rights, safety and well-being[6]. In this evaluation, the authorities basically consider the proposed protocol and supplementary documentation for research, whose proper conduction is intimately related to the success of a clinical study.

The team of researchers, physicians and technicians and the sponsors of the study, in dealing directly or indirectly with the study subjects, should base their actions on two grounds: the protection of the participants' rights and the guarantee of the security and confidentiality of the data generated during the collection, registration and statistical treatment processes. Ethical parameters rule the safety of the participants and the confidentiality of their information, while the adequacy to regulatory and technical quality criteria and the scientific validation are more related to the second item[11]. However, it is extremely important to highlight that the ethical and regulatory standpoints are complementary and inseparable, forming a fundamental binomial for the good conduction of clinical research in all its aspects.

Considering the trend of rapid growth in clinical research in countries like Brazil[11,12], the risk assessment applied to studies is becoming increasingly important[13]. International agencies and researchers have drawn attention to the need for effective management of this process[14], not only to avoid exposure to risk or even harm to the participants (caused by possible inefficiency of the structure or even of the teams), but also to strengthen the quality of the project management[3,15]. This concern is reflected in the recent updates of the Guide of Good Clinical Practices of the International Conference on Harmonization (ICH). These updates also influenced the Brazilian studies, since the country joined the ICH in late 2016. As part of a complex pharmaceutical development, the adequate governance of multiple activities requires an integrated and robust management[16] that can guarantee the efficient application of funds in the study. This is also imperative in the demand for an approach with minimal flaws and prediction errors.

During a clinical trial, safety issues related to the volunteers, as well as to the multidisciplinary healthcare team, can be transposed or readily adapted from the above routines of medical and pharmaceutical assistance already established at the centers, since, in essence, they do not differ as to the nature of the activities. In these cases, the gains in the safety of the participants have been regularly reported in the literature by various opportune risk analysis applied to medical care[14,17,18,19].

The adoption of effective monitoring techniques, associated with clinical trials in a landscape of growing general concern with safe medical services and the well-being of the patients, together with the pressure of regulatory instances, are producing a wave of support for risk-based monitoring (RBM)[20]. This approach aims to develop the best strategies to perform activities related to the clinical study within the research center. Artificially, two relevant moments can be considered for the risk approach in a clinical study:

- Risks in the design of the clinical protocol: related to the researchers' ability to predict and plan the clinical study, such as: (i) inaccurate prediction of safety-related events, like: the toxicity related to a drug test, which can lead to serious damage to the participants and the premature termination of the studies; (ii) inaccurate prediction of recruitment capabilities, which can lead to a not informative study; (iii) inaccurate estimate of the difference in the comprehensiveness of the proposed therapy or some effect from the planned interventions (an overrated effect can lead to an underestimation in the sample size required to achieve a statistically valid inference[21] or underestimated effect can lead to excessive recruitment and therefore unnecessary exposure of volunteers to risks)[15].

- Risks in implementing the clinical protocol: related to the dynamics of monitoring the study, which requires efforts to mitigate risks during the conduction of clinical procedures. By guiding the activities of the study through the research protocol and assessing the relevance of additional actions (e.g. training of clinical researchers and team,

clarification of the requirements of the protocol, etc.), the monitoring becomes a tool for process control. Bearing this in mind, we reinforce the idea that this is the most appropriate context for evaluating risks, since the results are essential to ensure the protection of individuals and the quality of the data in the locales they are generated or deposited[22].

The present study falls within the context of risk management to the protocol of an ongoing clinical study, whose aim is to establish a therapy with antiretroviral drugs (ARV) in patients with human immunodeficiency virus (HIV) and tuberculosis. This study, as well as the proposed risk assessment associated with your clinical protocol, was done in the Laboratory of Clinical Research in Micobacterioses (Lapclin-TB) of the Evandro Chagas National Institute of Infectious Diseases (INI), Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil. The objective was to provide instruments to reinforce the maintenance of the quality standard during this specific study as a means of safeguarding the clinical safety of the research participants and also of the study data. The increasing numbers of clinical studies managed by Lapclin-TB, as well as the complexity involved in quality management during clinical and laboratory procedures, justify pursuing ways to mitigate possible failures and the creation of safer routines. To achieve this objective, a set of procedures of the clinical protocol was modulated as a process. We then applied the Failure Mode Effects Analysis (FMEA) to the steps of the process to establish and highlight the potential risks associated with the procedures that make up such a process.

METHOD

The research project evaluated in this study involves the process of administering medicine to the participants of the survey, and also the complete chain of procedures throughout their clinical visits, as set out in the study protocol. The multidisciplinary study is underway in Lapclin's Tuberculosis Clinic-TB at INI Fiocruz, in Rio de Janeiro. During the study, this department received the visits of patients infected with HIV and tuberculosis to evaluate the pharmacokinetics of a tuberculostatic drug under increasing doses of ARV1/ARV2 (combination of antiretroviral drugs selected for testing). With its terms protected by confidentiality, the study in question fulfills all applicable ethical and regulatory approvals and is registered on ClinicalTrials.gov.

The FMEA was chosen because it is a structured tool with flexibility of use in processes structured by step-by-step coordination[23]. FMEA is a qualitative risk assessment tool that provides comparable results among themselves. These results can support decision-making and improve the process, based on risk mitigation[24]. The risk mapping was based on the document of the Americas (publication of the Pan American Health Organization on good clinical practices). The theoretical reference was the tripartite guide harmonized by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) on ICH Q9 risk management and its updated version (ICH E6 (R2) of 2016)[10,25].

The methodological development involved three integrated approaches. First, all processes of the study protocol involving the research participant were established within a flowchart, whose purpose was to demonstrate the concatenation of idealized steps as a basis for risk analysis. To this end, the protocol visits of the participants to the clinic were used as guiding events and central subject of the risk analysis. Next, the construction of the FMEA for the case under study was based on the three criteria to approach the failures: Severity, Occurrence (frequency) and Detectability (possibility to be detected). Within each criterion, the failures are evaluated and assessed according to a score between 1 and 10. For the Severity of the failure, the value 1 represents a safe risk and the value 10 can mean harm to the participant or even his/her death. In the Occurrence scale, the closer the value is to 10, the greater the chance of failure mode. Inversely, the value 1 for Detectability represents the highest probability of detecting the cause and/or mode of failure before or during the procedure and the value 10 corresponds to the impossibility of its detection in the process. The characterization of the FMEA is presented in Table 1. This process was carried out in brainstorming sessions with the team of professionals involved in the study: two coordinators, one physician, one pharmacist, two nurses and one nursing technician.

Once these matrices were prepared, the tool was applied to each procedure laid down initially. This also involved the dynamics of consensual brainstorming with the team, when all failures likely to put each procedure at risk were discussed. We calculated the Risk Priority Number (RPN) to rate each failure mode in the case under study by multiplying the three values obtained (severity x occurrence x detection). The maximum is represented by the value 300. For a prospect of the practical impact of the results, we classified the risk ranges as low (RPN ≤ 120), intermediary (121 ≤ RPN ≥ 200) and high (RPN ≥ 200).

RESULTS

The application of FMEA to the set of procedures comprised in the study protocol, with reference to the participant's visits to the study center, is summarized in Table 2. The first column presents the 25 different procedures performed in this study (according to chronological sequence), as deployed in 60 failure modes (numbered in the second column of Table 2). FMEA's approach to failure modes in the case of the present clinical study enabled us (i) to map potential failures within the processes in which the patient participates, (ii) to identify possible causes and the probability of occurrence of each failure mode, (iii) to assess the severity in case of failure and (iiii) to evaluate the system of failure detection. Overall, of the 60 failure modes listed on the table, 10 resulted in RPN above 200 (17%) and 19 were between 120-200 (32%) (Figure).

A comparative view of the results is presented in the Figure. It also includes a quick approach to the distribution and variability of the data obtained, represented by the values of the RPN of each failure mode.

Table 1. Assessment of failure modes according to Severity, Occurrence and Detectability criteria applied to participant's protocol visits to the Study Center.

Criteria (levels) for failure Severity	Index
Failure affects nothing (none)	1
Possible delay in procedure (minor)	2
Delay in procedure (low)	3
Probable loss of data and delay in the procedure. There may be some regulatory impact (low)	4
There will certainly be data loss and delay in the procedure (moderate)	5
Possible injury to the patient, data loss and delay in the procedure. There is regulatory impact (high)	6
Probable harm to the patient, data loss and delay in the procedure. There is regulatory impact (high)	7
Harm to the patient, data loss and delay in the procedure. There is high regulatory impact (high)	8
The potential failure mode affects the safety of the participant during the operation and/or leads to regulatory non-compliance. The procedure should be stopped until further action is taken to eliminate the hazard. Serious damage to the participant (high)	9
Death of the patient	10
Failure occurrence (frequency) scale	**Index**
Unlikely	1
Not likely, remote	2
Not common, but can happen	3
Less than once in ten procedures	4
Less than once in every four procedures	5
Less than once in every two procedures	6
More than once in every two procedures	7
Most of the time	8
Almost continuous	9
Constant, continuous	10
Failure detectability scale	**Index**
Almost sure of detection	1
Very high chance of detection	2
High chance of detection	3
Moderate to high chance of detection	4
Moderate chance of detection	5
Low chance of detection	6
Very high chance of detection	7
Remote chance of detection	8
Very remote chance of detection	9
No chance of detection	10

The distribution of the values obtained for RPN was plotted on a Box-Plot chart (inserted in the figure), in which we can see the median (central line) and the quartiles. Half of the failure modes with higher RPN (above the median of 108) included the highest variance of the data set, in a ratio of 2:1 compared to the variation of the RPN of the procedures below the median. The steps in the top quartile comprise 15 failure modes related to the highest RPN, which also comprise a greater dispersion of the data, producing also a wider variation in their set, as aligned in a descending order in the Figure. In this set of values, ten procedures with RPN > 200 (17% of total procedures) would deserve greater attention during the implementation of the clinical study, since they entail greater risks too.

DISCUSSION

Overall, the activities with the highest comparative potential risks (RPN > 200) and therefore highlighted as deserving more attention during the clinical study were: patient's compliance with the medicines and with the therapy through DOT-Plus, correction of the ICF process, appropriate records during blood sample collections and the measurement of weight and vital signs. The potential compromise in the ICF application process resulted in an RPN of 270, demonstrating the importance of performing this procedure adequately. This concern from the FMEA analysis is in line with the concerns of Good Clinical Practices regarding the quality of the consent process of volunteers to participate

Table 2. Application of Failure Mode and Effect Analysis (FMEA) at programmed visits in the clinical trial to establish therapy in HIV-Tuberculosis cases.

Process step[1]	Potential failure mode[2]	S	O	D	RPN	Preventive action
Screening visit						
I. Application of the Informed Consent Form	1. Lack of physician's signature	9	2	2	36	Reinforcing the team training in the study protocol and in Good Clinical Practices. Checking the coordinator at every new patient's consent.
	2. Lack of participant's signature	9	2	2	36	
	3. Obsolete version applied	9	3	4	108	Updating the spreadsheet frequently. Checking the coordinator at every new patient's consent. Keeping the obsolete versions separate.
	4. Version not approved	9	3	4	108	
	5. Consent process is impaired	10	3	9	270	Searching the physician's history in conducting other protocols (ABAC).
II. Confidentiality guarantee	6. Confidentiality revealed	6	3	3	54	Coding the randomized control of the patients. Training the team in Good Clinical Practices.
III. Assessment of medical history	7. Improperly executed or unperformed procedure	9	3	5	135	Creating a checklist and default templates to alert the physicians in their activities. Training physicians in the protocol and in the procedures before starting the study.
	8. Incomplete information in the CRF	9	4	5	180	
IV. Weight, height and vital signs measurement	9. Improperly executed or unperformed procedure	9	3	5	135	Updating the equipment control spreadsheet periodically (for example: weekly). Training and updating the nursing team.
	10. Wrong information collection	10	3	8	240	Intensifying training in laboratory procedures.
V. Complete physical examination	11. Failure to perform physical examination	10	2	2	40	Team training.
VI. Blood collection	12. Performed incorrectly	9	4	8	288	
	13. Wrong record of results	9	4	8	288	
	14. Wrong amount collected	4	2	8	192	Intensifying training in laboratory procedures.
	15. Patient not ready for the procedures	6	4	2	48	
	16. Collection performed incorrectly	9	3	8	216	
	17. Expired biochemical analysis material	7	3	2	42	Checking inventory periodically. Organizing the material to make it available before the expiration date.
	18. Infection of the participant with non-sterile material	9	3	5	135	Training the technicians responsible for continuously checking the sterile material vs. validity. Prepare SOP for collection.
	19. Replacement of collector tubes	7	3	8	168	Intensifying training in laboratory procedures. Separating tubes with reagents. Labeling before collection. Elaborating SOP.
	20. Contamination of collection tubes	7	3	8	168	Having a spare pipette available.
	21. Pipetting errors	6	4	8	192	Reinforcing the training of the technician and the nursing team in the study procedures. Using a different pipette for each visit.
	22. Incorrect centrifuging	7	4	8	224	
	23. Incorrect sample transportation	6	3	4	72	Reinforcing the training of the technician and the nursing team in the study procedures.
	24. Inadequate sample storage	6	4	3	72	
VII. Request for inclusion or not of the participant	25. Exams not requested or incomplete requests	9	3	2	54	Promoting a checklist, template with all the information that physicians should use to evolve in medical records.
	26. Exams not done by the participant	7	4	3	84	Promoting careful medical guidance and designating follow-up of the participant to the laboratory.
VIII. Evaluation of the inclusion and exclusion criteria of the participant	27. Non-evaluation of the criteria	8	2	2	32	Promoting a checklist, template with all the information that physicians should use to evolve in medical records.
	28. Misinterpretation of the criteria	9	2	6	108	Regularly training the medical staff in the study procedures and reinforcement.
	29. Corruption conflict of interest	10	2	8	160	
IX. DOT-phone	30. Incomplete DOT or DOT not done by the team	7	3	3	63	Double checking and/or two people performing this activity.

Continue

Continuation

	Visit n. 1 and Scaling up					
X. Windows	31. Participant did not initiate medication with ARVs of choice at appointment 1	8	3	5	120	Training staff on the specific aspects of the medication (information on specific form in the Operational Manual)
	32. Participant does not scale medication on the correct date	6	4	6	120	Training staff on the specific aspects of the medication (information on specific form in the Operational Manual) using DOT-phone.
XI. Omission of clinical information by the participant	33. No description of existing concomitant disease or new adverse events that have occurred since the beginning of the study	9	3	7	189	Promote good doctor-participant relationship. Alert in the participant's diary (which is kept in his/her possession) a list of possible adverse events caused by the medication, requesting notes made by him/her in his/her house.
XII. Concomitant medication	34. Participant taking medication prohibited by the protocol	8	4	3	96	Training staff on the specific aspects of the medication (information on specific form in the Operational Manual).
	35. No investigation on concomitant medication	8	3	7	168	Training the physician and making available a list of medicines for consultation at the appointment.
XIII. Medication dispensing	36. No dispensing of medication to the participant	10	2	3	60	Training the pharmacist.
	37. Incorrect guidance on medication administration	9	4	6	216	Training staff, establishing a well defined SOP and adopting medication control sheets.
	38. Quantitative dispensed wrongly, between a visit and another	8	3	3	72	Updating the form at every visit.
	39. Dispensation of expired medication or close to expiration	10	3	3	90	Checking the package before giving the medication to the patient.
XIV. Scaling up	40. Non-Scaling up	6	4	6	144	Improving pharmaceutical assistance. Telling physicians to make explanations simple and easy.
XV. Conducting safety exams	41. Failure to conduct exams	8	3	2	48	Regularly training the medical staff in the study procedures and reinforcement.
	Visit n. 2					
XVI. Window	42. Window loss 1-2 weeks after Scaling up	7	3	4	84	Updating the visit control worksheet. Confirming the appointment with the participant the day before the appointment, providing the necessary recommendations.
XVII. Serious adverse events	43. No monitoring of serious adverse events	10	2	9	180	Training the physician.
XVIII. Compliance with the ARVs (counting the tablets in the bottle)	44. Non-compliance with ARVs.	9	5	5	225	Monitoring the DOT with the participant by insisting on the importance of taking the medication correctly.
	45. Participant does not bring the medications for counting; or bring incomplete medication	6	5	5	150	Record in diary (DOT card) the need and importance of medication taken correctly.
XIX. Blood collection for pharmacokinetics	46. Lack of hospital bed for the day of pharmacokinetics	9	3	5	135	Booking the room in advance.
	47. Participant did not comply with 12-hour fasting regimen	6	4	5	80	Contacting the participant the day before, reminding him/her of the need for fasting.
	48. Participant did not take the last medication 12 hours before	6	4	5	80	Contacting the participant the day before, reminding him/her of the need for medication 12 hours before the appointment.
	49. Temperature deviation of collected sample	6	3	3	54	Creating a form for registration of arrival, departure, centrifuging and storage of the sample.
	50. Forms filled wrong	6	3	3	54	Intensifying training in laboratory procedures.
	51. Non-authorized people performing the activity	8	3	3	72	Continuously checking the delegation form and the activities assigned to each professional.
XX. Transporting the sample to the outside	52. Sample does not reach its destination	7	2	7	98	Preparing the documentation of the carrier and the researcher in advance. Applying a checklist of the documentation. Choosing a suitable carrier.
	53. Sample arrives at destination with inadequate quality	6	3	5	90	Applying a checklist to the documentation of the sponsor and the study center. Using preventive monitoring thermometer along with the sample.
	Visit n. 3					
XXI. Transport of the sample to the international laboratory	54. Non-availability of sample in a timely manner	7	3	7	147	Promoting traceability of the sample with the carrier.

Continue

Continuation

Visit n. 4						
XXII. Window	55. Window loss of 3-5 weeks	7	3	4	84	Updating the visit control worksheet. Confirming the appointment with the participant the day before the appointment, providing the necessary recommendations.
XXIII. Adhesion to DOT-Plus	56. Incorrect recording of the medication intake by the participant or the person chosen by the participant	7	6	7	294	Using new ways to communicate with the participant (for example: WhatsApp).
	57. Participant incorrectly informs the pharmacist or during the appointment	7	6	7	294	Improving communication and empathy with the participant.
XXIV. Compliance with the treatment	58. Non-compliance	9	5	4	180	Following the DOT, regularly urging the participant to take the medication correctly.
XXV. Inclusion of information in the clinical file in the CRF	59. Incorrect inclusion or non-inclusion	8	4	3	96	Constantly maintaining quality assurance to meet deadlines to release the data to the sponsor.
	60. Delay in including information in the CRF	7	4	3	84	Register the limit-date to include the information in the calendar (Google).

[1] The steps textually represent the flowchart of procedures designed for the visits during the clinical study. The term "window" refers to the interval between visits. "Scaling up" refers to the transpositions of doses of drugs as planned in the study protocol. During visits 2, 3 and 4, several steps either repeat procedures of visits 1 or of the immediately previous visit; these have been suppressed to avoid redundancies once they do not influence the risk classification per procedure as the final goal.
[2] In practice, failure modes were split according to their potential causes and the mechanism of occurrence of each failure was considered individually (data not shown).
[3] S: severity; O: occurrence; D: detectability; RPN: Risk Priority Number (S x O x D); CRF: Case Report Form; ARV: anti-retroviral; *ABAC: Anti-Bribery Corruption (act of the pharmaceutical industry to eliminate this specific risk); SOP: Standard Operating Procedures; DOT: Directly Observed Therapy.
Source: Developed by authors.

in a research project. The impairment of this process can have a significant impact on the context of ethics in conducting such research.

The biggest potential risks were found in the step regarding compliance with the DOT-Plus strategy (a procedure in step XXIII), which involves the direct participation of a family member or volunteer appointed to monitor and record each dose of medicine taken by the patient. The two failure modes associated with this procedure resulted in an RPN of 294: correctly recording medication intake and passing on false or misleading information to the responsible person. The DOT strategy (Directly Observed Therapy) is recommended by the World Health Organization[26] to improve compliance with the therapy. DOT-Plus[27] is adapted for the present study because it allows the participation of family members in the supervision of the treatment.

The steps involving blood collection in the screening visit (step VI) and during the pharmacokinetic tests (a procedure in step XIX) have 13 and 6 failure modes, respectively. In the first case, RPN values vary between 42 and 288, and in the second case, between 54 and 135, revealing significant qualitative differences. Thus, multiple sources of potential failures associated with the same step may pose different risk potentials depending on the consensus of the experts during the RPN evaluation and generation process. Additionally, some operations are repeated during different visits of the participant and can generate different RPN values. For example: the failure associated with the wrong record of the results of blood collection implies a high risk at the beginning of the study (maximum RPN = 288, failures VI.12 and VI.13), but only moderate risk at the pharmacokinetics step (maximum RPN = 180, failure XIX.46). Still, the smaller number of failure modes does not simply mean a lower or greater risk for a particular step. For example, in the structured visit process, there are six steps with only 1 failure mode pointed out (II.6, IX.30, XVI.42, XXII.55, XVII.43, XXI.55 and XXIV.58 in Table 2), with RPN varying between 54 and 180, representing relatively low and medium risks. In practice, it is important to consider the intermediate risks that are closer to RPN 200 (used as cutoff number for analysis) as well as relevant failure generators.

The use of FMEA in hospital activities and services in general is already a longstanding practice. Since 2001, the international accreditation organization Joint Commission on Accreditation of Health Care Organization – JCAHO (currently simplified as Joint Commission International - JCI), which is considered one of the most important in the world, has recommended the FMEA for the emergency activities of the hospitals with the aim of reducing the number of medical errors[28]. For example: the application of FMEA in the administration of medication in medical facilities has enabled the regulation of dosage windows and improved the management of the medicine distribution system[29]. It also enables the establishment of prescription, administration and adherence as basic issues to structure the risk analysis[30].

In a clinical study that aims to generate data to collaborate for the development and improvement of therapies, it is of great relevance to minimize errors in the records of medication administration. As important as the compliance with the therapy is the accuracy of the general records of a project. It is not enough to

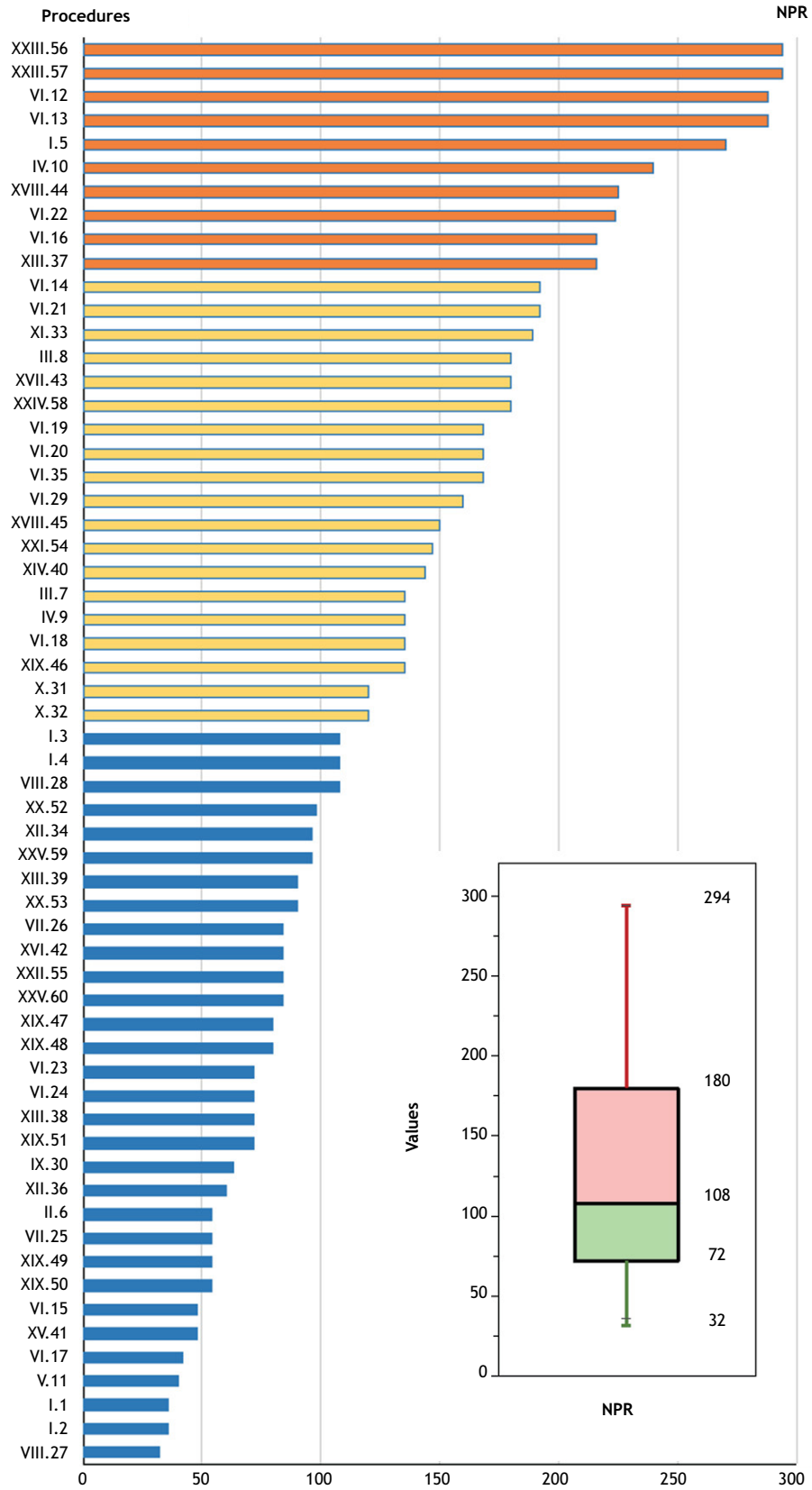

Figure. Risk Priority Number (RPN) classification using Failure Mode and Effect Analysis (FMEA) of failure modes (Arabic numerals) associated with the chain of procedures (steps) of the clinical study (Roman numerals). Top group: RPN > 200. Intermediate group: 120 < RPN < 200. Highlighted: Box-Plot chart of the distribution of the RPN values associated to the procedures involved in the study in question, highlighting the values of the median, minimum, maximum and between quartiles. Grubbs' test indicated that there was no outlier (P > 0.05) in the total data set.

ensure that the research volunteers are making proper use of the products under study; if the data is not accurate; the validity of the research may be jeopardized. In this sense, appropriate management of the risks inherent in the documentation is of great value.

In addition to technical issues, concern about the ethical impact of errors that are potentially avoidable is critical. In addition to the procedures related to compliance, therapy and appropriate data records, an important factor highlighted in the present analysis was the application of the ICF. Deviations of conduct with regard to the process of consent to participate in clinical studies are against some basic principles of good clinical practice and, more importantly, they impact the rights of research participants adversely.

Although recommended since 2001[31], the risk management applied to clinical studies was just recently incorporated into the guide of the ICH good clinical practices by an additive term in 4.2.5 and 4.2.6 items (ICH E6 (R2) 2016)[25]. This guide recommends that the guarantee of the protection of the participants and the qualification of the results in a clinical study begin with the mapping of the critical processes and identification of data. The identification of risks must be done already during the development of the protocol. In this sense, FMEA is quite appropriate, as demonstrated by the results obtained in the present study.

This study demonstrates that both clinical procedures and ethical care, and medical management practices, are important sources of failure modes. Some approaches suggest a previous categorization of risks involved in clinical research, according to variables associated with the different stages of pharmaceutical development, in order to facilitate the management by researchers and other stakeholders, aiming at the production of more accurate results[32].

The visibility offered by the structured procedures and the application of FMEA allowed scaling the risks associated with them, identifying those that are more vulnerable as focal points of priority corrective actions. These developments were important in the implementation of the monitoring plan for the study, and in the determination of the procedures most in need of adjustment by the redesign of the specific protocol or by the reinforcement in personnel training. Furthermore, the dataset allowed the elaboration of a specific Operational Manual for the study in focus, with the objective of supporting the monitoring the project activities. As feedback, this document also represented a tool to alert team members about the risks and urgency of mitigating the most serious risks. This enabled better control of corrective actions during the study.

CONCLUSIONS

The present study is aligned with the recently updated guidelines of international accreditation bodies[25], which recommend considering the risks both in the system approach (standard operating procedures, and customized informatics) and at the clinical level (study design, data collection and consent processes). On risk assessment, the sponsor of the study should identify the risks through: (i) the likelihood of failure occurrence; (ii) the extent to which such failures are detectable; (iii) the impact of such failures in the protection of the participant and the reliability of the results. In this context, FMEA has proven to be an effective tool and provider of due detail to the herein proposed analysis. The use of risk tools – in particular the FMEA – is universally recognized as effective in terms of the objectives it proposes[33]. Nevertheless, only recently has its application in clinical studies been reported more often[34]. This demonstrates that, despite being essentially qualitative, FMEA has proved extremely useful for use in clinical laboratories[35]. It has been increasingly recommended in international studies sponsored by JCI, a US-based health facility accreditation body[31,33].

The use of powerful tools to assist risk management in clinical research, as pointed out in this study, should be incorporated in the policies of such projects, aiming at greater effectiveness in producing results, optimization of resources, reduction of negative impacts for the research volunteers and to ensure the quality of the data generated.

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Conflito de Interesse

Os autores informam não haver qualquer potencial conflito de interesse com pares e instituições, políticos ou financeiros deste estudo.