Safety Requirements and Risk Analysis Related to Insulin Infusion Pumps: A Systematic Review

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Abstract. Diabetes mellitus is a metabolic disease characterized by high levels of blood glucose; in severe cases of diabetes, insulin infusion pumps are prescribed as treatment. Infusion pumps are automated devices with the purpose to simulate the functioning of the organism of a healthy person regarding the production and delivery of insulin, as this is a medical device, its operation must be reliable enough to avoid any risk to the patient's health and well-being. The aim of this article is to conduct a systematic literature review to investigate and perceive what are the risks implicated for the user of insulin infusion pumps also understand how safety and functional requirements for these devices have been treated, developed and studied.

1 Introduction

The most recent study from International Diabetes Federation (IDF) shows that 8.8% of the world population suffers from diabetes mellitus, and until 2045 this proportion should rise to 9.9%, reaching around 630 million people [1]. It is also estimated that 50% of diabetic adults are not aware of their disease, and the lower the average population income, the higher the non-diagnosed diabetics rate. The most common forms of the disease are classified as type 1 and 2; the *Diabetes Mellitus* is characterized by insulin resistance or a deficiency in producing it [2]. Approximately 4 million deaths of the population between 20 and 79 years old were due to diabetes in 2017, according to IDF estimates [1], diabetes represents 10.7% of the deaths on this age range. The condition may also lead to premature deaths and disabilities, like loss of vision and amputation of limbs, those are also known as "indirect tolls" of diabetes.

Considering all this information, diabetes has become one of the most challenging health issues of the present. Among the treatments advances, we can mention the development of insulin infusion pumps [3], automated devices that intend to simulate what happens in a healthy body regarding production and delivery of insulin for the user, keeping the hormone delivery stable 24/7 and maintaining the blood glucose concentration in regular rates for fasting periods and also during meals.

The operation of the insulin infusion pumps (IIP) must be reliable enough to ensure correct dosages of the medicine at the right moments, and any equipment misfunctioning may lead to an adverse event, producing underdose or overdose. Hence,

taking into account the significance of the IIP proper functioning, it was conducted a systematic literature review (SLR) to investigate and perceive what are the risks implicated for the user of insulin infusion pumps also understand how safety and functional requirements for these devices have been treated, developed and studied. Additionally, it was explored what the most common flaws and errors found on this equipment are and how those may be mitigated or eliminated.

In this paper, the results of the SLR are analyzed and discussed considering three approaches: (i) what the risks implicated for the user of the IIP while operating the equipment are; (ii) the safety and functional requirements of the IIP; (iii) what systems may be and are adopted to mitigate and eliminate the IIP errors and flaws. To the best of our knowledge, this is the first SLR on the risks and requirements for IIP.

This paper is organized as follows: Section 2 presents background and related works. The research methodology adopted to conduct the SLR is presented in Section 3. The results and analysis related to our research questions are presented in Section 4. Moreover, Section 5 summarizes the inferred conclusions of the SLR.

2 Background and Related Work

One of the most popular and relevant studies when it comes to medical errors is the book "To Err is Human: Building a Safer Health System" [7], first published by the Institute of Medicine (IOM) in 1999. A comprehensive analysis is exposed in this book regarding how government, healthcare providers, medical industries, and consumers can reduce preventable medical errors. The Quality of Health Care in America Committee of the IOM concluded that it is not acceptable for patients to be harmed by the health care system. Mistakes can be prevented by designing a safer health system. It is, therefore, of utmost importance that the development of the IIP identifies and creates systems and devices for the prevention of errors and failures.

Zhang et al. conduct an extensive analysis of possible risks that IIP may impute to its users [5]. The authors first propose a generic model of IIP to list the risks then, dividing them into sources of hazardous situations. These can be broadly categorized in terms of *therapeutic, energetic, biological/chemical, mechanical, and environmental*. From the identified risks, Zhang et al. discuss the safety requirements that must be considered in the development of the IIP software [8]. The authors categorize the safety requirements in six classes: *insulin administration, user interface, alarm system, event logging, battery management, and interaction with the environment*. The authors also relate those requirements with the risks previously identified.

Martins et al. propose the development of a low-cost IIP, mostly aiming the people with diabetes in Brazil [3]. In the study, the authors discuss a few hazards and safety requirements of such equipment, propose the elemental hardware composition and the software architecture to meet the functional requirements. Moving forwards in the IIP technology, some producers are developing the called "closed-loop system" for diabetes treatment, simulating a completely functional pancreas, with this therapy it is required minimum user interaction [9]. Quintal et al. and Ramkissoon et al. discuss some of the issues the AP [10, 11].

Neto et al. evaluate the medical equipment validation for the National Health Surveillance Agency (ANVISA) [12], Brazilian regulatory agency. The authors used the model of IIP to perform an example of ANVISA validation, showing that the certificate focus on productive process assessment, assuming that well-controlled and executed processes generate safe products.

3 Research Methodology

In this section, it is presented the design and the execution of the SLR. The research methodology to conduct this SLR was based and adapted from the one conducted by Martins et al. [4]. The need for this SLR (step 1) was presented in the Introduction (section 1) of this paper. Fig. 1 shows the research process that was adopted for this study and its steps, as better described in the next sections.

In Table 1, the research questions (step 2) considered relevant for this SLR are presented, also their aim. The research questions summarize what should be extracted from the selected studies and set the direction for further discussions.

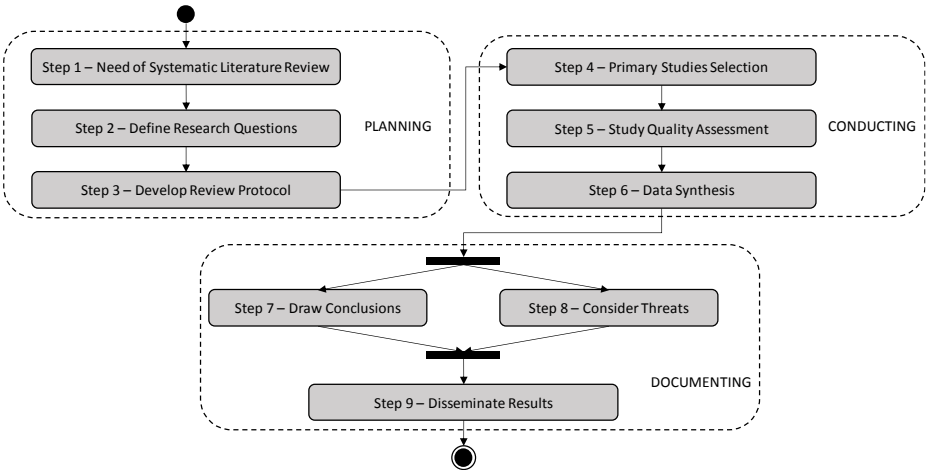

Fig. 1. Systematic review steps adapted from [4]

3.1 Search Strategy

For the identification of papers, it was adopted keywords, based on the research questions, used to compose the search string. A trial search was carried out to evaluate the quality of the proposed search string, analyzing the main results and the number of papers found. Performing a few rounds of search, the search string defined for this SLR was the one showed next: *"infusion pump" AND (safety OR hazard OR risk OR accident).*

Table 1. Research questions for the systematic literature review.

ID	Research Question	Aim
RQ 1.	What are the risks implicated for the user of Insulin Infusion Pump in diabetes treatment?	To identify and classify the risks implicated for the Insulin Infusion Pump user.
RQ 1.1.	How the Insulin Infusion Pumps deploy systems (software/hardware) that mitigate or attenuate the risks implicated in its use?	Identify what the systems/devices, especially software and hardware, proposed and used to mitigate the risks implicated on the Insulin Infusion Pump usage are.
RQ 2.	What are the safety and functional requirements for an Insulin Infusion Pump?	Identify the safety and functional requirements that have been used for Insulin Infusion Pump.

3.2 Review Protocol

A review protocol was developed for the execution of this SLR (step 3), in which the main elements were as follows: the *selected resources* were PubMed, ScienceDirect, and IEEE. The *search method* was based on researches through web search engines available in those digital libraries.

As *studies selection criteria,* it was determined that papers should be scientific articles from the last ten years and written in English. The *inclusion criteria* were defined as any study that presents or discuss safety or functional requirements of infusion pumps and also studies related to the analysis of hazards and risks in the usage of such equipment. The *exclusion criteria* were: studies that do not bring any discussion or analysis on requirements or risks related to infusion pumps.

3.3 Procedure for Studies Selection

The selection of primary studies was based on the inclusion criteria presented in Section 3.2. The search string presented in Section 3.1. was used to capture the primary studies from the selected resources, based on the review protocol, presented in Section 3.2. Initially, it was found 627 studies (phase 1), after applying the ten years filter, explained in Section 3.2, 313 studies (phase 2) were left, then analyzing the title and the abstract against the inclusion and exclusion criteria, 57 studies (phase 3) were selected for data extraction (Table 2). It is important to consider that the studies selection was executed around July of 2019.

3.4 Data Extraction

Table 3 shows the relation between the properties and the research questions. For all five properties (P1, P2, P3, P4, and P5), a list with expected values was defined previously. Those properties are shown below, and the complete list of definitions and possible values is available at http://shorturl.at/dlmrC.

Research methodology (P1). The studies were categorized according to the applied research methodology.
Context (P2). The studies were categorized into clinical and non-clinical cases.
Risk Assessment (P3). As explored by Zhang et al. [5], the hazardous situations for the IIP can be broadly categorized into five classes.
Systems Deployed (P4). Regarding the systems and devices to mitigate the risks, the studies were analyzed on which segment improvements are proposed.
Requirements Approach (P5). Zhang et al. conduct a general analysis of requirements for IIP [8] and categorize the requirements into six classes.

Table 2. Phases and quantity of selected studies.

Database	Phase 1	Phase 2	Phase 3
PubMed	430	204	35
ScienceDirect	148	77	18
IEEE	49	32	10
TOTAL	**627**	**313**	**57***

***Some repeated studies were found among the databases; those were not doubled on the final study selection count.**

Table 3. Extracted properties.

ID	Property	Research Question
P1	Research methodology	Overview of the studies
P2	Context	Overview of the studies
P3	Risks discussed	RQ 1
P4	Systems deployed	RQ 1.1
P5	Requirement approach	RQ 2

3.5 Study Quality Assessment

The study quality assessment (step 5) has the goal to help researchers conducting the SLR [13], offering direction in the interpretation of the finding from the selected studies. The study quality assessment conducted in this SLR was an evaluation of how well the studies were reported. Four questions were considered for each paper, those questions are presented in Table 4, along with the results, the questions were adapted from Unterkalmsteiner et al. [14] e Martins et al. [4].

3.6 Threats to Validity

During the execution of this SLR a few threats to validity were found: **Publication Bias; Identification of Primary Studies; Data Extraction Consistency.**

The complete discussion regarding the threats to validity is available at https://shorturl.at/hAJW8.

Table 4. Quality assessment adopted from [4, 14]**.**

ID	Quality Assessment Question	YES	PARTIALLY	NO
QA 1	Is the aim of the study addressing the RQs?	32 (56,1%)	25 (43,9%)	0 (0%)
QA 2	Is the presented approach clearly explained?	45 (78,9%)	9 (15,8%)	3 (5,3%)
QA 3	Is it clear in which context the study was carried out?	31 (54,4%)	23 (40,3%)	3 (5,3%)
QA 4	Are the results or findings clearly illustrated?	36 (63,1%)	16 (28,1%)	5 (8,8%)

4 Results and Analysis

A total of 57 studies discussing the risks and the safety and functional requirements of infusion pumps were considered and analyzed.

The documents were classified according to the research methodology (P1), presented in Section 3.4, as showed in Fig. 2. The studies context (P2) distribution, as presented in Section 3.4, is exposed in Fig. 3. 59.6% of the documents were conducted in a non-clinical setting. While the other 40.4% of the documents were conducted in a clinical setting, that showed a proper distribution among the possible contexts.

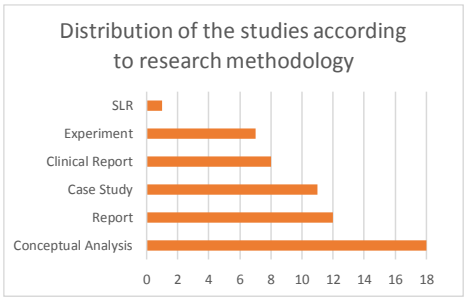

Fig. 2 Distribution of the studies according to research methodology

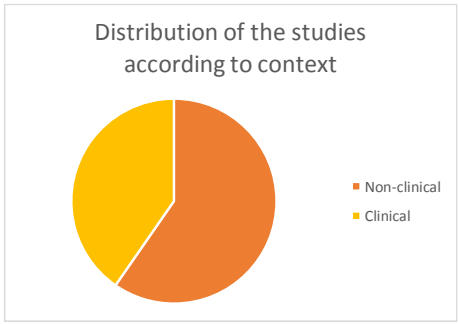

Fig. 3 Distribution of the Studies according to context

As in this SLR only studies from the last ten years were considered, it is possible to draw the distribution for the publishing year, shown in Fig. 4. It is observed that the documents are distributed among the year roughly evenly, with a small rise trend between 2009 and 2015, then a small drop in 2016 forward. Given the studies distribution according to the country of the author, exposed in Fig. 5, more than half of the studies were published by first authors from EUA (50.9%), the second country in publications is Brazil (8.8%), followed by United Kingdom (7.0%). This wide prevalence of the EUA in studies can be explained by the fact that only studies written in English were selected. Even with the proliferation of the English language around the world, it is easier for US natives to write a scientific paper in English. It is interest-

ing to notice Brazil in the second position on the published documents on the subject; this came as a surprise. It is also important to underline that most of the studies have more than one author, occasionally from different countries than the first author. Therefore there is the involvement of representatives of other countries than the ones listed, and this property only shows the origin of the first author.

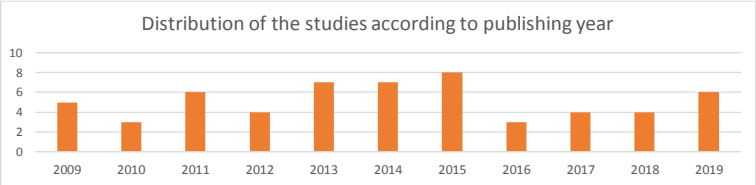

Fig. 4 Distribution of the studies according to publishing year

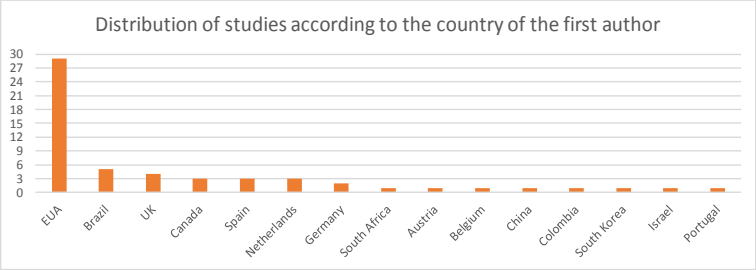

Fig. 5 Distribution of studies according to the country of the first author.

Many of the documents studied are related to hospital infusion pumps, the called smart infusion pumps (SIP), responsible for controlling the administration of several types of drugs in a clinical environment and may contain more complex than the IIP, equipment that initially motivated the execution of this SLR. This may be explained by the search string used, that did not contain the word “insulin,” this result was not planned. Still, anyhow, the data in the selected studies proved quite satisfactory, because the requirements and risks of the SIP are similar to the ones of the IIP, then it was decided to keep all the selected studies.

In the next sections, the results extracted from the selected studies regarding the research question presented in Table 1 are exposed.

4.1 Risk Assessment for Infusion Pumps (RQ1)

The aim of the RQ 1 was to identify what was the risks for the user on the use of the IIP, as shown in Section 3.4, the risks can be categorized in broad classes, the distribution of the studies according to the risk class discussed are presented in Fig. 6.

The least common risk reviewed is energetic related, with only ten studies citing this class. In contrast, the most common risks discussed in the studies are therapeutic related, with 56 of 57 studies considering this class risk.

The main risks discussed when it comes to drug administration are drug dosage below the specified and drug dosage above the specified. These situations may

lead to the interruption of insulin infusion, inducing hyperglycemia, or to overdosage of insulin that may head to hypoglycemia [11]. These effects are detailed below:
Hypoglycemia: occurs when the blood glucose level is below the normal thresholds, the main effects of hypoglycemia are excessive sweating, and fatigue, and dizziness, in more severe cases can lead to increased heart rate, blurred vision, and seizures.
Hyperglycemia: occurs when the blood glucose level is above the normal thresholds, the main effects of hyperglycemia are frequent urination, thirst and excessive hunger, fatigue, agitation, and in medium to long term, weight loss.

The most common risks discussed in the selected studies are those presented above, hypoglycemia and hyperglycemia [3, 11, 24–28, 16–23].

One of the causes found for the errors in infusion pumps is regarding the operational treatment of the equipment, that is, regarding the person controlling the equipment, for the SIP usually that is nurses and for IIP usually that the patient himself. The incorrect parameter adjustments in the infusion pumps may lead to incorrect dosages to the patient. Mason et al. showed that there is a considerable increase in patient safety when the nurses or users are familiarized with the infusion pump technology [29], so, before the beginning of the use of such equipment, it is necessary a previous presentation and training regarding its operation.

Another risk addressed concerns the error treatment of such equipment. In all automated medical devices, the error treatment is quite an important aspect, and it is not different for the IIP. If an error or fault is identified by the IIP software, it must emit an alarm to the user so that some action is taken. If the adverse events are not identified correctly, it is possible that the user does not notice the error when it occurs, on the other hand, if the device generates excessive alerts, the alarm fatigue may occur, that is the user disinterest when too many alarms are generated for an adverse event not quite critical. Therefore, the challenge in reducing alarms disinterest, increasing the percentage of clinically relevant alerts, is multifaceted [30].

4.2 Systems Deployed to Mitigate the Risks (RQ1.1)

RQ 1.1 aimed to investigate and understand what the systems deployed to try and mitigate some of the risks with infusion pumps. By system, it is meant any instrument, process, apparatus, or device that may mitigate or attenuate the risks were.

For P4, it was analyzed the studies regarding which "part" of the insulin pumps could be improved: software, hardware, both or none. Fig. 7 shows what the findings were, 36.8% of the studies treat the software part of the insulin pump, while 7.0% treat only the hardware part, 36.8% of the studies discuss systems to improve software and hardware. Eleven studies (19.3%) do not detail any system to improve the safety of infusion pumps [16, 24, 38, 26, 31–37], they only discuss the risks and its effects of such equipment, according to the inclusion criteria presented in Section 3.2, those studies were kept in the SLR as they still bring relevant data and information.

A quite popular method found in the studies to reduce safety risks is the human factor techniques [16, 34, 39–42], which may help to refine a product to attend the user expectations and reach the use intentions safely.

Russel et al. conducted a study to compare discrepancies between medical orders and bedside infusion pump settings before and after implementation of an interface between computerized physician order entry and pharmacy system [43], it shows the importance of a well-constructed interface to present the information.

Ray et al. and Ling et al. propose to use model-based engineering and model-driven engineering to identify and mitigate the risks of IIP [39, 44]. Usually used in the automotive and aerospace industry, with this approach, models are built from expected properties, and then the implementation occurs deriving out of those models.

Marinque-Rodrigues et al. And Sobral et al. propose the use of Failure Mode Effects Analysis (FMEA) for the risk assessment of IIP [45, 46]. FMEA aims to identify risks of processes and products.

Gerhart et al. propose the recommend the "intravenous clinical integration," that mixes safety aspects of a programmable infusion pump with software that provides overseeing with information in real-time regarding clinical infusion [47]. Concluding that this integration can help to reduce medication errors, improve patient care, reduce in-facility costs, and support asset management.

Van der Slujis et al. applied the lean methodology to study drug administration errors related to infusion pumps [48]. This methodology is derived from the Toyota Production System (TPS) that aims to eliminate wastes, concluding that despite the difficulty of applying this methodology in a clinical environment, it helps to reduce errors.

The creation of an infusion pump simulation is mentioned aiming for risks reduction by Elias et al. [49]. This simulation can be used as a way to introduce a wide range of clinical scenarios without putting the patient at risk.

Martins et al. adopted Fault Tree Analysis (FTA) to derive safety/functional requirements from the IIP [50], FTA is a well-known technique used to help requirements engineers understand hazards situations in the context of safety-critical software.

Kim et al. developed a set of generic safety reference models that can be used as reference standards and test harnesses to verify the safety of infusion pumps [51]. To do that, the authors formalized the model and the requirements using UPPAAL and TIMES tools.

Lin et al. proposed a profile in the Unified Modeling Language (UML) to design a language that is used to specify the design for the IIP [52], helping to identify the safety and functional requirements for the equipment.

Schraagen et al. used Impact Flow Diagram (IFD) to map methods to the way artifacts shape cognition and collaboration applied to infusion pumps [53]. IFD can be used to define a failure path for the uncritical use of infusion pump technology.

Amongst the selected studies, one of the main systems deployed to treat risk is the "drug library" [30, 54–59], which seeks to introduce thresholds for the drugs dosage setting, those thresholds may be soft limits (SL) or hard limits (HL). When the dosage is being selected on the pump, the system must confront the dose value with the SL and HL, if they are above the upper SL (usually SL do not have bottom limits), an alarm is generated to inform the user that has the permission to overwritten this alert and proceed with the infusion. On the other hand, if the dose value does not comply with the HL, the user must select another dosage, as the HL cannot get over-

written. These thresholds generally are specified by the infusion pump manufacturers together with professional clinical specialists in the affected medications.

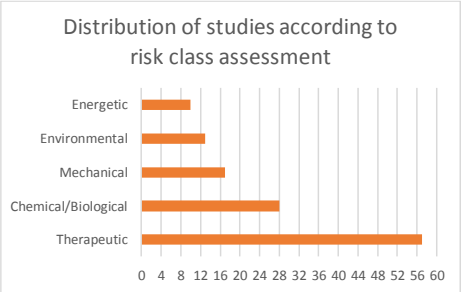

Fig. 6 Distribution of the studies according to risk class assessment

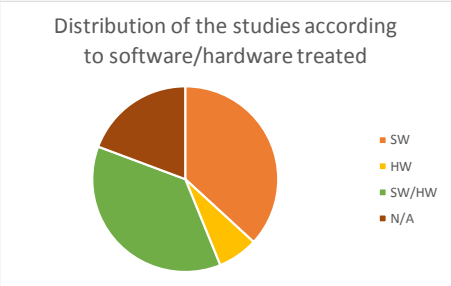

Fig. 7 Distribution of the studies according to software/hardware treated

4.3 Safety and Functional Requirements (RQ2)

With RQ 2, it was aimed to find out what are the most common safety and functional requirements for the development of IIP or at least try to divide those requirements into general classes, as presented in Section 3.4. Essentially the difference between safety and functional requirements is that the safety ones are non-functional requirements, meaning that those can be used to judge the operation of the system, rather than specific behaviors or functions. Fig. 8 exposes the distribution of the studies according to the requirement class discussed by the author in the study, the class that is treated in more studies is drug administration, with 38 studies considering this class, right behind is interaction with the environment with 35 studies reviewing this subtheme. The class with fewer studies discussing it is battery management, with four documents, making it clear that this matter must be better pondered by the IIP developers, Kuhadja is one author that address this topic and conducts a quite enlightening study using survival analysis to evaluate the battery efficiency of an infusion pump [60], showing that the power supply is an essential functional requirement for IIP.

Regarding software/hardware, the main concern found in the studies when it comes to software is the need for the IIP to ensure correct insulin dosage [11, 17, 21]. Jung et al. [18], Peterfreud et al. [19], and Tooke et al. [20] discuss the drug dosage but facing the hardware portion instead, analyzing syringes, catheters, and tubes.

Ramkinsoon et al. [11] cite the need for the called “fail-safe,” which is a feature that should ensure that if some error is found during operation, the equipment must enter a failsafe mode, to continue to deliver insulin to the user in a safe rate.

Cauchi et al., Ibey et al., Scott Evans et al. and Marwitz et al. [28, 61–63] raise the concern for the infusion pumps to possess the Dose Error Reduction System (DERS), integrated with event logs to help analyze and understand potential errors.

Paul et al. cite key security properties that have to be taken into account when developing the IIP software [64], those are the availability of the system, confidentiality of information, integrity of data, authentication of access, authorization of access.

As presented in Section 2.2, Zhang et al. conduct a comprehensive analysis on the safety requirements of the IIP [8], generation a list of the requirements relating them to the risk previously identified [5], the requirements are divided into six categories: insulin administration; user interface; alarm system; event logging; battery management and interaction with the environment.

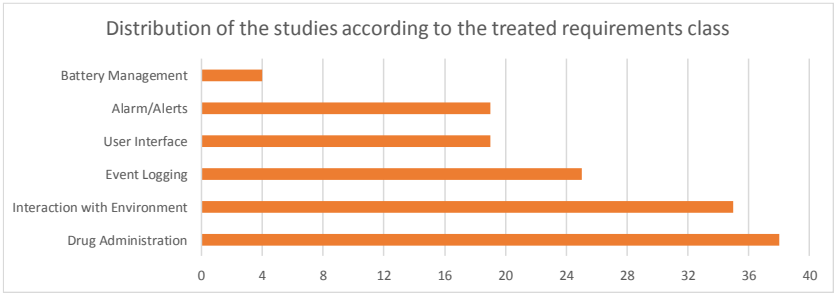

Fig. 8 Distribution of the studies according to the treated requirements class

4.4 Association Among Properties

In this section, the association among some of the properties extracted from the studies is draw to try and confirm the correlation.

One of the associations checked was between P3 and P5. A table was drawn, marking the studies that discussed concurrently specific risks class and specific requirements class. This is shown in Fig. 9. It is possible to observe that the most common combination is therapeutic risk and drug administration requirements, with 41 studies discussing these themes, this could be expected, therapeutic risks are regarding the medication use, and drug administration requirements treat the medication control. On the other hand, the least common combination is chemical/biological risks and battery management requirements, with only two studies addressing these themes concurrently, those were the only two studies discussing all the risks classes and all the requirements classes [5, 8], this result could also be expected, taking into account the distinctness of the two classes.

Another association tested was between P1 and P4. The results are shown in Fig. 10. From the figure is it possible to infer that the research methodology that more presents solutions for both software and hardware is conceptual analysis, with six studies, and the research methodology with more studies that do not present solutions is also conceptual analysis. This may be explained by the representation of conceptual analysis amongst the research methodologies, 18 of 57 studies. It is also interesting to observe that the only SLR amongst the studies selection does not present any solution of improvement for the risks of IIP.

As those two properties are qualitative, it is possible to run a Pearson's chi-squared test to check the magnitude of the association between P1 and P4 (1). Since some of the expected frequencies are less than five, the correction of Yates must be applied (2).

$$X^2 = \sum_{i=1}^{r}\sum_{j=1}^{s}\frac{(o_{ij}-e_{ij})^2}{e_{ij}}; T = \sqrt{\frac{\frac{X^2}{n}}{(r-1)\times(s-1)}} \quad (1)$$

$$X^2 = \sum_{i=1}^{r}\sum_{j=1}^{s}\frac{\left(\left|o_{ij}-e_{ij}\right|-0{,}5\right)^2}{e_{ij}} \quad (2)$$

Where: o_{ij} = observed frequencies; e_{ij} = expected frequencies; r,s = quantity of classes of each property

Then, calculating the Pearson's chi-squared with the Yates correction, it is found that **$T_{P1,P4}$ is equal to 0,3433**. This means that there is not a solid association between P1 and P4, but still, it is perceived a feeble association.

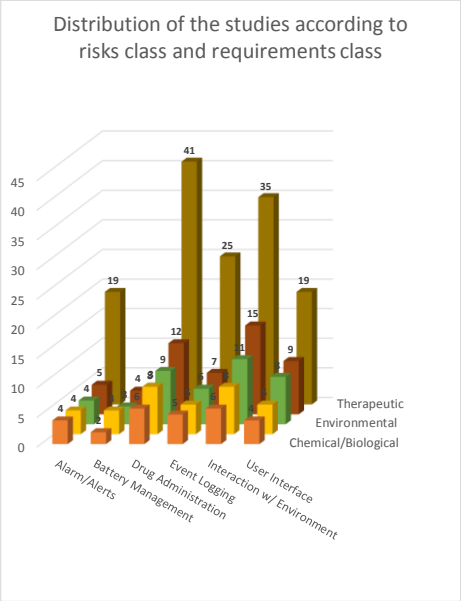

Fig. 9 Distribution of the studies according to risk class and requirements class

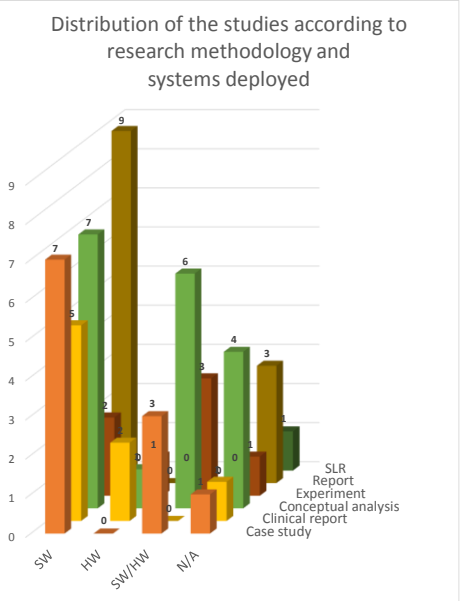

Fig. 10 Distribution of the studies according to research methodology and systems deployed

5 Conclusion

In this paper, it was conducted a SLR investigating studies related to the safety and functional requirements of the IIP also studies discussing and analyzing the risks implicated in the use of such equipment. The initial motivation of this SLR was to understand the risk presented by the portable IIP but with the studies selected it was possible to verify a greater amount of studies discussing the hospital's infusion pumps, the SIP, automated equipment, usually operated by nurses, responsible for the infusion of medications to the patients, allowing a wide range of different drugs. It is worth mentioning that this manifestation does not invalidate the aim of this SLR, because the SIP

and the IIP have the same operation principle, that is why the risks presented by both equipment are similar.

It was found with the results of this SLR that many authors discuss the safety and functional requirements for IIP, but they are not usually formally described, the aim for the development of such equipment is to construct it as safe as possible for the user. The main risks of the IIP mentioned by the authors, according to this SLR, are *hypoglycemia* and *hyperglycemia*, which can be caused by a wide set of reasons, like the malfunctioning of the equipment, poor algorithm development, damages on the infusion set even incorrect operation by the user. Some of the studies analyzed also propose a discussion regarding the validation of the IIP facing the reglementary agencies before its commercialization [12, 31, 65]. This is a point that was not initially considered by the SLR. However, it presented relevant, given the need that besides complying with all the safety and functional requirements of the state-of-the-art, it is necessary that the IIP complies with the requirements of the responsible agencies of the markets where the equipment will be commercialized. It is expected with the outcomes of this SLR new studies are motivated to treat and discuss the risks of the IIP, especially defining safety and functional requirements, leading to the development and implementation of increasingly effective and safe equipment for users affected by *diabetes mellitus*.

6 Acknowledgments

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8 Appendix

The SLR references are available at http://shorturl.at/fsCDP.