Design Approach of Medical Devices for Regulation Compatibility: A Robotic Rehabilitation Case Study

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Abstract: Regulations and normative framework strongly affect requirements and potential design constraints of devices, especially in critical environments like the medical field, characterized by a complex interaction among design, therapy procedures and user needs. In order to optimize the design process, the awareness of the designer about the compound information net generated by the required documentation becomes therefore fundamental. Depicting a custom mapping of required data and referring documents for the development and commercialization of a medical device as required by the Conformité Européenne (CE) marking process, this paper presents a design approach directly suitable for robotic rehabilitation systems, which aims at easing the regulations compatibility of the designed product. This method is applied to the illustrative case study of the LEPRE (LEg Programmable REhabilitation) robotic system, with particular attention to data collection and analysis for the evaluation of clinical background and demonstration of equivalence required by the device clinical evaluation report, according to MEDical DEVices (MEDDEV) 2.7/1 guidelines. Indications for the modifications required to adapt it to further application fields are also suggested.

1 INTRODUCTION

Health technologies such as medical devices are essential to guarantee good health care and the aging well possibility, and technological innovations in prevention and rehabilitative fields are gaining importance in funded research (Amici et al., 2016).

The medical, and in particular the rehabilitative, environment involves a complex interaction among design, user needs, and therapy procedures (Hagedorn et al., 2015). Considering the possible design methods for medical devices, literature suggested that both physician and engineer participate in the design phase of a rehabilitative device (Amici et al., 2016) since the earlier design phases: the physician defines the functional requirements of the system (i.e. maximum force or acceleration needed, movement to reproduce with the device), whereas the engineer develops the technical specifications of the device (i.e. kind of actuation, or structure). Then, the final user can support the process providing feedbacks along the development path.

The necessity of ensuring the patient benefit and safety led many countries to introduce regulatory instruments (Henschke et al., 2016) to demonstrate and guarantee safety and effectiveness of devices to be launched on the market (Kramer et al., 2020; Römer and Stuyt, 2007). Given the fundamental role of regulations in this process (Privitera et al., 2017), considering them from the earliest stages of the device design and project management should be good practice for manufacturers.

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In the European Union (EU), medical devices can be marketed across all EU member states after earning the Conformité Européenne (CE) mark; that guarantees streamlined trade, safety, and environmental standards (Council of the European Union, 1993), and defines essential requirements and recommendations concerning clinical evaluation and vigilance (Council of the European Union, 2007).

To obtain the CE mark, the MEDical DEVices (MEDDEV) set of documents (European Commission, 2016) is a helpful instrument, since represents non-binding guidance, which deals with the application of the directives on medical devices, such as consensus statements and interpretative documents (Fraser et al., 2011). Besides, since the clinical evaluation has become relevant for manufacturers ((Council of the European Union, 1993) consistent with (European Parliament; Council of the European Union, 2017)), the MEDDEV documents state the guidelines to correctly perform the clinical evaluation of a medical device and summarize it in the Clinical Evaluation Report (CER).

According to MEDDEV 2.7/1, the CER document includes, among others, two sections: i) clinical background, and ii) demonstration of equivalence. The first part produces as main output a systematic review of the current knowledge in the medical field of interest. Instead, the demonstration of equivalence can be fulfilled through different possible methods: a) comparing the new device with an equivalent certified device, b) collecting clinical evaluations to certify safety, performance, design characteristics, and intended purpose of the device, or c) thanks to a combination of these two options. Among the considered characteristics, the evaluation of clinical, technical, and biological factors is specifically required.

In this complex scenario, the design of rehabilitative devices should therefore consider not only technical but also normative requirements, which could introduce not negligible constraints since the device conceiving phase. This work presents an integrated design approach for medical devices, which aims at easing the regulations compatibility of the designed product, applied to the illustrative case study of the LEPRE (LEg Programmable REhabilitation) robotic system (Amici et al., 2019).

2 MATERIALS AND METHODS

LEPRE (PoliBrixia, Italy) is an end-effector based robotic device for limb rehabilitation and is characterized by two degrees of freedom that allow the implementation of every motion profile in the desired plane (Ceresoli et al., 2019). Within the current normative framework, the CER of this device was performed according to MEDDEV 2.7/1.

2.1 Interpretation of the Normative Framework

According to the MEDDEV 2.7/1 guidelines, the CER collects information from several areas of knowledge. Some of the required data partially overlap the informative content of other documents, mandatory as well for the CE mark earning. For instance, much of the information required in the device risk assessment is also stated in the risk analysis document (International Organization for Standardization, 2019) of the manufacturing company. For this reason, an analysis of the whole documentation regarding the device and the quality system of the manufacturing company (International Organization for Standardization, 2016) was performed, looking for consistency between data required according to MEDDEV 2.7/1 indications and already existing documents, with the final aim of optimizing the clinical evaluation process. According to this custom analysis, a mapping of required data and referring documents was then performed.

2.2 Clinical Background

The bibliographic research was conducted following the PICO systematic review strategy (Patient/Problem, Intervention, Comparison, Outcome) (Schardt et al., 2007) using as the main database PubMed (National Center of Biotechnology Information), and then extended to the ClinicalTrials (Clinical Trials) and Cochrane (Cochrane Library) databases. The optional fields Comparison and Outcome of the PICO technique were omitted. Table 1 collects the selected keywords for the Patient/Problem and the Intervention fields.

The identified keywords were combined in 5 search strings: s1) neurological AND (robotic AND rehabilitation); s2) orthopaedic AND (robotic AND rehabilitation); s3) rehabilitation AND robot-assisted; s4) upper-limb AND (robotic AND rehabilitation); s5) lower-limb AND (robotic AND rehabilitation). For each string and each database, an independent query was performed.

Inclusion criteria for the selection of the documents were: i) document type Review or Systematic Review; ii) document language English or Italian; iii) publication date between 01.01.1990 - 01.06.2020. Exclusion criteria were: i) references that

are not relevant in terms of population/reference pathology, ii) non-complete references, iii) too general references, iv) references without a real scientific contribution, v) duplicate references. No further restrictions are reported.

To assure the consistency of the query among the databases, the search strings were researched in all fields for PubMed and Cochrane databases. In the ClinicalTrials database, the query was implemented by assigning to the "Condition or disease" mask field the keywords search string of the PICO's P field, and to the "Other terms" mask field the keywords search string of the PICO's I field. For the Cochrane database, only intervention documents were selected. Queries were last updated on the 7th of July 2020.

The results of each query (five search strings for three databases) were filtered excluding duplicates and ordered by date (from newest records). Within the results of each query, the first ten products were selected, and the final set of documents was then analyzed by a trained operator. According to MEDDEV 2.7/1, a quantitative evaluation of the documents has been performed, considering four parameters: p1) publication date; p2) accordance with search string; p3) reference population; and p4) scientific consistency of the obtained results. For each of the defined parameters, the operator assigned a numerical value from 0 to 5 (0 not applicable, 5 fully consistent for the search), and for each document, a final score was computed as the sum of all the parameters' scores. Table 2 collects a synthesis of the guidelines for the parameters' score assignation. Two evaluators, experienced in clinical and technical context respectively, further checked the reasonableness of the results. Only documents presenting a final score higher than 14 were then selected and considered as significant for the clinical background.

2.3 Demonstration of Equivalence

For the LEPRE clinical evaluation, a free market analysis was performed to find potentially equivalent devices. Once identified the commercial names of those devices, further bibliographic research was conducted within the previously presented databases, to extract the relevant scientific literature currently available related to safety, performance, design characteristics, and intended purpose of the devices. The information gathered from those documents was then integrated with the data available on the websites of the manufacturers of the potentially equivalent devices. The information gathered from those documents was then integrated with the data available on the websites of the manufacturers of the potentially equivalent devices.

Table 1: Selected keywords for PICO's P and I fields.

Patient/Problem field	Intervention field
neurologic, orthopaedic, rehabilitation, upper-limb, lower-limb	robotic rehabilitation, robot-assisted

Table 2: Guidelines for the parameters' score assignation.

		[0-5](points) assignation strategy
Parameter	p1	5: document (published or) updated in 2020 4: document updated in 2019 3: document updated in 2018 2: document updated between 2017-2015 1: document updated between 2014-2010 0: otherwise
	p2	5: document very strongly related to the search string requirements 4: document strongly related to the search string requirements 3: document moderately related to the search string requirements 2: document weakly related to the search string requirements 1: document very weakly related to the search string requirements 0: document not related to the search string requirements
	p3	5: document with very generic sample of pathologic subject 4: document with generic sample of pathologic subject 3: document with moderate generic sample of pathologic subject 2: document with specific sample of pathologic subject 1: document with very specific sample of pathologic subject 0: document with not well-defined sample of pathologic subject
	p4	5: document with very strong theoretical and practical importance results 4: document with strong theoretical and practical importance results 3: document with moderate theoretical and practical importance results 2: document with weak theoretical and practical importance results 1: document with very weak theoretical and practical importance results 0: document with no theoretical and practical importance results

According to MEDDEV 2.7/1 indications, the biological equivalence was omitted, since the user is strictly required to wear gloves or socks when using

the LEPRE device, therefore no direct user-machine contact is necessary.

3 RESULTS

3.1 Interpretation of the Normative Framework

Figure 1 maps the required documents for the CE marking process. Within the scheme, an example of the data content interaction is provided, for the specific case of LEPRE CER. Documents containing the description of the device present a yellow dot, whereas data regarding the demonstration of equivalence are indicated with the green dot. The blue dot depicts risk analysis-related data, and the red dot is adopted for post-market surveillance information. This scheme represents a first level simplification of the data content interaction among documents sharing information with CER. For each document within the dashed boxes, further connections could be also identified.

3.2 Clinical Background

After the selection process, 37 documents emerged from the analysis of the PubMed, ClinicalTrials and Cochrane databases. Table 3 synthesizes overall results and post-filtering selected documents with respect to databases and search strings.

Comparing the results of the five queries performed within each database, 8 duplicated documents emerged for PubMed, 7 for ClinicalTrials and 28 for Cochrane, equal to 16,0%, 18,9% and 56,0% of the considered results for the specific database, respectively.

Figure 2 depicts the trend of the parameters' scores for all the products of the five queries, with respect to the three considered databases.

3.3 Demonstration of Equivalence

In order to cover all the functions provided by LEPRE, three medical devices emerged from the analysis and were selected as references in the demonstration of equivalence: device A, suitable for the evaluation of the functions related to the lower limb rehabilitation, device B, for the comparison of the upper limb-related functions, and device C for the evaluation of the cycloergometer-like features. The main factors adopted to compare the devices' characteristics, for both clinical and technical evaluation, are collected in Table 4.

4 DISCUSSION

The analysis of the informative flow among documents required by the normative framework surely can provide the designer with a general overview of requirements and potential constraints for the device development. Indeed, the awareness of the designer about this complex information net can for instance anticipate potential criticalities in technical solutions, like suggesting the exclusion of not biocompatible materials where needed. This scenario allows reducing resourcing, as time, costs and human resources otherwise devoted to the development of first attempt and not optimal solutions (Amici et al., 2016). Nonetheless, given that

Table 3: Results and post-filtering documents with respect to included databases and selected search strings.

	PubMed		ClinicalTrials		Cochrane	
Keywords Search String	Found results	Compatible results	Found results	Compatible results	Found results	Compatible results
s1: neurological AND (robotic AND rehabilitation)	149	6	29	5	24	2
s2: orthopaedic AND (robotic AND rehabilitation)	29	2	0	0	10	1
s3: rehabilitation AND robot-assisted	118	5	58	4	16	0
s4: upper-limb AND (robotic AND rehabilitation)	176	2	55	4	19	0
s5: lower-limb AND (robotic AND rehabilitation)	76	4	7	2	14	0
Total	548	19	149	15	83	3

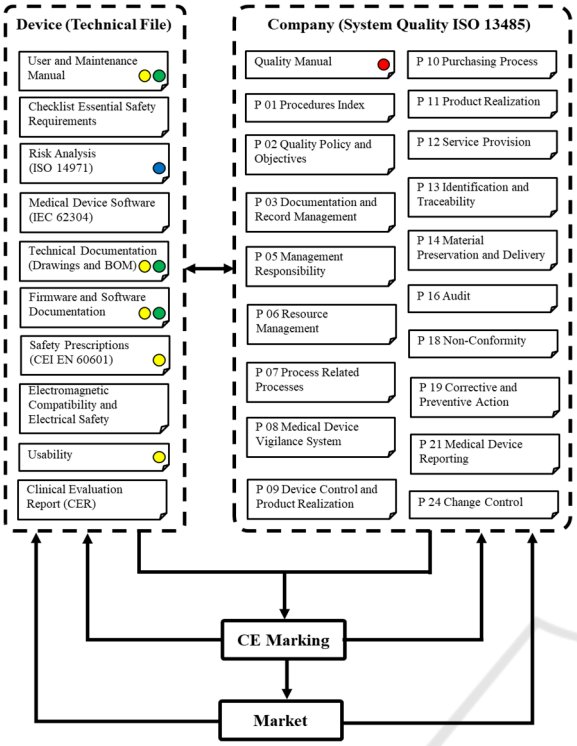

Figure 1: Schematization of information content and mandatory documents required for the CE marking process. The dashed boxes identify on the left the device-related information expected within the technical file, and on the right the manufacturer-related information required by the System Quality ISO 13485 regulation. The yellow dots indicate information referring to the description of the LEPRE device, the green dots data related to the demonstration of equivalence, finally the blue and red ones depict risk analysis and post-market surveillance information respectively.

those constraints derive from field-related regulatory instruments, analogous analyses should be performed when considering devices designed for different operational environments, e.g. industrial applications, according to a task-driven design strategy (Amici et al., 2020), or more in general, a design-for-X approach (Bause et al., 2019; Huang, 1996). In fact, the scheme depicted in Figure 1 represents a custom interpretation of the normative framework, specifically developed within the scenario of medical devices, designed for rehabilitative purposes, but also provides an illustrative application of a generally valid methodological approach. Besides, the need for the same informative content among documents suggests aiming for an optimization strategy also at a process management level, in the documents' definition. As a matter of fact, repeating the same information in multiple instances should be a deprecated strategy, since it leaves room for potential mistakes or incongruences. Conversely, overall knowledge of what information is required, for which document, and with which level of detail, allows the possibility of creating multi-purpose texts, suitable for integration in different documents, with a modular rationale.

Focusing on the illustrative case depicted in Figure 1, LEPRE CER emphasizes strong first-level connections with at least seven documents: for instance, the device description is expected in *User and Maintenance Manual*, *Technical Documentation (Drawings and Bill Of Materials – BOM)*, *Firmware and Software Documentation*, *Safety Prescriptions (CEI EN 60601)*, as well as *Usability document* within the documentation required by the device's technical file. In the same way, information related to the demonstration of equivalence will be surely included in the *User and Maintenance Manual*, *Technical Documentation (Drawings and BOM)* and *Firmware and Software Documentation*, although differences apply also at this first approximation level; for example, *Firmware and Software Documentation* deals with both clinical and technical equivalence, whereas the *Technical Documentation* mainly focuses on the technical characteristics. Besides, these interactions could be graphically schematized as double arrowed connections between two documents, since those relations should be considered mutual. In the same way, schemes and connections should be considered dynamic objects, since they evolve with the design phase along the development process. For instance, the introduction of a new attachment able to provide new training exercises would require an update of all the documents device- and company-related, but *P01 Procedure Index* and *P02 Quality Policy and Objectives*. Besides, also modifications at a software level only, like the introduction of a new training exercise which does not directly affect the device hardware, would affect all the documents but *Technical Documentation (Drawings and BOM)* in addition to the previously cited *P01* and *P02*. Still, this result should not surprise, given that the data interactions' net reflects the complexity of the design process (A.F. De Toni, 2007; A.F. De Toni and Tonchia, 2002). Within this scenario, methodological approaches aiming at the optimization of the design process such as concurrent engineering solutions could introduce considerable improvements in the overall efficiency of the design process (Loureiro and Curran, 2007).

Considering the CER developed for LEPRE, the PubMed, ClinicalTrials and Cochrane databases have been analyzed. Those databases present different

characteristics and aims, and collect therefore different kinds of data: the absence of duplicate documents in the results of the corresponding search strings among databases indicates that those databases integrate each other, supporting the appropriateness of analyzing them all. The analysis of the clinical background emphasized the interest of scientific research on this topic, especially in the last years, as the ascending trend of the parameter p1 scores for the PubMed and ClinicalTrials databases highlights. For the Cochrane database, a peak is revealed for value 2; this behavior can be justified considering that 2 points are assigned to a range of years (2015-2017), unlike higher values, which refer to single years. The high values of the p3 and p4 parameters support the suitability of the identified search strings as detectors of the results' clinical and technical relevance respectively, since they allow assessing population dimension, and importance and applicability of the proposed scientific results. Conversely, the p2 parameter can be considered a valid indicator of methodological quality of the investigation, since it expresses the correlation between expected requirements imposed by the search strings and actual content of the obtained documents. A potential limitation of the proposed approach is given by the evaluation of the ten most recent documents for each query and each database, but preliminary investigations suggested that this value represented a reasonable compromise between analysis quality and computational time. According to this rationale, the number of evaluated documents should be likely modified in case of analyses performed on different fields, for instance, increased when dealing with more traditional fields, like the mechanical or the industrial one, which could reasonably present a wider quantity of relevant documents.

For the demonstration of equivalence, three different devices had to be evaluated in order to provide for a complete analysis of LEPRE device's functions, since no device currently on the market provided a comparable set of features. The comparison between LEPRE and device A allowed demonstrating the clinical and technical equivalence of the functions related to the mobilization of the subject's lower limb, since no differences significantly affecting the equivalence can be detected between the devices. In the same way, the comparison with device B and device C allowed fulfilling the clinical and technical equivalence for the upper limb-related functions and the cycloergometer-like features respectively. No demonstration of biological equivalence was required since the user shall wear gloves or socks while performing the rehabilitative training with the LEPRE device. In fact, in case of direct contact between patient and device, MEDDEV 2.7/1 suggests the use of a biocompatible material (International Organization for Standardization, 2020) at a design process level, or

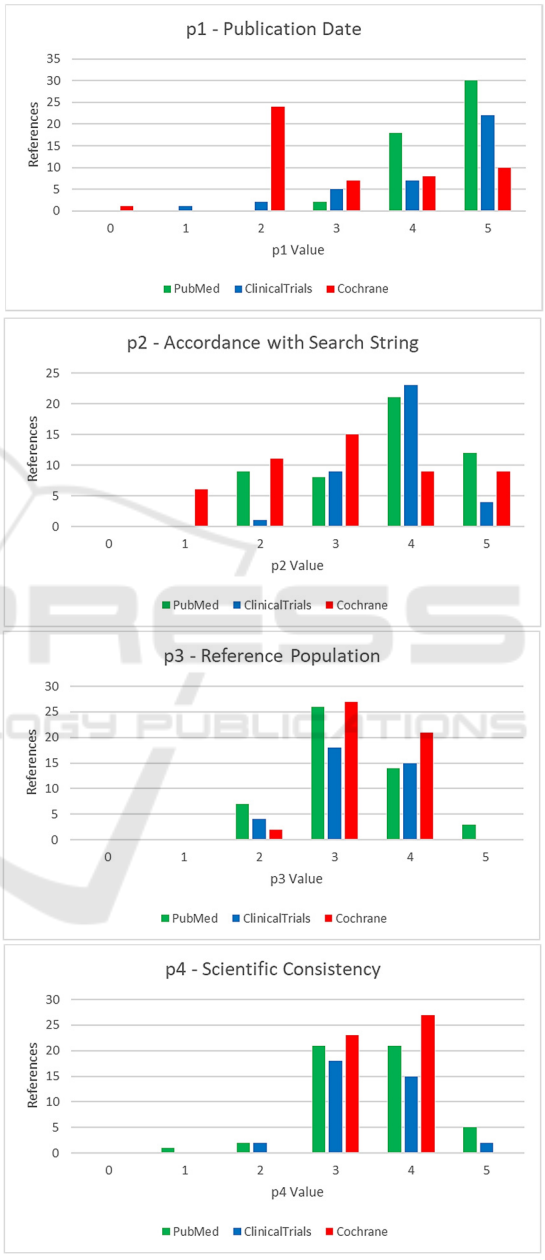

Figure 2: Bar plots of the assigned parameters' scores in aggregate form. From the top, the number of documents with respect to the score and database, for a) publication date (p1); b) accordance with search string (p2); c) reference population (p3); and d) scientific consistency (p4).

Table 4: Schematic comparison between LEPRE characteristics and devices A, B and C respectively, with respect to the parameters required for the clinical and technical evaluation. Green checkmarks indicate a complete overlapping of the characteristics between the devices, whereas yellow checkmarks indicate a partial equivalence: in the lower row of the table the detail of the observed differences is presented.

		A	B	C
Parameters for Clinical Evaluation	Clinical condition	✓	✓[1]	✓[2]
	Intended purpose	✓	✓	✓
	Site of the body involved	✓	✓	✓
	Reference population	✓[3]	✓[3]	✓
Parameters for Technical Evaluation	Design structure	✓	✓	✓
	Conditions of use	✓	✓	✓
	Specifications and properties	✓[4]	✓	✓
	Deployment methods	✓	✓	✓
	Principles of operation	✓	✓	✓
Differences Details	1. Device B can be adopted to also treat pathologies related to the pelvic diaphragm (e.g. incontinentia), currently excluded for LEPRE device. 2. Device C can be adopted to also treat pathologies such as hemodialysis, Alzheimer's disease/dementia, percutaneous coronary intervention (PCI), respiratory rehabilitation, or poliomyelitis/post-poliomyelitis syndrome, currently excluded for LEPRE device. 3. Reference population for the device also includes pediatric subjects, currently excluded for LEPRE device. 4. Device A presents overall dimensions and weight remarkably higher than LEPRE device, since it includes a seating system and supports for the patient, unnecessary in LEPRE device.			

the demonstration of biological equivalence at the final stage. Nevertheless, the no-contact operational condition assured by LEPRE also represents a favorable asset for the use of rehabilitation devices within the current scenario of the COVID-19 pandemic, easing the implementation of hygienizing and sanitizing protocols.

5 CONCLUSIONS

The design process of medical devices must integrate and optimize requirements related to technical and clinical factors, user needs, therapy procedures, and regulations' constraints. The optimization of the design process can be eased by the awareness about the complex information net required by the normative framework. Within this scenario, this paper presents a design approach which aims at easing the regulations compatibility of the designed product, based on the custom mapping of required data and referring documents for the development and commercialization of a medical device according to the CE marking process. This method is applied to the illustrative case study of the LEPRE robotic system, describing the data collection and analysis for the device CER, as suggested MEDDEV 2.7/1 guidelines, with particular a focus on the evaluation of clinical background and demonstration of equivalence. Since the proposed method grounds on the analysis of documentation that are strongly dependent on the product operational conditions, indications for the modifications required to adapt it to further application fields are also suggested.

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