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Original Article

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Article to reduce the adverse event reporting time in the development of vaccines

Artefato destinado a reduzir o tempo de relato de evento adverso no desenvolvimento de vacinas

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Abstract

The development of vaccines involves the need to control all adverse events, in order to monitor product safety under investigation in an agile and accurate manner. **Objective:** This research develops an artifact designed to reduce the reporting time of Adverse Events in a clinical trial for vaccine development. **Methodology:** Design Science Research was used as a conducting technique for the investigation, with the purpose of establishing an artifact designed to find a solution to the problem presented in the objective. Lean and Six sigma techniques were used as improvement tools in the Adverse Events reporting process in a phase 3 clinical trial for developing a vaccine. **Results:** As a result of the research, the proposed artifact reduced the average time of Adverse Event reporting from 30 days to 6 days and reduced the standard deviation from 33 days to 6 days. In this way, the total time in the Adverse Event reporting process started to be in compliance with the research center protocol, providing agility in the process, ensuring greater security, and quality of information, for the employees involved. **Conclusion:** The combination of Lean and Six sigma tools associated with control tools such as the control chart, Kanban and application form in the Check List pattern presented itself as an adequate strategy for the management of the Adverse Event reporting time, which can be a satisfactory resource for process optimization in clinical research or others in the health field.
Keywords: research institute; quality management; data reliability.

Resumo

O desenvolvimento de vacinas envolve a necessidade de se controlar todos os eventos adversos, visando monitorar a segurança do produto sob investigação de forma ágil e acurada. **Objetivo**: Esta pesquisa desenvolve um artefato destinado a reduzir o tempo de relato dos Eventos Adversos em um ensaio clínico para desenvolvimento de vacinas. **Metodologia**: Utilizou-se o *Design Science Research* como técnica condutora da investigação, com a finalidade de estabelecer um artefato destinado a encontrar uma solução para o problema apresentado no objetivo. Utilizou-se técnicas do *Lean* e do *Six sigma* como ferramentas de melhoria no processo de relato de Eventos Adversos, em um ensaio clínico fase 3 para desenvolvimento de uma vacina. **Resultados**: Como resultado da pesquisa, o artefato proposto proporcionou uma redução do tempo médio do relato de Evento Adverso de 30 dias para 6 dias, e redução do desvio padrão de 33 dias para 6 dias. Desta forma, o

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tempo total no processo de relato do Evento Adverso passou a apresentar-se em conformidade com o protocolo do centro de pesquisas, proporcionando agilidade no processo, garantindo maior segurança, e qualidade de informação, aos colaboradores envolvidos. **Conclusão**: A combinação de ferramentas do *Lean* e *Six sigma* associado com ferramentas de controle como a carta controle, o *Kanban* e aplicação de formulário no padrão de *Check List* se apresentou como estratégia adequada para a gestão do tempo de relato de Evento Adverso, podendo ser um recurso satisfatório para otimização de processos em pesquisa clínica ou outros na área de saúde.
Palavras-chave: instituto de pesquisa; gestão da qualidade; confiabilidade dos dados.

Introduction

The clinical trial is positioned as an investigation carried out in humans in order to identify the clinical, pharmacological and/or pharmacodynamic effect of a product, or to identify adverse reactions related to a product under analysis, establishing its safety and efficacy [1]. The development of the clinical trial seeks to identify possible Adverse Events (AE), and to assess whether the benefits outweigh undesirable effects [2].

The literature presents AE research addressing different topics, such as: introduction of a new weight loss medication [3], use of placebo [4], testosterone products [5], relevance of the event notification in patient safety [6] perinatal infection of 2019-nCoV [7]. This range of research topics reflects the importance and relevance of studies, with a focus on the protocols for the development of clinical trials and their Adverse Events. As highlighted by the Pan American Health Organization (PAHO), the clinical trial is characterized as a systematic study supported by scientific methods, establishing the importance of associating scientific rigor with the agility of presenting responses to society.

The clinical study involved in the vaccine development process establishes particular care and demands, in order to guarantee a high probability of immunization and low occurrence of AE. If the AE rates in the development of vaccines are higher than expected, the data of the experiment should be interrupted and evaluated, in order to guarantee the safety of its participants [8]. These aspects emphasize the importance of establishing protocols indicating how to perform the collection and registration of data, in order to guarantee its quality and reliability [9].

The importance and relevance of the development of the clinical trial and the timely registration of the respective Adverse Events related to the product under study, should stimulate the continuous advance of the processes, in order to speed up the punctuality of the arrival of the information to the sponsor of the product under investigation and all interested parties, aiming at the safety of voluntary research participants and, consequently, the response time for society. In this context, the objective of this research is to reduce the reporting time of Adverse Events in a clinical trial of vaccine development.

Materials and methods

In order to meet the research objective, Design Science Research (DSR) was adopted as the conducting technique of the investigation. Design Science Research establishes an interesting relationship between the rigor of scientific research, and the artifact resulting from the study [10]. Despite being a technique still in the expansion phase, it is possible to identify its use in the health area [11, 12, 13].

The DSR proposes the development of the experiment in five phases, namely: i) Identification of the need; ii) Logical design of the artifact; iii) Development of the artifact; iv) Initial tests of the artifact and; v) Validation of the artifact in the context of the end area [14, 15, 16]. The development of the DSR phases was supported by a set of tools called Six sigma of quality, aimed at

investigating and solving operational problems. Additionally, the tools referring to the Lean concept, which seeks to mitigate the losses and waste of the processes carried out by the institutions, were used in a substantiated manner [17].

Six sigma incorporates a set of techniques in a structured way, which aim to establish a high level of quality through a low variability in the execution of processes [18] aimed primarily at reducing costs and standardizing processes [19]. The techniques employed in this research are presented in association with the data found in the Results section, which appear next.

The use of Six sigma in health is associated with the seminal work carried out in an American hospital, with the purpose of reducing the waiting time in urgent and emergency rooms and improving the filling of medical records [20]. In Brazil, research started to be more applied in the health area as of 2000 [21]. Six sigma and Lean are positioned as a relevant instrument, employed in order to provide continuous improvement in performance, and in the quality of health services [22].

The place of study was that of the Aggeu Magalhães Research Institute, of the Fundação Oswaldo Cruz de Pernambuco (IAM / Fiocruz PE), an organ linked to the Ministry of Health. The activities were carried out with a phase 3 multicenter clinical trial team intended for evaluation effectiveness and safety of a vaccine. Among the products resulting from this institution, the vaccine with attenuated virus against yellow fever (which was patented), and a phase 3 study to prove the efficacy and safety of the quadrivalent dengue vaccine stands out. The development of this investigation did not involve contact with patients or other actors involved in the process under analysis, thus dispensing with the need to forward the research for approval by the ethics committee. In this context, the names of the components responsible for the actions to be performed were taken from the figures.

Results

This section presents the data obtained in the experiment, and the tools used to collect and process the information. In this sense, the data are presented in the sequencing effectively implemented by the researched institution.

The first stage aimed at identifying the need for the artifact, analyzed the documentation that addresses the flow of non-serious AE reports from a vaccine development study by the laboratory, over a four-month period (from December 2018 to March 2019). At this stage of the project, it was agreed that the AE reports with a term of more than seven days would be considered as overdue, because seven days was the maximum term established in the research protocol and recommended by the sponsor. During the analysis period, 144 reports of AE were identified, of which 64 (44.4%) were in a position to be late. The investigation of the origin of the delay identified two predominant causes. The first related to the difficulty of establishing telephone contact with the patient (voluntary participants of the research who had been vaccinated with the product under investigation), and the second due to the difficulty of the medical team in establishing contact with the participant in a timely manner (related with the large amount of activities they needed to perform).

From the identification of these first observations, a Project Charter was designed to establish goals to be achieved after the application of changes in the process. The Project Charter aims to manage the scope of the changes, the activities to be developed by the participants, the resources involved and to predict the deadlines for completion [23]. Figure 1 shows the Project Charter.

Figure 1. Project Charter for the implementation of improvements aimed at reducing the reporting time of adverse events.

LEAN SIX SIGMA PROJECT CHARTER

TITULO DO PROJETO:	**Redução do tempo de relato de eventos adversos em um ensaio clínico utilizando Lean e Six Sigma**				
Processo	relato de EA	**Data de Início**	**mar/19**		**Green Belt**
Depart.	**LAVITE - IAM/FIOCRUZ-PE**	**Data de Conclusão**	dez/19	x	**Yellow Belt**

CANDIDATOS GREEN BELTS	EQUIPE DE APOIO (Nome, Área)	SPONSOR	
		PROJECT CHAMPION	
		DONO DO PROCESSO	
		REVISOR FINANCEIRO	

Objetivos	**Indicador**	**Atual**	**Meta**	**% Melhoria**
Reduzir o tempo de relato de EAs infor. em contatos com participantes de um ERCT				
Diminuir o tempo total de relato dos Eas ao CRF	Número de dias	30 dias	9 dias	30%
Reduzir o número de EAs relatados com atraso (>7 dias)	N de Eas relatados com atraso	64 (61,5%)	45 (43,2%)	30%

Tipo de Projeto		**Centro**		**Administrativo**	**Ganho Financeiro Esperado**

Descrição Detalhada do Problema	**Base de Deficiencia do Processo**
Atualmente, o relato dos EAs no CRF frequentemente tem sido realizados com atraso, contrariando o que está recomendado no protocolo do estudo, que é de até 7 dias corridos, contados a partir da data do conhecimento do EA pela equipe do centro. Inicialmente, os colaboradores da equipe recebem o comunicado do EA pelo participante, a partir dos contatos telefônicos de rotina ou por meio de whatsapp, fazem o registro do contato e separam os prontuários com EA. Os médicos posteriormente, entram em contato com o participante, para obter informações mais detalhadas e analisar possível diagnóstico e intensidade, além de medicações utilizadas, relação causal com o PI e desfecho do EA, registrando tais informações no formulário de EA. E por fim, essas informações são registradas pela digitadora no CRF, quando cabivel (se relacionado ao PI ou até 21 dias pós vacina).	Dificuldade de conseguir contato telefônico com o participante para registro médico dos Eas; Dificuldade de estrutura fisica da sala onde são armazenados os prontuários; falta de padronização do arquivamento de prontuários pelo tempo de atraso; falta de monitoramento dos atrasos; existência de uma única pessoa para digitação dos dados no CRF.

Escopo do Processo:		**Objetivos Estratégicos Associados**
Inicio: recebimento da notificação do EA pelo participante	**Termino:** registro do EA no CRF	**Redução de desvios de protocolo notificados pelo estudo**

Site Champion	**Project Champion**	**Aprovacao do Patrocinador**
Aprovado por:	Aprovado por:	Aprovado por:
Nome:	Nome	Nome:
Cargo: PI	Cargo: co-PI	Cargo:
Data: 02/05/19	Data: 02/05/19	Data:

Grades. Legend: ERCT - Randomized Clinical Trial; EA - Adverse Event; CRF - Case Report Forms, PI - Principal Investigator e; Co-PI - Principal co-investigator.

As a proposition, the Project Charter provided fundamental information for the development of activities, - the objective of the project, - the list of stakeholders (actors), - the description of the problem, - the current performance of the indicators as well as the planned objectives and, - the intended deadline for completion.

Then, it was decided to use another tool to identify the problem and scope of the solution, but with the difference of identify the internal and external actors (customers) to be served with the implemented improvement. The tool in question was the Supplier, Input, Process, Output and Client - SIPOC which makes it possible to organize the visualization of the relationship with customers under different approaches [24]. Figure 2 shows the SIPOC carried out to accompany the project.

Figure 2. SIPOC built to define scope and control flow of inputs and outputs of the Adverse Event reporting process.

S.I.P.O.C.

Nome do Processo: registro de EA **Data emissão:**
Resp./Equipe: **Revisão:**

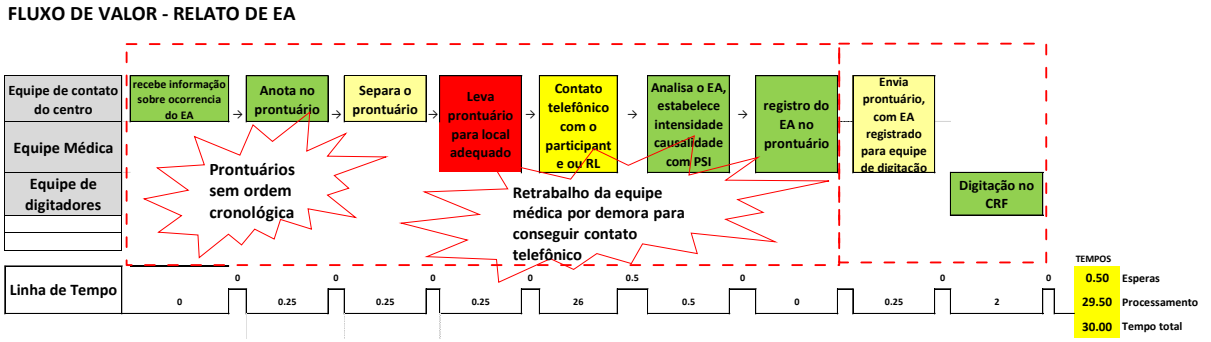
FORNECEDORES	ENTRADAS		PROCESSOS	SAÍDAS		CLIENTES
Provedores dos recursos	Recursos necessários ao processo	Requisitos numéricos das entradas	Descrição das atividades em nível macro	Fornecimentos do processo	Requisitos numéricos das saídas	Determinam os requisitos das saídas
	Método		Informação da ocorrência do EA pelo participante	EA relatado no prontuário	Até 5 dias corridos	Digitadora
coordenador de campo	POPs disponíveis	2 POPS disponíveis				
	Máquina:					
Suporte de TI do CRF	**Sistema CRF**	atualizado, disponível, em bom funcionamento		EA relatado no CRF	Até 7 dias corridos, S/N	Patrocinador
	Matéria Prima		Contato do médico e registro no formulário de EA			Digitador espera que o médico registre no prontuário em até 6 dias corridos.
Coordenador de campo	Formulário de EA	completo e correto				
monitor						Patrocinador: espera que o EA esteja no CRF em até 7 dias corridos, caso cabível.
	Meio Ambiente					
Coordenador do estudo	sala de arquivo de prontuários e para realização dos contatos	organizada, limpa, iluminada, espaçosa, silenciosa (5S).				
	Mão de Obra:		Registro do EA no CRF			
coordenador do campo	equipe de contato	qualificados e treinados - função				
	médico	tempo para contato				
	digitador	tempo para digitação				
	Medição:					
Monitor do estudo	Tempo do ciclo:	atualizado e				
	7 dias	padronizado.				

Grades. Legend: SIPOC - Suppliers Input Process Outcomes Control; CRF - Case Report Forms; EA - Adverse Events; SOPs - Standard Operating Procedures.

SIPOC indicated as main customers, the typist who needs to receive the reports of AE from the medical team, to include in the system, which starts the development of all necessary protocols, and informs the Sponsor, who needs the information to be available in the Case Report Forms - CRF to start analyzing the occurrence. Thus, the entire cycle of the process should ideally be completed in 7 days, the time recommended by the study protocol.

Faced with the identification of the need to improve results, the design phase of the artifact began. In this sense, we sought to identify the chaining of the stages of the process. To meet this demand, a Value Stream Mapping - VSM was developed, a Lean tool, with the purpose of representing the process in its current state (reality of the process) and the perspective of the future state (goal), after eliminating the waste (25). Additionally, the VSM allows to identify each of the stages of the process establishing its respective value (it is identified in many cases that that stage did not add value, positioning itself only as a waste of resources) and contribution to the result (26). Figure 3 indicates the VSM elaborated at the beginning of the research, in order to make it possible to understand the stages of the process.

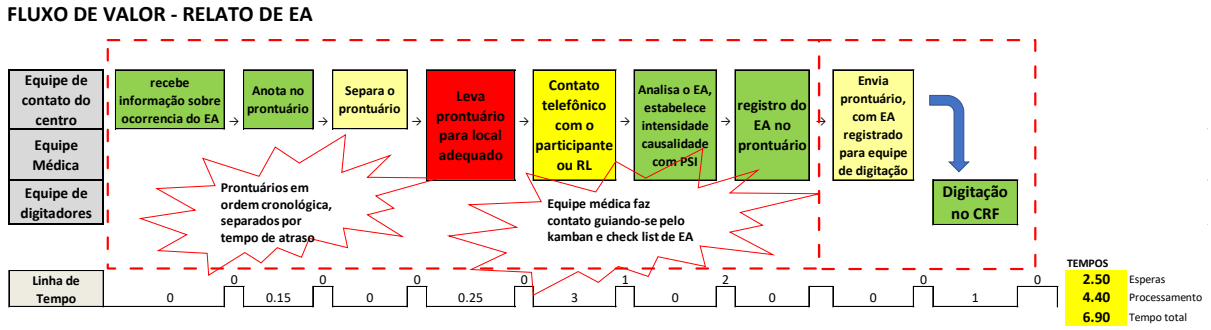
Figure 3. Mapping the value stream of the project to reduce the time of reporting an adverse event before improvements.



Grades. Legend: CRF - Case Report Forms; EA - Adverse Event; PSI - Product Under Investigation; VSM - Value Stream Mapping.

One of the characteristics of the VSM is also to establish the future situation to be achieved, that is, the goal of the process. In this sense, Figure 4 shows the expectation of what the process would be like after the implementation of the improvements.

Figure 4. Mapping the value flow (VSM) of the project to reduce the time of reporting adverse events after improvements.



Grades. Caption: CRF - Case Report Forms: PSI - Product Under Investigation; RL - Legal Representative.

The performance of the VSM made it possible to identify that one of the "bottlenecks" existing in the AE registration process was related to the need for the medical team professionals to have to take the medical records to an appropriate place to establish contact with customers, this dynamic was interpreted as waste of time, given that the contact could be made at the workplace. Another aspect identified as inefficient was the long waiting time observed in the attempt of telephone contacts (without success) between the professionals and the participants involved.

In order to expand the knowledge of the process carried out, the Process Map - PMAP was also adopted in order to identify the organizational flow, and the activities that are working properly, or not, thus facilitating the implementation of the improvement process [27]. It is noteworthy that the PMAP also has a relevant role of knowledge and the implementation of adjustments in the process and training of personnel [28]. Figure 5 shows the PMAP of the process under analysis.

Figure 5. Process Mapping (PMAP) of adverse event reporting

MAPEAMENTO DO PROCESSO (PMAP)

EA registrado corretamente pelo médico	Recebimento pelo digitador do EA registrado pelo médico		EA registrado corretamente pelo digitador no CRF	EA registrado corretamente e em tempo hábil (7dias) no CRF
Contato médico com o paciente ou RL	Análise e registro do EA	Separação do prontuário para equipe de digitação	Digitação no CRF	Envio do registro do EA para Patrocinador
P- Disponibilidade da equipe médica	C- Equipe médica	C- Equipe médica	C- Digitador disponível	P- Protocolo
!C- disponibilidade dos pacientes	C- Coordenador	C- Coordenador	!C- formulário completo	R- sistema funcionando bem
C- telefone disponivel	C- Telefone	!C- disponibilidade do digitador	R- Sala espaço	C- digitador
R- sala inadequada	R- sala inadequada	P- Prontuário do Paciente	P- Sistema CRF	C-coordenador
C- coordenador clínico	C- POP disponivel	R- Forma de Registrar		P- Sistema CRF
P - Formulário EA	P- Formulário de EA			

Note. Legend: C - Controllable; C - critical; EA - Adverse Event; R - Noise; P - Standard Operating Procedures; POP - Standard Operating Procedure; RL - Legal Representative.

As a result of performing the PMAP, it was initially evident that the critical point in the first stage of the AE registration process was related to the low availability of the patients involved, attending the medical team in an attempt to contact by phone. The second critical point identified in the process was the existence of only one digitizer to record the AE reports, a fact that on certain occasions delayed the introduction of the information in the system by up to two days. The third critical point identified was the absence of essential information on the form filled out by doctors. This lack of information demanded the need to return the document to the medical team, who needed to establish new contact with patients. In this regard, a measure that was diligently implemented was the change of the form, with the introduction of a new document prepared in the form of the Check List. The introduction of this new form, in addition to mitigating the possibilities of not answering relevant AE questions, also established control (history) of attempts to contact patients, a conduct that streamlined the process of conducting home visits to collect the necessary information, as well as to clarify to the involved the importance of carrying out the answer. It is worth mentioning that the proposition of this new form incorporates the phase of development of the artifact inserted in the methodology of Design Science Research.

In order to identify the possible current or future failures that occur in the EA report, the Failure Mode and Effects Analysis tool - FMEA, a Six sigma analytical tool, was applied. Through the FMEA it is possible to identify the risks involved in a process, at a point (moment) closest to its source of occurrence. This brevity in identifying any failure, makes it possible to establish actions aimed at preventing or mitigating the effects resulting from an eventual failure, a dynamic that is carried out through punctuation attributed to aspects related to severity, frequency of occurrence and detection of the failure [29]. The use of FMEA is also positioned as an important element in the development of the artifact, as it indicates points to be added in the current proposal. Figure 6 shows the FMEA elaborated in this study.

Figure 6. FMEA designed to identify failure modes in reporting Adverse Events.

FMEA DE PROCESSO

Nº Peça (Cliente)	Rev./Data do Desenho	Nome da Peça	Número da FMEA	Página
				1 de 1
Preparado Por		**Responsável pelo Processo -**	**Cliente**	
Organização		**Identificação do Produto**	**Número/Rev. Peça (Organização)**	
		Relato de EA		
Equipe			**Aprovado Por**	**Data**
Observações			**Data Início** / **Data Rev.**	**Data Chave**
			30/04/2019 / 30/05/2019	30/05/2019

Função & Requisitos do Processo	Modo de falha Potencial	Efeito Potencial da Falha	Sever	Causa / Mecanismo Potencial da Falha	Ocorr.	Controles Atuais do Processo Prevenção	Controles Atuais do Processo Detecção	Detec.	NPR	Ações Recomendadas	Responsável e Prazo	Resultado das Ações Tomadas	Sever	Ocorr	Detec.	NPR
Informa o EA à equipe	Não conseguir contato	Atraso do primeiro contato	7	Dificuldade financeira	5	Ligações periódicas pela equipe	Visita domiciliar	3	105	Elaborar uma planilha para controle de visitas domiciliares (VD)	C	Identificados casos com necessidade de VD e realizadas as VD pela equipe	7	2	1	14
	Informações incompletas ou incorretas	Atraso no registro do EA pelo médico	5	Dificuldade da equipe em colher as informações	5	Não tem	Não tem	10	250	Elaborar formulário tipo *check list* com informaçõs de EA para a equipe de contato utilizar	!	Facilitou e padronizou as informações permitindo identificar EAs atrasados e aqueles necessitando	5	1	1	5
Separar e organizar o prontuário	Prontuários desorganizados	Não possibilita identificar os mais atrasados	8	Falta método para organizar prontuários por atraso	10	Não tem	Não tem	10	800	Desenvolver padrão de organização dos prontuários por tempo de atraso (caixas com divisórias)		Permitiu identificar EA mais atrasados e tentativas de contato focada nos mais atrasados	8	2	2	32
	Não há identificação por tempo de atraso	Não possibilita identificar os mais atrasados	8	Falta método para alertar sobre os maiores atrasos	10	Não tem	Não tem	10	800	Desenvolver padrão de organização com alertas (post it ou lembretes) identificando os com maior atraso para passarem para caixa de visita domiciliar	Equipe de contato e equipe médica: prazo 10 dias	Identificar os EAs mais atrasados e realizar VD entre esses	8	2	2	32
	Não há espaço suficiente na sala	Dificulta a separação adequada de prontuários	8	Dificulta ordenar para alertar a equipe médica de por onde começar as tentativas de contato	10	Não tem	Não tem	10	800	Reorganizar as pastas para deixar sempre as caixas com divisórias disponíveis para serem colocadas no ambulatório aquela dos prontuários mais atrasados.		Identificar os EAs mais atrasados, permitindo que a equipe médica priorizasse tais contatos nos	8	5	1	40
Contato do médico com Pcte	Não conseguir contato	Atraso para registro médico do EA	10	Tentativas sucessivas do médico para obter os dados	7	Não tem	Não tem	10	700	Fazer um mutirão para tentar reduzir pendências com maior atraso, com ligações e visitas domiciliares	Equipe médica: prazo:30 dias.	Permitiu "zerar" as pendências dos meses anteriores à aplicação do plano de ação	#	1	1	10
	Não conseguir contato	Atraso para registro médico do EA	10	Tentativas sucessivas do médico de obter os dados	7	Não tem	Não tem	10	700	Após os primeiros 5 dias sem conseguir contato por telefone, separar o prontuário para colocar na lista de possível necessidade de visita domiciliar e monitorar quantidades de tentativas utilizando a ferramenta kanbam	E	Identificados casos com necessidade de VD e realizadas as VD pela equipe médica	#	2	1	20
	Não ter local adequado para realizar tentativa de contato	Atraso para registro médico do EA	3	Aumento do tempo gasto pelo médico no registro	5	Não tem	Não tem	10	150	Disponibilizar celular do recrutamento para o médico usar e descer diariamente para o ambulatório as pastas com maior atraso (caixa exclusiva)	Toda a equipe	Identificar os EAs mais atrasados, permitindo que a equipe médica priorizasse tais contatos nos intervalos de atendimento e de	3	2	2	12
Registra no formulário de EA	Dados incompletos para preencher o log de EA	Não consegue concluir o registro de EA e estabelecer a causalidade com o PI e ocasiona mais atraso	10	Dificuldade de obter informações completas no contato inicial (não médico)	7	Não tem	Não tem	10	700	Elaborar um formulário para contato inicial e gerenciamento de tentativas	N	Facilitou e padronizou as informações colhidas e permitindo identificar EAs com maior atraso e aqueles necessitando	#	1	1	10
Recebimento pela digitadora e devido registro no CRF quando cabível	Informações incompletas ou incorretas	Atraso do registro no CRF	10	Dificuldade do médico obter contato com pcte	7	Não tem	Não tem	10	700	Elaborar formulário com informaçõs de EA para a equipe de contato utilizar padronizando assim as informações coletadas.	!	Facilitou e padronizou as informações colhidas e permitindo identificar EAs com maior atraso e aqueles necessitando	#	5	2	100
	Excesso de prontuários para digitação	Atraso nas digitações	5	Existir apenas uma pessoa responsável pela digitação no CRF	7	Não tem	Não tem	10	350	Treinamento de mais digitadores.	P ((	Facilitou e gerou agilidade na digitação, reduzindo atrasos	5	2	2	20

Figure 6 presents the analyzed points, among which the most critical ones were those with the highest score on the NPR scale (NPR scale - Risk Priority Number, which combines: Severity, Occurrences and Detection). In this study, the activities that were most critical were: - medical records stored in a disorganized manner; - lack of organization of medical records due to time delay; - lack of space in the contact monitoring room; - difficulty in identifying the medical records with the most delayed reports of AE; - difficulty for the medical team to contact the participants; - medical records with incomplete or incorrect information obtained by the contact team and; - excess of medical records with incomplete data for typing.

The activities identified as critical were analyzed and proposed an action plan, which included the recommended actions, those responsible for implementation and the respective deadlines. This action plan was developed from the perspective of Kaizen, which is positioned as a tool designed to provide continuous improvement to the processes under analysis (30). Kaizen presents the quality of positioning itself as a planning focused on the actors and resources involved (31). For the execution of this project, a team for the development of kaizen was assembled, composed of ten professionals, being: 1 coordinator (physician of the institution); 2 medical underinvestigators of the clinical trial; 2 members of the clinical trial contact team; 1 clinical trial typist; 2 nurses from

the clinical trial; 2 health professionals from another department of the institution and not involved in the process. Figure 7 shows the plan adopted by the Kaizen team.

Figure 7. Action plan elaborated from Kaizen to reduce the reporting time of Adverse Events (AE) in a clinical trial.

***Kaizen* – Action plan**				
	Action	Data	Responsible	*Status*
1	Prepare form with EA information for the contact team to use.	15/05/19		
2	Develop pattern of organization of medical records by time delay.	10/05/19		
3	Develop an organization pattern with alerts (post-it or reminders) identifying the files with the longest delay to be transferred to the home visit box.	07/05/19		
4	Prepare worksheet to control family visits.	02/05/19		
5	Rearrange the folders to always leave the boxes with dividers available to be placed in the ambulatory those that the medical records are most delayed.	07/05/19		
6	Work together to reduce pending issues with greater delay, with calls and home visits.	20/05/19	Medical team.	
7	After the first 5 days without being able to contact the phone, separate the medical record to place it on the home visit list.	10/05/19	Medical team.	
8	Make the recruitment cell available for the doctor to use and download the folders with the greatest delay daily (exclusive box).	02/05/19	Contact team.	
9	Elaborate form for initial contact.	10/05/19		
10	Training of more typists.	110/05/19		

Implemented Actions
0 – It does not require knowledge.
1 – In training 25%.
2 – Able to perform the task 50%
3 – Get to know the background 75%
4 – Specialist can train others

The focal point of the project was the perspective of standardizing activities, dividing AE reports by time delay. Boxes were introduced to contain late AE reports, thus enabling those involved to identify the most critical cases.

The introduction of this modification marks the beginning of the initial testing phase of the artifact proposed by Design Science Research. As an initial measure, a task force was established to deal with the oldest cases, in order to enable an adequate standard, for the beginning of the activities adopting the new methodology. In addition, a Kanban was added to visually identify and monitor the progress of AE reports in categories. With this monitoring of tasks, it was possible for the whole team to view and signal, from the most recent reports, to the most delayed and that needed home visits. The term Kanban in Japanese means “board” and originally positioned itself as a mechanism designed to control the replenishment of items in production processes, eliminating waste, being a tool of the Lean philosophy [32], but which has also been used in the medical field [33], due to its characteristic of going through the entire process regardless of the existing organizational structures [34]. The adopted Kanban has a simple structure, composed of a table that divided the report of AE into five temporal categories: i) between zero and three days; ii) between four and six days; iii) with more than seven days; iv) needs home visits and; v) resolved cases. In these columns the numbers of the AE report are presented by means of a Post-it (for privacy reasons, the indication of the AE report is performed by means of numbering and not the patient's name, to preserve the confidentiality of the participants' identity of the study). Figure 8 expresses the Kanban model adopted.

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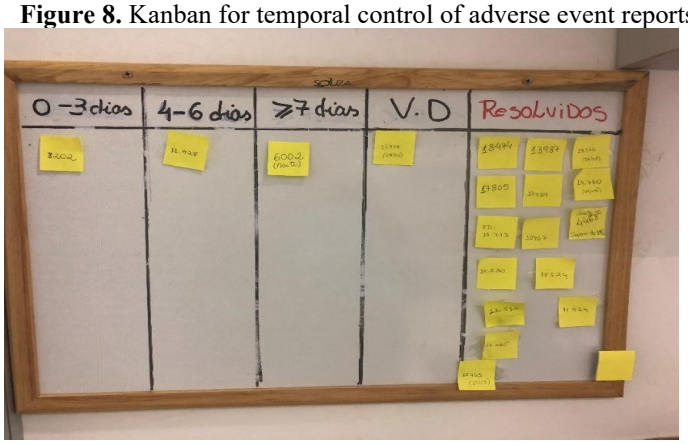
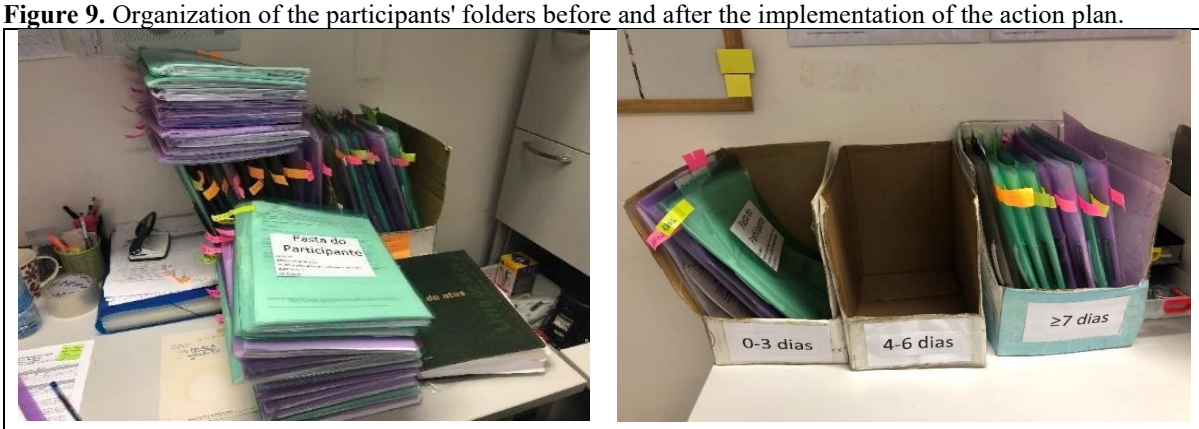
Figure 8. Kanban for temporal control of adverse event reports.



The measures adopted were analyzed in the following three months in order to identify the improvements that occurred in the process. The improvements were evidenced by comparing the NPRs raised in the development of the FMEA (Figure 6).

The results of the measures adopted showed a significant improvement in the items: - medical records stored in a disorganized manner; - lack of organization of medical records due to time delay; - difficulty in identifying the medical records with the most delayed reports of AE. Thus, the measures showed a 97% reduction in the risk analysis prepared by the FMEA (initially it was 800 points of PRN, and after the modifications it dropped to 24 points). For the items: - difficulty for the medical team to contact the participants; - medical records with incomplete or incorrect information obtained by the contact team and; - excess of medical records with incomplete data for typing; contemplated by the elaboration of a new form that standardizes data collection and monitoring of patients, the improvement was 87% (initially it was 700 points of PRN, and after the modifications it dropped to 90 points). The organization of the follow-up folders for AE reports, as shown in Figure 9, also established visual improvement in the workplace, valuing the activities of professionals in the area.

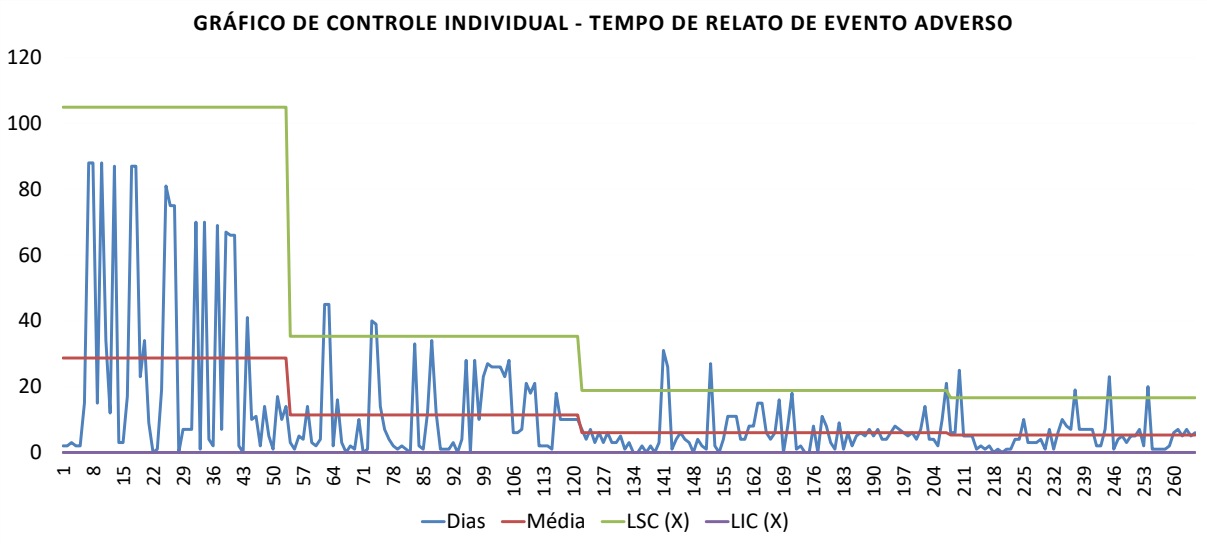
Figure 9. Organization of the participants' folders before and after the implementation of the action plan.



Antes das ações de melhoria | Após das ações de melhoria

In the last stage Design Science Research aimed at validating the artifact in the context of the end area, the results obtained through the actions developed were presented, with the help of a control chart of the average time involved in the AE report. The performance obtained during the realization of the project can be seen in Figure 10.

Figure 10. Control chart of the variation of the time of Adverse Event report in the period of realization of the project.



The improvement obtained in the development of the project was identified by reducing the time involved in the AE reporting activity. Considering the variability of the process, from the control charts (Figure 10) before the implementation of the improvements, the process had a high variability, with an initial average of around 30 days and an upper limit above 100 days. It is observed that in the first month after the improvements, the average dropped to around 7 days, with an upper limit of less than 40 days. In the second month, the average was close to 6 days, with an upper limit below 20 days. In the third and last month of analysis, there was a small drop in the average and upper limit, indicating the continuous improvement of the process, however the establishment of a standard for the process. The standard deviation showed a progressive reduction in value, since before the improvements, a standard deviation of 33 days was identified, changing to 13.3 days in the first month, then to 6.66 days in the second month, and finally to 6 days in the third month. The control chart is intended to analyze the centrality and the dispersion profile of the variables under analysis, enabling the understanding of the process (35). In this study, the variable under analysis was the time involved in the Adverse Event report.

In view of the results found, it is possible to state that the introduction of the artifact that embodies the Kanban, with a form in the Check List standard, in the management of the Adverse Events report in activities of analysis of clinical trials directed to the development of vaccines provides better management of the quality of the vaccine process, reduction of the time involved in the process, decrease in the waste of the process and better accuracy of the information.

The next section discusses the results found and the tools used in this study.

Discussion

This section discusses the data obtained, the tools employed and the developed artifact. The tools used within

the context of Design Science Research demonstrated in this study to be suitable for obtaining the desired artifact [10] positioning itself as an effective technique for the development of research in the health field [11, 12, 13]. The incorporation of Six sigma and Lean proved to be satisfactory within the context of health research, and in a way associated with Design Science Research.

The techniques used were also shown to be appropriate for health research. Project Charter positioned itself adequately in project management [23] and benefited from SIPOC in surveying the process flow [31], and from PMAP that described the process in detail [31], obtaining positive results as observed in clinical trials [36]. The use of VSM was fundamental to identify the value flow of the process, through the interpretation of the current state, and projection of the desired condition at the end of the implementation of the improvements [25, 26], so this study obtains the same positive results perceived in the health area [26].

The use of FMEA proved to be adequate for the purpose of identifying the critical points, and the potential failures, of the process [29], enabling the development of actions that mitigated the occurrence of problems. The adequacy of using the FMEA in this research is in line with similar results in activity in the chemotherapy service [37].

The adoption of kanban as an artifact intended to manage the Adverse Event report proved to be timely for the reality of the clinical trial in which it was applied, and can be extended to other clinical trials or other processes, whether in the development of vaccines or other pharmaceutical products, as well as in the other sectors of the health area [32, 33]. The benefits of introducing the artifact were evidenced through the control chart [35] that compared the initial performance of the process with the final condition reached. In this context, this study corroborates with others that indicated the appropriateness of using Lean and Six Sigma in the process improvement process in the health area [38, 39, 40].

The results obtained with the introduction of the kanban artifact and with the Protocol in the Check List model are relevant in reducing the time involved in reporting Adverse Events, in the vaccine development process, from clinical trials. The reduction of this time has benefits to speed up the process, and to guarantee the safety and well-being of the participants involved, as recommended by the precepts of good practices in clinical research.

Conclusion

The artifact that combines the control by the Kanban methodology, with the form in the Check List pattern, presented itself as an adequate resource for the management of the Adverse Event report. The developed artifact is suitable for use in other activities in the health field. The establishment of a working group using the resources of Lean and Six Sigma, shows the feasibility of using instruments from other areas of knowledge, in the area of health.

As a result of the research, the proposed artifact reduced the average time of development of the Adverse Event report from 30 days, to 6 days, and reduced the standard deviation from 33 days, to 6 days. The time involved in the Adverse Event reporting process is in accordance with the protocol of the study analyzed, and the vaccine development center, providing agility in the process, and ensuring greater safety and quality of information for the employees involved.

The results obtained show a process of significant continuous improvement, for the research institute that develops vaccines. In this sense, it is established as appropriate the application of the artifact developed in other activities in the health area, both systematically, as well as the use of the approach used in this study, in other processes in the health area, with the purpose of establishing improvement processes. constant.

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