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Analysis of the impact of clinical evaluation on the submissions of high risk medical devices to the Brazilian Health Regulatory Agency

Análise do impacto da avaliação clínica no registro sanitário de dispositivos médicos de alto risco

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ABSTRACT

Introduction: The clinical evaluation of medical devices is an important component in the evaluation of new technologies for sanitary registration purposes within the Brazilian Health Regulatory Agency and represents an important tool for regulatory decision-making to verify compliance with regulations that establish the need for proof of safety and efficacy of medical devices to perform sanitary registration. **Objective:** To evaluate and discuss the reasons for the rejection of registration requests motivated by deficiencies related to the clinical evaluation of high-risk medical devices. **Methods:** In the electronic system Datavisa, internal system for storage and analysis of data submitted to Anvisa, all the rejections occurred in 2017 within the scope of the General Office of Medical Devices (GGTPS) concerning the clinical evaluation of medical devices of risk class III and IV, both in the original cause of the refusal and related to the non-compliance with the legally established deadlines for meeting the requirements when at least one of the requirements involved clinical evaluation, were evaluated. **Results:** Data were collected from the expert opinion of the agency to construct the outline of the main characteristics related to the rejections in relation to the clinical evaluation offered in the registration dossiers by the companies responsible for the submission. The evaluations were divided according to the area responsible for the registry, involving implantable orthopedic materials submitted to the analysis of the Coordination of Implantable Materials in Orthopedics (CMIOR), materials for health use submitted to the analysis of the Office of Materials for Health Use (Gemat) and equipment submitted to the analysis of the Office of Equipment Technology (GQUIP) of Anvisa. **Conclusions:** Considering the sample of rejected health records, the findings suggest a heterogeneity in both the quality and the format of the data provided in clinical evaluations by companies submitting applications of medical devices, especially related to the methodological nature of the clinical trials presented, deficiencies in risk management, and other regulatory requirements connected to the clinical assessment scenario of medical devices and compliance with minimum design requirements.

KEYWORDS: Medical Devices; Clinical Evaluation; Sanitary Registration; Anvisa; Clinical Trials

RESUMO

Introdução: A avaliação clínica de dispositivos médicos é um componente importante na avaliação de novas tecnologias para fins de registro sanitário no âmbito da Agência Nacional de Vigilância Sanitária e representa uma ferramenta importante para a tomada de decisão regulatória para verificar a conformidade com as normativas que estabelecem a necessidade de comprovação de segurança e eficácia de dispositivos médicos para efetuar o registro sanitário. **Objetivo:** Avaliar e discutir as razões para o indeferimento de solicitações de registro motivadas por deficiências relacionadas à

avaliação clínica dos dispositivos médicos de alto risco. **Método:** Foram avaliados no sistema eletrônico Datavisa, sistema interno para armazenamento e análise de dados de processos submetidos à Anvisa, todos os indeferimentos ocorridos em 2017 no âmbito da Gerência-Geral de Tecnologia de Produtos para Saúde (GGTPS), que tiveram como causa aspectos relativos à avaliação clínica de dispositivos médicos de classe de risco III e IV, tanto na causa original do indeferimento, quanto relacionadas ao não cumprimento dos prazos legalmente estabelecidos para o cumprimento das exigências quando pelo menos uma das exigências envolvia a avaliação clínica. **Resultados:** Foram recolhidos dados dos pareceres construídos pelos especialistas da agência para construir o delineamento das principais características relacionadas aos indeferimentos em relação à avaliação clínica oferecida nos dossiês de registro pelas empresas responsáveis pela submissão. As avaliações foram discriminadas de acordo com a área responsável pelo registro, envolvendo materiais implantáveis em ortopedia submetidos à análise da Coordenação de Materiais Implantáveis em Ortopedia (CMIOR), materiais de uso em saúde submetidos à análise da Gerência de Tecnologia de Materiais de Uso em Saúde (Gemat) e equipamentos submetidos à análise da Gerência de Tecnologia em Equipamentos (GQUIP) da Anvisa. **Conclusões:** Considerando a amostra de indeferimentos de registro sanitário estudada, os achados sugerem uma heterogeneidade tanto na qualidade quanto no formato dos dados fornecidos em avaliações clínicas pelas empresas que submetem registros sanitários de dispositivos médicos, especialmente relacionado à natureza metodológica dos ensaios clínicos apresentados, deficiências no gerenciamento de risco e demais requisitos regulatórios relacionados ao cenário da avaliação clínica de dispositivos médicos e conformidade com os requisitos mínimos do projeto.

PALAVRAS-CHAVE: Dispositivos Médicos; Avaliação Clínica; Registro Sanitário; Anvisa; Ensaios Clínicos

INTRODUCTION

To use medical devices (MD) rationally, healthcare professionals must base their choices on the objective assessment of safety and clinical efficacy. Evidence provided by manufacturers when requesting authorization to market their high-risk devices should be publicly available, including performance data and pre-market clinical studies[1]. For physicians, access to this information supplements peer-reviewed scientific literature and may be essential for them to compare alternative devices. The development of new MD is a dynamic, fast and continuously incremental process. These devices are used in all facets of healthcare, improving disease prevention, diagnosis and treatment, as well as patient rehabilitation. However, these products may be associated with potential adverse effects and the lack of high-quality clinical data to demonstrate their efficacy[2]. To be launched on the market, a new MD must prove its safety and achieve the performance intended by the manufacturer. Unlike drugs that almost always use randomized controlled trials for efficacy and safety evaluation, there is no standardized methodology that determines the depth and extent of the clinical trials needed for MD[3].

The new European MD directive, for example, states that the manufacturer should prepare a summary of evidence for any implantable or high-risk device that can be marketed in the European Community[4].

The regulatory environment of the clinical evaluation of MD involves a number of questions about the degree of transparency and scientific basis of the requirements of health authorities around the world[5]. In order to assure end users that in clinical settings these devices work with the same safety and efficacy claimed by the manufacturer, and considering the great diversity of MD available today, it is particularly challenging to parameterize an optimal regulatory framework that is effective to ensure that devices can mitigate risks to the users while producing the benefit asserted by the manufacturer. In this context, a sound regulatory framework in the pre-market assessment of new technologies, as well as post-market surveillance that promotes continuous and integrated real-world observation are critical to meet MD users' needs and to ensure safe and effective use[6]. For example, the performance of an MD depends not only on the device itself, but also on the user's skills and experience. In an MD assessment report, it seems important to know how the learning curve was assessed or how operators were trained. Without this type of information, it may be difficult to establish the external validity of the study. External validity, which involves the generalization of the results, is the extent to which participants, the context of care, and interventions evaluated in the studies are representative or can be reproduced in healthcare[7].

The task of finding robust, global-scale evidence to support the safe use of MD for the indications that have been devised is particularly difficult because of the large investments required to build clinical trials, standardize care procedures, and other actions related to clinical trials. This conflicts with a product profile whose life cycle is often incompatible with patient observation and follow-up. It is important to know the meaning of clinical evidence in the regulatory context, as well as the process of data generation and clinical evaluation to produce such evidence. The requirements on the international arena are sometimes different considering the regulatory model for MD in each country[8,9].

There is a common perception about the need to relate the MD with the incorporated innovations and its relation to the target clinical condition. Many agencies require the manufacturer to demonstrate the equivalence of the proposed technology with the others in the market, in order to evaluate what clinical data will be required to subsidize the product's marketing

authorization. Many also have less stringent requirements for lower-risk products[10].

Evidence requirements for marketing authorization are determined via risk classification approach, based on the risk that the devices pose to patients. Depending on the region, there can be one to five risk categories. The safety requirements needed for reimbursement are always country-specific and may range from clinical studies to rigorous cost-effectiveness studies. For example, after a series of failures and device recalls, weaknesses were identified in the European approval process[5]. Those were related to very low safety standards for market access, the exclusion of efficacy assessments and the lack of transparency of regulatory processes and their evidence requirements. Thus, the call for new regulatory frameworks with more stringent and transparent evidence requirements has become stronger. However, while stricter regulatory frameworks lead to greater security, this in turn will limit early market access for some devices. Overall, there is a clear tension between fast access to new, often innovative products and the provision of high-level patient safety.

Considering the clinical evidence needed for MD marketing authorization in Brazil, this study aims to critically evaluate the landscape of rejections of MD submitted to the National Health Surveillance Agency (Anvisa) that were motivated by lack or insufficient information about clinical evaluation to demonstrate the safety and/or efficacy of higher-risk MD (class III and IV) as required by Resolution (RDC) n. 56 of April 6, 2001[1].

Considering the intrinsic nature of each set of devices, whether medical materials, equipment or in vitro diagnoses, the technical reasons for refusal vary depending on the non-compliance with the efficacy and safety needs of each device. These needs are described both in general standards like RDC n. 185 of October 22, 2001[11] and in specific standards to the device, as shown in Table 1.

A priori, *in vitro* diagnostic products have a distinct system of clinical evaluation, which is established through what RDC n. 36 of August 26, 2015[12] calls 'clinical performance'. This involves an assessment to establish or confirm the association between the analyte and the clinical or physiological condition. It includes a general summary of clinical evidence, comprising clinical sensitivity and specificity; expected values or reference values and clinical evidence evaluation report. Considering that these products have unique characteristics as to their clinical evaluation process, the present study aimed to outline the impact of traditional clinical evaluation. This type of evaluation is based on clinical data about health products that represent high-risk therapeutic intervention, namely medical-use materials, orthopedic implantable materials and health risk class III and IV equipment, as defined in RDC n. 185/2001[11]. Therefore, products for in vitro diagnostic are outside the scope of this assessment.

METHOD

This is a descriptive study that assessed, in the Datavisa electronic system - the internal system for storage and analysis of process data submitted to Anvisa - all refusals occurred in 2017 within the General Management of Technology of Health Products (GGTPS) that were motivated by aspects related to the clinical evaluation of risk class III and IV MD, both in the original cause of the refusal and those related to the non fulfillment of legally established deadlines when at least one of the requirements involved clinical evaluation. Data were collected from the opinions written by the agency's experts to establish the main characteristics related to the refusals and associated with the clinical evaluation provided in the dossiers by the companies responsible for the submission. The evaluations were divided according to the area responsible for the marketing authorization. That included implantable orthopedic materials submitted to the analysis of the Coordination of Implantable Materials in Orthopedics (CMIOR), materials for health use submitted to the analysis of Materials Technology for Health-Use Office (Gemat) and equipment submitted for analysis by Anvisa's Equipment Technology Office (GQUIP).

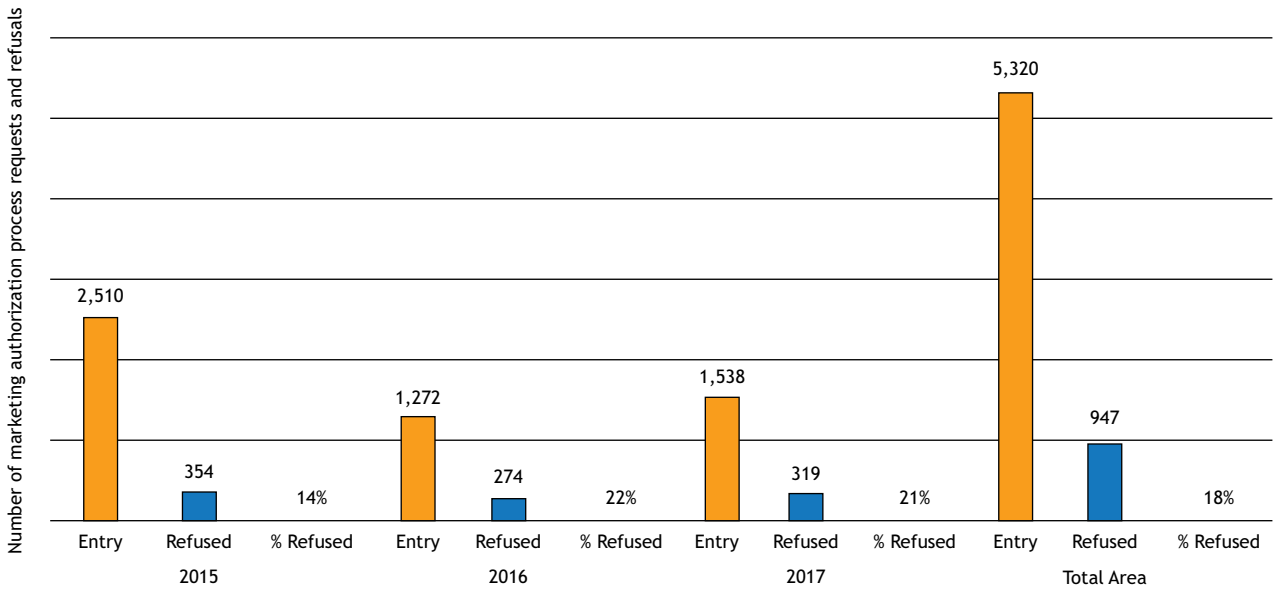
RESULTS AND DISCUSSION

The refusal of high-risk MD is related to non-clinical aspects related to device-specific characteristics and testing provided

Table 1. Anvisa's resolutions and guidelines that establish requirements for the marketing authorization of medical devices and set parameters related to the need for proof of safety and efficacy as per product framework.

Medical Device	Technical-Normative Reference
Medical Supplies	RDC n. 185/2001 RDC n. 56/2001 NT n. 004/2016/GGTPS/DIREG/Anvisa
Implantable materials for orthopedics	RDC n. 185/2001 RDC n. 56/2001 NT n. 004/2016/GGTPS/DIREG/Anvisa
Equipment	RDC n. 185/2001 RDC n. 56/2001
Products for in vitro diagnostics	RDC n. 185/2001 RDC n. 36/2001

GGTPS: General Management of Health Products Technology; DIREG: Health Regulation Board; Anvisa: National Health Surveillance System.



Source: Datavisa.

Figure. Ratio between entry of marketing authorization processes and refusals involving medical devices submitted to Anvisa in the 2015-2017 triennium.

Table 2. Number of marketing authorization processes submitted to Anvisa and refusals of marketing authorization requests for medical devices in 2017 that involved questions regarding clinical evaluation.

Medical Devices	Number of submitted processes	Number of refusals	Number of refusals attributed to missing or insufficient clinical evaluation information
Medical Supplies	536	170	43
Implantable materials for orthopedics	336	84	6
Equipment	260	11	0

for in technical standards, as well as to risk assessment needs associated with safety and efficacy profile. At GGTPS, the refusal ratio recorded in the Datavisa system for the three-year period of 2015-2017 (Figure) shows a ratio of 803 refusals to a total entry of 4,551 applications for marketing authorization of higher risk products (classes III and IV).

Considering the information contained in the technical opinions entered into the system in 2017, in which the largest number of refusals was found (Figure, Table 2), first we evaluated the ratio between the number of refusals by type of MD and their relation with the clinical evaluation.

To obtain further detail about the characteristics and profile of the refusals, Table 3 provides an outline of the MD submitted to Gemat (management responsible for the analysis of the submissions of MD) that received questions related to the clinical evaluation and were rejected based on such questions. Strictly speaking, there is a prevalence of lack of conclusive clinical data to support safety and/or efficacy. These data are sometimes referred to as pivotal and play a key role in the regulatory environment by gauging the clinical setting of MD insertion that is closer to the reality of its future use. This modality of clinical investigation of MD is the means to obtain evidence for the evaluation of data on the safety and performance of medical products in their intended use. This includes any risks or adverse effects/events presented by the product during use.

Another important aspect that is present in the perception of refusals involving clinical evaluation is the absence of Anvisa's consent to conduct clinical trials in Brazil, as established first by RDC n. 219, of September 21, 2004[13], and currently by RDC n. 10/2015[14], which determines the need for Anvisa's consent for clinical trials involving health products in Brazil. That is a necessary condition for Anvisa to monitor clinical trials considering health risk and good clinical practices, in addition to regulatory activities in the field of ethical evaluation by the Research Ethics Committees/National Research Ethics Commission (CEP/Conep) system. It is fundamental that researchers become familiar with the regulatory environment before starting clinical research involving MD. That's because even in the prototype phase or other developmental stages, the use of these devices poses risks that need assessment in both the health and ethical context. This becomes an essential factor both for the safety of research participants and to ensure the methodological quality of the data to be used in future marketing authorization.

Table 3. List of medical devices submitted to Gemat that were refused in 2017 because of aspects related to clinical evaluation.

Medical device	Number of medical devices by risk class		Nature of the refusal
	III	IV	
Surgical adhesives		1	Lack of connection between the clinical indications evaluated in the clinical trial and the proposed indications of the product, as well as absence of a contraindication profile based on the clinical trial exclusion criteria (related to safety aspects of the research participant).
Intragastric balloon	1		Lack of compilation of scientific literature with indexed publications related to clinical research conducted with similar products, with the same mechanism of action and clinical use, as an adjuvant to weight loss treatment, especially in the preoperative preparation of patients with "super" obesity (Index Mass Index - BMI> 50 kg/m2), with an association of aggravated and/or morbid obesity-triggered pathologies, in the form of a clinical evaluation report.
Metal head for hip arthroplasty	1		Lack of consistent clinical data to prove long-term safety for a metal-on-metal implant, especially regarding the release of metal ions of high toxicity.
Catheter with port for infusion	2		No clinical data, literature, or pertinent information was provided to support the proposed indications of use for the device.
Dressing	2	6	No data to support product efficacy for referenced use indications. Use of clinical data from other products that do not have the same composition as the product submitted for marketing authorization.
Artificial embolization device		1	Considering specific aspects of the product, no clinical data involving efficacy and safety of the product were presented, especially considering models that had pharmacological agents.
Endoprosthesis (vascular)		1	No clinical study with confirmatory methodological characteristics of safety and efficacy involving the device and its delivery system.
Surgical wires (barbed)		3	No clinical trial data for all clinical indications of the product.
Wound dressing gel		1	Absence of Special Communication (CE) issued by Anvisa authorizing the conduction of the clinical trial used to support the safety and efficacy of the medical device, as defined by RDC n. 10 of February 20, 2015. Methodological weakness related to the clinical trial presented considering aspects related to adequate sample calculation and absence of comparator.
Hemostatic dental dressing		1	No clinical trial involving a specific population covered by the proposed use of the product. Absence of the final report of the pivotal study on product safety and efficacy.
Eye implant for glaucoma treatment	1		Innovative product with insufficient data obtained from a clinical trial without statistical power to demonstrate confirmatory safety and efficacy of the device. Insufficient follow-up of patients.
Intradermal bulking agent for the treatment of stress urinary incontinence	1		Absence of Special Communication (CE) issued by Anvisa authorizing the conduction of the clinical trial used to support the safety and efficacy of the medical device, as defined by RDC n. 10/2015. Absence of report of the pivotal clinical trial done with the product
Antibiotic hemostatic dressing		1	Divergences between the clinical indications evaluated in the clinical evaluation report presented and the indications for use informed in the marketing authorization dossier.
Intraocular lenses	1		Absence of clinical evaluation report of the device.
Intimate lubricant		2	Absence of clinical evaluation report of the device. Absence of Special Communication (CE) issued by Anvisa authorizing the conduction of the clinical trial used to support the safety and efficacy of the medical device, as defined by RDC n. 10/2015.
Surgical soft tissue regenerative membrane		1	The clinical evaluation presented did not have sufficient clinical data to demonstrate the efficacy of the device requesting marketing authorization or similar devices in the proposed indications of use.
Heart occluder		1	Innovative product with no clinical data from a pivotal clinical trial and long-term patient follow-up, the pivotal clinical trial is ongoing.
Vascular prosthesis for repair or replacement of peripheral arteries		1	Absence of clinical evaluation report of the device.
Esophageal stent	1		No clinical data have been submitted to support the proposed new indications for use of the product.
Pharmacological stent for coronary arteries	4		Absence of a pivotal clinical trial to support the safety and efficacy of the product. Only feasibility clinical trials were presented without adequate statistical rationale to support the safety/efficacy of the device.
Pharmacological stent for peripheral arteries	2		Absence of a pivotal clinical trial to support the safety and efficacy of the product. Only feasibility clinical trials were presented, without adequate statistical rationale to support the safety/efficacy of the device. The confirmatory study was still ongoing at the time of dossier analysis.

To be continued

Continuation		
Intracranial stent	3	Weakness of the clinical evaluation report in demonstrating device equivalence to other commercially available devices, especially in functional, design and clinical indications. No pivotal clinical trial to support safety and efficacy of the product.
Renal and biliary stent	1	Inconsistency between the indications found in the clinical evaluation provided in the marketing authorization dossier and the indications claimed for the device.
Tympanic ventilation pipe	1	Absence in the clinical evaluation report of demonstration of equivalence between similar devices and the device submitted for marketing authorization.
Debridement hydrolytic gel	3	Absence of Special Communication (CE) issued by Anvisa authorizing the conduction of the clinical trial used to support the safety and efficacy of the medical device, as defined by RDC n. 10/2015. Absence of a pivotal clinical trial to support product safety and efficacy. The clinical trial presented did not have a comparator nor a rationale for calculating sample size.

Table 4. List of medical devices submitted to CMIOR that were refused in 2017 because of aspects related to clinical evaluation.

Medical device	Number of medical devices by risk class		Description of refusal involving clinical evaluation
	Risk class III	Risk class IV	
Absorbable osteosynthesis reconstruction plate		-	In the absence of a pivotal clinical trial to support product safety and efficacy, the clinical trial presented was a feasible clinical trial with small sample and failed recruitment.
Non-modular spinal disc prosthesis	1	-	Unfinished fundamental clinical trial for clinical evaluation.
Total hip prosthesis		1	The submitted clinical evaluation refers only to the femoral stem and did not evaluate the femoral head, whose material is innovative. Data were evaluated in a setting that cannot be characterized as clinical research.
Posterior column system for fixation to blade, pedicle, apophysis or joint mass	2	-	Fundamental clinical trial for clinical evaluation presents protocol deviation that hinders the accuracy of the safety and efficacy analysis of the device. No clinical trial required to prove safety and efficacy of proposed product use.
Metal head for hip arthroplasty	2	-	Absence of clarification of the origin of the values of the reported fatigue values related to the occurrence of osteolysis in the clinical evaluation report submitted in the marketing authorization dossier. Absence of consistent clinical data to prove long-term safety for a metal-on-metal implant, especially regarding the release of metal ions of high toxicity.

CMIOR: Coordination area of implantable materials for orthopedics

The marketing authorization requests made to CMIOR (area responsible for the analysis of implantable materials for orthopedics) include MD associated with prostheses for restoration of movements and pain relief in the vast majority of presentations. Therefore, the most relevant aspects associated with the clinical setting of these devices involve functional rehabilitation and aspects related to quality of life. With that, many of the innovations in this segment are associated with changes in the materials used, device design and dynamic structures that offer a better impact ratio on patients' routine activities. It is important to realize that the surgical technique employed has a great influence on the expected result of the use of such devices, which requires careful evaluation by the regulatory system integrating the care context in which the evidence was produced. Table 4 shows the characteristics that motivated the refusals in the area of orthopedic implants in 2017, with emphasis on clinical evaluation and evidence provided in marketing authorization dossiers submitted to Anvisa. The situations aforementioned in this article for medical materials are also found in the reasons for refusal of orthopedic implants. This highlights the importance of the quality of the evidence presented to ensure compliance with RDC n. 56/2011[1]. With respect to Table 4 we can also see the repeated submission of devices with serious safety concerns that have not yet been fully resolved with design changes. For example, there are "metal-on-metal" hip prostheses, which can cause adverse reactions to often highly-debilitating metal debris and lead to early surgical revisions. Technologies of this type require closer post-market follow-up considering the search for further evidence about the actual causes of the revisions, considering that surgical procedures for traditional hip replacement systems and reconstruction systems (*resurfacing*) have distinct characteristics, resulting in equally different learning curves. Furthermore, it would be necessary to build a profile of indications that could maximize clinical benefit in patients at high risk of revisions due to adverse reactions to metal debris[13,14,15,16,17].

One of the major challenges in building an appropriate clinical trial for MD that meets regulatory requirements is when

Table 5. Guiding documents produced by the International Medical Device Regulators Forum (IMDRF) related to the clinical evaluation of medical devices.

Document	Description	Access link
SG5/N2R8: 2007 *Clinical Evaluation* (Under revision)	The document proposes to provide manufacturers with guidance on how to conduct and document the clinical evaluation of a medical device as part of the conformity assessment prior to its marketing, as well as to support its ongoing monitoring. It is also intended to provide guidance to regulators and other stakeholders in assessing clinical evidence provided by manufacturers.	http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-2007-clinical-evaluation-070501.pdf
GHTF/SG5/N3:2010 *Clinical Investigations* (Under revision)	The document aims to provide guidance when there is a need to conduct clinical research to demonstrate compliance with the essential principles that are relevant to the development of a medical device, as well as to outline the general principles of clinical research involving medical devices.	http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf
SG5/N1R8:2007 *Clinical Evidence – Key Definitions and Concepts* (Under revision)	The document aims to present the concepts of clinical evaluation and clinical evidence, establishing the relationship between clinical research, clinical data, clinical evaluation and clinical evidence, in addition to being a guide to those who work in the generation, compilation and revision of clinical evidence that suffices to subsidize the marketing of medical devices.	http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf
IMDRF/SaMD WG/N41FINAL: 2017 - *Software as a Medical Device* (SaMD): *Clinical Evaluation*	The document provides guidance on the particularities of software as a medical device and the process for conducting the clinical evaluation of such devices, as well as the specific terminology used in the regulatory environment.	http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170921-samd-n41-clinical-evaluation_1.pdf

a confirmatory clinical trial is needed to support the safety and efficacy of the device for the intended use or validation of new indications. Often the design of clinical trials cannot avoid traditional biases because, unlike drug trials, blinding MD can be operationally challenging or ethically unacceptable. When blinding is not an option, an open study is the only feasible option. If an equivalent device is available, comparative efficacy studies may be conducted, for example, in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study, new-generation ventricular assist devices were compared with approved devices without the use of untreated comparator group. In the absence of an equivalent device, it may still be sustainable to design a study in which the results of single-arm studies are compared with results obtained in historical or contemporary controls accepted in a parallel marketing authorization. However, such a study may have shortcomings due to the differences measured or not between the cohorts[18].

Another relevant aspect is the level of technology assessment performed by Anvisa and the context in which this assessment is part of the Brazilian health system. The agency has precedence in the initial evaluation of MD before they can be marketed or made available for clinical trials[11] nationwide. This evaluation is distinguished from aspects related to the process of incorporation and reimbursement by health insurances and the Unified Health System[19]. It is based on the benefit/risk ratio of the device to the patients and the methodology used to measure outcomes that enable unambiguous decision-making. Refusals occur whenever the technical area does not receive consistent documentation to ensure compliance with the relevant essential principles in device design and there are gaps related to the clinical data produced. For high-risk devices, this uncertainty may pose a health risk because of the safety aspects of the device for users/patients, as well as its effectiveness in relation to a particular clinical condition, since the lack of efficacy of a device deprives patients of another intervention that could be more appropriate for their illness.

In the international arena we find several models similar to that adopted by Anvisa. The differences are associated with geo-economic and political characteristics and related to the development of a specific regulatory framework to evaluate the evidence necessary for the marketing of MD.

An initiative for international convergence is established in the International Medical Device Regulators Forum (IMDRF)[20], created in 2011 to discuss directions for harmonizing the MD regulatory environment. Formed by Brazil, Australia, Canada, China, Europe, Japan, Russia, Singapore and the United States, this forum has some important documents used as references for outlining both the clinical evaluation and the qualification of evidence required for submission to regulatory authorities (Table 5), always respecting the sovereignty of each jurisdiction in establishing specific norms related to the topic and considering the particularities of each healthcare system.

CONCLUSIONS

Although the timeframe of the present study only considers the year of 2017, we believe that the profile of the requirements involving clinical evaluation is recurrent and similar to that addressed in this paper. Despite its qualitative approach, the present study shows the concern of the agency's specialists about demanding robust data in order to know the risks arising from new technologies and to use the most qualified information in regulatory decision making. In the pursuit of greater transparency and guidance for future submissions, Anvisa plans

to prepare a guide for clinical evaluation of MD in accordance with topic 8.1 of the agency's regulatory agenda on marketing authorization, post-authorization, registration or notification of health products. The guide should show the agency's perspective as well as the technical benchmarks for building a clinical assessment report that meets regulatory needs for the safety and efficacy of MD, especially those that pose higher risks to patients.

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Conflict of Interest

The authors report that there is no potential conflict of interest with peers and institutions, nor political or financial conflicts in this study.

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