ETHICAL AND REGULATORY DIMENSIONS OF THE TECHNOLOGICAL DEVELOPMENT PROCESS OF A PORTABLE MEDICAL DEVICE FOR DIABETIC FOOT TREATMENT: FROM BENCH TO SCALE MANUFACTURING

VLADIMIR FRANÇA NOGUEIRA

DOCTORAL DISSERTATION IN ELECTRICAL ENGINEERING

DEPARTMENT OF ELECTRICAL ENGINEERING

TECHNOLOGY FACULTY

UNIVERSITY OF BRASÍLIA

University of Brasília
Technology Faculty
Department of Electrical Engineering

Ethical and Regulatory Dimensions of the Technological Development Process of a Portable Medical Device for Diabetic Foot Treatment: From Bench to Scale Manufacturing

PHD THESIS SUBMITTED TO THE GRADUATE PROGRAM IN ELECTRICAL ENGINEERING AT THE UNIVERSITY OF BRASÍLIA AS REQUIRED FOR OBTAINING THE PHD DEGREE IN ELECTRICAL ENGINEERING.

APPROVED BY:

_____

Prof. Adson Ferreira da Rocha, D. Sc. (UnB)
(Supervisor)

_____

Prof. Fátima Mrué, D. Sc. (UFG)
(External Examiner)

_____

Prof. Talía Simões dos Santos Ximenes, D. Sc. (Unicamp)
(External Examiner)

_____

Prof. Flavia Maria Guerra de Sousa Aranha, D. Sc. (UnB)
(Internal Examiner)

_____

Prof. João Yoshiyuki Ishihara, D. Sc. (UnB)
(Internal Examiner)

Brasília/DF, November of 2024.

CATALOGING-IN-PUBLICATION DATA

VLADIMIR FRANÇA NOGUEIRA

Ethical And Regulatory Dimensions of The Technological Development Process of A Portable Medical Device For Diabetic Foot Treatment: From Bench To Scale Manufacturing, [Federal District] 2024

PPGEE.TD 208/24, 210 x 297 mm (FT/UnB, Doctorate, Electrical Engineering, 2024). Doctoral Dissertation - University of Brasília. School of Technology. Graduate Program in Electrical Engineering.

1. Translational Health Research
2. Diabetic Foot
3. Rapha® Project
4. Brazilian Unified Health System
5. Health Policy

I. FT/UnB.

II. Ethical and Regulatory Dimensions of the Technological Development Process of a Portable Medical Device for Diabetic Foot Treatment: From Bench to Scale Manufacturing

BIBLIOGRAPHIC REFERENCE

NOGUEIRA, V. F. (2024). Ethical and Regulatory Dimensions of the Technological Development Process of a Portable Medical Device for Diabetic Foot Treatment: From Bench to Scale Manufacturing. Doctoral Dissertation in Electrical Engineering, Publication PPGEE.TD 208/24, Graduate Program in Electrical Engineering, School of Technology, University of Brasília, Brasília, DF, 146 p.

RIGHTS GRANT

_____

Vladimir França Nogueira

University of Brasília (UnB)

Darcy Ribeiro Campus

Faculty of Technology - FT

Department of Electrical Engineering (ENE)

Brasília - DF, ZIP 70.919-970

DEDICATION

"Science can tell us what is possible; it is up to technology to make the possible happen."
— Bertrand Russell

"Each scientific and technological advance is an attempt to alleviate human suffering; the true challenge is to ensure it is accessible to all."
— Albert Einstein

"Medicine advances with technological progress, and each new tool opens a new horizon to preserve and improve human health."
— Francis Bacon

"Technology that improves life and alleviates pain represents the triumph of the mind over human suffering."
— Hannah Arendt

To my family for their support, affection, and dedication, for always being there, believing in me, and standing by me every step of my life.

To my future wife whose love, support, and partnership have made this achievement even more special. Thank you for standing by me through the most challenging times and believing in my dreams as if they were yours.

ACKNOWLEDGMENTS

First and foremost, I thank God for the opportunity to achieve my academic career goals and extend my gratitude to my friends, my fiancée, and the professors who contributed to the development of this work.

I am grateful to my father, mother, sister, niece, and nephew, who have always been present, supporting, and participating in every moment of my life.

To my advisor, Prof. Dr. Adson Ferreira Rocha, for his support, guidance, encouragement, suggestions, friendship, and teachings throughout these years.

To Prof. Dr. Mário Fabrício Fleury Rosa and his wife, Prof. Dr. Suélia de Siqueira Rodrigues Fleury Rosa, who have spared no effort to help me and were present throughout the development of this entire work.

I am grateful to all the members of the Rapha® project for their ongoing support and contribution to the development of this topic.

ABSTRACT

Title: Ethical and Regulatory Dimensions of the Technological Development Process of a Portable Medical Device for Diabetic Foot Treatment: From Bench to Scale Manufacturing.

The development of new technologies applied to health is inherently complex. Consequently, academia, government, society, and industry have been striving to accelerate the transition from basic research to the availability of new products for the population. The Brazilian regulatory system for medical devices encompasses ethical, technical, regulatory, economic, and social considerations to ensure safety and minimum technical standards for effectively addressing the proposed solution in accordance with its intended use. In this context, Translational Health Research (THR) emerges as a field aimed at promoting, among other elements, a set of actions and activities to transfer findings from basic research to the approval of technology, making it available to users/patients. This is achieved through translational stages that underpin Brazilian regulatory processes. **Objective**: To develop the THR process within the ecosystem of research, development, and innovation at a Public University in Brazil, as well as within the ethical and regulatory environment associated with the development of new medical products for the Brazilian healthcare system, using the Rapha® device as a case study. **Methodology**: This study employed a structured approach to investigate the technological development process for medical devices, focusing on the Rapha® device. Initially, data were collected on the R&D&I ecosystem in public universities, identifying conditions for the social integration of technologies. Next, the translational research process was characterized, covering stages, markers, involved entities, and ethical and regulatory aspects, based on the Rapha® case study. Finally, the technological maturity and market potential of the device were evaluated using tools such as the SWOT matrix, Technology Readiness Levels (TRL), and Medical Device Readiness Levels (MDRL), ensuring an integrated analysis of the development and application of the device within the public healthcare system. **Results**: The transformation of knowledge generated at the University of Brasília into applied innovation resulted in the development of the Rapha® device, a product with potential for integration into healthcare services. This process led to patents and technology transfers, reinforcing their link to innovation. It was observed that THR operates as a non-linear process, as evidenced in the Rapha® case study. Among the challenges encountered were the "valleys of death," particularly during the regulatory and production transitions between the T3 and T4 phases, which are critical for making the technology available to the Brazilian market. The translational stages T0, T1, T2, and T3 were identified and complemented by an evaluation of the technological maturity levels using TRL and MDRL, as well as a strategic analysis with the SWOT matrix. **Conclusion**: The translation of knowledge generated by the university, represented by the Rapha® device, proved to be a successful case of applied research with the potential for a positive impact on Brazilian public health and the economy. Identifying the paths followed by the Research, Development, and Innovation (R&D&I) of this technology and its respective technological maturity levels reveals a replicable strategy for other academic innovations, highlighting the importance of a collaborative ecosystem for the development of technologies that benefit the population.

Keywords: Translational Health Research (THR), Diabetic Foot, Rapha® Device, Brazilian Unified Health System (SUS), Technological Maturity Level for Medical Devices (MDRL).

RESUMO

Título: Dimensões Éticas e Regulatórias do Processo de Desenvolvimento Tecnológico do Dispositivo Médico Portátil para Tratamento do Pé Diabético: da Bancada à Fabricação em Escala.

O desenvolvimento de novas tecnologias aplicadas à saúde é complexo, devido a isso a academia, o governo, a sociedade e as empresas têm se empenhado a fim de acelerar a realização da pesquisa básica e a disponibilização de novos produtos para a população. Sabe-se que o sistema regulatório brasileiro para equipamentos médicos envolve questões éticas, técnicas, regulatórias, econômicas e sociais a fim de garantir segurança e condições técnicas mínimas para atender a solução proposta de acordo com indicação de uso de forma eficaz. Nesse sentido, a Pesquisa Translacional em Saúde (PTS) emerge como uma área que procura promover, entre outros elementos, um conjunto de ações e atividades com o intuito de transferir os resultados encontrados a partir da pesquisa básica até a aprovação da tecnologia para ser disponibilizada aos usuários/pacientes por meio das etapas de translação que ajudaram a embasar os processos regulatórios brasileiro. **Objetivo:** Desenvolver o processo da PTS no ecossistema de pesquisa, desenvolvimento e inovação da Universidade Pública do Brasil e do ambiente ético e regulatório associado ao desenvolvimento de novos produtos médicos para o sistema de saúde brasileiro, usando como base o estudo de caso do equipamento Rapha®. **Metodologia:** Este estudo utilizou uma abordagem estruturada para investigar o processo de desenvolvimento tecnológico de equipamentos médicos, com foco no equipamento Rapha®. Inicialmente, foram levantados dados sobre o ecossistema de Pesquisa, Desenvolvimento e Inovação (PD&I) em universidades públicas, identificando condições para a inserção social de tecnologias. Em seguida, caracterizou-se o processo de pesquisa translacional, abrangendo etapas, marcadores, entidades envolvidas e aspectos éticos e regulatórios, com base no estudo de caso do Rapha®. Por fim, avaliou-se a maturidade tecnológica e o potencial mercadológico do dispositivo, utilizando ferramentas como a matriz SWOT (*Strengths, Weaknesses, Opportunities e Threats*), TRL (*Technology Readiness Levels*) e MDRL (*Medical Device Readiness Levels*), garantindo uma análise integrada do desenvolvimento e aplicação do equipamento no sistema de saúde público. **Resultados:** A transformação do conhecimento gerado na Universidade de Brasília em inovação aplicada, resultando no desenvolvimento do equipamento Rapha®, um produto potencialmente assimilável pela assistência à saúde. Este processo gerou patentes e transferências tecnológicas, reforçando seu vínculo com a inovação. Observou-se que a PTS opera como um processo não-linear, evidenciado no estudo de caso do Rapha®. Entre os desafios enfrentados, destacaram-se os "vales da morte", especialmente nas fases de transição regulatória e produtiva entre T3 e T4, que são essenciais para disponibilizar a tecnologia ao mercado brasileiro. Foram identificadas as etapas translacionais T0, T1, T2 e T3, complementadas pela avaliação do grau de maturidade tecnológica utilizando TRL e MDRL, além da análise estratégica com a Matriz SWOT. **Conclusão:** A translação do conhecimento gerado pela universidade, representada pelo equipamento Rapha®, mostrou-se um caso bem-sucedido de pesquisa aplicada, com potencial de impacto positivo para a saúde pública brasileira e a economia. A identificação dos caminhos percorridos pela PD&I desta tecnologia e seu respectivo grau de maturidade tecnológica revela uma estratégia replicável para outras inovações acadêmicas, destacando a relevância de um ecossistema colaborativo para o desenvolvimento de tecnologias que beneficiem a população.

Palavras-chave: Pesquisa Translacional em Saúde (PTS), Pé Diabético, Equipamento Rapha®, Sistema Único de Saúde (SUS), Grau de Maturidade Tecnológica para Dispositivo Médico.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS

A_f	Final Area
A_i	Initial Area
UHI	Ulcer Healing Index
UCR	Ulcer Contraction Rate

GLOSSARY

ACT – Technology Commercialization Agency

ANVISA – National Health Surveillance Agency

CEP – Research Ethics Committee

CG – Control Group

CONEP – National Research Ethics Commission

CONITEC– National Commission for the Incorporation of Health Technologies in SUS

CTD – Center for Technological Development

DF – Federal District

DFU – Diabetic Foot Ulcers

DM – Diabetes Mellitus

EG – Experimental Group

EU – European Union

FDA – Food and Drug Administration

FUB – University of Brasília Foundation

GMP – Good Manufacturing Practices

GRI – Granulation Red Index

HRAN – Asa Norte Regional Hospital

HRG – Gama Regional Hospital

HRL – Human Readiness Levels

HRT – Taguatinga Regional Hospital

HTA – Health Technology Assessment

IDF – International Diabetes Federation

IEEE – Institute of Electrical and Electronics Engineers

INMETRO – National Institute of Metrology, Quality, and Technology

INPI – National Institute of Industrial Property

JAMA – Journal of American Medical Association

LED – Light-Emitting Diode

MDRL – Medical Device Readiness Levels)

MH – Ministry of Health

NASA – National Aeronautics and Space Administration

PCB – Product Certification Bodies

PubMed– Publisher Medline

R&D&I – Research, Development, and Innovation

RDC – Collegiate Board Resolution

RRL – Regulatory Readiness Levels

SBAC – Brazilian Conformity Assessment System

SES/DF – Federal District's Department of Health

SF-6D – Short-Form 6 Dimensions

ST&I – Science, Technology, and Innovation

SUS – Unified Health System

SWOT – Strengths, Weaknesses, Opportunities, and Threats

THR – Translational Health Research

TRL/MRL – Technology Readiness Levels/Manufacturing Readiness Levels

UnB – University of Brasília

URC – Ulcer Contraction Rate

CHAPTER 1

INTRODUCTION

1.1. Contextualization and problem formulation

The introduction of new technology into the healthcare system involves multiple stages, including ethical, regulatory, technical, scientific, and budgetary requirements. This complex process is time-consuming, marked by a high failure rate, and requires significant human and financial resources, both public and private (FUDGE *et al*., 2016; HELEN, 2016). In the early stages of basic research, the proposed solutions undergo rigorous testing before advancing to clinical research. Even after the completion of clinical trials, less than half of the results are often published in the first year, making it difficult to disseminate and apply these findings within the healthcare system (DEVITO; BACON; GOLDACRE, 2020).

In this context, science plays a fundamental role in developing health technologies, which necessarily encompasses basic and applied (clinical) research on products and processes (CCATES, 2019). Basic research seeks knowledge discovery and information generation in fields like cellular and molecular biology, physiology, and pathology, among others. On the other hand, applied research aims to develop technologies and practical applications of knowledge, representing innovations for preventing or altering the course of diseases (BIGDELI *et al*., 2014; ZERHOUNI *et al*., 2018). Although advances in science have been observed in recent decades, the literature suggests a need for the application of knowledge to generate more beneficial results and technologies that better meet the health needs of society (LUPATINI *et al*., 2020).

The development of new health technologies is complex. For this reason, the academic, government, society, and companies have strived to accelerate the execution of basic research and the availability of new products to the population, representing translational research. Since 2009, Abrasco has intensified discussions on the "commitment of science, technology, and innovation to the right to health" from the perspective of the science, technology, and innovation sector and/or quadruple helix (state – university – industry – society) (MINEIRO, 2019). The university is crucial in identifying societal problems and bringing innovative solutions through researchers. At the same time, companies transform the research and creativity of researchers into products to be used and commercialized in society, and finally, the government assists with

legislation and financial support (DO AMARAL; RENAULT, 2019). Thus, the process of technological development depends on intense interaction between government, academia, and companies to generate innovation and capitalize on economic and social advances (BOSIO *et al*., 2019, p. 49).

In this context, Translational Health Research (THR) emerges with the aim of reducing the time between knowledge generated through basic research and its clinical application in healthcare, making it available in the market (BARRETO, 2019; KHOURY *et al*., 2010). Often associated with the expression "from bench to bedside," translational research aims to integrate various stages of research and knowledge, seeking to make practical applications available that result in societal benefits (LEFANT, 2003; WOOLF, 2008). Furthermore, it is referred to as "translational medicine" and "translational science," although each definition has its nuances (MOREL, 2020). The first translational research model referenced two stages (basic and applied research) in a unidirectional sense. Subsequently, new stages were incorporated into the model with bi- and multidimensional directionality, involving, for example, evidence synthesis, knowledge translation, dissemination, implementation, and technology evaluation, as well as the assessment of the impact of its use in health systems (FORT, 2017; LUPATINI, 2022). Broadly, this type of research establishes the link between discovery, development, regulation, and its practical use (WAGNER; KROETZ, 2016).

The introduction of new technology into the healthcare system requires numerous stages, processes, and activities from various actors. These stages include ethical, regulatory, technical, scientific, and budgetary impact requirements. This represents a complex process that requires significant time before the new technology reaches the end user in the healthcare system. A low success rate marks it and requires substantial resources of various kinds (human, financial) and types (public and private) (FUDGE *et al*., 2016; HELEN, 2016). In the early stages of basic research, the investigative solution must pass several tests before entering the clinical research phases. In this sequence, results are collected, and clinical trials are often discontinued until adjustments are made to meet sanitary registration requirements. Clinical trial results must be published to the scientific community as an ethical obligation and moral conduct. Still, studies indicate that less than half of the results are published within one year after the conclusion of the studies (DEVITO; BACON; GOLDACRE, 2020). Therefore, scientific publications highlight results that can be used in clinical and management decision-making processes. However, significant barriers exist to accessing, interpreting, regulating, and applying research evidence in decision-making processes (OLIVER *et al*., 2014; ORTON *et al*., 2011; TRICCO *et al*., 2015).

It is known that the process of transforming laboratory, clinical, and humanistic findings into interventions that promote public and individual health improvements — from converting diagnostic and therapeutic interventions or products into procedures and behavioral changes — is described as translational science (FELIPE *et al*., 2020). When conducted by the university, this process requires the assimilation of results into health systems through private initiatives (industries, companies, startups, and spin-offs) for their introduction into these systems. In this context, THR is essential to mitigate the "valleys of death" [1] between Research, Development, and Innovation (R&D&I) and market availability for large-scale production, especially regarding ethical and regulatory dimensions, such as regulations from the Brazilian Health Regulatory Agency (ANVISA, abbreviated from Portuguese, “Agencia Nacional de Vigilância Sanitária”), according to the Collegiate Board Resolution (RDC, abbreviated from Portuguese, “Resolução da Diretoria Colegiada”) (ROSA, 2022).

Science, Technology, and Innovation (ST&I) are crucial for overcoming crises and are among the main topics in public debate and national public policy agendas in the global system (GADELHA *et al*., 2022, p. 119). In this regard, investments in R&D&I in the health sector were essential in addressing the COVID-19 pandemic, given the challenges posed by the health emergency. This fostered additional financing mechanisms for both academic research related to COVID-19 and direct support for public and private R&D&I activities, aiming to develop vaccines and other health technologies (DUARTE *et al*., 2020, ROSA *et al*., 2021; VARGAS; ALVES; MREJEN, 2021).

An example of the quadruple helix in the context of THR, with the effective participation of the university, is the project developed at the University of Brasília (UnB), which saw the translation stages of knowledge in the Portable Medical Device for Tissue Neoformation (Rapha®). This technology aims to treat one of the complications of Diabetes Mellitus (DM). This disease represents a serious public health issue and directly impacts the individual's quality of life, with high rates of morbidity and mortality (Saeedi *et al*., 2021). It is estimated that the number of people diagnosed with DM will increase from 537 million (2021) to 783 million in 2045 among individuals aged 20 to 79, according to the International Diabetes Federation (IDF)

[1] Death Valley is a desert valley located in eastern California, north of the Mojave Desert, along the border with the Great Basin Desert in the United States. It is one of the hottest places on Earth at the height of summer, comparable to deserts in the Middle East. Consequently, it is an inhospitable place, where only the best-adapted organisms have a chance of survival. When the concept of a “Death Valley” is applied within the R&D&I process, it serves as an analogy for the failure to transform a technology’s proof of concept into a final product that meets regulatory requirements. In the context of translational research, however, the analogy extends further: the Death Valley represents the failure to integrate research outcomes into healthcare systems (ROSA, 2022).

(IDF, 2016). According to the Ministry of Health (MH), the prevalence of DM diagnoses in Brazil increased from 6.3% of the population in 2010 to 6.9% in 2022 (Brazil, 2023). In the Federal District, this prevalence increased from 4.4% in 2010 to 5.2% in 2022 (BRASIL, 2023). DM is associated with various complications in essential organs. Among these, Diabetic Foot Ulcer (DFU) is a primary concern due to the high number of hospitalizations and the significant rate of lower limb amputations (YAZDANPANAH; NASIRI; ADARVISHI, 2015), as wound healing in diabetic feet is hampered by prolonged inflammation (FREITAS, 2002). The Rapha® device showed promising results for DFU treatment, using a latex biomembrane associated with a Light-Emitting Diode (LED), promoting the reduction of free radicals in the injured tissue and angiogenesis, among other effects (REIS, 2013; ROSA *et al*., 2019; ROSA *et al*., 2020). This way, it accelerates the healing process and wound closure in less time than conventional treatments (BALTZIS; ELEFTHERIADOU; VEVES, 2014; HOURELD, 2014; ROSA, 2019; HUANG, 2020). It is worth noting that Rapha® has overcome the "valleys of death" since its ethical approval and is currently in the registration phase with ANVISA.

Given the long duration of this process, it is crucial to integrate and optimize the stages so that the benefits provided by the Rapha® device can be available and accessible to society. From this perspective, identifying the phases, entities involved, and regulation in the Brazilian context is justified, as the generation of information can identify gaps and opportunities for improvement in R&D&I, ethical, and regulatory processes, as well as support decision-making, particularly within the Brazilian Unified Health System (SUS, abbreviated from Portuguese, “Sistema Único de Saúde”).

This study focuses on diabetic foot complications, specifically the development and translation of a medical device. This innovative portable medical device, called Rapha®, was created to accelerate wound healing in diabetic feet.

Innovation in healthcare is traditionally associated with the production of new equipment, clinical procedures, and preventive measures. However, to broaden this perspective, the entire process of implementing new ideas, services, and products involves different levels of management competencies with translational goals. Thus, the research problem addressed in this study consists of presenting the translation of Rapha® device from the laboratory to ANVISA registration and its subsequent availability in the Brazilian healthcare system.

The outcomes proposed by this doctoral research, conducted at a public university, aim to contribute to translational research and related fields such as science, technology, and innovation, in addition to health technology assessment based on its technological maturity and market potential. This is achieved using tools such as the SWOT matrix (Strengths, Weaknesses,

Opportunities, and Threats), TRL (Technology Readiness Levels), and MDRL (Medical Device Readiness Levels), ensuring an integrated analysis of the development and application of the device within the public healthcare system. In this context, public universities play a crucial role as drivers of economic development through the creation of health solutions, exemplified by the Rapha® device. The application of this knowledge within the Brazilian context can enable rational, cost-effective, and timely access to new technologies for the population, while also contributing to R&D&I in biomedical engineering.

CHAPTER 2

CONCEPTUAL FRAMEWORK AND OBJECTIVES

2.1. Research Question

How can the technical and regulatory challenges in developing new medical technologies in Brazilian public universities be overcome, considering market demands and the national regulatory environment?

2.2. Hypothesis

This doctoral research aims to generate results that will assist in the ongoing clarification of the processes, difficulties, and opportunities associated with the development and translation of new health technologies in the context of Brazilian public universities. Using biomedical engineering techniques and based on a case study of the development of the innovative Rapha® medical device, the research seeks to understand how technologies can be translated from academia to the healthcare system.

The Rapha® case study focuses on translating knowledge generated at the university into a product that combines healthcare features with commercial viability, aiming to meet the needs of the SUS. By analyzing the translational aspects involved, including ethical and regulatory challenges, the research aims to fill knowledge gaps regarding the process of integrating university-developed technologies into the market, benefiting both the population and the Brazilian economy.

Thus, this work's hypothesis is based on the Rapha® project case study. It aims to understand the THR process applied to the development of medical equipment, considering ethical and regulatory aspects that enable its availability in the Brazilian healthcare system through private initiatives (industries and companies).

The qualitative research will include document analysis and fieldwork, providing evidence that will contribute to developing theoretical-methodological models and frameworks on the topic. The single case study of Rapha® will serve as a foundation for anchoring the development of these models, given its development and licensing process at the UnB.

2.3. Objectives

2.3.1. General Objective

This work aims to develop the Translational Health Research (THR) process through the case study of Rapha® device within the Research, Development, and Innovation (R&D&I) Ecosystem of the Brazilian Public University and the ethical and regulatory environment for the Brazilian healthcare system.

2.3.2. Specific Objectives

a) Collect data and documents related to the technological development of medical devices conducted by universities.
b) Characterize the stages, markers, entities, and policies of translational research related to new technologies in Brazil for medical products, as well as ethical and regulatory aspects, using the development of the Rapha® project as a case study through document analysis and field approach.
c) Describe and analyze the technological development of the Rapha® device according to THR, covering phases T0 to T4 and detailing the challenges encountered in each phase.
d) Demonstrate the practical application of the Rapha® medical device in clinical settings, evaluating its efficacy and outcomes in preclinical and clinical phases. e) Evaluate the technical, regulatory, and ethical aspects involved in the development and technology transfer of the Rapha® medical device by the public university.
e) Assess the perception of the technological maturity and competitive intelligence of the Rapha® device for the market (SWOT Matrix, TRL and MDRL), considering R&D&I, ethical, regulatory, and market aspects.

2.4. Outline

This work is organized into seven chapters, including this one.

Chapter three presents an overview of the theoretical framework, aiming to understand translational health technologies' concepts, protocols, and processes. Additionally, the chapter incorporates bibliographic research information on state of the art regarding models for developing medical systems. The following topics are addressed in the chapter: (i) Diabetes

Mellitus (DM), (ii) Health Technologies, (iii) Translational Health Research (THR), (iv) Research, Development, and Innovation (R&D&I), (v) Ethical and Regulatory Aspects for Medical Devices and (vi) Tools for Technology Maturity Assessment.

Chapter four details the methodology used in the qualitative research, which combines document analysis and fieldwork into a single case study.

Chapter five describes the results and discussion obtained from the development structure of translational research for incorporating health technology in the Rapha® device case study under Brazilian ethical and regulatory aspects.

Chapter six discusses the most important points of this study's and presents the work's final conclusions.

Finally, chapter seven presents the future works of the doctoral thesis based on the ideas presented in this document.

CHAPTER 3

THEORETICAL FRAMEWORK

3.1. Diabetes Mellitus (DM)

DM is considered one of the most prevalent chronic diseases affecting contemporary humans (SAEEDI *et al*., 2021). It is estimated that the number of patients diagnosed with this condition will increase from 537 million in 2021 to 783 million by 2045 among individuals aged 20 to 79, according to the IDF (IDF, 2016). According to the MH, the prevalence of DM diagnosis in Brazil was 6.3% of the population in 2010 and reached 6.9% in 2022 (BRASIL, 2023). In the Federal District, this prevalence rose from 4.4% in 2010 to 5.2% in 2022 (BRASIL, 2023).

DM is one of the most significant health issues today due to its high morbidity and mortality rates. It is a chronic and complex metabolic disorder characterized by impaired glucose metabolism and other energy-producing substances, and it is associated with complications in vital organs necessary for life maintenance, such as non-traumatic amputations of the lower and upper limbs (BRASILEIRO *et al*., 2005; FREITAS *et al*., 2002).

Due to its chronic nature, the severity of its complications, and the necessary measures for managing them, DM represents a highly costly disease, not only for affected individuals and their families but also for the healthcare system. Individuals with diabetes have higher hospitalization rates compared to non-diabetics, as well as more extended hospital stays to address the same health issues. Hospitalizations consume a significant portion of healthcare resources, representing 55% of the direct costs of type 2 diabetes in Europe, 44% in the United States, and 10% in Latin America (MORAES *et al*., 2020). From 1999 to 2001, in Brazil, the hospitalization rate for diabetes was 6.4 per 10,000 inhabitants, while in the United States, this rate was 20.0 per 10,000 inhabitants in 2000 (ROSA *et al*., 2007).

3.1.1. Complications of Diabetes

Among the complications of DM, there can be reduced sensitivity (neuropathy) and decreased blood perfusion (vasculopathy). The feet are often among the first areas of the body to be affected by this loss of sensation. Patients experiencing this issue lose the primary protective mechanism of the body — pain — making them susceptible to developing foot

ulcers. Due to compromised blood circulation, these ulcers can reach alarming sizes, making management and healing difficult. Additionally, the loss of sensation renders patients vulnerable to trivial injuries, which can serve as entry points for bacteria, potentially leading to severe and silent infections if not treated early. These neurovascular complications alter the normal biomechanics of the foot, resulting in areas of high pressure on the metatarsal heads, heels, and toes (CAVANAGH; ULBRECHT; CAPUTO, 2000).

According to the literature, the origin of foot ulcers is strongly associated with increased pressure in specific areas and with foot and toe deformities, such as high or flat arches, bunions, claws, or hammer toes. These deformities contribute to increased pressure on the plantar surface. For this reason, it is crucial to identify these areas through pressure measurement tools to prevent foot injuries by using custom insoles that redistribute plantar pressure across regions of higher concentration during patient gait (ZEQUERA *et al*., 2003).

3.1.2. Diabetic Foot Ulcers

Diabetic foot is characterized by a range of changes resulting from neuropathies and micro- and macro-vasculopathy. Due to biomechanical alterations leading to deformities, there is increased susceptibility to infections. It is considered one of the most severe complications of DM, ranking among the most significant global health issues due to the often-devastating outcomes of ulcerations, which can lead to amputation of toes, feet, or legs (MACEDO; PEDROSA; RIBEIRO, 2001).

Lesions typically arise from trauma and frequently progress to gangrene and infection, caused by failures in the healing process, potentially resulting in amputation when early and adequate treatment is not provided (PEDROSA *et al*., 1998). The risk of lower limb amputation in DM patients is approximately 40 times higher than in the general population (ASSUNÇÃO; SANTOS; GIGANTE, 2001).

It is estimated that 14 to 20% of patients with foot ulcers undergo at least one amputation, and 50% of non-traumatic lower limb amputations are attributed to diabetes. At the same time, about 20 to 25% of diabetic patients will develop lower limb ulcers at some point in their lives (SINGH; ARMSTRONG; LIPSKY, 2005). Data from North America indicates that 9 to 20% of individuals with diabetes required a second amputation within twelve months of the first, and in the five years following the initial amputation, between 28 and 51% of survivors will need another intervention on the same limb. Another relevant factor is mortality; when a patient undergoes a primary amputation, the survival rate is 50% after 3 years, decreasing to 28% at five years (MANAMAYA; DEVI, 2017).

These rates can be attributed to various sociocultural practices, such as walking barefoot, using inappropriate tools for diabetic foot care, wearing improper footwear, and inadequate socioeconomic and educational conditions (VIJAY; SNEHALATHA; RAMACHANDRAN, 1997). Additionally, factors such as age, type, and duration of DM diagnosis, poor metabolic control, smoking, alcohol consumption, obesity, and hypertension, along with poor dietary and hygiene habits in foot care, are significant and strongly influence the risk of this complication. These factors favor the formation of ulcers, infections, and gangrene, potentially culminating in amputation (ZANGARO, 1999).

In addition to physical problems, ulcerations can lead to high mortality rates, reduced quality of life, and prolonged hospitalizations. These factors also impose a significant economic burden, especially regarding frequent hospitalizations, prolonged treatments, absenteeism, and early retirement. The loss of the ability to continue working or limitations in professional performance during peak productive age are direct consequences of these complications, resulting in work interruptions and often an inability to return to work (REGGI JUNIOR; MORALES; FERREIRA, 2001; ASSUNÇÃO; SANTOS; GIGANTE, 2001). These economic impacts are compounded by the fact that DM patients consume at least twice the healthcare resources compared to non-diabetics, leading to additional costs for the healthcare system (PEDROSA *et al*., 1998). Reflecting this, in Brazil, the total annual medical costs of the SUS for diabetic foot patients are estimated at R$ 586.1 million, potentially ranging from R$ 188.5 million to R$ 1.27 billion in sensitivity analyses. Of this total, 85% of costs are allocated to treating patients with neuroischemic foot ulceration, amounting to R$ 498.4 million (BAHIA, 2023).

Consequently, the high demand for medical resources, coupled with the severity of chronic complications, highlights the importance of incentives and investments directed toward research development and new technologies. These are essential for enhancing disease prevention and proper management, aiming to minimize the impact on patients' quality of life and reduce excessive treatment costs.

3.1.3. Conventional Treatments

The treatment of diabetic foot depends on the degree of limb commitment, considering the presence and/or severity of ischemia and/or infection. Currently, there are numerous options for treating lesions, including dressings with various types of coverings, debridement of devitalized tissues, revascularization, local application of growth factors, oxygen therapy,

multiple procedures for human skin replacement, and extremity amputation — the latter being the most frequently adopted option (HADDAD *et al*., 2005).

Among these options, a simple and effective approach to monitoring foot condition is conducting a physical examination to assess plantar pressure. This examination helps identify areas of overload, which are often painful, calloused, or even ulcerated. Evaluating pressure distribution on the plantar surface provides essential information on the functional impairment of the foot and ankle during gait, which may indicate the need for redistribution and reduction of tissue pressure in specific areas of the foot (HESS, 2002; BRASILEIRO *et al*., 2005).

In the public health system, diabetic foot treatment follows a specific protocol established by the MH with standardized guidelines. The Diabetic Foot Manual provides detailed guidance for treatment management, such as (HEALTH, 2016):

a) Topical intervention to accelerate wound healing and prevent recurrence. Topical treatment aims to keep the ulcer clean, moist, and covered, promoting the healing process;
b) Routine wound assessment by nurses or physicians to identify whether there is involvement of viable tissues (granulation and epithelialization) or nonviable tissues (dry and wet necrosis);
c) Patient and/or caregiver guidance for daily secondary dressing changes;
d) Use saline-moistened gauze (0.9% saline solution) and other dressings that cover the wound and promote a moist environment.

Dressings should be selected based on the predominant tissue type and the treatment priority at the time of wound assessment in cases of:

a) Tissue epithelialization without exudate: The area should be protected from sun exposure, and alcohol-free moisturizer should be applied. A thin layer of hydrocolloid can be used as a covering for up to 7 days, and essential fatty acids can be applied 1 to 2 times per day;
b) Granulating tissue with minimal or no serosanguineous exudate: Apply gauze moistened with 0.9% saline solution for 24 hours and change it daily. A thin layer of hydrocolloid can be used as a covering for up to 7 days;
c) Granulating tissue with moderate to heavy serosanguineous exudate: Apply gauze moistened with 0.9% saline solution for 24 hours and change it daily. Cover with calcium and sodium alginate, changing upon saturation or at least every 7 days;

d) Granulating tissue with moderate to heavy sanguineous exudate: Apply gauze moistened with 0.9% saline solution for 24 hours and change it daily. Cover with calcium and sodium alginate, changing every 2 to 3 days;
e) Dry necrosis / Eschar without exudate: The patient should be referred to an outpatient service for surgical debridement.

In summary, according to the MH protocol recommendations, to ensure effective and protective coverage of the diabetic wound, the material used must have the following properties: be capable of removing excess exudate (a protein-rich product released during the inflammatory process); maintain moisture between the wound and dressing; allow gas exchange; protect against infections; provide thermal insulation; be free from particles and toxic contaminants; and allow removal without causing local trauma (SILVA, 2021).

SUS protocol for diabetic foot management, proposed by SES-DF (2018), involves using appropriate coverings and applying occlusive dressings on the wound area. The coverings vary according to the ulcer's characteristics and may include alginate fiber, silver hydrofiber, silver foam (gold standard), petrolatum gauze, or activated carbon with silver. This medical protocol covers wound cleaning and dressing application, aiming to protect, absorb, and drain skin ulcers. The MH mandates that essential supplies for treating acute and chronic wounds be available in all Basic Health Units across the country (HEALTH, 2016; CALHEIRA, 2021).

Diabetic foot management is performed according to the risk presented, and the analysis and characterization of the ulcer determines the dressing type. The SUS uses four risk classifications: no additional risk, at risk, high risk, and the presence or absence of ulceration or infection (SES-DF, 2018).

3.2. Health Technologies

According to the MH, the concept of health technology refers to any intervention that can be used to promote health. This concept includes organizational and support systems within which healthcare is provided, as well as technologies that interact directly with patients, such as medications, equipment (biomedical technologies), and medical procedures, including anamnesis, surgical techniques, and technical standards for equipment use, which, together with biomedical technologies, are referred to as medical technologies (BRASIL, 2009; AMORIM *et al*., 2010).

In recent decades, improvements in quality of life and reductions in overall mortality have resulted from advancements in disease prevention, diagnosis, and treatment, which are

directly related to the increase in the production and adoption of new technologies. Despite the benefits achieved, this scenario has led to higher healthcare costs, such as the increase in per capita expenditure between 2001 and 2005 of 23% in Brazil, 29% in the United States, and 37% in Spain (SANTOS, 2010). This situation is justified by two main factors: the higher acquisition costs and the cumulative nature of health technologies. The former is due to the extensive research and development process, strict regulatory requirements, the technological complexity involved, and the low production scale. These combined elements significantly increase the market price of these technologies. The latter, the cumulative aspect, refers to the fact that, unlike other sectors where the introduction of new technology often replaces older ones, healthcare institutions commonly maintain, update, and operate both new and existing technologies. This increases operational costs, and each new technology may incur additional training, maintenance, and infrastructure expenses, thus aggravating total implementation costs (CAMPOS; DA MOTTA; ALBUQUERQUE, 1999).

The introduction of these technologies requires preliminary research to determine the clinical outcomes of interventions regarding efficacy (demonstrated benefit in controlled environments, such as clinical trials), safety, and effectiveness (benefit in real-world studies) before their application in healthcare systems (AMORIM *et al*., 2010). In this context, evidence-based medicine emerged, a term introduced by a group of researchers from McMaster University in Canada (JAMA, 1992). EBM is defined as the conscientious, explicit, and judicious use of the best available scientific evidence for appropriate decision-making in individual patient care (SACKETT *et al*., 1996). Evidence-based clinical practice established a new model for medical practice, replacing the previous one based on intuition, unsystematic individual clinical experience, and pathophysiological justifications without proper scientific validation (LOPES, 2000).

As a result of this new approach and the experiences in R&D&I of health technologies and, consequently, clinical practice, it has been observed that the National State generally acts as both an entrepreneurial and regulatory entity. As an entrepreneur, the state operates through funding, exchange rate adjustments, implementation of public policies aimed at the development and technological innovations in health, as well as specific budget forecasts for strategic project execution (MAZZUCATO, 2014). In its regulatory role, the state establishes norms to ensure the safety and efficacy of developed technologies, supervising the approval of drugs and medical devices through regulatory agencies, such as ANVISA in Brazil or the Food and Drug Administration (FDA) in the United States, and defining technical standards that companies must follow to bring their products to market.

Simultaneously, universities act as developers of products, using their scientific and technological expertise to conceive new technologies. The private sector, in turn, participates as the element that transforms scientific and technological developments into solutions that meet consumer needs while also ensuring compliance with the various regulatory requirements involved in this process. Lastly, society assumes the role of beneficiary of this cycle. However, it is known that the interaction between these entities alone does not ensure success; it is essential to implement strategies capable of overcoming challenges and bridging existing gaps (ROSA, 2022).

Innovation in health is traditionally linked to the production of new equipment and clinical procedures, as well as new preventive measures. To broaden the concept of innovation, it can be stated that the entire process of implementing new ideas, services, and products is involved in the process of competencies at different management levels with translational objectives (SILVA *et al*., 2014).

According to Salge (2012), *innovation* can be defined as the generation, development, and adaptation of new ideas in the form of new products, services, and processes. These definitions highlight the broad scope of innovation activities within institutions. It is essential to note that although technology is a valuable tool, it alone has not been able to solve issues of incompetence, negligence, and inaccessibility, particularly for low-income citizens (DOMINGUEZ, 2005). Given this scenario, Health Technology Assessment (HTA) emerged in the 1970s, serving as a link between scientific evidence and health service managers to generate reliable, transparent, and validated information that supports decision-making (BATTISTA; HODGE, 1999; BANTA; JONSSON, 2009). HTA aims to provide support for decisions regarding the dissemination and adoption of these technologies by managers, healthcare professionals, and patients. It is a multidisciplinary and interdisciplinary field that compiles knowledge about the application of health technologies in society, highlighting their short-, medium-, and long-term impacts. Within this field, reviews are conducted to encompass all existing scientific evidence, including aspects such as technical characteristics, safety, efficacy, effectiveness, cost, cost-effectiveness, implementation impact, as well as sociocultural, ethical, and legal considerations regarding the technology under evaluation (BANTA, 1997; GABBAY; WALLEY, 2006; AMORIM *et al*., 2010).

HTA has a strong connection with evidence-based medicine. However, while EBM primarily focuses on analyzing clinical outcomes to support decisions for individual patients, HTA conducts a broader evaluation, considering how the technology will be incorporated into healthcare systems, in addition to considering economic aspects (KRAUSS-SILVA, 2004).

Considering this integration, the MH has implemented two interconnected processes in the management of health technologies: (i) the production, systematization, and dissemination of HTA studies, and (ii) the establishment of a flow for the incorporation, exclusion, or modification of new technologies within the SUS. These processes are part of the National Policy for Health Technology Management, approved in 2009, with the objective of "maximizing health benefits to be achieved with the resources available to the system, ensuring equitable access for the population to effective and safe technologies" (SILVA; PETRAMALE; ELIAS, 2012).

Within this context, the present study highlights diabetes-related complications associated with diabetic foot, emphasizing the production and translation of innovative technologies such as the Rapha® medical device. Developed to accelerate wound healing in diabetic patients, Rapha is a portable device currently in Phase III clinical trials. The relevance of producing and translating effective technologies like Rapha® is directly aligned with the objectives of this work, which aims to explore public incentive policies and the R&D&I ecosystem that enable the creation of accessible and safe health solutions for the population.

3.3. Translational Health Research (THR)

2.3.1. Concept and Definitions

The advent of scientific research in health occurs in various forms, ranging from the description and conception of technology through pre-clinical laboratory research (basic research), observational studies, and clinical trials (clinical research) to its direct application to the population (patients). It is understood that a direct transition from studying individual cells or organ systems to patient testing is unsafe, introducing the field of translational research. This research bridges basic research and health innovation to ensure technology development through products like vaccines, drugs, non-pharmacological therapies, equipment, as well as services and policies that may benefit the population. In this context, translational research aims to apply laboratory findings and pre-clinical studies to the design and development of clinical trials, which are subsequently applied in clinical practice (DESANTANA, 2022; ARAUJO-JORGE; FERREIRA, 2022).

Discussions on the link between basic scientific knowledge and the development of innovative products and processes have roots in longstanding investigative practices but gained momentum with the Human Genome Project, launched in 1990. This milestone propelled the research field, which was consolidated with the publication of an editorial in the Journal of the

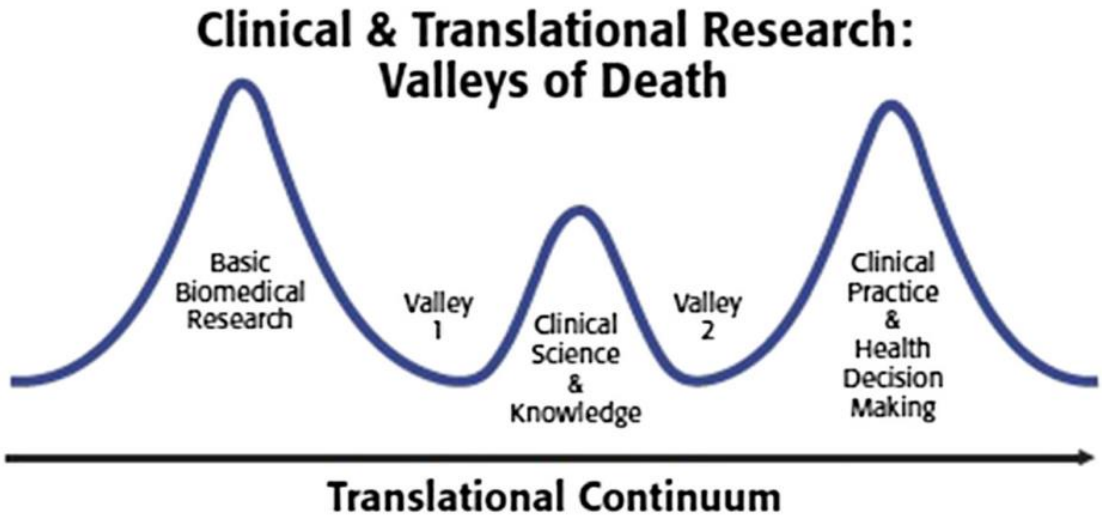
American Medical Association (JAMA) in 2002. The editorial emphasized the importance and necessity of applying advancements from basic research to improve patient health, thereby fostering innovations in the areas of disease prevention, diagnosis, prognosis, and treatment (ZERHOUNI, *et al*., 2005; DESANTANA, 2022).

Over the years, translational research has expanded beyond an exclusively clinical research field, broadening its scope and accelerating the development of new health technologies. The significance of this evolution is evidenced by the Publisher Medline (PubMed) index, which, through Medical Subject Headings, classified Translational Research as a subarea of Biomedical Research under the term "translational medical research" (WEHLING, 2006; BARRETO *et al*., 2019; SILVA, 2021).

This broadening of the translational research field has brought numerous benefits, such as an increased number of individuals participating in research and a more patient-centered approach. However, it has also revealed significant challenges, such as the high cost of projects, limited funding, and slow achievement of results. Considering these challenges, the symbolic expression "Valley of Death" emerged, alluding to the gap between the idealization of technology and its actual implementation, especially considering regulatory dimensions. In translational research, this analogy refers to the difficulty of incorporating research results into healthcare systems. Thus, whether in R&D&I or THR, the term reflects the failure to complete the entire cycle of scientific innovation development and application, demonstrating an inability to ensure that findings translate into tangible benefits for patients and the healthcare system (KASLOW *et al*, 2018; ROSA, 2022).

Figure 1 illustrates the Valleys of Death, as described by the Canadian Institutes of Health Research. The two proposed valleys may arise between the three phases of translational research. The first, "Valley 1," refers to the limited capacity to translate results or findings from basic research in the lab into clinical practice, while the second, "Valley 2," points to the limited ability to synthesize, disseminate, and integrate research results into health decision-making and clinical practice (REIS; MCDONALD; BYERS, 2008; CIHR, 2011; FARRAGHER *et al*., 2015).

Figure 1 - “Valleys of Death" in Translational Research



Source: Reis; Mcdonald; Byers, 2008; Cihr, 2011; Farragher *et al*., 2015.

Fernandez-Moure (2016) delves deeper into this issue by identifying two "Valleys of Death" in the translational context, emphasizing the importance of funding at different stages of the process. The first, "Valley 1," addresses the lack of resources to advance proven technologies to the human testing stage, while "Valley 2" relates to the shortage of funding in the costliest phase: human trials.

Kaslow *et al*. (2018) further observes that innovative products risk failing to progress beyond the proof-of-concept stage due to a lack of market interest, especially for emerging diseases predominantly affecting populations in poor and developing countries. Seyhan (2019), in turn, emphasizes the growing gap between basic and clinical research, referring to the "Valley of Death" in translational research. This gap highlights the challenge of transforming laboratory findings into practical human applications, a central concern for academia and industry.

The "valley of death" is saturated with programs, practices, procedures, products, and policies supported by research and evidence established by health experts. Simultaneously, many of these findings remain unimplemented, awaiting incorporation into real clinical practice settings. Parallelly, it is estimated that 30% to 40% of patients lack access to treatments with proven efficacy, while 20% to 25% are subjected to unnecessary or potentially harmful interventions (MCGLYNN *et al*., 2003; GEEST *et al*., 2022).

Balas and Boren (2000) pointed out that only 14% of published evidence reaches clinical practice, and the gap between discovery and effective implementation typically lasts an average of 17 years. This inertia increases waste associated with research (GEEST *et al*., 2022).

Translational research plays a fundamental role in overcoming the so-called "valleys of death" in science and medicine. With an integrated and patient-centered approach, it serves as an indispensable link between laboratory discoveries and their practical application in clinical settings. Although challenges exist, such as high costs, slow results, and funding barriers, this type of research undeniably offers a more effective solution for translating scientific evidence into tangible clinical interventions. By accelerating the implementation of proven-effective treatments and reducing unnecessary or potentially harmful interventions, translational research contributes to optimizing patient care, reducing research waste, and maximizing returns on investment in science and innovation. In sum, it is a vital tool for bridging the gaps of the "valleys of death," ensuring that scientific discoveries promptly meet the needs of patients and the healthcare system as a whole (SEYHAN, 2019).

3.3.2. Stages of Translational Research

THR can be understood as a set of actions and activities aimed at transferring results obtained in basic research to the approval of technologies that are then made available to users/patients. This research demonstrates the interdependence and integration among the stages in the production chain for developing a health technology (GUIMARÃES, 2013). In this sense, THR emerged to reduce the gap between basic research and its clinical application. Translational research is divided into five temporal stages, identified as T0 to T4, which must be completed for research to yield practical health outcomes that benefit society. This structure is promoted by the NIH Roadmap, an initiative developed by the National Institutes of Health (NIH) and launched in 2004. The NIH Roadmap aims to accelerate the discovery, development, and application of new technologies and approaches in biomedical science and clinical practice.

Among theoretical approaches to THR, T-time is used as a guiding model for translation. One example is the study by Khoury *et al*. (2010), which defines the "epidemiology and phases of translation and knowledge synthesis—from discovery to impact on population health," as illustrated in Table 1, adapted from Rosa (2022).

Table 1 - Translational model with phases T0 to T4.

Phase	Details	Role of Epidemiology	Examples in Genomics
T0	Description and Discovery	Role of Epidemiology by place, time, and person; identifying determinants of health outcomes through observational studies.	Describing patterns of health outcomes concerning inbreeding, migration, and family history to generate hypotheses about genetic factors; genome-wide association studies as a tool for gene discovery.

T1	From discovery to health applications (tests, interventions)	Characterizing discovery and evaluating potential health applications using clinical and population studies.	Assessing prevalence, associations, interactions, sensitivity, specificity, and predictive value of testing for genetic risk factors.
T2	From health application to evidence-based guidelines	Assessing the effectiveness of interventions to improve health and prevent disease through experimental, observational studies.	Evaluating the clinical utility of genetic risk factors in improving health outcomes.
T3	From guidelines to health practices	Evaluating the implementation and dissemination of guidelines in practice.	Assessing factors associated with the implementation of BRCA testing in practice.
T4	From health practice to population health outcomes	Evaluating the effectiveness of interventions on health outcomes.	Assessing the effectiveness of neonatal screening programs.
Knowledge Synthesis	Systematic review of what is known, unknown, and how it is known.	Knowledge synthesis applies to all phases of translation through evidence synthesis and systematic reviews.	T1 - Assessing the credibility of genetic associations and evaluating genetic effects and interactions (via HuGENet). T2 - Systematic reviews on the clinical validity and utility of genomic applications for specific intended uses (via EDAPP assessment).

Source: Adaptation of Khoury *et al*. (2010) by Rosa (2022).

According to Rosa (2022), the above model includes the element of knowledge synthesis or systematic review in addition to T4, a tool used in epidemiology. This concept was incorporated into THR to support the formation of its scope by intercalating phases from T0 to T4. The model presented by Khoury *et al*. (2010) represents the epidemiological process for interpreting translation and has been adopted in previous studies to map THR in other areas of translational research. Thus, knowledge synthesis does not follow rigid temporal linearity, but rather, it is used to review aspects of different phases in the research cycle and enhance technology development within the context of epidemiology.

The THR process encompasses laboratory, clinical, humanistic findings, and interventions, which are applied both in public health and individual healthcare settings. These findings and interventions may include results from basic research, such as studies with cells, tissues, or animal models; results from clinical trials conducted on humans to test the efficacy and safety of new therapies, diagnostics, or interventions; elements related to the impact of interventions on patients' quality of life, including social, behavioral, and ethical factors; and products and processes like diagnostics, therapies, medications, behavioral changes, and medical procedures, always aiming to improve disease diagnosis, treatment, and prevention. This concept is based on the definition provided by the National Center for Advancing Translational Sciences, which describes this process as involving various interconnected stages, emphasizing the focus on health outcome improvement and innovation.

In this context, it is essential to encourage and enhance R&D&I projects, promoting interdisciplinary and multidisciplinary integration and collaboration between research institutions and the business sector, both public and private. Support can come from funding sources and calls for proposals with projected outcomes for this type of basic research related to an effective connection with the subsequent research or development stage. In this research production environment and product safety assessment for health, the T0 stage represents the initial phase, focused on the conception, description, and discovery of new interventions, technologies, or therapies. Next, T1 and T2 stages correspond to preclinical and clinical studies, where findings' feasibility, safety, and efficacy are tested, initially in the laboratory and later in clinical trials with larger populations. In T3, results are integrated into regulatory systems, infrastructure, and health sector practices to facilitate the technology's implementation and commercialization. Finally, in T4, the technology is made available to the healthcare system and evaluated in terms of its impact on society, measuring its practical effectiveness and contribution to public health (FELIPE, 2020).

The transition from T2 (clinical trials) to T3 (effectiveness research, regulatory approval, and product commercialization) consolidates the initial stages' outcomes, culminating in the product's registration by the ANVISA and the National Institute of Metrology, Quality, and Technology (INMETRO, abbreviated from Portuguese, “Instituto Nacional de Metrologia, Qualidade e Tecnologia"). It is known that the shorter the time required to bring a product to market, the better the practical application of scientific knowledge, especially in multicenter studies involving collaboration from various research centers. This means that by reducing the time it takes for a new technology or treatment to reach the market, scientific results can be applied more quickly and effectively, benefiting more people. However, this process directly depends on various factors, such as funding actions, public health policies, industry involvement, and technology integration into healthcare systems, among others, which directly influence the success of THR. Additionally, the success of clinical study approval depends on protocol validation by ANVISA and INMETRO, as well as minimizing technical requirements and additional corrections, which can delay the product registration process (FELIPE, 2020; ROSA, 2021).

Finally, it is noted that translational research does not follow a linear path; this is a fundamental characteristic for appropriating the theoretical-methodological model of THR in biomedical engineering (ROSA, 2021), as exemplified by knowledge production, which occurs in parallel with preclinical and clinical analyses. Therefore, establishing evaluation metrics for THR becomes essential to frame each stage and monitor technology development properly.

3.3.3. Average Duration of THR

The duration of THR is a determining factor for effectively applying scientific discoveries to benefit patients. However, the time required for these innovations to be incorporated into clinical practice can vary significantly between countries, reflecting disparities in regulatory systems, research infrastructures, and public and private investments (ARAUJO-JORGE; FERREIRA, 2022).

The scientific literature reveals that drug development, particularly for oncology, is among the most extended processes within THR. Studies indicate that the average time to bring a cancer drug to market ranges from 10 to 11 years, depending on the type of cancer. For instance, the development of drugs for breast, lung, and prostate cancers took an average of 11, 10, and 10.4 years, respectively (UYGUR *et al*., 2017). Moreover, a broader analysis of studies on general biomedical research shows that the average time from initial discovery to clinical application is 17 years, underscoring the slow pace of the translational process (UYGUR *et al*., 2017).

In Brazil, translational research faces similar challenges. Between 2012 and 2019, the SUS included five biological agents for treating rheumatoid arthritis, with an average timeline of 11 to 13 years from clinical development to SUS utilization. This timeline is comparable to that observed in other international contexts. However, Brazil has specific requirements, such as evaluation and approval by the ANVISA and the National Commission for the Incorporation of Technologies in the Unified Health System (CONITEC, abbreviated from Portuguese, “Comissão Nacional de Incorporação de Tecnologias no SUS”), which may add additional steps to the process (LUPATINI, 2022).

In the United States, the process is similarly lengthy and costly, with timelines ranging from 10 to 15 years and requiring millions of dollars in financial investment. Additionally, regulatory approval from the FDA is needed (MORGAN *et al*., 2011). Studies show that approximately 12% of experimental drugs entering clinical trials are eventually approved by the FDA, highlighting the high failure rate in advanced phases of clinical testing (SCHUHMACHER; GASSMANN; HINDER, 2016). Therefore, translational research in the U.S. faces significant challenges in terms of time and cost, impacting the speed with which new therapies reach the market (VAN NORMAN, 2016).

In Europe, the scenario is similar, although there are coordinated efforts to optimize the translational research process. The European Commission, the European Medicines Agency, the Innovative Medicines Initiative, and the European Infrastructure for Translational Medicine

are some of the primary entities seeking to facilitate the transition from basic research to clinical application (AARDEN *et al*., 2021). Studies show that, in Europe, the average time for translating scientific discoveries into clinical practice can also be as long as 17 years, depending on the type of medication and the complexity of the disease (BUXTON *et al*., 2008; HANNEY *et al*., 2020).

Translational research is vital for health innovation but faces considerable challenges regarding time and cost. In response to these temporal challenges, efforts have been directed toward reducing the average translation time through initiatives that involve multidisciplinary cooperation, the conduct of robust clinical trials, and the improvement of regulatory efficiency (CONTOPOULOS-IOANNIDIS *et al*., 2008; AARDEN *et al*., 2021; ARAUJO-JORGE and FERREIRA, 2022).

In summary, although THR involves a long and complex process, its benefits for public health justify efforts to optimize each stage and ensure that scientific advancements reach patients more quickly and efficiently.

3.3.4. Actors in Translational Research

The healthcare sector possesses characteristics that make its innovation system unique. Direct interaction with various actors—including research institutes, industries, the three levels of government, municipal, state, and federal councils, professional commissions and boards, and civil society representatives—is essential for discussing and fostering participation in decisions regarding the creation, dissemination, and use of new knowledge in research (COSTA *et al*., 2016; RIVERA; ARTMANN, 2012). Additionally, the health field is distinct from others by incorporating innovations and technologies that often do not replace but complement existing ones, contributing to rising costs. For instance, innovations such as tomography and ultrasound did not eliminate the use of X-rays. In this context, the HTA presents itself as an indispensable tool to aid managers in decision-making regarding adopting new technologies and avoiding the introduction of technologies with uncertain cost-benefits for healthcare systems. Health technologies include any intervention aimed at health promotion, disease prevention, diagnosis, or treatment, as well as rehabilitation and long-term care (TOPFER; CHAN, 2006). It is crucial to systematize available information to guide decision-makers and policymakers (SILVA *et al*., 2010; CAVALCANTI, 2019).

When addressing the use of new knowledge, Gibbons *et al*. (1994), in their book *The New Production of Knowledge*, discuss new forms of knowledge generation, contrasting the former mode of production, called Mode 1, with the new Mode 2. Mode 1 is associated with

the classic form, generated within a disciplinary and cognitive context, more closely linked to conventional academic practices. Mode 2, on the other hand, encompasses broader social and economic contexts and is characterized by interdisciplinary relationships, as observed in translational research programs.

In the context of Mode 2, research programs, such as translational programs, face numerous challenges, spanning from research and knowledge production to program management and technological development, which must be overcome to ensure the effective implementation of new technologies. It is important to emphasize that the effective implementation of new technologies for the benefit of the population is a particularly complex challenge, especially in healthcare. The challenging interaction between healthcare systems — particularly those where the state plays an almost monopolistic role in serving the most vulnerable populations — the domestic and international health industry and development sectors in Brazil presents significant challenges for translational research initiatives. Certain actors play a transversal role throughout the entire process, such as universities and research institutions, in addition to government agencies like the MH, the ANVISA, and private institutions. These actors are not limited to a single phase or function but are broadly involved in all crucial areas of the process, ensuring a connection between science, innovation, and public policy (CAVALCANTI, 2019).

The connection between scientific research and the productive sector, represented by private enterprise, is fundamental. In Brazil, due to historical processes, the R&D&I sector has developed more strongly within the public sector, while the private sector, considered the "natural cradle" of innovation, has played a smaller role. Universities and research institutes are key actors in the production, dissemination, transformation, and advancement of scientific and technological knowledge, and they are also committed to transferring technology to society (CAVALCANTI, 2019). Furthermore, partnerships between the MH and universities are essential for developing and producing technologies to meet the population's health needs. These collaborations encourage the transformation of ideas into products, processes, and protocols that can be incorporated by both the public healthcare system and the private sector. Disseminating these initiatives is essential to promote innovation and ensure that technological advancements benefit the largest number of people possible (FELIPE *et al*., 2019).

Innovation can also be understood as a system integration model realized through cooperation networks between private initiatives and institutions. This model involves the complementation and collaboration of different actors in the innovation process, who, through continuous learning, accumulate knowledge and interact systemically (BRITTO, 1999;

CAVALCANTI, 2019). A recent example of this concept is Industry 4.0, which illustrates how advanced technology integration and collaboration among various sectors can drive innovation. The interaction between these actors and the productive system is a channel with great potential to promote industrial, technological, and economic development through THR.

3.4. Research, Development, and Innovation (R&D&I)

The concept of R&D&I is widely recognized in Brazil and supported by various laws, manuals, and guidelines. According to the Basic Manual for R&D&I Partnership Agreements (2010), R&D&I encompasses both basic and applied research, along with experimental development, always adhering to a specific plan and in compliance with established regulations (PIMENTEL, 2010). R&D&I involves applying technical and scientific knowledge in economic sectors to create new materials, equipment, products, processes, or services through inventions or enhancements (CARVALHO, 2016).

This study establishes the adopted concept of technological innovation in Article 17, paragraph 1 of the Good Law, Law No. 11,196, dated November 21, 2005. This legislation defines innovation as the creation of a new product or manufacturing process, as well as the addition of new functionalities that result in substantial gains in quality or productivity, ultimately leading to increased market competitiveness (BRASIL, 2005).

Unlike conventional projects, R&D&I projects are characterized by their long-term and high-risk nature. Many of these projects span decades and set ambitious goals, which may not always yield the expected results. As such, managing these projects demands caution and continuous commitment to ensure their progress and desired outcomes (MANFREDINI, 2018).

The relationship between SUS and Science and Technology policies in health evolved nearly parallel to SUS's own development. A significant milestone was the first Conference on Science and Technology in Health, held in 1994, which, among its highlights, established that health Science and Technology policy is part of the national health policy. Additionally, the creation of a specific department within the MH was proposed, which was only realized in 2003. In 2004, the second conference, held in Brasília, outlined a policy and an agenda of research priorities (BRASIL, 2017).

Health research policy within SUS includes: (1) health-disease transitions, covering basic, individual, and collective determinants; (2) health systems and policies; (3) intersectionality and the relationship between health, society, and development. Research within SUS must encompass biomedical, clinical, epidemiological, and social sciences components, including health policy, planning, and management. This perspective highlights

the importance of a clear connection between SUS managers and the formulation and promotion of health research in Brazil, given SUS's significant role in the health market (GUIMARÃES *et al*., 2019).

SUS plays a crucial role as it is responsible for approximately one-third of the pharmaceutical market, 90% of the vaccine market, half of the medical equipment market, and the entirety of constitutionally guaranteed health services for the population. Furthermore, according to National Council for Scientific and Technological Development data, human health is strongly represented in most graduate programs, with the largest contingent of students, professors, and researchers dedicated to research lines (GUIMARÃES *et al*., 2019).

In biomedical research, challenges arise in attempting to understand disease complications, including non-communicable chronic diseases. The Brazilian public health sector intertwines with the evolution of national scientific and technological development, dating back to 20th-century sanitary and bacteriological medicine, emphasizing experimental research (ROSA; DOMÍNGUEZ; GUIMARÃES, 2017).

R&D&I projects are primarily conducted at universities in partnership with industry, encouraged by national and state policies. This cooperation connects government, industry, and academia (BARBALHO, 2008).

Within the academic environment, articles, papers, courses, and outreach activities are considered technical and technological products arising from R&D&I efforts. However, more tangible innovations, such as patents and technology transfers, represent the transformation of research into practical products for healthcare systems, which depends on private-sector collaboration. The relevance of innovation becomes more evident when research moves beyond the laboratory and aligns with regulations, such as those established by ANVISA, paving the way for implementation within healthcare systems.

The concept of the Triple Helix, which emphasizes the interaction between government, universities, and industry, has become a central pillar in scientific and technological development (ETZKOWITZ, 2009). This model was later expanded to include society, not only as the final recipient of innovation but as an active agent and co-creator within the innovation ecosystem. Thus, the Quadruple Helix concept emerged, integrating society as the fourth and vital pillar. This paradigm reflects the importance of genuine co-creation, open dialogue, and collective knowledge-building, aiming for more democratic and adaptive innovation systems. However, the continuous advancement in understanding innovation has introduced the Quintuple Helix, which, in addition to the previously mentioned actors, incorporates the

environment or ecology, recognizing that genuinely innovative solutions must be sustainable and benefit society and the environment (MINEIRO, 2019).

In sum, R&D&I represents a strategic pillar for Brazil's socioeconomic advancement, with profound influence and impact on the health sector, guided by collaborative models such as the triple, quadruple, and quintuple helixes.

3.5. Ethical and Regulatory Aspects for Medical Devices

According to Gomes *et al*. (2012), clinical research in Brazil is overseen by two main regulatory bodies: the National Health Council and ANVISA. The National Health Council is a permanent deliberative council composed of government representatives, service providers, healthcare professionals, and users. Its primary function is to formulate strategies and oversee the execution of health policies in Brazil, in addition to regulating issues related to the ethical aspects of clinical research in the country. ANVISA, in turn, is the authority responsible for formulating and enforcing sanitary regulations[2] related to conducting clinical trials in the country. Its primary duties in this area include implementing and monitoring trials aligned with good clinical practices, reporting adverse events, granting import licenses, approving studies and sites, and evaluating the methodological criteria of clinical protocols.

The regulation of clinical studies in Brazil began only in 1996 with the publication of Resolution 196/96, although the first attempt to standardize the ethical aspects of clinical research occurred in 1988. In addition to creating the National Research Ethics Commission (CONEP, abbreviated from Portuguese, "Comissão Nacional de Ética em Pesquisa"), this resolution established the requirement for prior study approval by Research Ethics Committees (CEP, abbreviated from Portuguese, "Comitê de Ética e Pesquisa"). Important criteria were also established for conducting the studies, such as the prohibition of compensation for volunteers and ensuring access to the benefits resulting from the research. The CEPs are responsible for the initial review of clinical research's ethical implications, and they may be organized into one or more units of analysis, depending on the needs of research institutions. Additionally, CONEP may designate another institution to analyze the protocol when the institution conducting the research does not have its own CEP (GOMES *et al*., 2012).

---

[2] The main difference between ethical and sanitary regulation is that the former evaluates any epidemiological study, while only those aimed at product registration are subject to sanitary regulation. From an analytical perspective, however, the common purpose —protecting the research subject — can lead to overlapping responsibilities. In practice, any ethical issues identified by ANVISA are usually referred to CONEP.

The creation of the CEP/CONEP system was considered a significant advancement, contributing to the development of clinical research capacity in Brazil and the country's integration into the international R&D&I market, particularly regarding the development of new health products and technologies in the late 1990s and early 2000s (GOMES *et al*., 2012).

ANVISA initially considers the pertinence of regulating a device, depending on whether it falls within the scope of medical devices requiring regulation (BRASIL, 1976).

According to ANVISA's RDC No. 185/2001, the classification of medical devices must consider their primary purpose. These devices may be intended for the prevention, diagnosis, treatment, or rehabilitation of diseases, injuries, or disabilities, as well as for contraception, non-superficial aesthetic modifications, or for the cleaning and disinfection of other medical technologies.

Still, according to RDC 185/2001, there are cases where confusion may arise between classifying a product as a medical device or a medication, depending on the technology used. Regarding technology, a medical device cannot have pharmacological, immunological, or metabolic mechanisms as its primary mode of action, although it may be supported by these means. In cases where the primary function is achieved through pharmacological action, the product will be classified as a medication. However, if the device fulfills its primary function through its physical characteristics, it will be considered a medical device, even if it uses pharmacological substances complementarily (FARIAS, 2022).

Medical devices are divided into two major groups: medical-use materials and healthcare equipment, excluding in vitro diagnostic products, which have specific regulations. The latter include reagents, calibrators, standards, controls, sample collectors, and other materials used in in vitro analyses of human samples to provide diagnostic information, monitoring, screening, or compatibility with potential blood, tissue, and organ recipients (ANVISA, 2001).

Medical products can be further subdivided into two main categories. The first includes non-active medical devices, which do not rely on electrical or any energy source other than that generated by the human body or gravity. Examples include orthopedic implants, surgical instruments, heart valves, stents, and condoms, among others. The second category refers to healthcare equipment that requires electrical or another energy source to operate, using it to perform its functions. This category includes medical devices used for diagnostics, rehabilitation, monitoring, or therapy for both medical and aesthetic purposes. Examples include physiotherapy, dental, and laboratory equipment. Finally, there are non-active medical

devices, such as wheelchairs, hospital beds, and surgical tables, which are essential to healthcare support but do not require energy sources for operation (FARIAS, 2022).

In conclusion, the regulation of medical devices in Brazil, conducted by ANVISA and supervised by the CEP/CONEP system, plays an essential role in ensuring that health products are developed and applied safely and effectively. From rigorous classification, considering both function and technology involved, to the clear distinction between medical devices and drugs, this regulatory system is fundamental to ensuring that technological innovations in healthcare benefit society ethically and responsibly. Furthermore, the development and regulation of medical products and technologies, combined with good clinical practices and ethical reviews, reflect Brazil's commitment to integrating into the international R&D&I landscape, promoting advances that are essential for both public health and the private sector.

3.5.1. ANVISA Regulation

According to ANVISA Resolution RDC 185:2001 requirements, the regulatory process for health products must follow a classification-based procedure, depending on the type of device or equipment. Products are classified according to the intrinsic risk they could carry to the health of consumers, patients, operators, or third parties involved and are categorized into Classes I, II, III, or IV, from lowest to highest risk. Moreover, classification rules are determined based on invasiveness, duration of contact between the material and the patient, and the anatomy of the affected area, which are essential criteria for the proper use of the device. Among the fundamental principles considered for classification are the possible consequences for the body in case of failure, the purpose of its application, and the technology used in its development. Once the product is correctly classified and its field of use understood, the health product can be appropriately categorized. According to ANVISA Resolutions RDC 185:2001, RDC 40:2015, and RDC 270:2019, the regulatory processes for medical devices with ANVISA are divided into two groups based on their risk classification: low- and medium-risk products, classified as Risk Classes I and II, which are subject to Notification processes, and high- and maximum-risk products, Risk Classes III and IV, which must undergo Registration processes.
According to the requirements of ANVISA RDC 40:2015 and RDC 270:2019, the documentation for the Notification process includes a Petition Form with the product's technical and commercial information, accompanied by an attached file with images and graphic and additional information, if necessary. The documentation also includes copies of technical-administrative documents, such as the Certificate of Good Manufacturing Practices for Medical Products and the Manufacturer's Authorization Letter. For imported products, a Certificate of

Compliance is required, according to the requirements of the Brazilian Conformity Assessment System (SBAC, abbreviated from Portuguese, “Sistema Brasileiro de Avaliação da Conformidade”). Thus, the regulatory holder must keep the technical documentation available to health authorities, even if prior submission to ANVISA is not required. Required documents include the Project and Development report, including relevant validations, manufacturing details and controls applied, Models of Instructions for Use and Labeling, and evidence related to Risk Management, among others. A Clinical Evaluation is also required, consisting of (1) a general summary of clinical evidence, which is applicable when clinical evidence is required due to the demonstration of safety and efficacy for technological innovations and new usage indications, and (2) relevant clinical literature, specifically for Class II Risk products. In some cases, additional documents are necessary to demonstrate product safety and efficacy, especially in situations of public health risk or when the product is considered strategic by the MH (FARIAS, 2022).

In the Registration process for medical devices, according to ANVISA RDC 185:2001, a more extensive set of documents is required. Thus, the registration of a medical device must include: (1) Manufacturer or Importer Form for Medical Products, containing commercial and administrative information about the products and company; (2) Labeling Model; (3) Instructions for Use Model; (4) Technical Report; (5) Comparative Table of Products, in cases of varied commercial presentation or product family; (6) Certificate of Compliance, for products subject to mandatory certification under SBAC; (7) Manufacturer’s Authorization Letter, in the case of imported products; (8) Free Sale Certificate in the country of origin, also for imported products; and (9) Certificate of Good Manufacturing Practices and Health Product Control, for the manufacturing units/locations of the product in question.

Additionally, the Technical Report document is noteworthy, as it must meet the requirements of Appendix III.C of ANVISA RDC 185:2001. This document must be prepared by the regulatory holder in Portuguese in a confidential manner and contain complete technical information on the evidence related to the safety and efficacy of the medical device for regulation purposes. This document includes contextual information about the medical device and information related to the clinical evaluation of the device per safety and efficacy requirements set by ANVISA, currently outlined in ANVISA Resolution RDC 546:2021. Also included are all indications and contraindications for use, adverse events, and other relevant information for the product’s use, detailed in the Instructions for Use and User Manual. Finally, data related to preclinical and clinical trials must be presented (ANVISA, 2001; ANVISA, 2021).

Evidence of compliance with essential requirements should not be limited to a statement from the manufacturer affirming that the requirement has been fulfilled. Certificates, reports, test results, validation outcomes, manufacturing and control procedures descriptions, information on design features, comparative studies, special specifications for raw materials, and others must be provided as evidence of compliance with essential requirements. All documents submitted to prove compliance with fundamental requirements must have technical and scientific backing to be accepted as a valid justification. When there are not enough scientific publications, the company must present its own studies that resulted in the product specifications (ANVISA, 2001; ANVISA, 2021).

ANVISA verifies notification processes on a sampling basis, while Registration processes are analyzed by agency experts (ANVISA, 2019). Thus, the analyses conducted by the Agency may be approved or rejected according to regulatory requirements. When gaps or additional information needs are identified, ANVISA may issue a Technical Requirement, a technical-administrative procedure requesting data supplementation by the manufacturer or importer. This procedure, while necessary to ensure the device's safety and efficacy, can extend the review time and reduce the efficiency of the regulatory process, primarily due to the uniqueness and complexity of each process, as well as the specific clinical evidence required for approval (NASCIMENTO, 2019; ANVISA, 2022a).

According to Technical Note 004 from ANVISA's General Management of Health Product Technology, issued in 2016, specific clinical trials must be presented for innovative or Class III and IV products in the following cases:

> *"I – Innovative health products, regardless of their risk class (innovation in design, raw material, intended use, among others); II – Class III and IV health products that, due to their unique nature and performance closely linked to material design and manufacturing process, require verification of safety and efficacy using specific clinical data of the requested product."*

Regarding valid safety and efficacy measures, the specific clinical investigation must present a methodology that enables the intended clinical performance to be achieved. In this context, process approval will be based on the level of required evidence, device characteristics, indications, contraindications, and degree of innovation, for instance (FARIAS, 2022).

Therefore, the regulation of medical devices with ANVISA depends on a range of factors, including preclinical and clinical research results, indications, contraindications, and

product complexity, mainly when intended to treat specific or rare clinical conditions. Attention to safety and efficacy criteria is essential for successful regulation of these devices.

3.5.2. INMETRO Product Certifications

As established by ANVISA in RDC 546:2021, certain medical devices are subject to certification under the SBAC as one of the requirements to demonstrate compliance with the essential safety and efficacy standards set by ANVISA. Under SBAC, the INMETRO is responsible for managing Conformity Assessment Programs.

INMETRO is a federal agency linked to the Special Secretariat for Productivity, Employment, and Competitiveness within the Ministry of Economy and is responsible for regulating and overseeing the accreditation process for Product Certification Bodies (PCB), also known as certifiers. These certifiers carry out activities related to product certification and are responsible for issuing compliance certificates validated by INMETRO. Certification activities include product testing, analyzing test reports conducted by international laboratories (for products manufactured abroad), and conducting audits. Additionally, it is the responsibility of INMETRO, through its ordinances, to regulate the requirements for the operationalization of activities to be carried out by certifiers in response to the need for product certification, as required by ANVISA (INMETRO, 2022).

It is important to note that both ANVISA and INMETRO have responsibilities in the compulsory certification process for medical devices (INMETRO, 2022). ANVISA determines the need for mandatory certification of medical devices through the publication of specific RDC. At the time of product regularization with ANVISA, the Certificate of Compliance submission is mandatory (ANVISA, 2001). Examples of products subject to compulsory compliance certification in Brazil include breast implants, syringes, electromedical equipment, infusion sets, and latex male condoms.

In summary, the certification process for medical devices in Brazil, regulated by ANVISA and managed by INMETRO, plays a crucial role in ensuring the safety and efficacy of products used in the healthcare system. Through rigorous assessment and conformity mechanisms, such as testing, audits, and analysis of technical reports, it is ensured that medical devices, from electromedical equipment to implants, meet the required quality standards before being made available on the market. This collaboration between ANVISA and INMETRO not only reinforces trust in certified medical products but also protects public health by ensuring that only safe and effective technologies are used in the country, thereby playing a vital role in technological development and innovation in the healthcare sector.

3.6. Tools for Fechnology Maturity Assessment

The development of innovative technologies requires a careful and systematic maturity analysis using tools that evaluate essential strategic, technical, and regulatory aspects for product market entry. Tools such as the SWOT matrix (Strengths, Weaknesses, Opportunities, and Threats), TRL (Technology Readiness Levels), RRL (Regulatory Readiness Levels), HRL (Human Readiness Levels), and MDRL (Medical Device Readiness Levels) contribute to organizing and executing targeted strategies at each stage of maturity. These approaches are fundamental to guiding decisions that drive technological advancement, especially in sectors that demand rigorous market and regulatory entry (MANKINs *et al*., 1995; SOUZA *et al*., 2013).

For a technology to establish itself competitively in the market, it is necessary to map its advantages and challenges from the early stages of development. Among these tools, the SWOT matrix, also known as Strengths, Opportunities, Weaknesses, and Threats, stands out for offering a valuable strategic framework to assess both the internal and external environments of technology, identifying strengths and weaknesses in terms of competitiveness and innovation (Souza *et al*., 2013). The SWOT matrix is divided into four main components: strengths represent the technology's internal advantages, such as innovation or skilled resources; weaknesses indicate internal limitations, such as lack of experience or resource scarcity; opportunities are favorable external factors, such as increased demand or positive regulatory changes; and threats represent external risks, such as new competitors entering the market or restrictive regulations (SOUZA *et al*., 2013; BENZAGHTA *et al*., 2021).

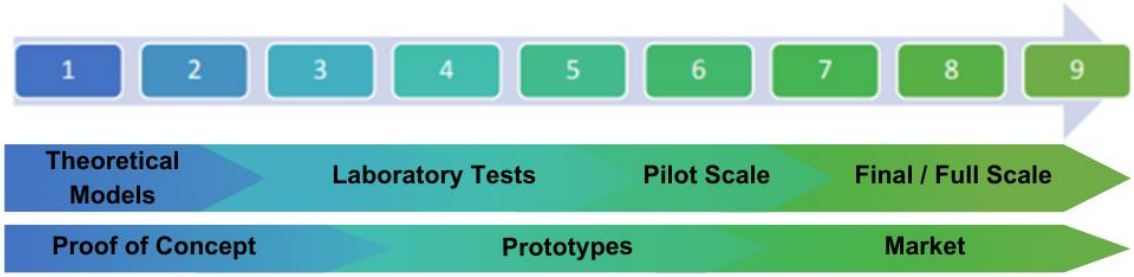
When applied in the context of technology maturity, this tool allows researchers and managers to identify contextual factors that directly influence the feasibility and acceptance of emerging technologies, enabling adjustments in development according to market needs (CAPDEVILLE *et al*., 2017; BENZAGHTA *et al*., 2021). Thus, SWOT becomes essential alongside technical tools such as the TRL, RRL, HRL, and MDRL scales, assisting in creating adaptive strategies that ensure the technology progresses toward commercialization and market sustainability.

With the strategic diagnosis provided by the SWOT matrix, it is possible to move forward to a technical analysis that guides development based on technology maturity stages. The Technology Readiness Levels/Manufacturing Readiness Levels (TRL/MRL) scale, described by Mankins *et al*. (1995) and adapted for different sectors, structures the

technological and regulatory maturity stages necessary to ensure the final product's maturity and safety.

The TRL tool, developed by National Aeronautics and Space Administration (NASA) in the 1970s, aims to standardize the innovation process in technology companies by using a technological maturity scale (MANKINS *et al*., 1995). This tool assesses a technology's maturity level across nine levels, ranging from initial research to proven implementation, as shown in Figure 2. This allows detailed monitoring of technological development, evaluating progress at each stage and highlighting specific technical needs for the technology to advance levels, as well as enabling direct comparisons between different products (VALENTE, 2021). Capdeville *et al*. (2017) point to the effectiveness of TRL in sectors that require continuous monitoring and precise organization of readiness levels.

Figure 2 - R&D&I Program and Technology Readiness Levels.



Source: Author's Own Work.

Despite its relevance, TRL has limitations when applied to specific sectors, such as medical devices, due to its origin in aerospace engineering. In response, the US Army Medical Research and Materiel Command attempted to address this limitation by mapping TRL descriptions for health product development (U.S. Department of Defense, 2009). A simplified example of this adaptation can be seen in a therapeutic candidate, which progresses through TRLs 1 to 4, involving basic research and preclinical studies; advances to TRL 5, which includes clinical trials; and passes through TRLs 6 to 8, covering clinical trials and submission for approval by regulatory agencies, culminating in the product's launch (TRL 9), followed by post-marketing studies and surveillance.

Although the TRL adapted by US Army Medical Research and Materiel Command is helpful, it still does not offer the necessary detail for academic researchers to advance with regulatory requirements to make medical devices available within the healthcare system. According to Webster and Gardner (2019), the TRL scale, when applied to the pharmaceutical sector, lacks the granularity and depth necessary to cover the quality requirements and clinical

guidelines needed for drug development, especially between TRLs 4 and 7, stages known as the "Valley of Death," where many projects fail to reach commercial potential. It is suggested that this lack of detail explains its relatively low acceptance in pharmaceutical and academic development programs.

An adaptation of the TRL scale with a greater emphasis on regulatory stages could substantially improve decision-making in translational research. Harris and O'Reilly (2020), in their studies, identified that many academic researchers and specialists lack the training, knowledge, or experience necessary to engage in regulatory pathways, and there is a lack of clarity about the regulatory requirements associated with commercializing basic scientific research, making it essential to introduce a simplified tool to assist them in the regulatory process.

In response to this need, the RRL maturity scale tool was developed by Mcgowran and Harris (2020) to assess the regulatory readiness stage of a technology or product, especially in fields like healthcare. It functions as an adaptation of the TRL tool, which measures technological maturity but specifically focuses on the regulatory stages required for commercializing and using technologies. The primary goal of the RRL is to guide researchers and developers from the early stages of development through to meeting all stages required by regulatory agencies, such as ANVISA in Brazil or the FDA in the United States. This tool enables researchers and developers to identify gaps and map key areas in the regulatory process, that is, areas that have not yet been adequately addressed and that could compromise product approval. This aspect is crucial to prevent the project from facing irreversible obstacles in the approval stages, which could result in failure or significant delays, especially in critical development phases like the so-called "Valley of Death."

As with TRL, the initial work conducted by Mcgowran and Harris (2020) led to the creation of a simplified version of RRL, focused on the pharmaceutical sector. The tool comprises nine levels (RRL 1 to 9), which reflect the development stage of the technology in terms of meeting regulatory requirements, as shown in Table 2. The RRL levels range from the initial stages of research and development to final approval and post-marketing surveillance. At each level, the RRL maps regulatory progress, indicating which criteria have already been met and which still need to be fulfilled for the product to advance on the scale. The RRL tool was designed to be practical and accessible, even for researchers with little or no familiarity with the complexities of the regulatory process. By providing a structured and easy-to-understand guide, the RRL facilitates navigation through the requirements imposed by regulatory

authorities, offering a clear pathway to comply fully with the requirements for product commercialization.

Following its initial development, the RRL tool was tested in its beta version by a group of industry professionals and an academic group, both of which focused on the commercialization of innovative products. The positive feedback resulted in constructive suggestions to enhance the tool's functionality and usefulness. Among the improvements implemented were the expansion of RRL levels, providing more detailed information on the expected steps at each level. Additionally, hyperlinks were incorporated to relevant regulatory guidelines, such as ANVISA and FDA guidelines, which guide researchers on the specific requirements for each development phase. These guidelines cover crucial aspects such as safety specifications, clinical studies, manufacturing requirements, and quality standards, ensuring that researchers have access to up-to-date information and can conduct their research in alignment with regulatory demands.

Table 2 - RRL Scale with Corresponding Activities Compared to the TRL Scale.

TRL	Expansion of Activities	RRL Scale
TRL 1	• Reviewed scientific discoveries characterizing new technology.	RRL 1
TRL 2	• Generate research ideas "paper studies"; • Develop research plans; • Hypotheses are formed to identify candidates for proof of concept and/or therapeutic drugs.	RRL 2.1 – 2.3
TRL 3	• Test hypotheses – evaluate technologies supporting drug development; • Initial synthesis of candidates, limited in vitro and in vivo research models – initial proof of concept; • Characterization of hits in preclinical studies.	RRL 3.1 – 3.3
TRL 4	• Demonstrate proof of concept and safety of candidate drug formulations; • Preclinical studies (animal models) to assess potential safety and toxicity issues, adverse events, and side effects; • Exploratory studies of hits/leads to define formulation, routes of administration, synthesis method, physical and chemical properties, metabolic fate and excretion/elimination, and dose variation.	RRL 4.1 –4.3
TRL 5	• Non-clinical and preclinical research studies; • Collection and analysis of parametric data in well-defined systems; • Candidate drugs in pilot batches are produced for further development, providing a basis for a transferable manufacturing process compatible with cGMP pilot batch production; • GLP safety and toxicity studies to evaluate PK/PD of candidate drugs. • Compiled data packages from animal pharmacology and toxicology studies, proposed manufacturing information, and clinical protocols for Phase 1 clinical trials.	RRL 5.1 –5.5
TRL 6	• Phase 1 evaluation request submitted and approved; • Phase 1 Clinical Trial (CT) conducted; • Production technologies demonstrated through qualification of cGMP plant at production scale; • Clinical safety PK and PD data generated to support Phase 2 CT design.	RRL 6.1 – 6.4

TRL 7	• Phase 2 CT conducted (initial efficacy and additional data on safety, toxicity, and immunogenicity); • Final product dose, dosage range, schedule, and route of administration established; • End of Phase 2 CT; • Pre-Phase 3 meeting with agencies to discuss phase/phase 2 results, clinical parameters and/or surrogate markers of efficacy, and testing plans; • Phase 3 CT or surrogate testing plan prepared; • Application and clinical protocol to support Phase 3 CT trials or surrogate testing plan submitted.	RRL 7.1 – 7.5
TRL 8	• Safety and efficacy in Phase 3 CT or surrogate tests; • Evaluate the overall risk-benefit of candidate product administration and provide a basis for drug labeling; • Process validation completed, followed by batch consistency and reproducibility studies; • Dossier prepared and submitted to the agency.	RRL 8.1 – 8.3
TRL 9	• Approval received; • Product launch and market monitoring.	RRL 9.1 – 9.2

Source: Adapted from Mcgowran and Harris (2020).

The tool is still in the development phase based on a Microsoft Excel program, with the inclusion of a set of yes/no questions that allow the RRL level achieved to be evaluated. It is important to highlight that this tool is designed to bridge Ireland's regulatory gaps, with a particular focus on the pharmaceutical industry. However, in the Brazilian context, where there are specific regulations, particularly for medical devices, adaptations would be necessary for the tool to be fully applicable. Since it has not yet been finalized or made available, it will not be used in this study; however, the importance of regulatory aspects for THR is noteworthy to ensure the technology's maturation.

Another important tool developed from the TRL is the HRLs scale, which was designed to evaluate the readiness level of a technology in terms of its interaction and usability by humans (ACOSTA, 2010; ENDSLEY, 2014; PHILLIPS, 2010; SALAZAR *et al*., 2020; SEE *et al*., 2017). While TRL assesses whether a technology is technically ready for implementation, according to the Human Factors and Ergonomics Society, 2021, the HRL was developed to evaluate, track, and communicate whether this technology is safe, effective, and comfortable for human use. HRLs function as a scale with different levels, indicating the progress of a technology throughout its development in terms of human factors integration. Each HRL level addresses a specific phase of human factors evaluation, such as usability, comfort, and user safety. This tool is used throughout the development cycle of a technology to ensure that, from the earliest stages, the needs of end users are considered. This includes everything from initial research activities, where potential human needs are evaluated, to advanced development stages, where the technology is tested directly with users to ensure it meets safety and comfort requirements. For example, in the development of a medical device, HRLs would help assess

whether physicians can use it safely and effectively, if patients can operate the device with ease and intuitively, and if it elicits the desired emotional responses, such as confidence in treatment (HUMAN FACTORS AND ERGONOMICS SOCIETY, 2021).

It has been noted, however, that HRLs are not fully integrated into regulations for medical product development, making it challenging to compare technological maturity levels and compromising managers' decision-making regarding future investment plans. Furthermore, while HRLs acknowledge end-user needs in the development process, they still do not me*et al*l regulatory requirements for technology translation (LEE; BOYER, 2019). In this sense, medical product developers who ignore these requirements and release their products prematurely may suffer reputational damage due to the need for technical assistance or recalls over safety and efficacy concerns (HWANG *et al*., 2016).

Another important point is that although tools like HRLs and TRLs provide a technical and maturity assessment of a technology, they do not consider market acceptance parameters, such as user satisfaction. One example demonstrating the importance of this consideration is the Pillcam Colon, which presented itself as a substitute for colonoscopy. Besides meeting clinical needs, the product succeeded by fulfilling patient desires and offering a less painful and more comfortable procedure (TAPIA-SILES; COLEMAN; CUSCHIERI, 2016). Effectiveness and user satisfaction were key factors in market acceptance, showing that this integration is essential for success in the final translation stage. Therefore, the absence of these factors in HRL and TRL tools limits a complete assessment of a technology's maturity, especially regarding its adoption and commercial success.

Post-marketing assessment is also critical to ensuring the safety of high-risk medical equipment. Device users, hospitals, and healthcare professionals are required to report adverse events related to device use to regulatory bodies and manufacturers (VAN NORMAN, 2016). Post-marketing surveillance in Brazil, known as technovigilance, is a regulatory health surveillance activity established with the creation of ANVISA, and it aims to continuously monitor the performance, safety, quality, and efficacy standards of products throughout their life cycle. Post-market surveillance actions are the responsibility of all entities within the National Health Surveillance System (MELCHIOR, 2020).

A recent study developed by Seva *et al*., 2023, proposed a framework that integrates regulatory requirements in technology with HRL assessment based on the regulations of the FDA, as it is considered more stringent than the European Union (EU) standards (MAREŠOVÁ *et al*., 2020). The needs were identified through the interaction of medical devices with various users, such as patients, healthcare professionals, and support teams. Five critical dimensions,

stipulated in several medical device regulatory documents or considered necessary for market adoption, were considered: safety, clinical efficacy, usability, comfort, and affective response. These dimensions were mapped to stakeholders, considering the factors that affect their interaction with the medical device. In this sense, the most critical consideration for medical device development is the patient who receives the medical intervention. Although medical procedures sometimes cause discomfort, they are generally tolerated by the patient in pursuit of a positive health outcome. The patient is usually a passive recipient of the medical device, while the healthcare professional handles it according to established usage standards.

In response to this need, inspired by the TRL scale, MDRL scale was developed, consisting of nine levels, and designed to assess the readiness level of a medical device throughout its development cycle, focusing on both technical and regulatory criteria. MDRL expands the concept of TRL and HRL to include elements specific to medical devices, such as safety, clinical efficacy, commercialization, and market use. Table 3 shows the levels and definitions of MDRL concerning the TRL and HRL structures (HUMAN FACTORS AND ERGONOMICS SOCIETY, 2021).

Table 3 - Comparison of TRL, HRL, and MDRL.

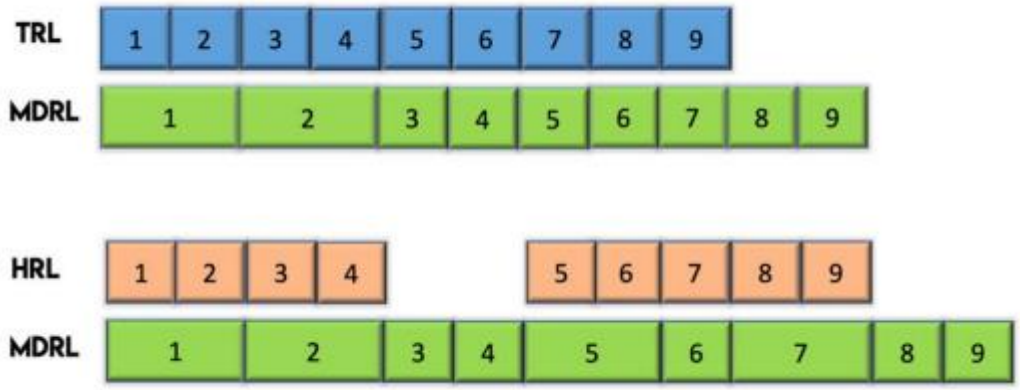
Scale	TRL	HRL	MDRL
1	Basic principles observed and reported	Relevant human capabilities, limitations, basic human performance issues, and risks identified	Needs assessment. Identification of scientific and design principles to address an existing medical challenge in terms of safety, clinical efficacy, system integration, human performance, and satisfaction.
2	Concept of technology and/or application formulated	The concept of operations is defined with a human-centered focus, establishing human performance design principles	Prototype development. Development of a functional prototype illustrating scientific and design principles to address safety and efficacy. Potential user performance and system integration issues are identified to improve design.
3	Critical function and/or characteristic of concept analytically and experimentally validated	Requirements to support human performance established	Bench Testing. Bench tests are used to identify performance issues in the mechanical, electrical, and biological engineering of the device, including animal or human tissue ex vivo, in vitro, and in situ, as well as animal carcass or human cadaveric testing. en
4	Component and/or breadboard validation in a laboratory environment	Modeling, partial task testing, and commercial design concept studies completed for human systems	Animal Testing. Initial evidence of the medical device's safety is established, including performance when used in a living system. Device operator performance issues were identified as a means of enhancing design.
5			

	Component and/or breadboard validation in a relevant environment	User evaluation of prototypes in goal-relevant simulations to inform design	Pilot Testing. Device safety is established in a small sample of healthy individuals. Patient-system integration issues identified to enhance design.
6	System/subsystem model or prototype demonstration in a relevant environment	Fully matured human system design influenced by human performance analyses, metrics, prototyping, and high-fidelity simulations	Feasibility Testing. Clinical efficacy was established in a small sample of patients with the health condition. Performance issues involving patients, healthcare professionals, and support staff in device use, as well as system integration issues, were identified to enhance design.
7	Prototype system demonstration in an operational environment	Thoroughly tested and verified human systems design in an operational environment with system hardware and software, plus user representativeness	Essential Testing. The device was tested in a large sample of patients with the health condition to identify rare and adverse effects. Statistical significance of results established. User performance and system integration issues were resolved.
8	The actual system was completed and qualified through testing and demonstration.	Full human system performance is thoroughly tested, validated, and approved in operations, using complete system hardware and software with user representation.	Market Acceptance. Full human system performance was thoroughly tested and validated, the regulatory authority approved a device, and discomfort in device use was mitigated. At a minimum, device tolerance is achieved, and at a minimum, discomfort is non-distressing.
9	Actual system proven through successful mission operations	The system is successfully used in operations across the entire operational envelope with systematic human performance monitoring.	Post-market Surveillance. The device is entirely accepted in the market with high satisfaction rates and positive evaluations.

Source: Adapted from Seva *et al*. (2023).

Figure 3 illustrates the relationship between MDRLs, TRLs, and HRLs. It is observed that human system integration and performance issues are identified from MDRL 1 through to the end of the development process. TRL and HRL levels 1–2 and 2–3 were incorporated into MDRL levels 1 and 2, respectively. Levels 8–9, however, address an exclusive approach within MDRL. At higher levels, TRL and HRL focus on mission success and full system integration, while MDRL primarily targets market acceptance. HRL was not mapped to MDRL levels 3–4 due to the absence of human involvement in these stages (SEVA *et al*., 2023).

Figure 3 - Mapping MDRL Progress Compared to TRL and HRL Levels



Source: Seva, *et al*., 2023.

The MDRL was initially designed for Class III devices under the FDA's most stringent standards. However, the MDRL can also be used to assess the readiness of Class I and II devices by excluding irrelevant levels. For example, not all Class II devices require premarket notification, eliminating the need for clinical trials (MDRL 4–7) if the manufacturer can demonstrate substantial equivalence to an already legally marketed device (KAPLAN *et al*., 2004; SEVA *et al*., 2023).

The MDRL thus aims to guide technology managers in successfully transitioning from research to commercial application. Technology maturity evaluation using MDRL considers regulations for medical device manufacturing at various stages, such as the requirement for three clinical trials for high-risk devices, FDA approval before deployment, and post-market surveillance to monitor safety and effective clinical evaluation. To address market adoption and sustained use considerations, dimensions of comfort and affective response were included in the MDRL as exit criteria. The proposed exit criteria provide clear targets for technology managers to reach each exit level and guide them in identifying suitable strategies and metrics to achieve their goals. At each exit point, it is ensured that the requirement has been met and high-level issues are addressed to progress to the next level (SEVA *et al*., 2023).

Regarding the criteria for each level, the relationship between the positioning of the criteria and the TRL structure was mapped. The main criteria for medical device maturation are presented below (SEVA *et al*., 2023):

a) MDRL 5 – Safety: Parameters must be validated to ensure safety before the first clinical trial with human participants, such as performing safety tests, including toxicity and biocompatibility;

b) MDRL 6 – Clinical Effectiveness: Parameters related to the technology's mission and objective. The device must prove it meets its therapeutic goals, such as providing accurate imaging in a colonoscopy or functioning correctly as a prosthesis;

c) MDRL 7 – Usability: Parameters that represent issues arising from interaction with the medical device's interface that may cause errors, such as unclear instructions, inconsistent screens, poorly designed interfaces, etc;

d) MDRL 8 – Comfort: Parameters related to mitigating discomfort in the medical device's use by the end user, such as contact stress, poor fit, and acute or chronic pain;

e) MDRL 9 – Affective Response: Assessment of users' emotional response when using the technology, including feelings of confidence or emotional comfort, such as joy, surprise, embarrassment, fear, and trust.

Additionally, these criteria were grouped into fundamental (MDRL 5–7) and advanced (MDRL 8–9) dimensions to differentiate regulatory aspects before and after FDA approval. The fundamental dimension includes safety, clinical effectiveness, and usability as basic requirements for promoting the medical device in the market. The advanced dimension focuses on higher stakeholder needs related to market acceptance and sustainability—factors that can determine a product's market success or failure. It is worth noting that technologies at MDRL stages 8 and 9 are designed to achieve greater market acceptance, as system users are less likely to experience discomfort while using the technology and tend to respond positively to it emotionally (SEVA *et al*., 2023).

These MDRL dimensions, grouped into fundamental and advanced aspects, provide a structured path for safe and sustainable medical device development, distinguishing criteria before and after regulatory approval. This broader focus enables technologies to achieve technical compliance as well as wider market acceptance, minimizing risks and increasing commercial success potential.

The availability of various tools, such as SWOT, TRL, MDRL, and RRL, provides developers with a comprehensive and detailed view of the technological maturation process, covering everything from the initial strategic analysis to the final regulatory requirements. As noted by Seva *et al*. (2023), this diversity of approaches allows researchers to choose the most appropriate tools for their product's context, accurately mapping challenges and opportunities at each development stage. The possibility of jointly applying these tools creates a complete

and flexible evaluation framework, ensuring that technological innovations progress with safety, effectiveness, and greater market acceptance.

For the Rapha® device, TRL and MDRL are essential tools for this research, given the need for a rigorous, specific evaluation aligned with ANVISA standards, considering the device's risk group. These tools allow technical and regulatory progress mapping, directly contributing to THR by guiding each development phase according to translational requirements. Thus, TRL and MDRL help mitigate the "valleys of death" throughout the process, addressing both the fundamental and advanced maturation dimensions that promote technical safety as well as regulatory and market acceptance.

CHAPTER 4

METHODOLOGY

4.1. Study Delimitation

The methodology of this thesis was designed to address the specific objectives previously outlined. The study was divided into several stages, beginning with the collection of data, documents, and public policies that encourage the technological development of medical devices within public universities. This phase was essential for mapping the R&D&I ecosystem and identifying the conditions that promote the social integration of medical technologies, highlighting their benefits to society. The analysis focused on the role of universities as catalysts for innovation, as well as on the incentives and barriers encountered in the process. The primary goal of this phase was to identify an ecosystem capable of fostering the social integration of these technologies, emphasizing their societal benefits.

The second stage involved a critical analysis of the translational environment applied to the development of medical devices in Brazil. This included characterizing the stages, markers, and entities involved in translational research while also addressing ethical and regulatory challenges. The case study of the Rapha® device was used to illustrate these dimensions, with particular emphasis on the technological maturity of the device.

Subsequently, a detailed examination of the development process of the Rapha® device was conducted, comparing it with other technologies available within the Brazilian SUS for treating wounds associated with diabetic foot. This analysis enabled the identification of challenges faced in each translational phase (T0 to T4) and the evaluation of the technological maturity and competitive intelligence of the device using tools such as the SWOT matrix, TRL and MDRL.

Finally, the feasibility of incorporating the Rapha® device into the Brazilian healthcare system was analyzed, considering the time elapsed from the start of its development to its market introduction. This stage included an assessment of the impact of public policies, partnerships with the private sector, and the regulatory environment in accelerating the innovation process.

Another critical aspect was the evaluation of policies related to translational research, which also addressed ethical and regulatory challenges. The case study of the Rapha® device was utilized to illustrate these elements, while also exploring its technological maturity level.

Subsequently, the development process of the Rapha® device was described, with special attention to comparing this new technology with other healthcare solutions already integrated into the SUS for treating wounds associated with diabetic foot. Additionally, the perception of the technological maturity and competitive intelligence of the Rapha® device was assessed using the SWOT matrix, TRL, and MDRL tools, in alignment with the RDC/ANVISA standards for different development stages.

Finally, the feasibility of incorporating the Rapha® technology into the Brazilian healthcare system was analyzed, taking into account the time elapsed from its initial development to its market introduction.

4.2. Methodological Delimitation

Data collection was conducted through the acquisition and processing of information derived from academic and scientific outputs, following a qualitative approach. The data collection included both document analysis and field approaches. For data processing, thematic content analysis was employed to highlight elements relevant to the research subject, based on the translational research process of the Rapha® device.

In the document analysis, macroprocesses and subprocesses were identified with their respective specificities. It is important to note that, although these processes do not occur linearly or sequentially, they tend to follow this pattern over time. Additionally, the field approach reinforced these processes and their corresponding outcomes. Consequently, the T0, T1, T2, T3, and T4 phases were identified as results of the translational process of the Rapha® device over time.

In the academic environment, articles, papers, courses, and extension programs were considered technical and technological outputs resulting from R&D&I efforts. However, more tangible innovations, such as patents and technology transfers, represent the transformation of research into practical products for healthcare systems, often requiring collaboration with the private sector. The significance of these innovations becomes even more apparent when research extends beyond the laboratory environment and aligns with regulations, such as those established by ANVISA, paving the way for their implementation in healthcare systems.

Among the key elements identified during data collection, values were assigned, and the results of translational research across the T0 to T4 phases were compared. Data collection

encompassed aspects such as product conception, approval by the CEP/CONEP, patents, technology transfer, and registration with INMETRO and ANVISA, aiming for the eventual availability of the device in the Brazilian market.

As a result, it was necessary to explore the interaction model between agents linked to the national R&D&I system, as verified in the development of the Rapha® device, considering the Quadruple Helix models that emphasize the collaboration between academia, government, society, and the private sector in advancing the project. Subsequently, the phases completed by the Rapha® device were identified and described based on the traditional stages of THR.

The research characterized the translational phases (T0-T4), identifying key markers, actors, and public policies related to the development of medical technologies in Brazil. A critical analysis of the translational environment was conducted using the case study of the Rapha® device, highlighting ethical and regulatory aspects. This phase enabled detailed mapping of the R&D&I process, focusing on collaboration between academia, government, and the private sector, and on adapting technologies to national (ANVISA, INMETRO) and international (FDA) standards. Finally, an evaluation of the time required for each phase of the THR was performed, including considerations on overcoming "valleys of death" and optimizing translational timelines.

Additionally, ethical and regulatory aspects were analyzed in detail. The research did not require submission to the CEP/CONEP as it utilized secondary public domain data and adhered to all ethical procedures from previously approved studies by competent bodies. The researcher’s participant observation also contributed to enriching the theoretical-methodological framework.

The efficacy of the Rapha® device was evaluated in preclinical and clinical studies conducted at partner institutions. Randomized double-blind clinical trials demonstrated the practical application of the device in treating wounds associated with diabetic foot, highlighting its feasibility as an innovative technological solution. This phase also compared the performance of the Rapha® device with existing technologies in the SUS, validating its potential impact within the context of Brazilian public health.

In summary, the research examined the technical aspects related to the design, functionality, and efficacy of the Rapha® device, the regulatory requirements for its validation (ANVISA, INMETRO), and the ethical challenges encountered during the R&D&I process. The analysis considered the role of public policies and partnerships with the private sector in advancing technology, emphasizing how these interactions can accelerate the translation of medical devices to the market.

To evaluate the technological maturity of the Rapha® device, a methodology based on TRL and MDRL tools was applied. Initially, appropriate assessment instruments were selected, using the TRL scale developed by NASA and the MDRL scale specific to medical devices, according to FDA requirements. Information on the theoretical development, creation, and testing of the device was then collected. The intellectual property analysis included verifying patents, scientific articles, and licensing or technology transfer processes related to the Rapha® device.

The application of TRL and MDRL scales allowed for an evaluation of the device's technological and regulatory maturity levels, tracking progress from initial research to technological validation. The data obtained were interpreted to provide a comprehensive view of the Rapha® device's technological evolution, documented and communicated through detailed reports and presentations. This process enabled the review and adjustment of development processes and identified opportunities for future initiatives and collaborations in THR, aligning with the translational phases. Thus, challenges associated with "valleys of death" were mitigated, considering the fundamental and advanced dimensions proposed for the Rapha® device.

The SWOT matrix was employed as a strategic and market analysis tool for the Rapha® device. This methodology facilitated the identification and assessment of the strengths, weaknesses, opportunities, and threats related to the project. The application of SWOT provided a comprehensive understanding of internal and external factors influencing the device's success, enabling informed decision-making and the development of strategies to optimize translational research. By highlighting strengths such as interdisciplinary collaboration and technological innovation, and acknowledging weaknesses and threats such as regulatory challenges and market competition, the SWOT analysis offered a solid foundation for directing the effective development and commercialization of the Rapha® device.

It is important to emphasize that the primary objective of applying these tools was to assess the technology's maturity level through a dynamic and detailed analysis of the variables involved, enriching the data foundation for informed decision-making. Exhaustive measurement of all possibilities related to this technology was not sought. The inclusion of this activity in the specific objectives was motivated by the need to deepen the understanding of the translational process, aiming to improve the translational research model for biomedical devices proposed in this work. Consequently, the content analysis based on simple thematic elements revealed that the case study achieved the expected maturity and translational levels according to technical, ethical, regulatory, and market aspects.

Finally, the total time from the initial prototype development to its availability in the healthcare system was considered a dependent variable, while disease characteristics, device specifics, and socioeconomic factors were treated as independent variables. This holistic approach not only mapped the technological progress of the Rapha® device but also provided valuable insights for overcoming the challenges of translating research into clinical practice, ensuring a well-defined strategy for its future implementation in the healthcare market.

4.3. Ethical Aspects of the Research

In this study, the researcher is part of the group involved in the translational process of the Rapha® device. In this context, it is necessary for the researcher to clarify their role in the research subject, utilizing participant observation as an integral component of the theoretical-methodological framework of the qualitative research.

From an ethical perspective, according to Resolution No. 510, dated April 7, 2016, in Article 1: "The following will not be registered or evaluated by the CEP/CONEP system: [...] II – research that uses publicly accessible information, under Law No. 12,527, of November 18, 2011; [...] VI – research conducted exclusively with scientific texts for literature review; VII – research aimed at theoretical deepening of situations that emerge spontaneously and contingently in professional practice, provided that no data is revealed that may identify the subject; [...]". In this sense, the doctoral research was not submitted to an ethics committee for the above reasons. Additionally, previous studies had been approved by the Research Ethics Committee of the Faculty of Health Sciences at the UnB under the ethical review certificate 94910718.5.0000.0030. Furthermore, the project was approved by the CEP of the Foundation for Education and Research in Health Sciences, under the Federal District's Department of Health (SES/DF, abbreviated from Portuguese, "Secretaria de Estado de Saúde do Distrito Federal"), given that the project is linked to the Federal District Health Secretariat (ROSA, 2019).

The clinical trial was a randomized, double-blind, comparative study involving the treatment of diabetic foot ulcers using a natural latex-derived biomembrane and an LED-emitting device known as the Rapha® Protocol. The screening of diabetic patients was conducted at the Asa Norte Regional Hospital (HRAN, abbreviated from Portuguese, "Hospital Regional da Asa Norte") and the Gama Regional Hospital (HRG, abbreviated from Portuguese, "Hospital Regional do Gama") and Taguatinga Regional Hospital (HRT, abbreviated from Portuguese, "Hospital Regional de Taguatinga"), located in the DF. The experiment was divided into two trials, with the treatment duration for patients ranging between 45 and 90 days.

Participants were randomly assigned to two groups: Control Group (CG) and Experimental Group (EG). The CG received the standard treatment offered by SUS, which included calcium alginate and silver foam dressings. On the other hand, the EG performed daily self-care at home using the Rapha® system, which included dressings with a natural latex-derived biomembrane combined with red LED phototherapy, applied for 30 minutes daily. EG patients received instructions from the responsible team and were visited by the nursing team twice weekly in their homes. Additionally, every two weeks, they attended multidisciplinary evaluations at the hospital (ROSA *et al*., 2019).

CHAPTER 5

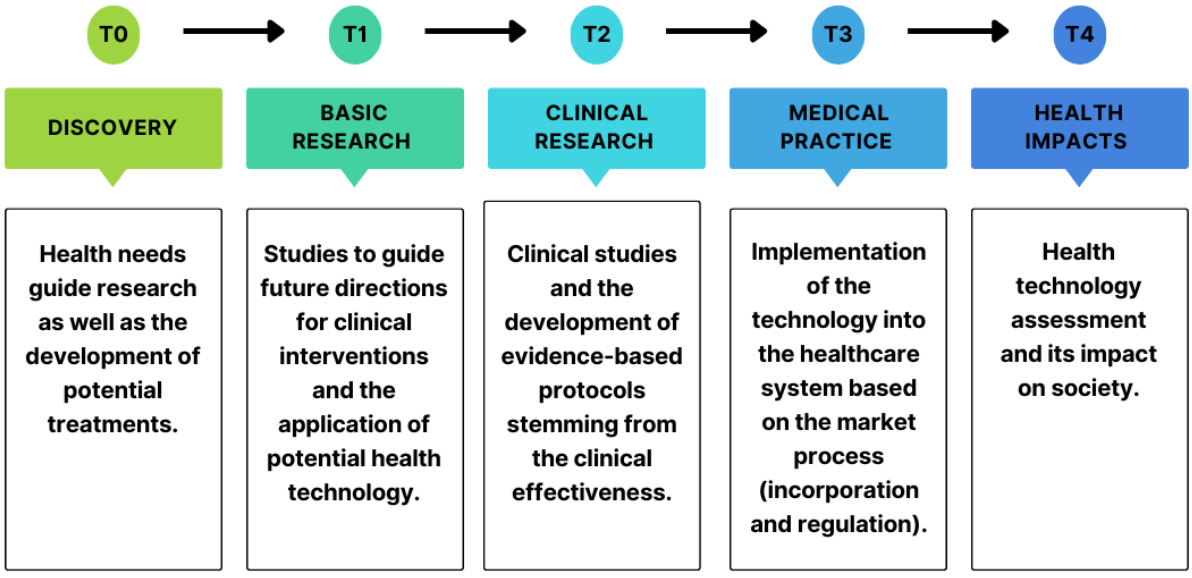
RESULTS AND DISCUSSION

5.1. Stages, Markers, and Entities in Translational Research

Translational models aim to capture and convey the multifaceted complexity of real-world phenomena. To achieve this, these models employ empirical data that allow for the identification and characterization of distinct stages, as well as for estimating the average time required for each. Another essential aspect is identifying the key agents involved at each stage. These translational phases are organized into specific temporal periods, referred to as T0, T1, T2, T3, and T4, with each milestone representing a distinct phase in the process of converting research into tangible health benefits, following the NIH Roadmap framework.

The translational model proposed by Khoury *et al*. (2010) is widely applied in THR and was chosen to illustrate the trajectory of the Rapha® equipment, as shown in Figure 4. It is important to note that while the model presents these phases from T0 to T4, it does not imply a rigid linearity in research development. Instead, the translational process can involve dynamic interactions and reversals between stages, reflecting the inherent complexity of health-related development.

Figure 4 - Translation model presenting phases T0 to T4 in developing the Rapha® device.



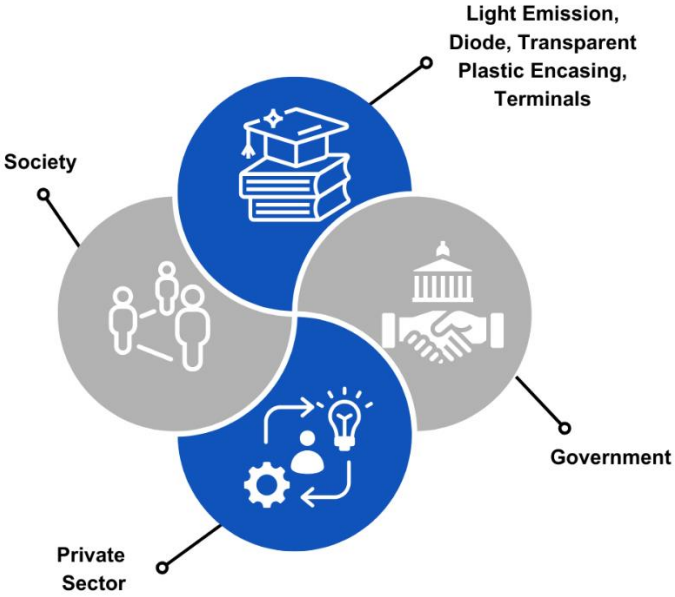
Source: Adapted from Khoury *et al*. (2010) for the Rapha® device.

Within the macroprocesses, there are distinct subprocesses with unique characteristics and particularities. Additionally, it is essential to understand that these processes or markers do not constantly develop in a linear or rigid sequence; however, generally, they tend to follow this trajectory over time.

In the documentary analysis, macroprocesses and subprocesses with considerable specificities were identified. It is important to note that these processes occur non-linear and non-sequential; nonetheless, they generally follow this pattern over time. Furthermore, the field approach highlights these processes and their respective outcomes. Thus, the stages T0, T1, T2, T3, and T4 were identified as the temporal phases in the translation of the Rapha® device over time.

Historically, scientific and technological development has been driven by the triad composed of government, universities, and the private sector—a concept widely known as the "triple helix." However, the National System of ST&I has expanded this model by incorporating civil society, thereby creating the "quadruple helix," where society, in its various facets, directly influences innovation outcomes, as shown in Figure 5. An example of this can be seen in Science and Technology Parks, organized environments that promote innovation and technological development through collaboration between universities, companies, and research centers. These parks function as innovation ecosystems with active participation from civil society, whether through entrepreneurship and startup creation or direct influence on technological demands. Additionally, Science and Technology Parks frequently involve society in advisory boards and events, facilitating the social appropriation of knowledge and strengthening the role of civil society within the 'quadruple helix' model. Nevertheless, even with this synergy, success is not guaranteed. Effective strategies have been required to overcome obstacles and gaps, particularly the "valleys of death," and to ensure that science and technology translate into tangible benefits for society.

Figure 5 - Key Actors in THR.



Source: Author's Own Work.

It is crucial to highlight that some actors play a continuous and comprehensive role throughout the translational research process. Notable examples include universities, research institutions, and governmental agencies, such as the MH and ANVISA. However, for a more didactic and schematic representation, we chose to emphasize actors whose activities and competencies are predominant in specific research stages, as well as in the macro and subprocesses.

5.1.1. T0 Stage

Phase T0 represents the foundation of the translational process, serving as a critical stage for identifying the initial feasibility of the medical device, which, in this specific study, is the Rapha® device. During this phase, fundamental data are collected regarding the problem to be addressed (such as the treatment of diabetic foot) and the conceptual development of the device.

In this context, data collection, evaluation of preexisting technologies, product lifecycle analysis, and systematic reviews/meta-analyses were conducted. The articulation of R&D&I proved essential, as it allowed for the identification of all stakeholders and potential users of the technology. Based on this data, it was possible to structure a research project management plan, facilitating the identification of requirements, specification definitions, recognition of stages, actors, and inherent risks, as well as technical detailing. This planning is fundamental for securing support from funding institutions, as outlined in Phase T0. Once approval was obtained from the CEP/CONEP, it was possible to proceed with prototype development and

initiate preclinical testing. If rejected, prior steps, such as project specifications, would need to be revised for resubmission to CEP/CONEP.

Before initiating any tests involving human subjects, it was imperative to obtain approval from the Research Ethics Committees, including CEP/CONEP, to ensure the protection and integrity of participants in accordance with ethical guidelines.

This phase involved extensive data collection to translate the T0 phase. This stage emphasized detailed descriptions of the device and findings that indicate patterns in health outcomes, considering variables such as location, timeline, and actors involved in the research development. In this context, the conceptualization of the device during the T0 phase of THR was also outlined.

The main protagonists in this process were researchers affiliated with universities and other research institutions, whether public or private. Additionally, research participants played a vital role. Funding for these investigations came from various sources, including internal budgets, agencies, and institutions dedicated to promoting science and innovation, such as the National Council for Scientific and Technological Development, Research Support Foundations, the Funding Authority for Studies and Projects, the National Bank for Economic and Social Development, the Research Program for SUS, and state foundations such as the Federal District Research Support Foundation and the São Paulo Research Foundation. It is also important to highlight the role of the Department of the Health Industrial Complex and Innovation in its mission to promote the development and innovation of health inputs.

This initial organization and the evaluations conducted during T0 established the foundation for the preclinical analyses carried out in Phase T1.

The initial discovery and functional modeling allowed the proposed technology to have a solid scientific basis, justifying investments in subsequent stages. This phase was crucial for establishing the relevance of the technology and defining a functional prototype that could be evaluated under controlled conditions. Without a robust scientific foundation, the product could not advance to the more specific tests of later phases.

5.1.2. T1 Stage

Preclinical testing in Phase T1 evaluates the safety and initial efficacy of the device in laboratory and animal models. During this phase, biocompatibility studies, cytotoxicity assays, intracutaneous reactivity evaluations, and other toxicological tests were performed. These tests established the safety of the device before any human exposure, ensuring that risks were minimized. They also provided critical data to guide the design of clinical trials in Phase T2.

For the Rapha® device, the objective was to catalog findings and evaluate potential healthcare applications through animal studies. Initial limitations for the use of the device were also identified. This phase encompassed both basic and preclinical research, from its conception to its development.

As in Phase T0, synergy and collaboration among stakeholders were fundamental. During this phase, researchers associated with universities and research institutions played a prominent role. Additionally, funding agencies and institutions assumed a crucial role by providing financial support for these preclinical trials.

5.1.3. T2 Stage

In Phase T2, the device was tested in humans through clinical trials divided into three main phases. The first clinical trial, known as Phase I, aimed to assess the safety of the device in a small group of participants. This stage analyzed aspects such as potential adverse reactions and device tolerability, establishing an initial foundation for subsequent phases. In Phase II, the objective was to determine the initial efficacy of the device in a larger group of participants, enabling the collection of data on dosage, response, and preliminary clinical efficacy. This stage also contributed to adjusting operational parameters for larger-scale testing in the next phase. In Phase III, the goal was to confirm the device's efficacy in a broader population and compare its performance with existing treatments, when applicable. This stage was crucial to validate safety and efficacy under real-use conditions and is often used as a basis for regulatory submissions to agencies such as ANVISA.

Clinical trials were necessary to demonstrate that the device is safe and effective under real-world conditions. Dividing the trials into three phases ensured a progressive evaluation of each aspect, reducing risks and ensuring ethical compliance.

For the specific case of the Rapha® device, emphasis was placed on clinical analysis, focusing on health interventions and central guidelines to evaluate intervention efficacy. This evaluation aimed to improve patient health and prevent the progression of diabetic foot wounds through both observational and experimental studies. The device was tested on patients with diabetic foot, with the primary goal of assessing the safety, tolerability of the latex blade, and the effects of continuous use.

Key collaborators in this phase included regional hospitals such as HRAN, HRG, and the HRT affiliated with the SES/DF, along with active participation from civil society. The clinical and research teams were composed of nurses, physicians, researchers, and academic members. Additionally, funding institutions and laboratories supported the clinical trials. At this stage,

the involvement of ANVISA was essential, as the agency was notified at the conclusion of the tests, contributing to the subsequent technology registration process.

When it comes to surveillance and healthcare, the actions of the Health Surveillance Secretariats and the Health Care Secretariat are essential, with ANVISA also playing a fundamental role. At this stage, other strategic actors, such as CONITEC, the National Supplementary Health Agency, universities, and research institutions with expertise in HTA—some of which are part of the Brazilian Network for Health Technology Assessment—began to participate actively. Additionally, technical departments within the Ministry of Health, such as the Department of Science and Technology, the Department of Technology Management and Incorporation, and the Department of Health Economics, Investments, and Development, were prominent. Active collaboration among these entities is crucial for overcoming the typical challenges of the clinical research phase, often referred to as "valleys of death."

5.1.4. T3 Stage

In this phase, the focus was on standardizing the production process to introduce the technology to the market, obtaining certifications (such as INMETRO), and securing regulatory approval (ANVISA). Once all the necessary information was presented and the requirements of these regulatory bodies were met, ANVISA proceeded with its evaluation and, if approved, granted the sanitary registration. Simultaneously, INMETRO evaluated the device and, where appropriate, certified it for human use. Additionally, technology transfer was conducted to industries that would carry out large-scale production. This stage is critical to ensuring that the device is ready for production and distribution with quality and safety, in compliance with all regulatory and technical standards.

As in previous phases, a holistic evaluation of the healthcare sector requires ongoing collaboration and coordination among the various stakeholders involved. These include administrators from different levels of governance, researchers affiliated with universities and research institutions, and the private sector, which is responsible for incorporating the technology. It is also essential to adhere to the protocol of the INMETRO PCB and secure registration with ANVISA.

In alignment with the SUS guidelines, effective integration and communication among various levels of management are crucial. Policies, programs, and actions are materialized at the territorial level. In this context, the importance of the Bipartite and Tripartite Intermanagers Commissions is emphasized, as they play a key role in deliberating and agreeing on policies as well as defining financial responsibilities within the healthcare sector.

5.1.5. T4 Stage

The final phase consists of introducing the device into the market and the public healthcare system, including the Brazilian SUS. At this stage, the clinical, economic, and social impacts of the device are evaluated. Incorporation ensures that the benefits of the device reach the population in an accessible manner, promoting improvements in public health and generating a positive impact on both patients' quality of life and the economy.

In the context of this study, the transition from the conclusion of regulatory stages to large-scale implementation in the healthcare system represents one of the most critical "valleys of death" in the translational process. This point is a common barrier in the integration of innovative medical technologies due to the need to align complex regulatory requirements, validate large-scale results, and structure efficient distribution networks.

As of the present time, because Phase T3 is still in progress, the Rapha® project has not yet advanced to Phase T4, which refers to the device's entry into the Brazilian market and the evaluation of its impact and acceptance by society.

As in the previous phase, collaboration and synergy among the various stakeholders involved are fundamental. In this phase, partnerships and involvement with the private sector, CONITEC, National Supplementary Health Agency, and the Brazilian Network for Health Technology Assessment are highlighted. These entities, through HTA, aim to consolidate innovative practices and methods in the sector. In addition to these organizations, the Ministry of Health, through its departments, plays a crucial role, ultimately aiming for the successful integration of the technology into SUS after rigorous validation and assurance of its excellence and efficacy.

Beyond the previously mentioned stakeholders, there are others whose involvement does not follow the strict linearity of the translational research process. Many of these stakeholders, though affiliated with universities and research institutions, have their participation directly conditioned by the results, processes, and validations throughout the research. A clear example of this is the Intellectual Property Center of the Coordination for Innovation and Technology Transfer at the Center for Technological Development (CTD) of the UnB. This center plays a crucial role in patent registration with the National Institute of Industrial Property (INPI, abbreviated from Portuguese, "Instituto Nacional da Propriedade Industrial") and subsequent technology transfer. Other important entities in this context include the Technological Innovation Center at CTD, the Department of Intellectual Property at UnB, and various research laboratories, which are discussed in greater detail in Phase T0.

By identifying key temporal bottlenecks and points in the process with the greatest fluctuations, it becomes feasible to strategically direct efforts and allocate resources. In doing so, it is possible to refine and accelerate procedures that consume more time than necessary, promoting a more efficient and effective execution.

Based on the measures taken so far, such as robust scientific validation, the submission of documentation for certification, and strategic partnership planning, there are concrete prospects of overcoming this challenge and surpassing the “valley of death.” Although the development time elapsed since the device's initial conception is significant, it remains within the average for medical devices of similar classification, especially considering the rigorous safety and efficacy standards required in the sector. Thus, the case of the Rapha® device reflects the necessary balance between technological advancement and regulatory compliance, serving as an example of translational potential to benefit public health.

5.2. First Stage of Technology – Description and Discovery (T0)

5.2.1. Location, People, Facts, Occurrences, and Frequencies

This work presents a documentary analysis and conceptual approach to translate the Rapha® device, which was approved by the Ethics Committee of Foundation for Education and Research in Health Sciences, SES-DF, under protocol no. 052/2012-CEP/SES/DF, and the Ethics Committee of the Faculty of Health Sciences at the UnB, with certificate 085906/2018 and Certificate of Presentation for Ethical Appreciation no. 94910718.5.0000.0030 in 2019. The study was conducted by an interdisciplinary and multidisciplinary group affiliated with the Graduate Program in Biomedical Engineering, under the guidance of Prof. D. Sc. S. R. F. Rosa and Prof. D. Sc. A. F. Rocha, who acted as collaborators in the Diabetic Foot clinics associated with the HRG, HRAN, and HRT hospitals, with daily follow-ups at patients’ homes.

The study began at the UnB, at the Gama Campus, in the LIPIS and LAPPIS laboratories, in partnership with the Optical Spectroscopy Laboratory of the Institute of Physics at the UnB – Darcy Ribeiro Campus, the Biology Laboratory at the UnB – Planaltina Campus, and CERTBIO at the Federal University of Campina Grande. It was based on the doctoral thesis of D. Sc. Maria do Carmo Reis, who developed, alongside the research group, a system composed of an LED light-emitting circuit and natural latex that induces tissue neoformation for treating diabetic feet. The device consists of a healing insole and an electronic circuit for tissue regeneration. The healing insole is derived from natural latex from the Hevea brasiliensis rubber tree and is customized according to the characteristics and dimensions of each patient.

Later, adhesive latex sheets were used for better application on patients with diabetic foot ulcers. Thus, the healing of these ulcers, through tissue regeneration and neoformation, was achieved by the combined and simultaneous action of latex biomaterial and low-intensity LED irradiation.

Following the initial results, the study continued with the research group, resulting in various publications, final course projects, master's theses, and doctoral dissertations aimed at refining the equipment and outcomes obtained, in addition to analyzing the entire process's social impact, which received awards from SUS.

This research was essential for fostering collaboration among researchers within UnB and other Higher Education Institutions, including freelancers and other civil society members. These contributors helped improve the device and deliver better patient outcomes through interdisciplinary processes in science, technology, and innovation. Meetings were held both in person and virtually, as well as via WhatsApp groups. Thus, the contributions of various stakeholders in each research line facilitated a conceptual discussion of the technology and its subsequent development, identified in translational literature as T0.

The R&D&I scenario demonstrated a multidisciplinary integration within the research group, aimed at reducing the number of people with diabetic feet. Most participants were institutionally affiliated, including faculty, researchers, and students (doctoral, master's, and undergraduate levels) from UnB. However, some participants were not affiliated with HEIs and were identified as volunteers. This data suggests the involvement of freelance professionals and/or representatives from the private and/or public sectors interested in contributing to the Rapha® R&D&I. This group included representatives from private companies and the hospitals where initial technology tests were conducted. Thus, it was possible to observe the interdisciplinary and multidisciplinary process of participants, both through institutional affiliation and the advanced educational background of some members, with engineering, health sciences, and biological sciences working together.

This integration was fundamental for Rapha® R&D&I to surpass the T0 phase of translational research, where the concept of the technology took shape through the integration of different fields. It is worth noting that most project participants did not follow the entire translational path of the technology; however, each one's contribution was significant to the device's development.

5.2.2. Device – Technical Concept of the Technology

The portable device consists of a mobile electronic system for tissue neoformation based on phototherapy principles, designed to aid in wound healing by accelerating the scarring process. Its light-emitting circuit comprises two modules: a control module and an LED matrix module. Currently, low-power LED phototherapy has demonstrated effectiveness in treating various conditions. In this context, the Rapha® device is regarded as a new phototherapy modality, noted for its low cost and ease of use. Additionally, the Rapha® device is portable and simple to operate, emitting an LED beam for a predetermined time of approximately 35 minutes. Technically, the device consists of two boards: the LED board and the time control board.

5.2.2.1. Latex Membrane

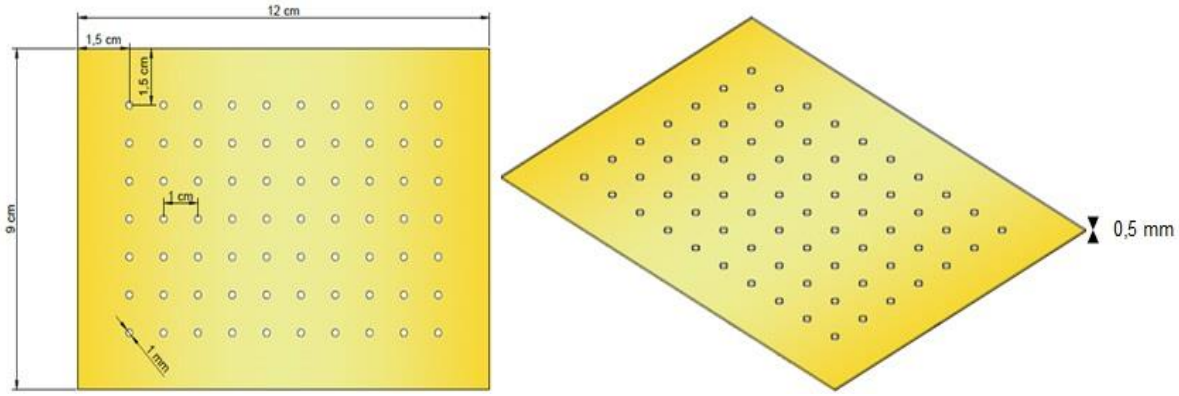
Natural rubber latex is a milky fluid obtained from the Brazilian rubber tree, *Hevea brasiliensis*. It is a colloidal system that contains 50% water, 30-45% rubber particles (cis-1,4-polyisoprene), and 4-5% non-rubber constituents (such as proteins, lipids, and carbohydrates) (NEVES-JUNIOR *et al*., 2006). Latex has been shown to be biocompatible, capable of stimulating angiogenesis and the formation of extracellular matrices, as well as promoting cellular adhesion, tissue replacement, and repair (AZEVEDO BORGES *et al*., 2014). In this case, the natural latex biomembrane was used as an alternative dressing for treating skin ulcers, offering an effective, economical, and easy-to-handle solution that accelerates healing. Furthermore, it has debriding and neoangiogenic potential, making the scarring process dynamic and rapid—an essential aspect in ulcer healing for diabetic patients (FRADE *et al*., 2004).

In the adhesive production process, the latex must first undergo a 60% centrifugation process to reduce the amount of naturally occurring proteins, many of which are responsible for allergic reactions. The same requirements apply to sulfur and resin suspensions to impart the necessary elasticity and resistance to the final compound (MRUÉ; CENEVIVA, 1996).

The latex membrane is produced by the CERTBIO Laboratory in Campina Grande (PB), an INMETRO-accredited laboratory under ABNT NBR ISO/IEC 17025:2017, which strictly adheres to quality standards. The Rapha® development team explained the technology to CERTBIO, which then made the necessary adjustments to meet the standards required for ANVISA product approval.

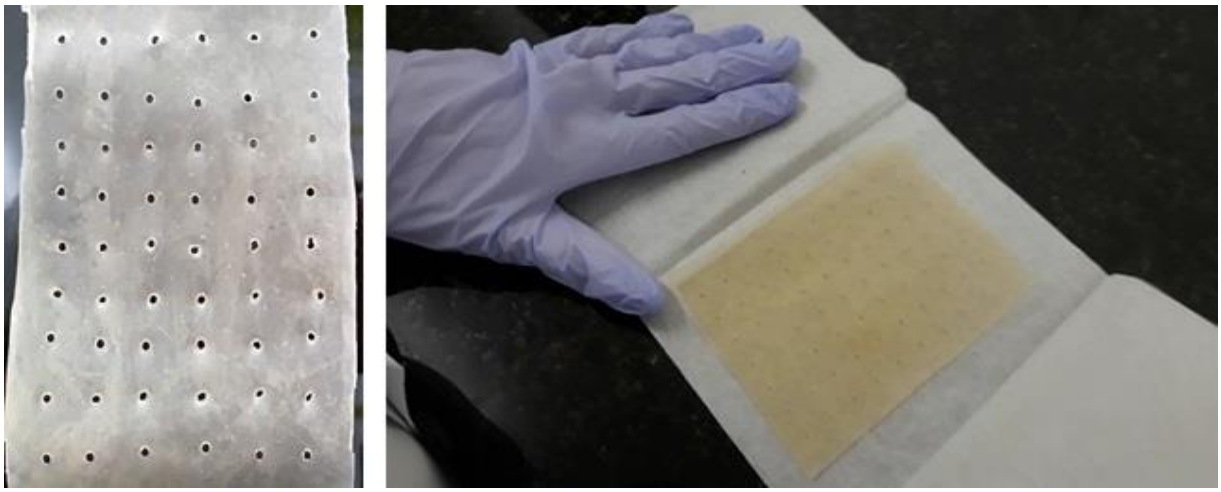
To produce latex biomembranes under uniform and controlled conditions, ensuring product quality consistency, specific quality control measures were followed for the raw material. After the raw material was approved, the latex was vulcanized. Figure 6 and 7 show the dimensions of the latex sheet and its packaging to preserve production characteristics.

Figure 6 - Diagram of the Arrangement of Circular Perforations in the Latex Biomembrane.



Source: Author's Own Work.

Figure 7 - Perforated membrane placed on parchment paper.



Source: Nunes, 2017.

5.2.2.2. LED Light Emission Device

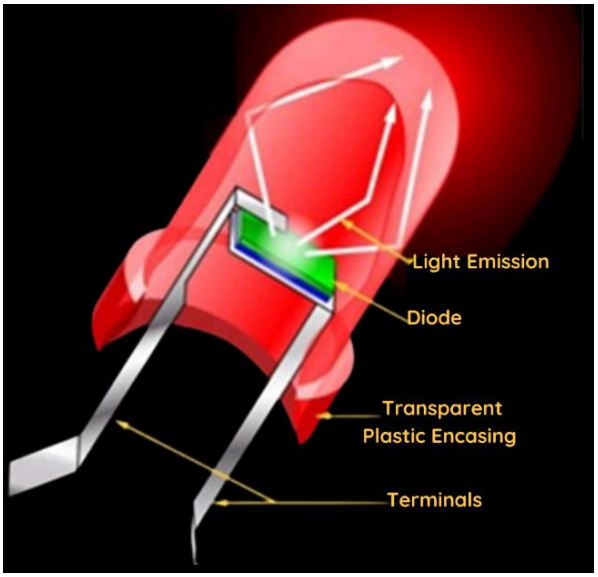
The Rapha® device is a portable tissue regeneration system based on phototherapy principles, designed to assist in the healing of diabetic foot wounds. Its circuit is controlled by a timer operating a panel of red LED lights. The device comprises two modules: the Irradiance Module, or LED Panel, and the Control Module:

a) The **Irradiance Module**, or **LED Panel**, contains 30 red LEDs, as illustrated in Figure 8;

b) The **Control Module** includes a timer circuit that activates a microcontroller, programmed to keep a green LED blinking as a time-count indicator, and the LED panel illuminated, emitting red light for 35 minutes. At the end of this period, a buzzer sounds, emitting audible waves to signal the automatic shutdown of the system.

The components described above are integrated into a robust structure molded from black ABS PA757 plastic. This housing also contains two 9V alkaline batteries that power the circuits and features an on/off switch to activate the system. The complete design of the device, including dimensional specifications, is illustrated in Figure 9 and 10. For effective application, the Rapha® is attached to the patient's body using an elastic bandage made of self-adhesive cotton.

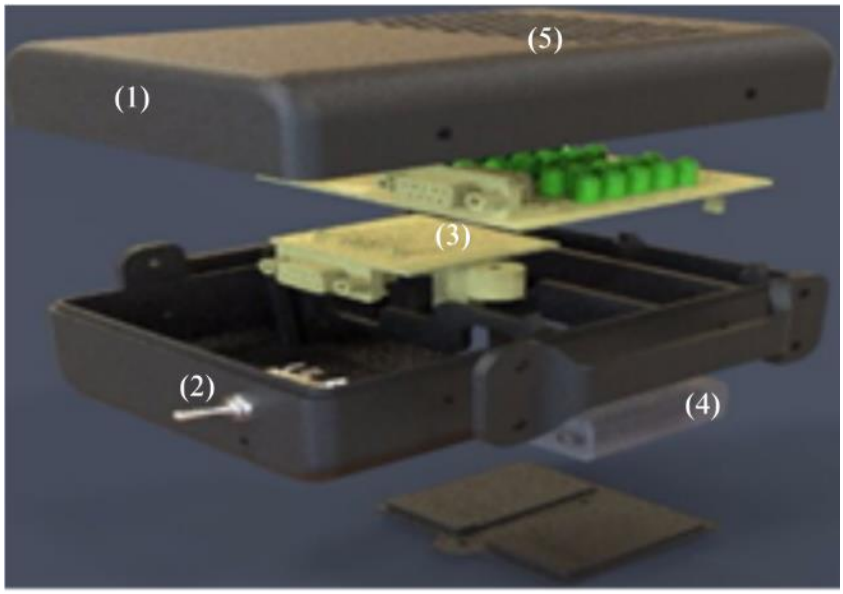
Figure 8 - LED Composition.



Source: Author's Own Work.

The figure illustrates its terminals and diode, which, when energized, release photons, illuminating the surrounding area.

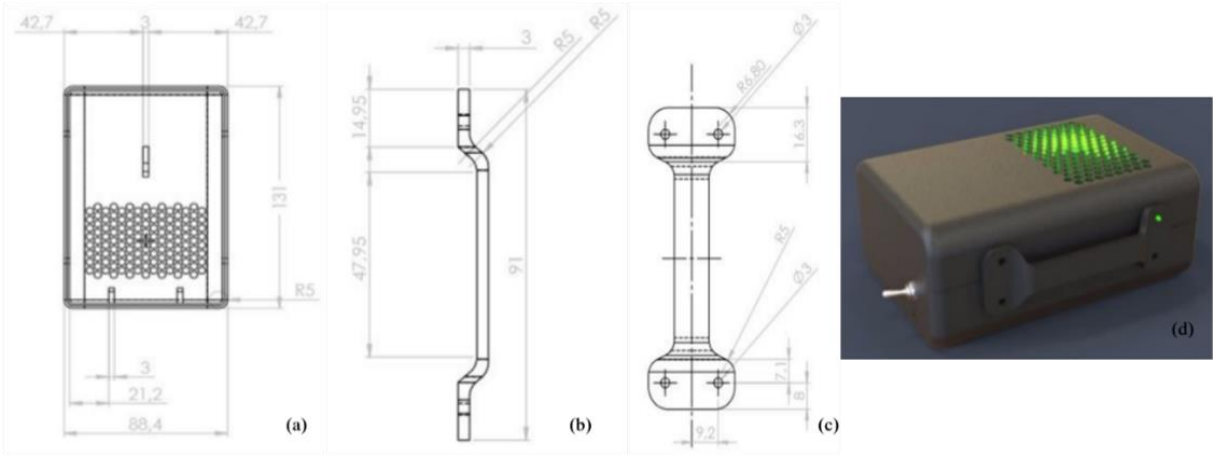
Figure 9 - Rapha® Device, LED Light Emitter.



Source: Adapted from ROSA *et al.*, 2023.

Point 1: Casing; Point 2: On/Off Switch; Point 3: Electronic Circuit Board; Point 4: Rechargeable Battery; Point 5: LED Light Apertures

Figure 10 - Perspective of the Rapha® Device.



Source: Adapted from ROSA *et al.*, 2023.

This figure shows the main parts of the equipment, as well as its dimensions in perspective.

(a) LED Light Emitter; (b) Side Handle – side view; (c) Side Handle – front view; (d) Image of the closed electronic device.

The software was developed for the PIC16F4A microcontroller and represents the latest firmware, with the function of activating the LED matrix (irradiance module) for a set time of 35 minutes; in this firmware, this time cannot be reprogrammed. While the irradiance module is operating, a blinking LED indicates that the device is functioning. At the end of the operating time, the buzzer emits an audible alert, signaling the end of the cycle.

Regarding the operation process of the Rapha® device, the PIC microcontroller was programmed to activate the LED panel at a frequency of 1 Hz for a period of 35 minutes while the patient maintains the device on the latex membrane in direct contact with the diabetic foot wound, as shown in Figure 11. During this period, the irradiance module operates at maximum intensity. Once the stipulated period has elapsed, the irradiance module shuts off, the buzzer is triggered, and the signaling LED turns off.

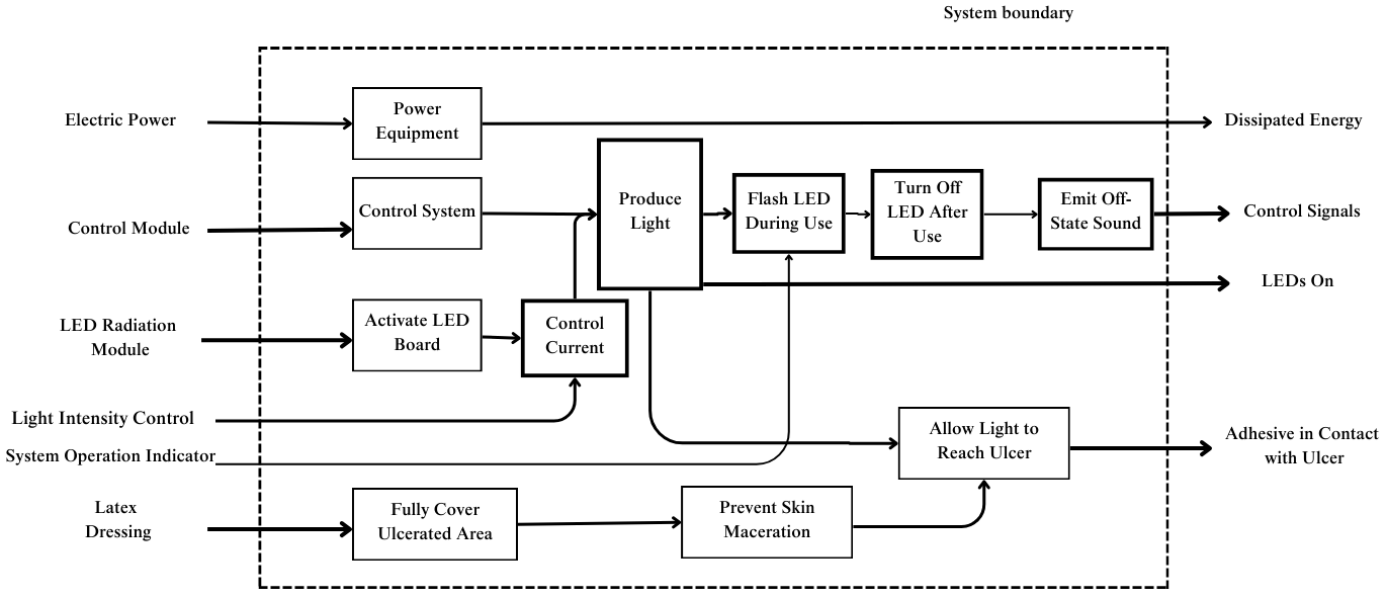
Figure 11 - Rapha® device in use: application on the patient during tissue regeneration treatment.

Source: Rosa, 2019.

5.2.2.3. Functional Modeling

In order to obtain a functional model for the Rapha® device, several versions were generated, with the chosen model being the one presented in Figure 12. This model was considered the most functionally suitable as it provides a clearer depiction of the operational activities of the device. Furthermore, the breakdown of the global function in this model enabled not only the generation of partial functions but also an additional breakdown into elementary functions.

Figure 12 - Functional Modeling of the Rapha® Device: Breakdown of the Global Function into Partial and Elementary Functions.

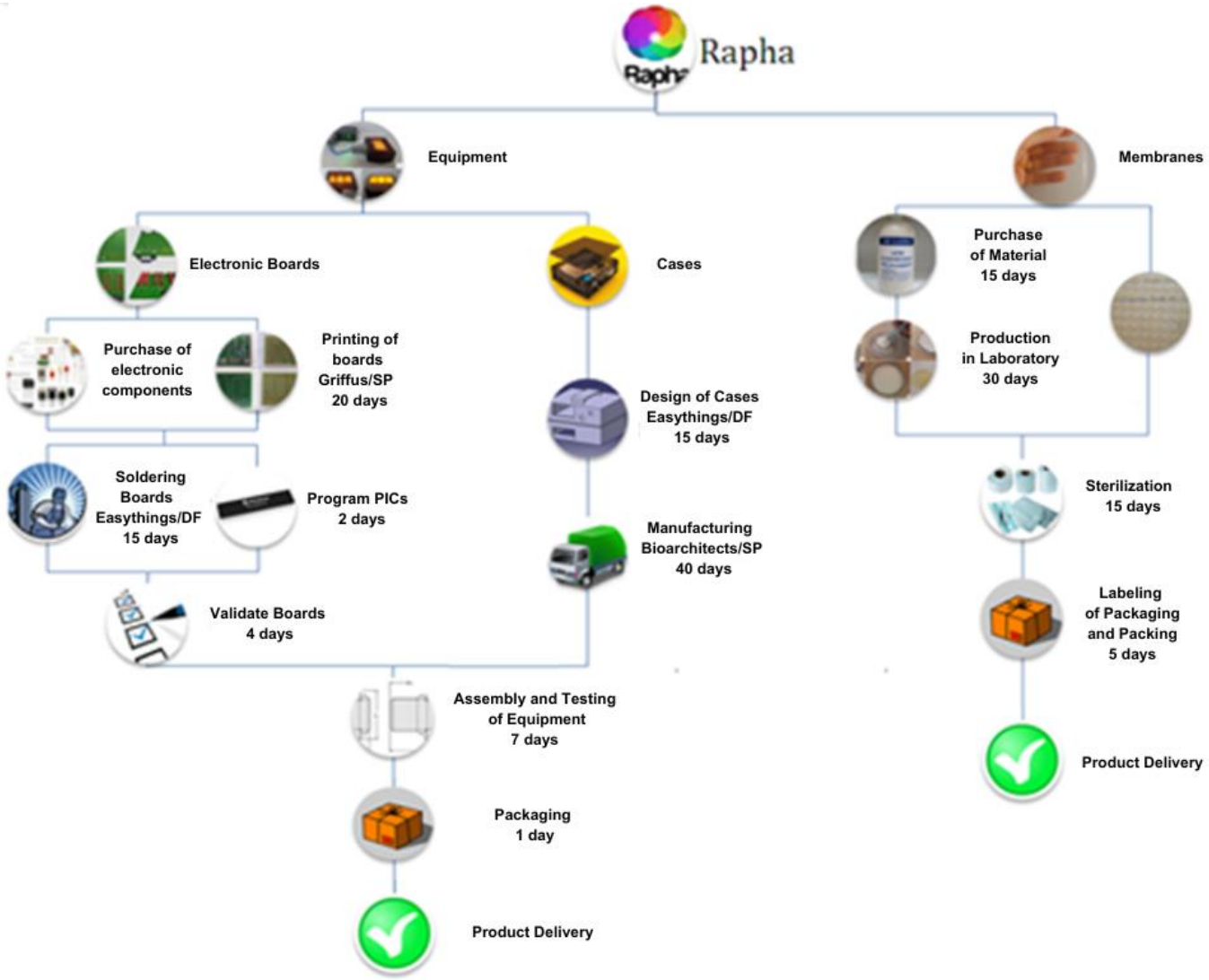


Source: Adapted from Rosa, *et al.,* 2023.

5.2.2.4. LED Device Production Process Specification

The production flowchart was developed by the Rapha® project team, with support from the Biomedical Engineering Laboratory at the University of Brasília. The production process for the Rapha® device encompasses various stages, focusing on the manufacturing of two main components which, when combined, form the final product: the device itself and the application sheets. The first stage involves producing the device, which is composed of two modules housed within a plastic casing, a switch, and two alkaline batteries. These modules undergo assembly, verification, and packaging. The second stage pertains to the production of the application sheet, which includes sourcing the material and its fabrication in both factory and laboratory settings, followed by sterilization, labeling, packaging, and final packing. Verification tests are conducted at each stage of the development process to detect potential errors. Additionally, the production stages are independent of each other and, in some cases, can be conducted in parallel, as illustrated in Figure 13 which provides a visual schematic of these stages.

Figure 13 - Flowchart of the Rapha® Manufacturing Process, Detailing the Production Stages.



Source: Adapted from Rosa, *et al.,* 2023.

5.2.2.5. Concept – Clinical Protocol and Patent Filing Text

Patent filing is one of the initial steps undertaken when seeking translation. The concept was materialized by a multidisciplinary group in the fields of engineering, health, and biology, representing the T0 phase, in which patents were identified according to protection number, registration date, title, managing institution, inventors/authors, academic units, department, type of protection, and classification by group and subgroup, as detailed in Table 4.

Table 4 - Patents Related to Rapha® Specifications Equipment.

PROTECTION NUMBER	FILING DATE	TITLE	MANAGING INSTITUTION	INVENTOR/ AUTHOR	ACADEMIC UNIT	DEPARTMENT	TYPE OF PROTECTION	CLASSIFICATION GROUP	CLASSIFICATION SUBGROUP
PI 1103692 3	07/18/2011	Shock-Absorbing Insole for Diabetic Feet	FUB	Maria do Carmo dos Reis	Faculty of Technology - FT	Department of Electrical Engineering - ENE	Invention Patent	Health	Medical-Hospital Equipment and Devices
				Suélia de Siqueira Rodrigues Fleury Rosa					
				Adson Ferreira da Rocha	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA			
PI 1103691 5	07/18/2011	Sensorized Insole for Diabetic Feet	FUB	Maria do Carmo dos Reis	Faculty of Technology - FT	Faculty of Technology - FT	Invention Patent	Health	Medical-Hospital Equipment and Devices
				Suélia de Siqueira Rodrigues Fleury Rosa					
				Adson Ferreira da Rocha	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA			
				Edson Alves da Costa Júnior	Faculty of Technology - FT	Department of Electrical Engineering - ENE			
PI 1103690 7	07/18/2011	Healing Insole for Diabetic Feet	FUB	Maria do Carmo dos Reis	Faculty of Technology - FT	Faculty of Technology - FT	Invention Patent	Health	Medical-Hospital Equipment and Devices
				Suélia de Siqueira Rodrigues Fleury Rosa	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA			
				Adson Ferreira da Rocha	Faculty of Technology - FT	Department of Electrical Engineering - ENE			
BR 10 2016 019963 8	08/29/2016	Micro-Perforated Adhesive Made of Latex, Associated with LED Light Sources for Direct Application in Human Internal and External Inflammatory Processes	FUB	Suélia de Siqueira Rodrigues Fleury Rosa	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA	Invention Patent	Health	Biomaterials and Biomolecules
				Mário Fabrício Fleury Rosa					
				Pedro Henrique Gonçalves Inazawa	Faculty of Technology - FT	Department of Electrical Engineering - ENE			
				Aroldo Kenkichi Inazawa					
BR 10 2017 014239 6	06/29/2017	Structural Design Applied to Foot Prosthesis with Elastic and Shock-Absorbing Characteristics and Its Method for Quantifying Mechanical Energy to Be Reused	FUB	Suélia de Siqueira Rodrigues Fleury Rosa	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA	Invention Patent	Health	Assistive Technology
				Danilo dos Santos Oliveira					
BR 13 2021 001944 0	02/02/2021	Latex-Based Biomembranes (Hevea brasiliensis) Containing Liposome with Curcumin (Curcuma longa) and Papain (Carica	FUB	Marcella Lemos Brettas	UnB Planaltina Faculty - FUP	UnB Planaltina Faculty - FUP	Certificate of Addition	Health	Biomaterials and Biomolecules
				Franciéle de Matos da Silva					
				Wellington Rodrigues	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA			
				Suélia de Siqueira Rodrigues Fleury Rosa					

		papaya) and Its Use Associated with LED Therapy for Treating Chronic Ulcers and Diabetic Wounds		Breno Amadeus Sales Marinho de Sousa	Institute of Biological Sciences - IB	Institute of Biological Sciences - IB			
				Cesar Romero Soares Sousa					
				Ricardo Bentes de Azevedo					
				Thamis Fernandes Santanta Gomes	Institute of Biological Sciences - IB	Department of Genetics and Morphology - GEM			
				Jaqueline Rodrigues da Silva					
BR 10 2022 007175 6	04/13/2022	Portable Photodynamic Therapy Transducer for Use on Infected Wounds in Diabetic Feet	FUB	José Carlos Tatmatsu Rocha	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA	Invention Patent	Health	Medical-Hospital Equipment and Devices
				Suélia de Siqueira Rodrigues Fleury Rosa					
				Ludmila Evangelista dos Santos					
				Adson Ferreira da Rocha	Faculty of Technology - FT	Department of Electrical Engineering - ENE			
				Micael Felisberto de Noronha					
				Diogo de Oliveira Costa					
BR 51 2022 001637 0	07/01/2022	Claucia (Ulcer Classification Using Artificial Intelligence)	FUB	Marcella Lemos Brettas Carneiro	UnB Gama Faculty - FGA	UnB Gama Faculty - FGA	Software Program	Health	Diagnostic

Source: Author's Own Work.

Table 4 presents the various inventions developed based on the Rapha® Device, which have contributed knowledge and development across different contexts from 2011 to the present. It confirms the validation of phase T0, with the first patent registration in 2011 derived from Dr. M. C. Reis's doctoral thesis, along with subsequent contributions and improvements to the device. This process highlights the nonlinear nature of translational research. Furthermore, the work conducted demonstrates interdisciplinary collaboration across biomedical engineering, health, and biology fields, in conjunction with Technological Innovation Center at CTD, the Department of Intellectual Property at UnB, which managed the various processes and stages required for patent filing. Consequently, the nonlinear progression of research stages to achieve translation is evident in phases T2 and T3; the former involves clinical research, and the latter encompasses regulatory aspects and technology transfer. These phases depend exclusively on ethical clearance and patent filing. Therefore, activities related to phases T2 and T3 were previously incorporated by phase T0, through the clinical protocol actions and patent filing, following a nonlinear chronological logic.

5.3. Second Phase of Technology – Pre-Clinical or Non-Clinical Testing (T1)

Pre-clinical tests were conducted with both *in vitro* and *in vivo* samples. The following tests are presented by topic.

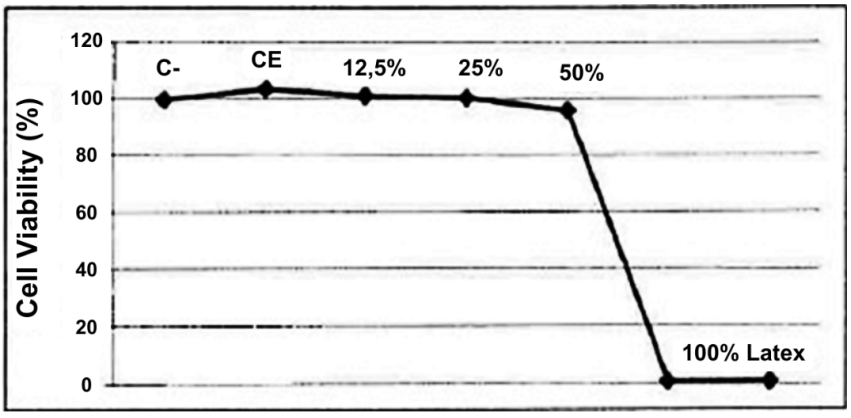
5.3.1. Biocompatibility Tests

Biocompatibility tests were performed on the natural latex membrane. The LED equipment does not make direct contact with the patient's skin during treatment, as the latex membrane acts as a barrier between the device and the skin. Thus, the device was exempted from these tests.

5.3.2. *In Vitro* Cytotoxicity Potential Assessment

The cytotoxicity of the natural latex membranes was evaluated in V-79 cell lines. These fibroblasts were cultured in plates and exposed to various concentrations of the extraction medium (100%, 50%, 25%, and 12.5%) for 24 hours. After this period, an MTT solution (1mg/ml) was added, and samples were incubated for an additional 2 hours, followed by the addition of isopropanol. Absorbance analysis was performed at 570 nm, with 650 nm used as a reference. The results indicated that the natural latex membranes did not exhibit cytotoxicity toward V-79 cells at concentrations of 50%, 25%, and 12.5%, as cell viability remained close to 100%. However, at a 100% concentration, a drastic reduction in cell viability to approximately 0% was observed, representing a reduction of nearly 100% relative to the control. This outcome indicates extremely high cytotoxicity at this concentration, nearly eliminating the viability of V-79 cells, as illustrated in Figure 14**.**

Figure 14 - Reduction in cell viability of the natural latex membrane sample at concentrations of 100%, 50%, 25%, and 12.5% after 24-hour exposure.



Source: Adapted from ROSA *et al.*, 2023.

5.3.3. Intracutaneous Reactivity Toxicological Test in Rabbits

The objective of this test was to evaluate the skin reactivity of natural latex membranes through intradermal injections in rabbits (*Oryctolagus cuniculus*). Following the depilation of the dorsal region along the spine, a sample was prepared with a proportion of 0.1 g of latex diluted in 1.0 ml of sterile saline solution and subjected to a water bath at 37°C for 72 hours. Three rabbits were administered with 5 injections on the left side with the sample and 5 injections on the right side with the control solution. Observations were made at intervals of 1, 24, 48, and 72 hours post-injection. After 1 hour, edema was observed in both the sample and control areas, with complete regression within 24 hours. No systemic toxicities were identified. The resulting score, comparing the sample reaction with the control, was 0.0. It was concluded that the natural latex membranes did not demonstrate intracutaneous reactivity in the tested rabbits.

5.3.4. Skin Sensitization Test in Guinea Pigs – Buehler Method

This test aimed to evaluate the potential for skin sensitization of natural latex membranes in guinea pigs (*Cavia porcellus*). The animals were divided into two groups: an EG with 10 animals (5 males and 5 females) and a CG with 5 animals (3 males and 2 females).

The animals' flanks were shaved. In the EG, latex was applied to the left flank, while the CG received only gauze dressings. These applications, each lasting 6 hours, were performed weekly over three consecutive weeks, constituting the "induction phase." After an 11-day interval, a "challenge" was conducted on the 28th day, during which both the sample and control were administered to the right flank of the animals. Evaluations were conducted 24 and 48 hours after the dressings were removed, focusing particularly on the presence of erythema and edema, according to the parameters established by the Guidelines for Testing of Chemicals: Skin Sensitisation (406) (BRAZIL, 1985).

No cutaneous irritation reactions, erythema, or edema were observed on the right flanks of the animals following the challenge phase. Thus, under the test conditions, the natural latex membranes were classified as non-sensitizing to the skin of guinea pigs. Table 5 provides information on the sensitization assessment during the induction period and 24 and 48 hours after removing the dressings in the control and EGs (SHIMADA, 2018; ROSA *et al*., 2023).

Table 5 - Sensitization Assessment during the Induction Period and 24 and 48 Hours after Dressing Removal in the CGs and EGs.

Group	Animals	Sex	Skin Evaluation		
			Clinical Signs	24 h	48 h
Control	1	Male	N/A	0	0
	2		N/A	0	0
	3		N/A	0	0
	4	Female	N/A	0	0
	5		N/A	0	0
Experimental	6	Male	N/A	0	0
	7		N/A	0	0
	8		N/A	0	0
	9		N/A	0	0
	10		N/A	0	0
	11	Female	N/A	0	0
	12		N/A	0	0
	13		N/A	0	0
	14		N/A	0	0
	15		N/A	0	0

Source: Adapted from SHIMADA, 2018.

5.3.5. Dermal Toxicity Test with Repeated Doses (28 Days) in Rats

The study, approved by the Ethics Committee on Animal Use of ALS Laboratories Ltd., aimed to elucidate the potential systemic toxic effects resulting from dermal exposure to latex membranes over 28 days in Wistar rats. The study included anatomopathological, hematological, and biochemical analyses.

The test was conducted in accordance with ISO 10993:11 – Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity, 2017.

During the experiment, 20 young, healthy adult Wistar rats, consisting of 10 males and 10 females, were divided into groups of 5 animals per sex and subjected to repeated applications, five times per week, over a 28-day period, totaling 20 applications of the latex membranes, which were applied topically to the experimental (n=10) and control (n=10) groups. The EGs were exposed to latex membranes measuring 2.5 x 2.5 cm (6.25 cm^2 area) on a pre-trimmed body surface. Meanwhile, the CG was exposed to sterile gauze moistened with demineralized water, applied directly to the shaved skin and covered with a semi-occlusive dressing for five consecutive days, monitored over a 28-day period.

Throughout the study, the rats' weight and food consumption were monitored, along with individual clinical observations. At the end of the experiment, blood samples were collected for analysis, and macroscopic and histopathological evaluations were conducted.

Exposure to the latex membrane, evaluated over a 28-day period following the final exposure, did not induce mortality in the animals from the EGs. No evident clinical signs of toxicity associated with the test item exposure were observed during the study period. No clinical signs or mortality were observed in the CG either. Food consumption and weight gain in both the experimental and CGs did not show statistically significant differences. Additionally, during necropsy, no macroscopic changes were found in the organs and tissues evaluated in both control and EGs across sexes.

Exposure to the latex membranes did not induce significant changes in body weight, food consumption, hematological, or biochemical parameters, except for isolated variations in some indices in females. Notably, no mortality or clinical evidence of toxicity was observed in either the ECs or CGs. Moreover, microscopic evaluations revealed no histological lesions in the organs and tissues of the animals, suggesting no toxicity. In summary, the results, based on multiple assessments and measurements, refute the hypothesis of toxicity associated with exposure to latex membranes.

The data obtained from this study are described and annexed to the study: Development and Application of Therapy Based on Latex Biomembranes *(Hevea Brasiliensis)* Containing Liposome with Curcumin (*Curcuma Longa*) and Papain *(Carica Papaya)* Associated with LED Therapy for Wound Treatment in Diabetic Wistar Rats *(Rattus Norvegicus)* (SANTANA, 2021).

5.4. Third Phase of Technology – Clinical Trials in Humans (T2)

This clinical study is part of the Rapha® project and aimed to evaluate the clinical progression of ulcer healing in two distinct groups: the EG and the CG. The first group used the Rapha® technology daily at home, with in-person assistance from the research team once a week, daily remote monitoring, and biweekly evaluations at the clinic. The second group (CG), however, received treatment following the SUS protocol, with weekly dressings or as needed, under the responsibility of the clinic nurses.

5.4.1. Regulatory Aspects for the Clinical Phase and Private Sector Involvement in the T2 Translation Phase

The results of clinical studies are essential for the regulatory approval process, as they help ensure the safety and effectiveness of medical products and healthcare equipment. Due to the importance and characteristics of clinical studies, regardless of the funding institution, they involve commercial or scientific motivations that may occasionally conflict with issues related

to the protection of research patients. In this context, ethical approval is of paramount importance, as is the approval of clinical trials by ANVISA.

Technical Note No. 004/2016/GGTPS/DIREG/ ANVISA establishes requirements and guidelines for conducting clinical trials on medical devices seeking registration and certification with ANVISA, aiming to ensure their safety and efficacy. According to the technical note, clinical trials conducted in Brazil for innovative products—regardless of risk class—as well as for risk classes III and IV products, due to their complexity and potential health impact, must be supported by robust clinical studies that demonstrate the specific safety and efficacy of the product, in accordance with RDCs 10/2015 and 548/2021 or preceding standards (ANVISA, 2016).

These clinical studies must follow Good Clinical Practices and meet ANVISA's methodological requirements, being divided into phases: pilot studies to evaluate initial safety and feasibility, and pivotal studies that confirm efficacy and safety in a larger population. The documentation submitted to ANVISA must include a detailed protocol, covering aspects such as study design, inclusion and exclusion criteria, primary and secondary safety and efficacy outcomes, statistical analysis, and sample size justification. Furthermore, it should be noted that for clinical trials conducted in Brazil, obtaining a "Special Notice" is mandatory for higher-risk products (classes III and IV), or a "Specific Special Notice" for lower-risk products (classes I and II) from ANVISA. The absence of these notices in the registration dossier may lead to additional technical requirements or even invalidation of the clinical data submitted for product registration or certification (ANVISA, 2015; ANVISA, 2021).

Given this, clinical studies must necessarily have their design defined before submission and approval by the regulatory agency, in the form of the aforementioned protocol. This document outlines the study plan, objectives, methodology, and statistical considerations to enable evaluation and monitoring of the tests. In this context, the participation of qualified private sector entities in the T2 phase is crucial to overcoming the "valley of death." The involvement of the private sector at this stage can have a significant impact on market approvals, helping to accelerate the translation process and guiding the research toward production and manufacturing of the health equipment in compliance with Good Manufacturing Practices (GMP), as an example.

From a market and regulatory perspective, the Rapha® device benefited from the involvement of the company INOVATIE, which guided the clinical trials and the development of the investigator’s brochure to meet the necessary regulatory and ethical requirements for market entry. Initially, another private company significantly contributed to the development of

production and manufacturing designs, with direct involvement in the research. However, this company did not continue with the market development of the equipment, which was completed by the research team in partnership with INOVATIE. This collaboration helped overcome the "valley of death" and complete the phase III clinical trial. The notification of the clinical trial's completion was filed with ANVISA under protocol number 2505352.1222-2021-2019, reference 80131 (Appendix I). To date, ANVISA has not provided a response to this notification.

Finally, three clinical studies were conducted to assess the efficacy and safety potential of the Rapha® Device. These studies are described in the following sections.

5.4.3. First Clinical Trial

A significant milestone in medical research took place at the HRT in Taguatinga – DF, with the first clinical trial using the preliminary version of the Rapha® device. This study not only assessed the safety of this innovative system but also estimated its efficacy.

The study design strictly adhered to Resolution 196/96 of the National Health Council and received approval from the CEP of the Health Sciences Teaching and Research Foundation of the Federal District Health Department, under protocol No. 052/2012-CEP/SES/DF. Between August and December 2013, six participants with a total of eleven ulcers participated in the research program. The studies disclosed below present findings from Reis, 2013 and Rosa *et al*., 2016, among others cited throughout the text.

The ulcers were divided between a CG, treated according to the standard SUS protocol, and an EG, treated with the Rapha® system.

In the CG, ulcers received traditional treatment for at least 30 days, with weekly follow-ups by the medical team. Following meticulous debridement and cleaning, a silver alginate-releasing foam dressing was applied, creating a moist environment crucial for healing, as noted by Brem *et al*., 2004. The dressing was changed every five days at home by the patient or a family member. However, on clinical evaluation days, the nurse responsible at the clinic performed the dressing change.

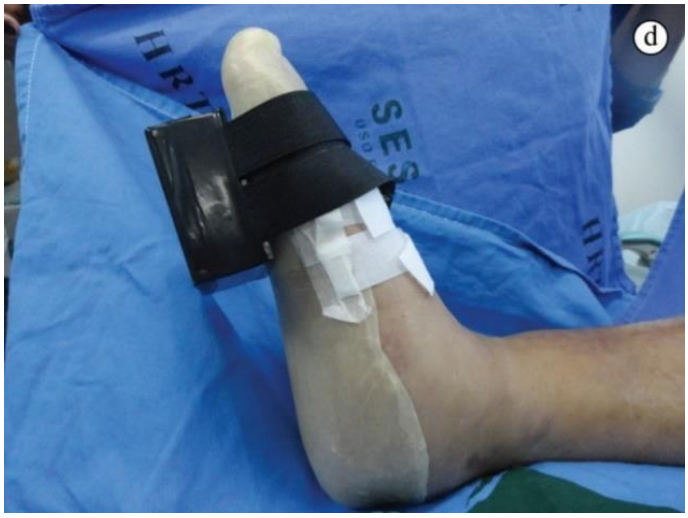
Conversely, the EG was treated with the tissue neoformation induction system, which consisted of a healing insole and an electronic tissue regeneration circuit and was followed weekly by the research team for varying periods. Once selected for the EG, the process began with taking a mold of the patient's foot to manufacture a personalized insole. Next, participants received detailed instructions on how to use the system at home, as the tissue neoformation induction system was designed exclusively for home use, requiring patients to clean the ulcer

with saline and gauze before application. The weekly follow-up by the healthcare team included debridement and re-cleaning of the ulcer, ensuring continuous and effective care.

The process involved inserting a sterilized latex sheet into the insole to cover the wound, positioning the LED cell (Rapha® device) over the ulcer, and covering it with cling film. The circuit was activated to emit light for 35 minutes, after which an alarm signaled the end. After use, the insole was covered with gauze and bandage to absorb secretions, and was worn for at least 10 hours daily, while the sheet remained in contact with the wound for 24 hours. The sheet was cleaned and replaced daily, with the insole being changed weekly.

It is recommended that the wound size be equal to or smaller than the surface area of the LED panel on the Rapha® device. In cases of larger wounds, it is advised to segment the treatment into successive applications over each part of the wound.

Figure 15 - Illustrates the use of the device by a participant in the EG.

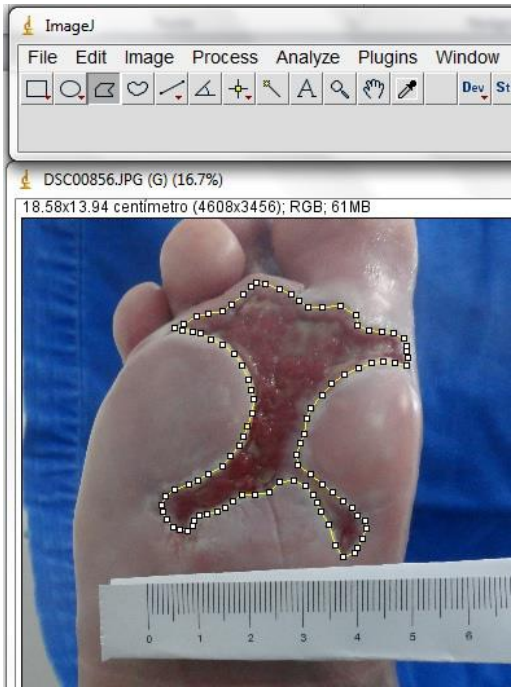


Source: Reis, 2013.

The medical team instructed participants from both groups to follow important recommendations, including glycemic control, the use of adapted or offloading footwear (or a wheelchair, depending on the location of the lesion), rest, and self-care for the wounds, such as avoiding wetting them during bathing and refraining from wearing inappropriate footwear. Adherence to these recommendations is essential for ulcer healing.

All participants were evaluated weekly, with data collection always conducted in person. Digital images of the ulcers were captured weekly throughout the treatment to quantify the total area of the lesions and monitor healing progress. The analysis of these images was performed using the ImageJ® software, as illustrated in Figure 16.

Figure 16 - Ulcer edge delineation using ImageJ® software.



Source: Reis, 2013.

After calculating the total ulcer area, the Ulcer Healing Index (UHI) was determined according to *Equation 1* below:

Equation 1

$$UHI = \frac{(A_i - A_f)}{A_i}$$

Where,

UHI – Ulcer Healing Index;

Ai – Initial area;

Af – Final area.

The UHI, as proposed by Robson *et al*., (2000), presents the following analyses (Reis, 2013; Rosa *et al*., 2016):

UHI = 1: represents total re-epithelialization (complete healing);

UHI = 0: no signs of re-epithelialization;

UHI > 0: reduction in ulcer area;

UHI < 0: increase in ulcer area.

The ulcer contraction was also evaluated as a percentage using the formula proposed by Al-Watban (2003) and Yu (1997), as shown in *Equation 2* below:

Equation 2

$$UCR = \frac{(A_i - A_f)}{A_i} \times 100$$

Where,

UCR – Ulcer Contraction Rate;

Ai – Initial area;

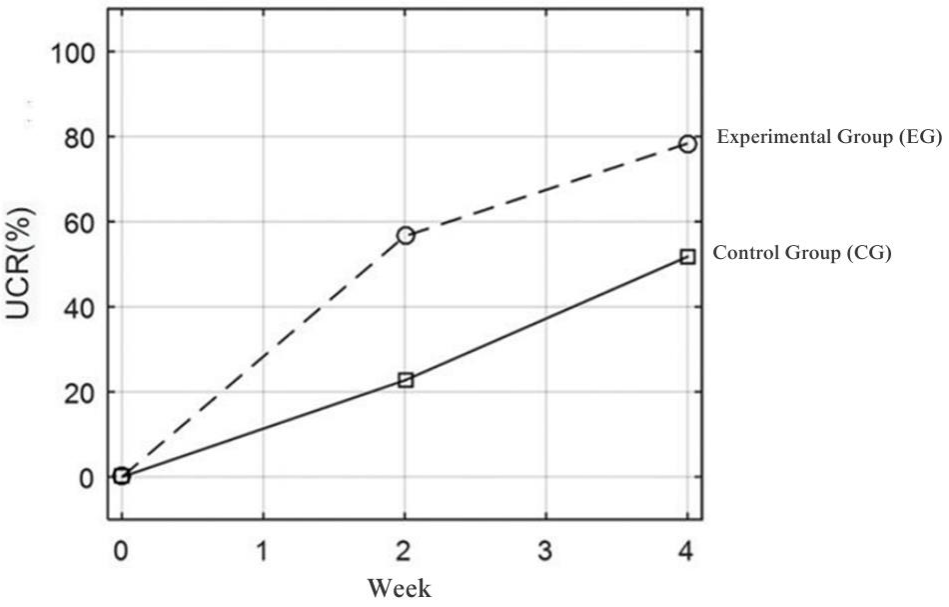
Af – Final area.

In general, most participants followed the recommendations to assist in healing (rest, use of offloading or appropriate footwear, and ulcer self-care). No side effects were reported or observed during the study with the tissue regeneration-inducing system. The only inconvenience reported by participants while using the system was a mild odor, attributed to the natural smell of rubber (latex) combined with skin perspiration.

Specialist physicians considered the results obtained by the tissue regeneration-inducing system to be very satisfactory. This positive feedback is supported by the qualitative and quantitative analyses of clinical tests, which indicated that the EG showed better results than the CG. Therefore, the combined analysis of the results and data suggests that this system could be an effective treatment for diabetic foot ulcers, thanks to its high healing-inducing potential, ease of application, potential for home use, and low cost.

Figure 17 illustrates the percentage healing progress of ulcers (UCR%) in the EG and CG over four weeks of treatment. The chart shows the initial situation and the healing progress at weeks 2 and 4, indicating that the difference between the results of the two treatments was statistically significant ($p<0.001$), with a faster recovery rate in the group treated with the Rapha® system compared to the CG. These results represent the first evidence related to the safety and efficacy of the Rapha® system.

Figure 17 - Ulcer border delineation using ImageJ® software.



Source: Rosa *et al*., 2016.

5.4.4. 2nd Clinical Trial

This second clinical trial, a randomized, controlled, double-blind study, was approved by the Human Research Ethics Committee of Foundation for Education and Research in Health Sciences and conducted at outpatient clinics in HRAN and HRG, as well as in the homes of 94 qualified patients. These patients, suffering from neuropathic diabetic foot ulcers, had lower limb lesions and showed no hypersensitivity to latex. The study presented below references the studies of Reis, 2013 and Rosa *et al*., 2023.

The participants were divided into three groups:

a) **Group I (GI):** Participants received treatment with RAPHA®, applied daily at their residence. Nurses conducted home visits twice a week, and every two weeks, the participants underwent an evaluation at the wound care clinic of the HRC-DF

b) **Control Group (GII):** Participants were treated with calcium alginate or silver foam dressings, applied by nurses at the wound care clinic twice a week, following the standard protocol of the Brazilian SUS.

c) **Group III (GIII):** Participants self-applied RAPHA® daily at their residence after receiving training. Every two weeks, they underwent a clinical evaluation at the wound care clinic of the HRC-DF.

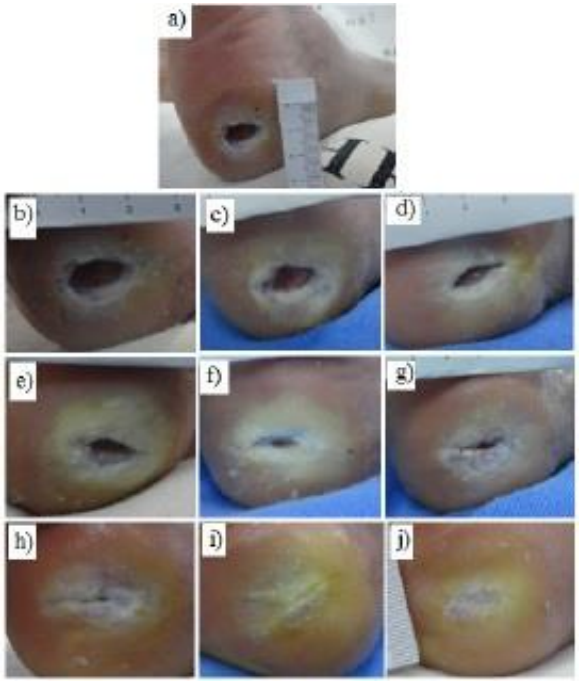
During the study, records and text messages related to each participant were collected to gather as much information as possible and create a timeline of the body's responses to the treatment. These data allowed for a detailed assessment of aspects related to comorbidities, inspection of lesions, and quality of life for patients in both groups. Comorbidities and lesion status were analyzed based on the Texas Brodsky Scale criteria, while quality of life was measured using the Short-Form 6 Dimensions (SF-6D) Quality of Life Questionnaire – Brazil. Pain was assessed during dressing changes and its impact on daily life, considering the burdens caused by the presence of the wound.

In the sample, 60.18% were men and 39.82% were women, with an average age of 60 years. Lesion evaluation revealed that 60% were superficial, 26.7% involved tendons, and 13.3% were infected. Ankles and feet were the most affected areas. The average duration of lesions was 25 months, with a minimum of two months and a maximum of 120 months. The most notable quality of life impairments involved functional capacity, social aspects, general limitations, and pain.

Additionally, 46.7% of participants had undergone amputations due to ulcers that had persisted for approximately five years. It was observed that 60% reported mobility dependency. All ulcers included in the study were neuropathic.

Figures 18, 19 and 20 illustrate the healing progression under the intervention of Rapha®.

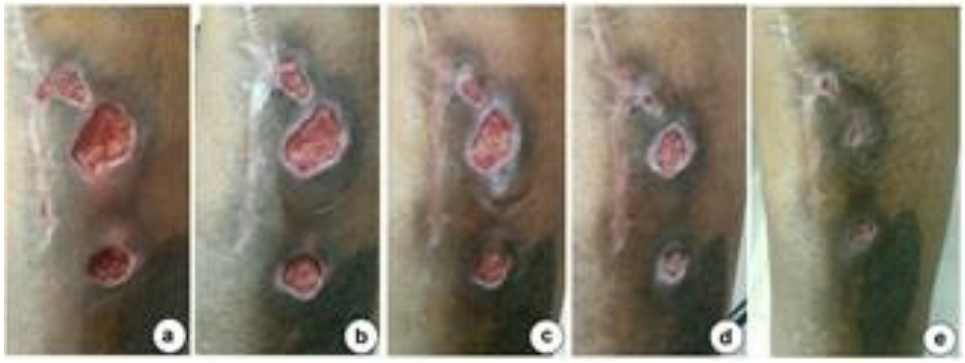
Figure 18 - Photographic record of the clinical follow-up of a participant from the EG.



Source: Reis, 2013.

(a) Initial image of the ulcerated area; (b) condition of the ulcer before treatment initiation; (c) progress after 1 week of treatment; (d) after 2 weeks; (e) after 3 weeks; (f) after 4 weeks; (g) after 5 weeks; (h) after 6 weeks; (i) after 7 weeks; (j) after 8 weeks, showing progressive wound closure throughout the treatment.

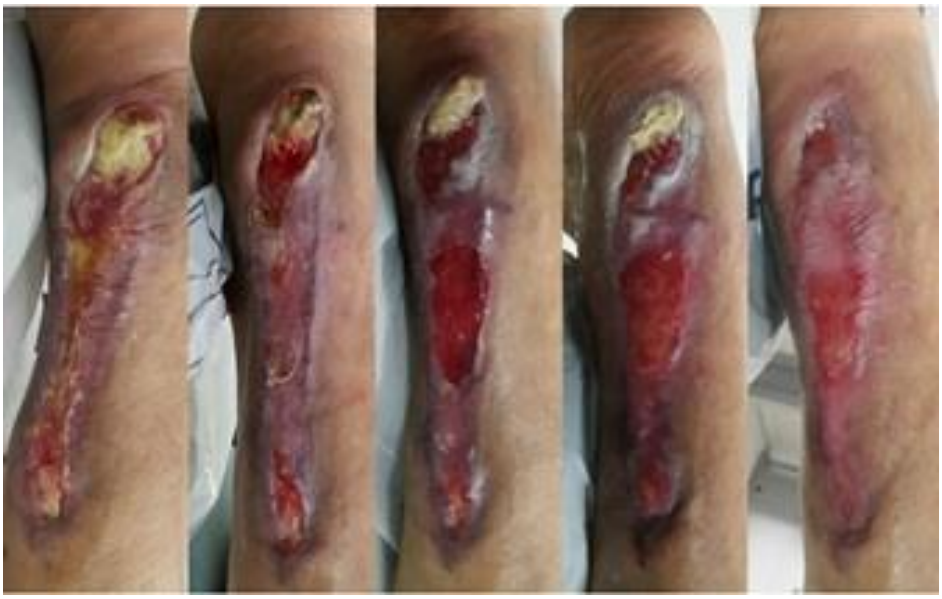
Figure 19 - Photographic Record of the Healing Process of a Participant from the EG.



Source: Rosa, *et al.,* 2023.

(a) Condition of the ulcer before the start of treatment; (b) progress after 1 week of treatment; (c) after 2 weeks; (d) after 4 weeks; (e) after 6 weeks.

Figure 20 - Photographic Record of the Healing Process of a Participant from the EG.



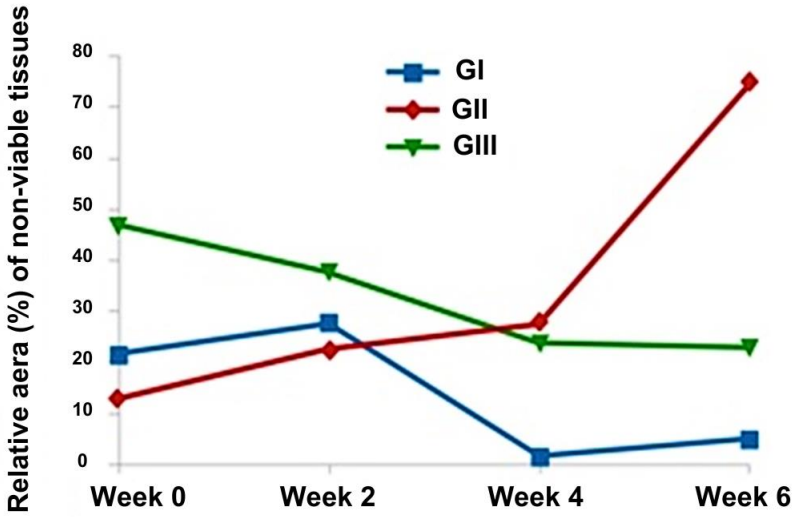
Source: Rosa, *et al.,* 2023.

(a) Condition of the ulcer before the start of treatment; (b) progress after 1 week of treatment; (c) after 2 weeks; (d) after 4 weeks; (e) after 6 weeks.

The latex biomembrane showed good adhesion, facilitating keratinocyte proliferation and consequent tendinous and dermal reconstruction. During the study, 33% of participants in both groups (EG and CG) developed new ulcers. This phenomenon can be attributed to the complex causes of diabetic ulcers. Notably, patients treated within the public healthcare system (SUS) exhibited more pronounced hemodynamic and metabolic imbalances, making them more susceptible to new lesions. Other observed causes included micro-traumas, prolonged static posture, and inappropriate footwear.

Systemic effects of photobiomodulation were observed, with a significant, albeit short-term, increase in T lymphocyte proliferation. A progressive reduction in the percentage of non-viable tissues was noted throughout the study in participants treated with the Rapha® Equipment (EG). Conversely, an increase in the proportion of these non-viable tissues occurred in the lesions of individuals undergoing conventional treatment (silver foam dressings, Group II – CG), resulting in significantly higher values – Group II (74.7%, $p<0.05$) compared to those observed in Group I (4.9%) and Group III (23.1%) after six weeks of therapeutic procedures, as shown in Figure 21.

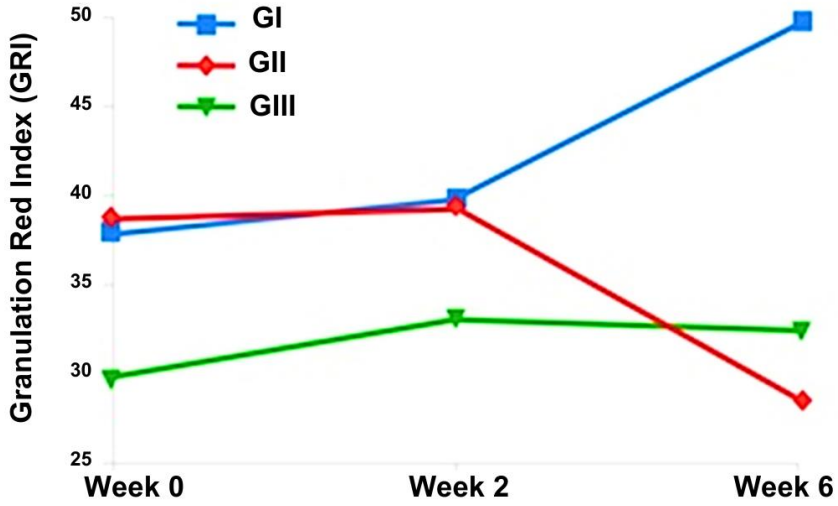
Figure 21 - Relative areas (%) of non-viable tissues on the wound surface of diabetic participants undergoing a clinical trial after 2, 4, and 6 weeks.



Source: ROSA *et al*., 2023.

The quality of granulation tissue was evaluated using the Granulation Red Index (GRI). According to Figure 22, there was an increase in the GRI in all groups after one week of treatment. However, after 4 weeks, only the groups treated with Rapha® (Group I and Group III) maintained improvement in the GRI. Conversely, the group following conventional treatment (Group II) showed a significant decrease in this index, with values of 28.3, which were significantly lower than those in Group I (49.4, $p<0.05$) and Group III (32.1, $p<0.05$).

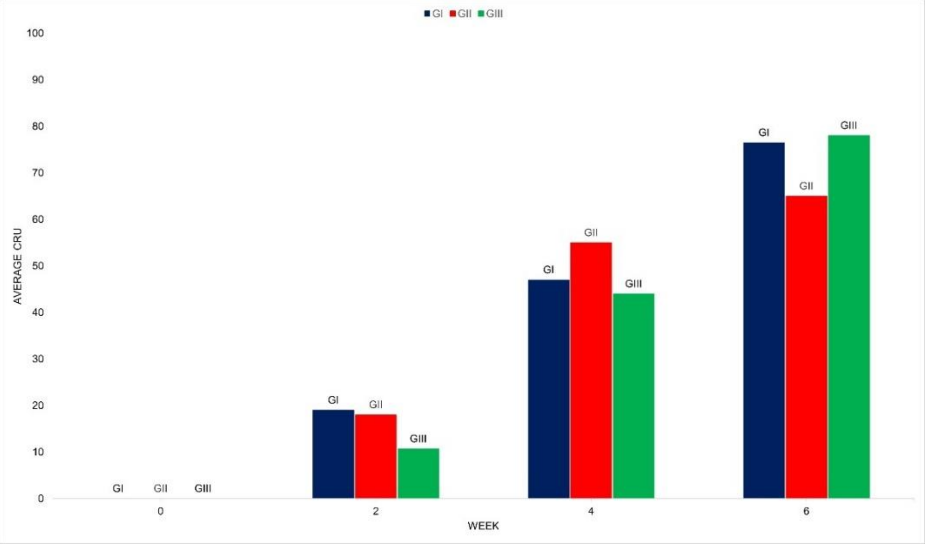
Figure 22 - Evolution of the GRI of ulcers in participants undergoing a clinical trial over a period of 6 weeks.



Source: ROSA *et al*., 2023.

Six weeks after the start of treatment, a reduction in ulcer area is evident in all groups. Figure 23 - illustrates the average UCR (Healing Rate Index) of ulcers for each group at weeks 0, 2, 4, and 6, highlighting the healing progress throughout the treatment.

Figure 23- Healing rate index of the ulcer healing process for the same treatment weeks.



Source: ROSA *et al*., 2023.

The Mann Whitney test was used to discern statistical differences between the initial and final areas of ulcers in different treatment groups. The EGs treated with the Rapha® system (Group I and Group III) showed significant statistical differences ($p = 0.017$ and $p = 0.050$, respectively). In contrast, the group receiving conventional treatment (Group II) showed no statistical difference ($p = 0.421$).

These data underscore the effectiveness of the Rapha® system in accelerating the healing of diabetic foot ulcers compared to the standard protocol of the SUS adopted in HRAN and HRG hospitals. It is important to note that the Rapha® system consistently met the operational standards set by national quality regulations.

The benefits of the Rapha® system are even more apparent when comparing the progress of Groups I and III to Group II. The first two groups experienced significant improvements in all stages of healing: granulation tissue formation, reduction of non-viable tissues, wound contraction, and edge closure. A more in-depth analysis of these results can be found in the study by Rosa *et al*., 2023.

5.4.5. 3rd Clinical Trial

Another randomized, double-blind clinical trial was conducted to evaluate the efficacy and safety of the combined use of the latex-derived biomembrane (Hevea Brasiliensis) and the LED light-emitting device on diabetic ulcers of the lower limbs. Preliminary tests were also conducted using LEDs of different colors, but the main focus was on red LED. This study was developed in the later stages and incorporated into the researcher's brochure for protocol submission to ANVISA.

The study chose to compare the Rapha® system with the standard SUS treatment instead of using a placebo due to ethical considerations. Thus, the system's efficacy was assessed in comparison to the standard treatment provided by the SUS, similar to the experiment described in section 4.3.2 of this work.

The primary objective of this trial was to evaluate the efficacy of combining latex biomaterial (biomembrane derived from natural latex) and the red LED light-emitting device, with a wavelength range of $\lambda = [650 \pm 20$ nm, 500 mW], to determine, within this therapeutic range, the optimal amount of J/cm² provided by each wavelength and its effect on fibroblast cell proliferation. Additionally, initial tests were performed on a smaller number of wounds using the Rapha® device with LEDs in blue, yellow, and green colors.

The sample involved 94 participants, representing 113 ulcers, from HRAN and HRG. Participants were divided into five treatment groups, but this analysis primarily focused on the CG and the group treated with the Rapha® system using red LED.

Participants remained in the study for approximately 90 days and were randomly assigned to treatment groups according to a computer-generated randomization list. Randomization was conducted in blocks of 2 and 4 and was stratified by center and ulcer size in the diabetic foot (1–10 mm², 11–20 mm²). Allocation concealment was ensured by using opaque, sealed, and sequentially numbered envelopes.

The research groups consisted of five: CG – standard SUS protocol; EG – Rapha® protocol with red LED light emitter; EG– Rapha® protocol with blue LED light emitter, EG – Rapha® protocol with yellow LED light emitter, and EG – Rapha® protocol with green LED light emitter. However, this section focuses only on the two main groups: the CG (CG) and the group using the Rapha® protocol with red LED (EG). The analysis with these two groups will support the ANVISA approval request.

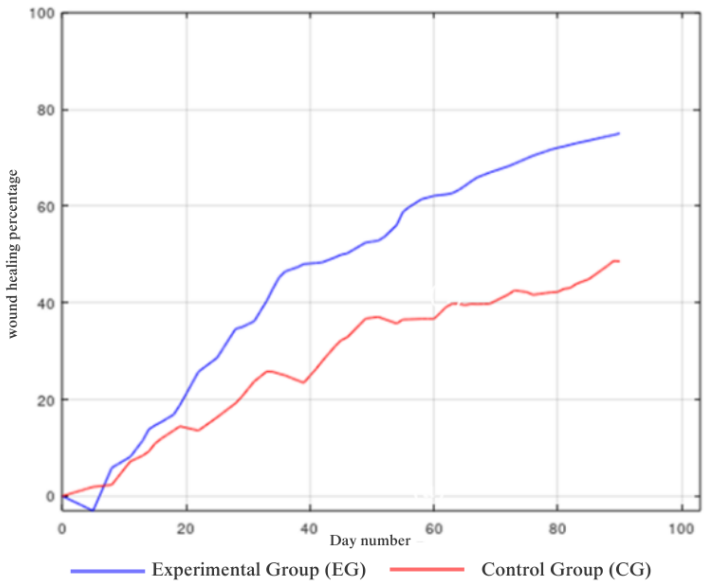
The treatment protocols varied. The CG used standard SUS dressings, while the EG used the biomembrane and phototherapy from the red LED emitting device, with patients self-

administering at home and receiving visits from research team members. The evaluation period lasted for 90 consecutive days, and the collected data were analyzed both qualitatively and quantitatively. Treatment in both the EG and CG followed a similar protocol to a previous section of the study, using the UCR (%) parameter to evaluate wound area.

In the analysis, the EG was treated with the Rapha® system with red LEDs, totaling 72 volunteers with an average height of (169.46 ± 10.36) cm (mean ± standard deviation). The EG included a relatively large group of wounds with areas significantly larger than those in the CG, resulting in a higher average value, which skews the results as larger areas tend to require a longer period for complete healing. For a more accurate assessment of healing, data from wounds larger than 20 mm² were excluded, and, as previously mentioned, non-randomized wounds were disregarded. After these adjustments, the EG, composed of 26 men and 13 women, recorded a total of 65 wounds. The CG presented 22 wounds, with participants having an average height of (165.9 ± 6.9) cm. The initial mean area of their wounds was (8.05 ± 5.99) mm².

Figure 24 presents the mean curves of the CG and the EG volunteers with initial wounds of up to 20 mm², as represented by Equation (2), which relates the percentage of closed area to the number of days since treatment initiation, a widely used metric in healing assessments. Over 90 days, the average wound closure was 48% in the CG, while the EG achieved 74%, highlighting the efficacy of the Rapha® device.

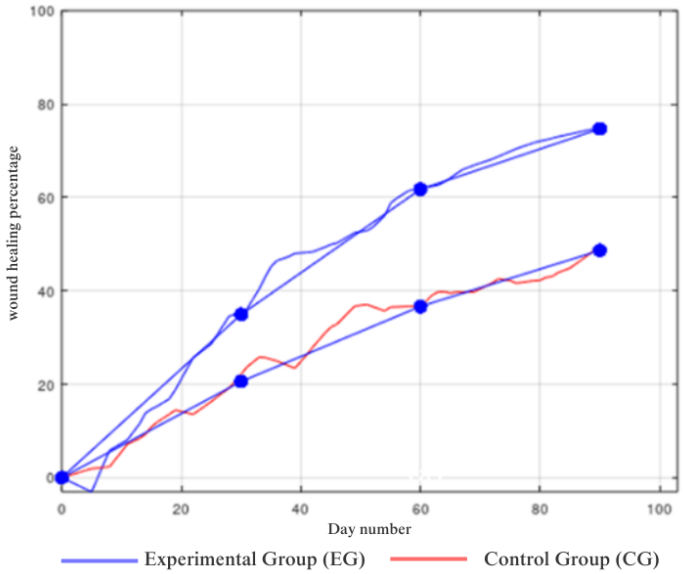
Figure 24 - Healing progress percentage of EG and CG.



Source: Rosa, *et al.*, 2023.

The results in Figure 25 show that the healing rate is visually higher for the EG than the curve for the CG. To highlight this more clearly, the values of the curves on day 30, day 60, and day 90 were extracted for Table 6.

Figure 25 - Evolution of the percentage of wound area healed over time, highlighting the average values of each curve on days 30, 60, and 90.



Source: ROSA *et al.*, 2023.

The averages on these days are presented in Table 6.

Table 6 - Average curve values for GC and GE after 30, 60, and 90 days.

	GC (%)	GE (%)
Day 0	0	0
Day 30	20,587	34,940
Day 60	36,665	61,748
Day 90	48,649	74,682

Source: Rosa *et al.*, 2023.

The results presented in Table 6 are promising. However, observing Figure 25, we see that the curves are outlined by the averages of the interactions in groups GE and GC. Thus, it becomes essential to perform hypothesis tests to discern the statistical significance of these variations. In the presence of differences between points on two trajectories, we can resort to Student's t-test (parametric) for data with a Gaussian distribution or the Wilcoxon test (non-

parametric) in alternative situations. To determine the most appropriate method, the Lilliefors test, an adaptation of the Kolmogorov-Smirnov test, was used. The Lilliefors test is employed to verify data normality. It is particularly useful for small sample sizes, as it is more sensitive than other tests in identifying deviations from normality. Thus, the outcome of this test guides the choice between parametric and non-parametric tests. The specifics of the Lilliefors test, when applied to the curves of the percentage of healed area in GE volunteers with initial areas up to 20 mm², are detailed in Table 7.

Table 7 - Normality Tests and appropriate test decisions.

	GC (%)	GE (%)	GC (%) + GE (%)	GC (%)	GE (%)
Day 0	0	0	0	-	-
Day 30	20,587	34,940	14,353	0,500 (t-test)	< 0,4633 (t-test)
Day 60	36,665	61,748	25,083	0,500 (t-test)	< 0,001 (Wilcoxon)
Day 90	48,649	74,682	26,033	0,1124 (t-test)	< 0,001 (Wilcoxon)

Source: Author's Own Work.

The results in Table 7 show that all data for GC and the data for day 30 in GE can be adequately tested with Student's t-test (parametric). For GE data on days 60 and 90, the most suitable test is the Wilcoxon test.

Table 8 - Normality Tests and appropriate test decisions.

	GC (%)	GE (%)	GC (%) + GE (%)	GC (%)	GE (%)	GC (%) + GE (%)
Dia 0	0	0	0	-	-	-
Dia 30	20,587	34,940	14,353	< 0,001 (t-test)	< 0,001 (t-test)	< 0,011 (t-test*)
Dia 60	36,665	61,748	25,083	< 0,001 (t-test)	< 0,001 (t-test)	< 0,001 (t-test*)
Dia 90	48,649	74,682	26,033	< 0,001 (t-test)	< 0,001 (t-test)	< 0,001 (t-test*)

Source: Author's Own Work.

In Table 8, line 1 presents the hypothesis tests to assess changes between Day 0 and days 30, 60, and 90. The results for GC and GE are shown in the fifth and sixth columns, respectively,

while the sixth column also indicates whether there were statistical differences between GC and GE on these days.

The results in Table 8 allow for the following conclusions:

a) The traditional treatment, applied to GC, resulted in statistically significant improvements: the increases in healed area on days 30, 60, and 90 were, respectively, 20.587; 36.665; and 48.649.
b) The treatment with the Rapha® device, applied to GE, also resulted in statistically significant improvements. The increases in healed area for GE were substantially higher and statistically significant: 34.940; 61.748; and 74.682 on days 30, 60, and 90, representing gains of 69.7%, 68.4%, and 53% higher than those observed in GC, respectively.

The final comparisons led to the following conclusions:

f) The clinical trial results indicate excellent treatment efficacy;
g) No side effects related to the system's use were observed;
h) Home treatment proved effective, making the system attractive, especially as it aligns with the concept of deinstitutionalization, which is gaining significant importance.

This Phase III efficacy and safety study was approved by CONEP and the involved Ethics Committees, and its execution was reported to ANVISA. Upon study completion, the technical information and necessary documents related to the Rapha® product are being submitted to ANVISA for registration as a new health product in the country.

5.5. Fourth Phase of Technology – Technology Transfer, INMETRO Certification, ANVISA Registration, and Technology Incorporation (T3)

The R&D&I process for Rapha® has yet to complete its translation, as it is currently in the registration submission phase with ANVISA. The T3 phase of translating the Rapha® device encompasses four main aspects: (i) transferring the technology to a qualified private company that meets the minimum necessary requirements; (ii) certification with INMETRO; (iii) registering the device with ANVISA for commercial use; and (iv) incorporating the ANVISA-approved technology into public and private healthcare systems.

It is important to note that only a private company, through its business registration (CNPJ), can submit the technology for ANVISA's review, as universities lack this prerogative

in the case of the Rapha® device. This limitation applies to various universities, as many do not have accredited or qualified laboratories and environments for manufacturing and making the technology available on the market. Thus, while the university possesses the technical and scientific knowledge necessary for research and development, industrial-scale manufacturing must meet and be conducted in accordance with regulatory requirements, a role fulfilled by the private sector. Some exceptions to this rule exist, such as public research centers like the Oswaldo Cruz Foundation, the Butantan Institute, and the Scientific, Technological, and Innovation Institution), which have a complete R&D&I ecosystem structured to incorporate and develop technologies capable of covering the entire production and regulatory chain until ANVISA approval.

According to ANVISA's RDC 546/2021, certain medical devices are subject to certification within the SBAC framework as part of the proof of compliance with the essential safety and efficacy requirements established by ANVISA. For the Rapha® device, an INMETRO Compliance Certificate is required because the device has a LED, categorizing it as phototherapy equipment, which requires compliance with specific safety requirements. Thus, the qualified private company must submit the compulsory certification of medical devices in accordance with RDC 546:2021 and RDC 27:2011 to the PCB, established in Brazil and accredited by INMETRO.

For ANVISA registration submission, it is essential that the device already possesses the INMETRO Compliance Certificate and the “Investigator’s Brochure.” This document presents the technology from conception to manufacturing, ensuring the safety and efficacy of its application in the healthcare system. In this context, there is an integration between the research and development carried out by the university (including regulatory, ethical, and statistical aspects) and the regulatory process of large-scale production conducted by the private sector. After validation of the Investigator’s Brochure, the private company’s documentation, and the INMETRO Compliance Certificate by ANVISA, the technology receives official registration with ANVISA.

The incorporation of the technology into the healthcare system occurs through the registration and commercialization of the device for hospitals, medical centers, and, in some cases, pharmacies, depending on the nature of the healthcare product. This incorporation may be limited to the private system but can also be extended to the public health system if the technology is acquired by the MH for distribution to municipal and SES, or if it is nationally incorporated by the SUS through the CONITEC, a body linked to the MH. One of the ultimate

goals of the Rapha® device research is to enable its incorporation into SUS to benefit the public healthcare system.

Thus, private sector participation is essential in the T3 stage to facilitate the entry of the technology into the healthcare system after transferring the technology from the university to the company and registering it with ANVISA.

5.5.1. Technology Transfer

In the context of the Rapha® device, efforts began to identify capable companies to manufacture and commercialize the technology, aiming to fulfill the translation stages and integrate it into the Brazilian healthcare system. This process is enabled through technology transfer, or knowledge transfer, which involves transferring knowledge generated at the university to the productive sector, allowing it to be converted into products and services with a positive impact on society. To this end, initial conditions were defined to facilitate the licensing of the patented technology. The technology commercialization agency of the CTD at UnB evaluated that the technology was ready for licensing, allowing interested companies to obtain a license to manufacture and market the Rapha® device. In this process, a technology licensing agreement was established, a modality that authorizes the licensee to use the technology under the terms outlined in the contract, including various uses such as testing, scaling, and commercial exploitation. This type of technology transfer reduces risks and uncertainties associated with innovation absorption by the licensee, facilitating its transformation into a product or service for society.

Various actions and initiatives implemented by the Rapha® device development team demonstrate the efforts made by UnB to turn an R&D&I project into a new solution for diabetic foot ulcers. Among these was the selection of a company interested in the Rapha® device and qualified to manufacture and market the technology. This company was required to have an operating license issued by the state or municipality, as well as the authorization to operate and the Certificate of Good Manufacturing Practices and Health Product Control, both granted by ANVISA. The operating license, known as the operating permit, declares the legality of the company's operation, the authorization to operate authorizes the company to perform activities described for healthcare equipment, and the Certificate of Good Manufacturing Practices and Health Product Control certifies compliance with GMP. Thus, the company’s regulatory compliance with Health Surveillance through these documents is an essential requirement for registering the device with ANVISA, representing an essential initial step in the translation process during the T3 phase.

The production of the latex membrane was integrated into the translation process during phases T0 (concept), T1 (preclinical), and T2 (clinical), with support from CERTBIO at the Federal University of Campina Grande. This laboratory, accredited by ANVISA and INMETRO for biomaterial development and evaluation, is recognized as a Reference Center in Science and Engineering of Biomaterials in Brazil, operating sustainably and according to technological advancements by introducing quality management practices and developing products with national technology. It also plays a key role in the scientific training of undergraduate and graduate students.

The laboratory developed the necessary biomaterial units to meet the preclinical and clinical phases of the device. Meanwhile, the LED light-emitting device was initially developed by the research team. Subsequently, the company Easyglic - EasyThings Serviços em Tecnologia Ltda offered to take on the responsibility of advancing the device's development, contributing to the technological progress. The company carried out the technology transfer with CTD but did not complete the stipulated work plan to continue with the T3 phase of translation. As a result, another company, Life Care Medical Indústria e Comércio – Eireli, was sought out and assumed responsibility for continuing the technology transfer process and incorporating Rapha® into the Brazilian healthcare system. In 2022, a Confidentiality Agreement and a Technology Licensing Agreement for commercial use and exploration were signed between UnB/CTD and Life Care. These two legal instruments were conducted by Technological Innovation Center at CTD, the Department of Intellectual Property at UnB regarding the intellectual property rights for the use, development, and testing of the technologies “Sensorized Insole for Diabetic Feet” and “Healing Insole for Diabetic Feet,” filed with the INPI under no. PI 1103691-5 and PI 1103690-7, respectively, and exclusively owned by the University of Brasília Foundation (FUB, abbreviated from Portuguese, “Fundação Universitária de Brasília”).

Having completed this stage, the company committed to obtaining the INMETRO Compliance Certificate and preparing the “Investigator’s Brochure” for ANVISA registration. Currently, the company has already submitted the required documentation to obtain the certificate from INMETRO and has received support from the research group and the company INOVATIE to develop the “Investigator’s Brochure” for ANVISA registration. However, the risks related to incorporating the technology into the healthcare system still depend on the validation of documentation by INMETRO and ANVISA, as well as successful negotiations with healthcare systems. The Rapha® device thus faces the "valley of death" in the T3 phase,

with processes still ongoing, as these developments were not completed by December 2023, hence no conclusive results were reported in this study.

5.5.2. INMETRO Certification

Certain medical equipment requires an INMETRO Compliance Certificate or a Consolidated Test Report for regularization with ANVISA. For the Rapha® device, it is necessary to certify the LED device according to the criteria established in Normative Instruction No. 49, dated November 22, 2019. The specific legislation governing Certification and the Consolidated Report includes Resolution - RDC No. 27, dated June 21, 2011, and Ordinance No. 384, dated December 18, 2020. Therefore, compliance certification for this equipment or issuance of the aforementioned report must be conducted by PCB, accredited by INMETRO.

According to Ordinance No. 384, dated December 18, 2020, the requirements apply to medical, dental, laboratory, or physiotherapy equipment — including their parts and accessories — intended for diagnosis, treatment, rehabilitation, and monitoring of human beings, as well as equipment for aesthetic and beautification purposes.

The conformity assessment process consists of several stages, each following a specific sequence of procedures. Ordinance No. 384, dated December 18, 2020, establishes the RDC for certification based on Certification Model 5. This model includes type testing, evaluation, and approval of the manufacturer’s Quality Management System requirements, with follow-up audits and tests on samples selected or conditioned by the manufacturer, as determined by the PCB. The samples must be traceable and representative of the design and pilot production, being evaluated, audited, and approved according to the product’s Risk Management carried out by the manufacturer. The manufacturer must provide a summary of the product's Risk Management in accordance with item 3 of ABNT NBR ISO 14971, as well as include applicable Quality Management System documents.

Thus, the manufacturer must meet the established requirements and, depending on the type of equipment and its medical purpose, apply the items 6.2.2.1.2 of Ordinance No. 384, dated December 18, 2020, as well as the evaluation requirements of ABNT NBR ISO 14971, and the verification standards ABNT NBR IEC 60601-1:2010/2013, ABNT NBR IEC 60601-1-6:2011/2013, ABNT NBR IEC 62366:2010, ABNT NBR IEC 60601-1-9:2010, and IEC 62304:2015, when applicable. Accordingly, the licensed company for the Rapha® device must comply with all requirements and prepare the documents and tests in collaboration with the PCB to ensure certification in accordance with safety and efficacy requirements.

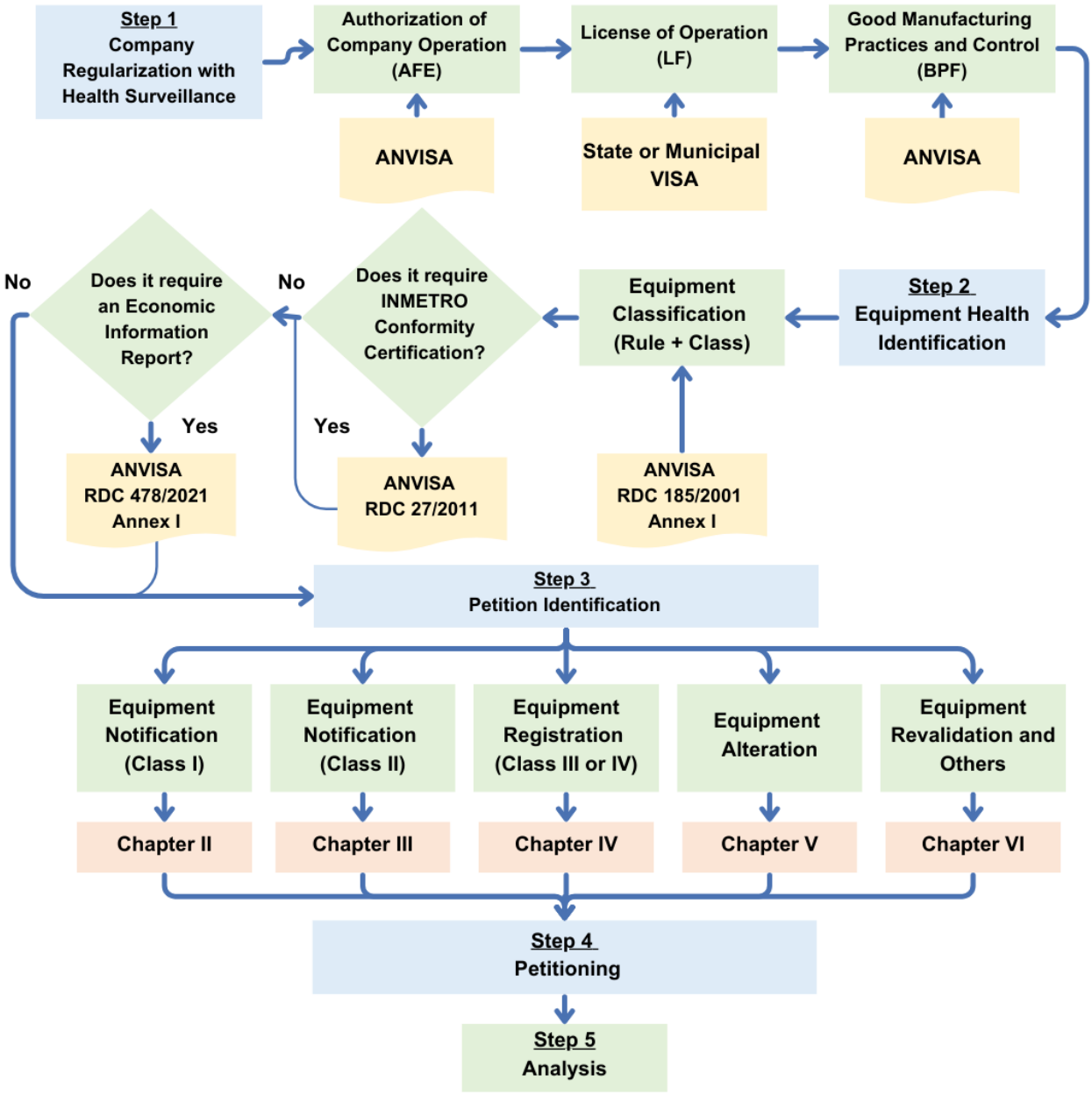
5.5.3. ANVISA Registration

The registration and notification of products with ANVISA are regulated by specific resolutions according to the nature and risk class of each product. The notification of health products classified as risk class I is governed by RDC No. 270/2019, and for class II risk products, RDC No. 40/2015 and RDC No. 423/2020 apply. For medical devices classified as risk class III and IV, registration follows the guidelines of Resolution - RDC No. 185, dated October 22, 2001, although complementary legislation may also apply to the process.

The process of registration or notification with ANVISA is carried out by submitting a petition, which includes documents and information specified in ANVISA resolutions RDC No. 40/2015 and No. 270/2019 (for notification) and RDC No. 185/01 (for registration), among other relevant legislation. Once submitted, the process is forwarded for technical review by the ANVISA team, which may request additional information and documents if necessary. After the review, the granting of the registration or notification is formalized with publication in the Official Gazette of the Union for registrations and notifications on the ANVISA Portal for notifications if the process is approved.

The product's registration or notification with ANVISA can be understood as depicted in Figure 26, according to the sequence of steps 1 to 5. Notably, each granted registration, or notification is represented by a unique numeric sequence generated automatically and electronically.

Figure 26 - Flowchart of ANVISA notification or registration process.



Source: Adapted from Manual for Medical Equipment Regulation (ANVISA, 2021).

The registration process for the Rapha® device with ANVISA was previously initiated by the research group with support from the company INOVATIE. Initially, the purpose of Rapha®—focused on healing diabetic foot wounds—was assessed to determine its regulatory framework and risk classification. It was established that the device falls under Rule 4, item (b), of Non-Invasive Products in ANVISA's RDC No. 175/22:

> *"Non-Invasive Devices*
> *Rule 4*
> *All non-invasive devices that come into contact with damaged skin or mucous membranes are classified as:*
> *a) Class I, if intended to be used as a mechanical barrier, for compression, or for exudate absorption;*
> *b) Class III, if primarily intended to be used on skin wounds that have resulted in dermis or mucous membrane rupture and can only heal by secondary intention;*
> *c) Class II, if primarily intended to control the microenvironment of the damaged skin or mucous membrane; and*
> *d) Class II in all other cases. This rule also applies to invasive devices that come into contact with damaged mucous membranes."*

Thus, Rapha® was classified as a high-risk, Group III device due to its action altering the chemical or biological composition of bodily fluids. As a result, it was necessary to follow the registration procedures outlined in Chapter IV of ANVISA's RDC No. 175/22.

With this classification, efforts were directed towards creating the Investigator's Brochure, as required by ANVISA, in collaboration with the licensed company Life Care Medical Indústria e Comércio – Eireli, which had already signed a confidentiality agreement with CTD/UnB. Furthermore, the completed clinical study and access to research data contributed significantly to the development of the investigator's brochure using the database, statistical analyses, and the study's final report. This documentation will follow ANVISA's current guidelines for Life Care, which will review the documentation in accordance with the ANVISA registration process through gap reports. Subsequently, the medical device registration will be submitted under Risk Class III for commercialization.

In summary, the T3 phase will be consolidated after the investigator's brochure is reviewed by the company's technical team, allowing the Rapha® to be registered with ANVISA. Thus, the conclusion of this phase will be achieved upon ANVISA's registration and release of the technology and the integration of the Rapha® device into both private and public healthcare systems. It is expected that the registration application for the technology will be filed by February 2024, with registration anticipated to be granted within the year, enabling the

start of phase T4, intended for the integration of the technology into healthcare systems. Lastly, it is worth noting that the HTA process will be necessary during this final phase to evaluate the technology through various variables and decide on its retention or discontinuation in healthcare systems.

Therefore, the Rapha® R&D&I has not yet completed phase T3, as the university does not have the institutional role to carry out this phase, making it the responsibility of the private sector due to regulatory requirements. Similarly, phase T4 will depend on private sector and/or public agencies. However, the university retains the responsibility to promote a culture of translational research, managing the translational objectives to monitor the phases and mitigate the "valleys of death," with the goal of delivering societal benefits derived from the scientific knowledge developed.

5.5.4. Regulatory Documentation Manuals

To meet the regulatory requirements of this phase, two manuals were developed, detailing the necessary documentation for the market introduction of medical devices. These manuals outline the fundamental requirements that must be submitted to regulatory bodies, such as ANVISA and INMETRO, including the Product Technical Dossier, validation reports, certifications, technical reports, and other essential items for evaluation, based on the case study of the Rapha® device.

The purpose of these manuals is to facilitate the understanding of regulatory requirements and provide a practical reference for researchers, developers, and manufacturers of medical devices. The manuals reflect efforts to organize information in an accessible manner, promoting technical compliance and overcoming regulatory barriers in the translational process.

The complete list of documents is provided in Appendix II and III of this study, organized to separately detail the requirements of ANVISA and INMETRO. These appendices were structured to allow for practical and immediate consultation, serving as a complementary tool to the main content of this work.

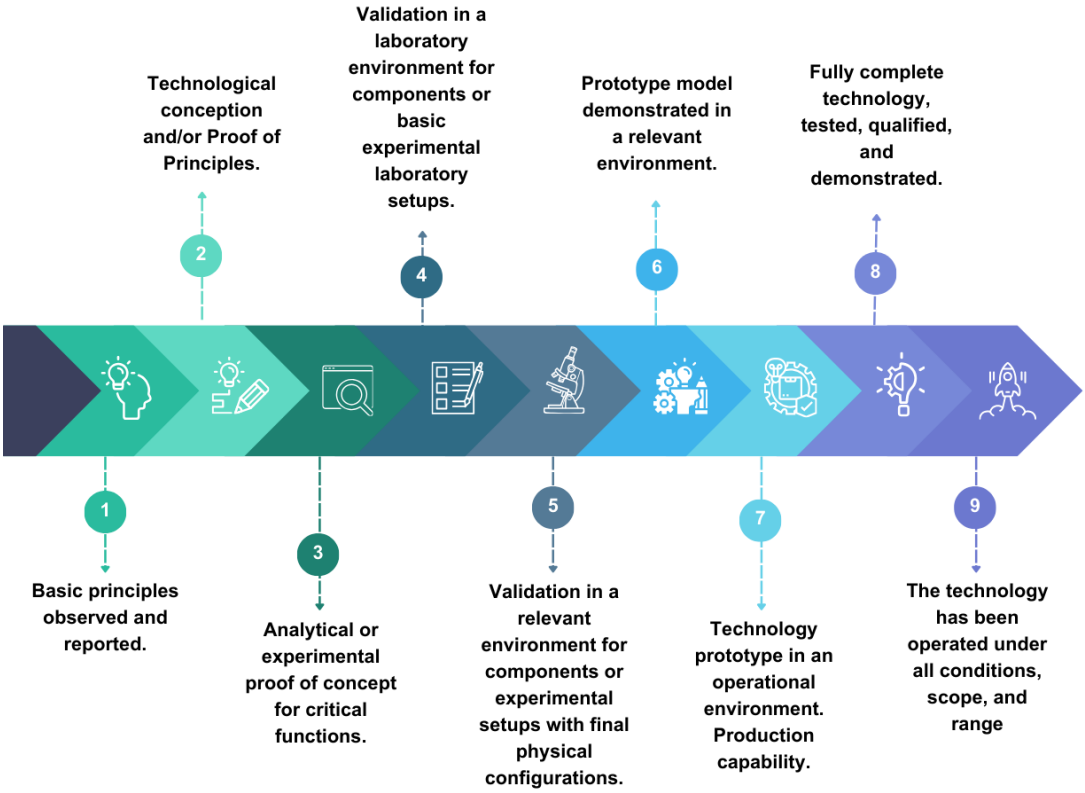
5.6. Evaluation of the Technological Maturity of the Rapha® Device

Assessing the technological maturity of the Rapha® device is a crucial step to verify the hypothesis of this doctoral research. In this context, an academic effort was made to use tools

that aid in assessing and forecasting the degree of technological maturity for the market. These tools include TRL, developed by the NASA of the United States, and the recent maturation scale for medical devices, known as MDRL, established based on the FDA regulatory process. Both tools consider internal and external factors related to market perspectives.

The technological maturity assessment of Rapha® was conducted based on the TRL scale levels (MANKINS *et al*., 1995), which aim to monitor the stages of the research, development, and validation process to measure the technology. In this sense, the theoretical model developed for proof of concept, the prototype used in tests, and the scale development for market availability were analyzed. Furthermore, aspects such as developed intellectual property, patents, scientific articles, and the licensing and/or technology transfer process described in sections 4.2.2.5 and 4.4.1, respectively, were evaluated, representing R&D&I results of the technology. This assessment enabled a comprehensive analysis of the technology's evolution, facilitating the understanding of the translation process and its relationship with each phase, as illustrated in Figure 27.

Figure 27 - Flowchart with the nine levels of the TRL scale.



Source: Adapted from Mankins *et al*. (1995).

This research concluded that the Rapha® technology has reached level 7 on the TRL scale (technology prototype in an operational environment with production capability), characterizing it as an advanced stage. This is due to the completion of preclinical and clinical tests, resulting in patent applications, publications in journals, participation in conferences, and awards. Additionally, the technology was incorporated by the private sector to complete phase T3 and begin phase T4, involving large-scale production and enabling its integration into the healthcare system. Thus, the technology has surpassed the scientific and technological research phase and is currently in the regulatory approval phase (ANVISA) to commence production and availability in the healthcare system.

Moreover, according to Malveira (2018), INPI/PR Resolution No. 220, of May 25, 2018, which establishes phase II of INPI's Pilot Project for processing patent applications filed by Scientific, Technological, and Innovation Institution (art. 1), allows for the participation of the Institution patent applications with a TRL above 4. It can therefore be inferred that the Rapha® technology is in the final stage and/or ready for market implementation (healthcare system), as the licensed company is responsible for certification with INMETRO and registration with ANVISA.

The MDRL scale, based on the TRL scale, was also adopted. This scale was selected due to its specific design for medical devices classified as FDA Risk Class III, a process characterized by a higher level of rigor than ANVISA. MDRL addresses intrinsic regulations for manufacturing such devices at various stages. It is noteworthy that the Rapha® device fulfilled the requirement of three clinical trials as stipulated by the FDA for high-risk devices. Regarding the criteria for each level, the relationship between the criteria placement on the MDRL structure for the Rapha® technology case study was mapped to represent a compatible scale for the translational process of biomedical devices. The following outlines the maturation levels on the MDRL scale, specifically adapted for biomedical devices, illustrating the Rapha® R&D&I case study. These stages are extensible and may be relevant for assessing other biomedical devices.

a) **Discovery**: This phase refers to identifying needs and researching the scientific principles and design required to address medical challenges, focusing on safety, clinical efficacy, system integration, human performance, and user satisfaction.
b) **Prototyping**: Similar to the prototype development phase, this stage involves creating a functional prototype that demonstrates scientific and design principles, addressing safety and efficacy issues while identifying system integration and usability concerns.

c) **Bench Testing**: In this phase, bench tests are conducted to assess the device's mechanical, electrical, and biological engineering performance, including tests with ex vivo, in vitro, and in situ tissues, as well as testing with animal carcasses or human cadavers.

d) **Preclinical**: This stage consists of animal testing, where initial evidence of device safety and efficacy in living systems is established, along with usability issues for operators to improve design.

e) **Pilot Clinical Trials**: This stage involves pilot trials where the device's safety is evaluated in a small sample of healthy individuals. Patient-system integration issues are identified to enhance device design.

f) **Main Clinical Trials**: Similar to the feasibility testing phase, this stage involves evaluating the device's clinical efficacy in a small sample of patients with the target health condition, identifying performance issues for patients, healthcare professionals, and support staff, as well as system integration issues.

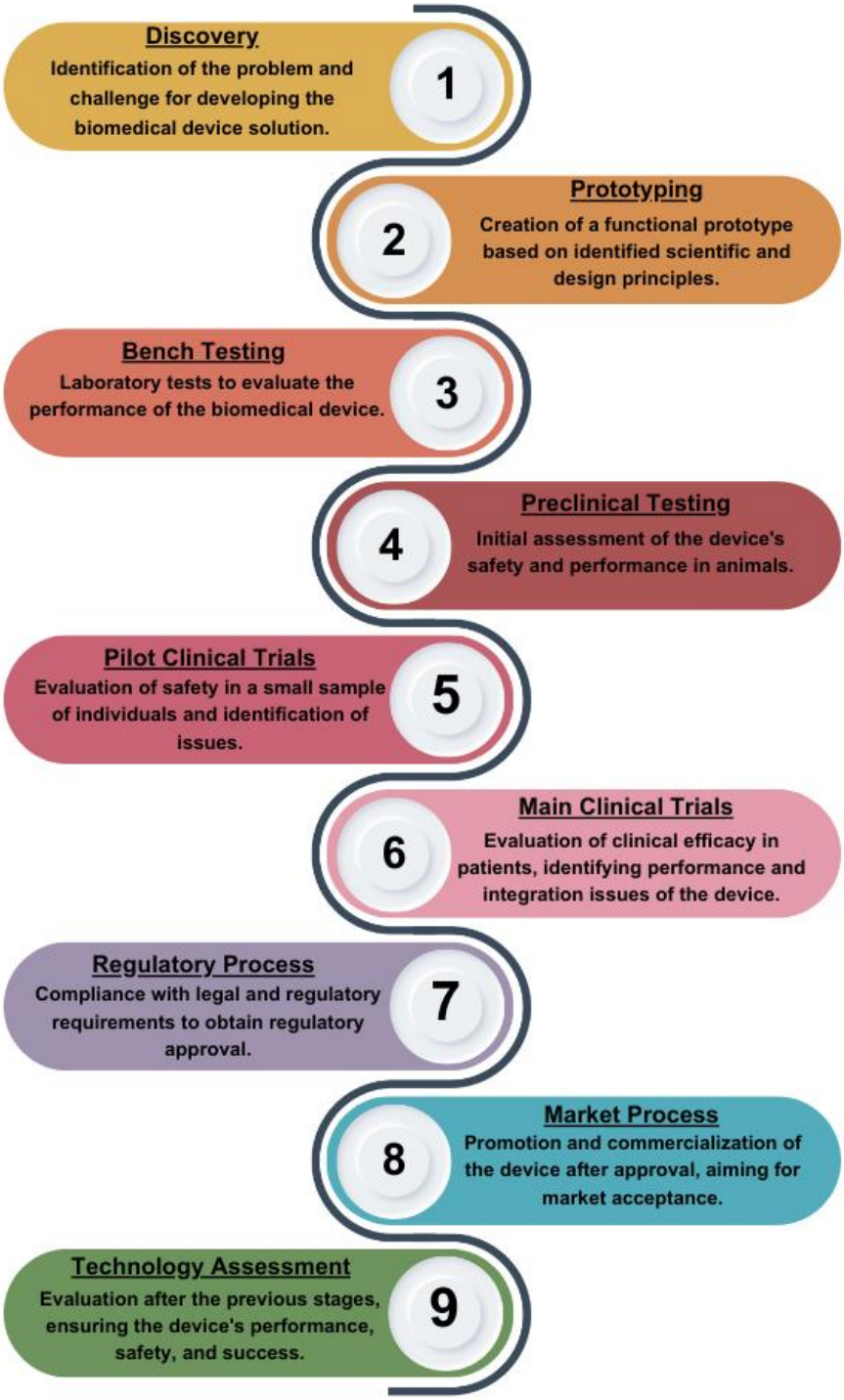
g) **Regulatory Processes**: This phase focuses on the regulatory processes required to obtain device approval from regulatory agencies, ensuring that all legal and normative requirements are met.

h) **Market Processes**: Corresponding to market acceptance, this stage involves promoting and marketing the device following regulatory approval, with the goal of achieving broad market acceptance and minimizing user discomfort.

i) **Technology Assessment**: This phase represents the overall assessment of the technology after all previous stages, ensuring that the device has achieved the required performance and safety levels to be considered a success.

Figure 28 presents the flowchart in a didactic manner to visualize the main stages and key criteria for the maturation of a biomedical device.

Figure 28 - Flowchart with the nine levels of the MDRL scale.



Source: Adapted from the study by SEVA *et al*., 2023.

Currently, the Rapha® device is classified at MDRL level 7 within the regulatory process, aiming to meet all necessary requirements to subsequently progress to the marketing and HTA phases. This latter phase represents a post-regulatory stage, analogous to the T4 phase in translational research. It is important to highlight that at the MDRL 7 stage, safety, clinical

efficacy, and usability are assessed as essential components of the core dimension. In these evaluations, functionality and safety are confirmed by the device's approval from regulatory entities, which are essential criteria for the introduction of the biomedical device to the general market.

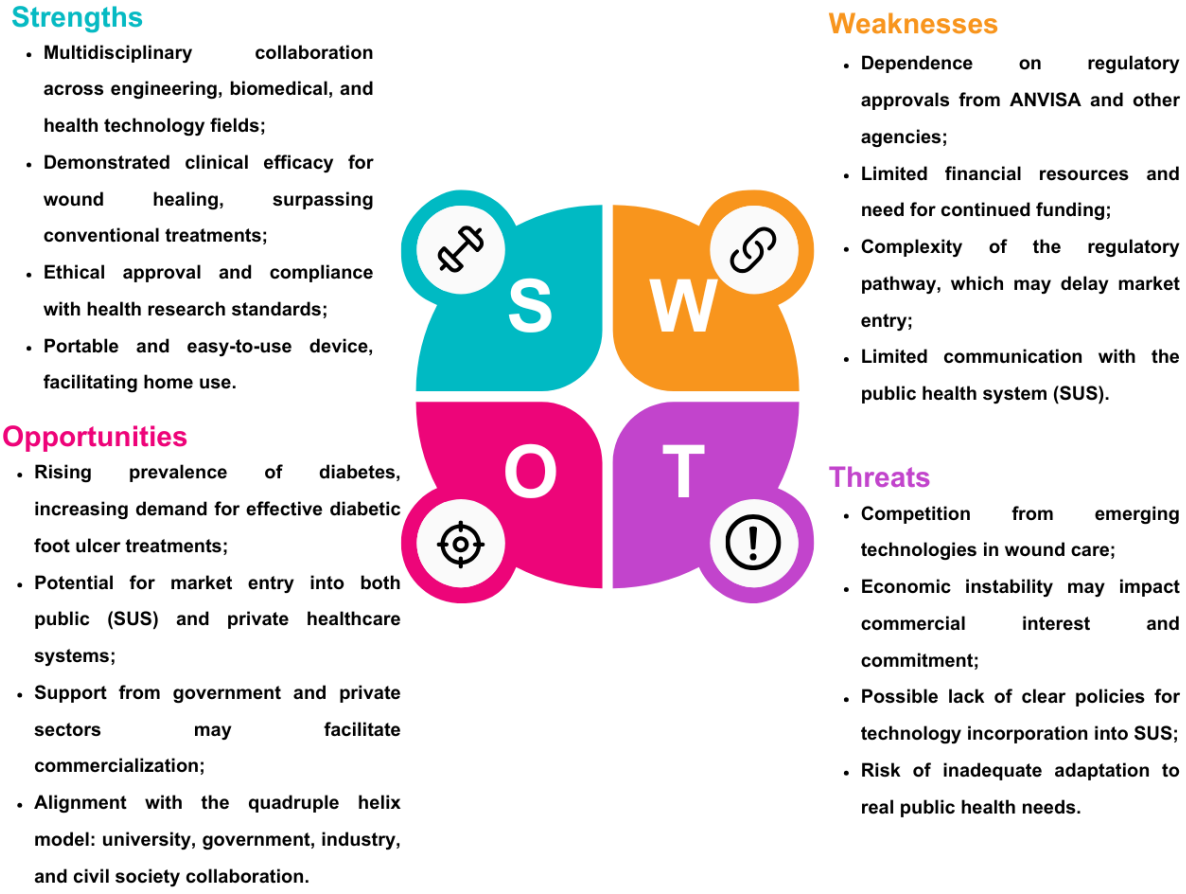
In the subsequent marketing phase, increasing stakeholder demands are considered, with a focus on prolonged and consistent device use. It should be noted that devices at MDRL level 8 are designed to achieve broad market acceptance, as they minimize potential discomfort for users. Similarly, devices classified at MDRL level 9 are expected to attain greater market penetration, as they tend to evoke positive emotional responses from users.

In summary, MDRL emerges as an essential tool to guide researchers, technology managers, and other stakeholders in the effective transition from research to practical application. By evaluating the technological maturity of Rapha® through MDRL, a comprehensive approach is achieved, encompassing manufacturing regulations for medical devices across various phases, mandatory regulatory approval prior to commercialization, and ongoing post-market surveillance to continually ensure its safety and clinical efficacy. Finally, incorporating dimensions such as comfort and affective response within the MDRL framework reflects the emphasis on sustained market adoption, reinforcing the quadruple helix concept. These output criteria establish not only concrete goals for technology managers but also support translational research by defining strategies, metrics, and mitigating the "valley of death."

5.7. SWOT Analysis Matrix of the Rapha® R&D&I Project

The SWOT matrix is a widely used strategic analysis tool to identify the strengths, weaknesses, opportunities, and threats of a project or business. According to SEBRAE, this tool is essential for making an organization more efficient and competitive by addressing its deficiencies. In the case of the Rapha device, developed by the UnB, applying the SWOT methodology is crucial to understanding and enhancing the translational research of the device. Figure 29 presents the main topics of the SWOT matrix related to the Rapha® device.

Figure 29 - SWOT Matrix of the Rapha® Device.



Source: Author's Own Work.

The Rapha® project stands out due to its strong interdisciplinary foundation, involving researchers from electrical engineering, biomedical engineering, and health technology. This multidisciplinary collaboration is essential for technological innovation, as evidenced by the creation of a device that combines a latex biomembrane with LEDs to promote tissue regeneration. Institutional support from both government and private companies can facilitate the commercialization and integration of the device into public and private healthcare systems. The interaction among university, government, companies, and civil society — known as the quadruple helix — has the potential to drive the research and development of the device.

Moreover, the project has ethical approval, ensuring compliance with health research standards. The rising incidence of DM increases the demand for effective treatments for diabetic foot ulcers, creating various opportunities for the Rapha® project. The device's clinical efficacy is a major advantage, with promising results in healing diabetic foot ulcers, outperforming conventional treatments. In addition to its proven clinical efficacy, the project has ethical approval, ensuring compliance with health research standards. The innovative nature of the

device, its portability, and ease of use are significant advantages, making it accessible and practical for patients, with significant potential to revolutionize healthcare.

However, the project also faces significant threats that could impact its development and market viability. The possibility of regulatory rejection by ANVISA or other agencies may delay or prevent the device's commercialization. Additionally, competition with other emerging technologies in the wound care market places Rapha® in a constant position of market share competition. The lack of clear policies for technology integration into the SUS, coupled with insufficient communication with this system, may result in inadequate adaptation to actual public health needs. Finally, economic instability represents an additional challenge, potentially affecting the commercial interest and commitment of partner companies.

The SWOT analysis of the Rapha® device from UnB reveals a project with great strengths and opportunities but also facing significant challenges. Translational research, which cannot be separated from production cycles and is essential to the project's development, requires continuous support and well-defined strategies to overcome weaknesses and mitigate threats. Interdisciplinary collaboration, technological innovation, and the clinical efficacy of the device are strengths that should be maximized. On the other hand, resource acquisition, navigation through the complex regulatory process, and ensuring institutional support are areas needing attention and improvement.

The SWOT matrix not only identifies areas for improvement but also highlights the importance of a proactive and collaborative approach to ensure translational research success. For the Rapha project, this means not only understanding the challenges and opportunities but also continuously adapting strategies to maintain competitiveness and relevance in the healthcare field.

CHAPTER 6

CONCLUSION

This study delved into the process of THR, using the development of the Rapha® device as a case study within the R&D&I ecosystem of a Brazilian public university. The research analyzed the ethical and regulatory aspects involved in the development of medical technologies targeted at the Brazilian healthcare system, highlighting the collaboration between academia, public and private entities, and the government, all of which play essential roles in promoting technological innovation.

The data and document collection was critical to understanding the strategic role of Brazilian universities in the technological development of medical devices. This phase revealed the existence of significant public policies that foster innovation but also highlighted institutional and regulatory barriers that need to be overcome for technologies developed in academia to reach the market and benefit society. This mapping underscored the necessity of strengthening the innovation ecosystem through more integrated policies and a more efficient alignment among the involved stakeholders.

The development of the Rapha® technology allowed for an in-depth evaluation of the translational phases, from T0 (discovery and description) to T3 (technology transfer, ANVISA registration and INMETRO certification). The integration of ethical and regulatory aspects, contextualized through the Rapha® project, demonstrated that translational research in Brazil still faces significant challenges, such as complying with ANVISA's regulatory requirements and adapting to international certification standards. This analysis reinforced the importance of a collaborative environment among academia, government, and the private sector to overcome these barriers.

The study provided a detailed examination of the technological development of Rapha®, from its initial conception to validation in clinical trials. The in-depth analysis of the translational phases identified challenges encountered at each stage and proposed strategies to mitigate the so-called "valleys of death," critical junctures where innovative projects often face difficulties advancing. The results demonstrated that Rapha® possesses a robust structure to address these barriers and progress to the final stages of validation and commercialization.

The inclusion of details about the device's functionality and the results of the conducted studies is justified by the need to provide researchers and stakeholders with a practical and

comprehensive understanding of the phases and challenges of the translational process. Furthermore, the technical description of the device and the clinical results serve as concrete examples, helping to illustrate how each translational phase unfolds in practice.

This level of detail allows stakeholders to observe the breadth and complexity of the studies conducted, understanding how the results obtained at each phase influence subsequent decisions and ensure the safety, efficacy, and regulatory viability of the device. Additionally, this approach facilitates the visualization of obstacles encountered at each stage, demonstrating how overcoming these challenges impacts the translation of innovative medical devices into clinical practice.

By including these elements, the study not only documents the translational process but also provides a didactic and applied example, contributing to a deeper understanding of the practical and strategic nuances involved in similar trajectories. This enhances the scientific and practical value of the study, broadening the understanding of the topic addressed.

The practical application of Rapha® was evidenced by its efficacy in clinical settings, particularly in the treatment of wounds related to diabetic foot. Preclinical and clinical studies showed promising results, proving the device's viability as an innovative and accessible solution for Brazilian public healthcare. Additionally, the technical, ethical, and regulatory analysis highlighted the device's robustness concerning compliance with regulatory requirements, from initial development to the stages of technology transfer.

The completion of preclinical and clinical trials demonstrated the technology’s efficacy, culminating in patent filings and scientific publications. The T2 phase has not yet been finalized due to pending regulatory procedures with ANVISA, which, once completed, will allow progression to the T3 phase, ensuring the registration and certification necessary for scaled production and incorporation into the Brazilian healthcare system. The translational process exemplified by the Rapha® device underscores the importance of interaction among academia, government, and the private sector to enable innovation and the introduction of new technologies into the healthcare market.

The evaluation of technological maturity, using the TRL and MDRL scales, indicated that the Rapha® device achieved Level 7, corresponding to a prototype capable of production in an operational environment. This result reflects an advanced degree of maturity, highlighting the device’s technical and regulatory robustness. Additionally, the SWOT matrix was applied as a strategic tool to identify the key strengths, weaknesses, opportunities, and threats associated with the project. Strengths included technological innovation and interdisciplinarity, while

regulatory challenges and competition in the medical device market represented threats to be addressed.

Public policies, along with the roles of universities and public and private entities, were crucial in fostering innovation and ensuring the necessary support for the development and commercialization of Rapha®. Brazilian universities, through their policies to encourage research and innovation, have significant potential to play a much more critical role in the development of new health technologies. The partnership with the private sector, which assumed responsibility for the certification and production phase of the device, strongly suggests the effectiveness of the collaborative model among sectors in overcoming barriers related to technology transfer and accelerating the innovation process.

Finally, the translation of knowledge generated by the university, represented by the Rapha® device, proved to be a successful case of applied research with the potential for positive impact on Brazilian public health and the economy. The identification of the pathways taken by the R&D&I of this technology reveals a replicable strategy for other academic innovations, emphasizing the importance of a collaborative ecosystem for the development of technologies that benefit the population. Thus, the results of this research point to a promising future for the application of translational research, with positive impacts on public health and the economy, reaffirming the potential of Brazilian universities as catalysts for technological innovation.

.

CHAPTER 7

FUTURE WORK

Based on the results obtained and the limitations encountered in the present study, the following activities are proposed as suggestions for future research:

a) Completion of Phase T4 and Monitoring of Impact on the Brazilian Health System: Completing the fourth stage of the translational process (T4) for the Rapha® device is crucial for its definitive integration into the market and the SUS. Detailed documentation of this phase is recommended, focusing on the clinical and economic impact of the technology, considering the reduction of diabetes-related foot complications and improved patient quality of life;

b) HTA and Comparison with Conventional Methods: A comprehensive analysis of the HTA impact of the Rapha® device is suggested, comparing indicators such as efficacy rate, cure rate, and other health metrics with conventional methods. Future research may also explore continuous improvements to the Rapha® technology based on clinical feedback and performance across different patient populations;

c) Analysis and Systematization of Ethical and Regulatory Processes for Medical Devices in Brazil: A detailed study is proposed to systematize the ethical and regulatory aspects involved in the translation of medical devices in Brazil, focusing on the regulatory procedures for the Rapha® device. This work would contribute to creating a standardized regulatory guide that could serve as a reference for other biomedical innovations;

d) THR Model for Brazilian Universities: Developing a replicable THR model that can be implemented in other Brazilian universities, integrating the public health system and the medical device market. Such a model could include guidelines to optimize interaction among academic research, technological development, clinical validation, and market entry, as well as promote collaboration among government, universities, and companies.

e) Development of Tools for Technological Maturity Assessment in the Brazilian Context: Considering the specificities of the Brazilian health system, creating a model for assessing technological maturity adapted to Brazil is recommended. This model should consider regulatory, market, and cultural aspects and include specific

indicators for the public health system (SUS). This model would help identify bottlenecks and accelerate the country's technological innovation process;

f) Integrated System for THR in Brazil: Creating an integrated THR system linked to SUS and public universities would allow greater synergy between academic research and the needs of the Brazilian population. A centralized national system would facilitate the coordination and acceleration of new medical technologies and development, promoting technological advancements directly impacting public health quality and access;

g) Application of Artificial Intelligence in the Translational Process: Applying Artificial Intelligence in the Research, Development, and Innovation process could be an innovative strategy to optimize clinical data analysis, accelerate regulatory and managerial decision-making, and mitigate risks associated with the “valleys of death” in technology translation. It is suggested that the use of AI be explored to automate stages of the translational process, such as analyzing preclinical and clinical data, identifying patterns in research outcomes, and predicting market performance;

h) Creation of an Innovation Hub for Medical Devices in Brazil: Proposing the creation of a national innovation hub for medical devices to centralize collaboration among universities, companies, government, and the health system. This hub could provide a space to accelerate the development, assessment, and commercialization of new technologies, facilitating the exchange of knowledge and resources among various actors in the innovation ecosystem;

i) Economic Impact Study of Innovative Technologies in SUS: Conducting a detailed economic analysis of the impact of innovative technologies like the Rapha® device within SUS. This study could address the economic benefits in terms of cost reduction in the treatment of diabetic foot complications and the impact on public finances and population well-being.

j) Exploration of Disruptive Health Technologies for Prevention and Treatment: Beyond developing the Rapha® device, it is recommended that future research explore the use of other disruptive technologies, such as biotechnology and nanotechnology, for treating chronic conditions like diabetes. These studies could bring significant advancements in therapeutic approaches and personalized health care.

These suggestions aim not only to continue developing the Rapha® technology but also to advance Brazil's health innovation ecosystem, focusing on creating impactful solutions.

REFERENCES

AL-WATBAN, F. A. H.; ANDRES, B. L. Polychromatic LED therapy in burn healing of non-diabetic and diabetic rats. *Journal of Clinical Laser Medicine and Surgery*, v. 21, n. 5, p. 249-258, 2003. Cited 1 time in page 72.

AMORIM, F. F. *et al.* Health technology assessment: historical context and perspectives. *Science Communication in Health*, p. 343-348, 2010. Cited 3 times in pages 12, 13, and 14.

ARAUJO-JORGE, T. C.; FERREIRA, R. R. Translational research in Chagas disease: perspectives in nutritional therapy emerging from selenium supplementation studies as a complementary treatment. *Memórias do Instituto Oswaldo Cruz*, v. 117, e220001, 2022. DOI: 10.1590/0074-02760220001. Cited 2 times in pages 21 and 22.

ASSUNÇÃO, M. C. F.; SANTOS, I. S. dos; GIGANTE, D. P. Primary care in diabetes in Southern Brazil: structure, process, and outcome. *Revista de Saúde Pública*, v. 35, p. 88-95, 2001. Cited 2 times in pages 9 and 10.

AZEVEDO BORGES, F. *et al.* Natural rubber latex: study of a novel carrier for Casearia sylvestris Swartz delivery. *International Scholarly Research Notices*, v. 2014, 2014. Cited 1 time in page 56.

BAHIA, L. The high cost of diabetic foot in Brazil. 2018. Available at: https://www.diabetes.org.br/publico/ultimas/1609-o-alto-custo-do-pe-diabetico-no-brasil. Accessed on January 5, 2023. Cited 1 time in page 10.

BALTZIS, D.; ELEFTHERIADOU, I.; VEVES, A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Advances in Therapy*, v. 31, n. 8, p. 817-836, 2014. Cited 1 time in page 4.

BANTA, D.; JONSSON, E. History of HTA: introduction. *International Journal of Technology Assessment in Health Care*, v. 25, n. S1, p. 1-6, 2009. Cited 1 time in page 14.

BANTA, H. D. Report from the EUR-ASSESS project EUS-ASSESS-Introduction to the EUR-ASSESS report. *International Journal of Technology Assessment in Health Care*, v. 13, n. 2, p. 133-143, 1997. Cited 1 time in page 14.

BARRETO, J. O. *et al.* Translational research in public health: challenges of an evolving field. *Saúde em Debate*, Rio de Janeiro, v. 43, special issue, p. 4-9, 2019. Cited 2 times in pages 2 and 16.

BATTISTA, R. N.; HODGE, M. J. The evolving paradigm of health technology assessment: reflections for the millennium. *CMAJ*, v. 160, n. 10, p. 1464-1467, 1999. Cited 1 time in page 14.

BENZAGHTA, M.; *et al.* SWOT analysis applications: An integrative literature review. *Journal of Global Business Insights*, v. 6, n. 1, p. 55-73, 2021. Available at: https://scholarcommons.usf.edu/globe/vol6/iss1/5. Accessed on October 26, 2024. Cited 2 times in pages 32 and 33.

BIGDELI, M. *et al.* Medicines in health systems: advancing access, affordability, and appropriate use. Geneva: World Health Organization, 2014. Available at: https://www.who.int/alliancehpsr/resources/publications/9789241507622/en/. Accessed on December 14, 2022. Cited 1 time in page 1.

BOSIO, C. G. P. *et al.* Translational Research: the performance of the National Institutes of Science and Technology in health. *Saúde em Debate*, v. 43, special issue 2, p. 48-62, 2019. Cited 1 time in page 2.

BRAZIL. Law No. 6,360, of September 23, 1976. Provides for the health surveillance of medicines, drugs, pharmaceutical inputs, and related products, cosmetics, sanitizers, and other products, and other measures. *Official Gazette of the Union*, Brasília, DF. Cited 1 time in page 27.

BRAZIL. Law No. 9,782, of January 26, 1999: Defines the National Health Surveillance System, establishes the National Health Surveillance Agency, and other measures. *Official Gazette of the Union*, Brasília, DF. Cited 1 time in page 8.

BRAZIL, Ministry of Health. Health technology assessment: tools for SUS management. Brasília, 2009. 112 p. Cited 1 time in page 12.

BRAZIL, Ministry of Health. Methodological guidelines: performance evaluation of health technologies. Brasília, DF: Ministry of Health, 2017. Available at: http://conitec.gov.br/. Accessed on March 6, 2021.

BRAZIL, Ministry of Health. Meeting of experts to standardize the use and reuse of disposable medical-hospital materials in the country. Brasília, 1985.

BRAZIL, Ministry of Health. Diabetes (diabetes mellitus), 2023. Available at: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/d/diabetes. Accessed on January 20, 2023.

BRAZIL, Ministry of Health. Morbidity and risk factor indicators: D.11 Prevalence rate of diabetes mellitus: Qualification sheet. *DATASUS*, 2023. Available at: http://tabnet.datasus.gov.br/cgi/idb2000/fqd11.htm. Accessed on January 20, 2023.

BRASILEIRO, J. L. *et al*. Diabetic foot: clinical aspects. *Brazilian Vascular Journal*, v. 4, n. 1, p. 11-21, 2019.

CALHEIRA, B. F. Mathematical modeling of diabetic foot healing: performance analysis of the Rapha® protocol. 2021. 45 f. Undergraduate Thesis (Bachelor's in Electronic Engineering) — University of Brasília, Brasília, DF, 2021.

CAMPOS, F. E.; DA MOTTA E ALBUQUERQUE, E. Contemporary specificities of work in the health sector: introductory notes for a discussion. In: *Collective Bargaining in Health Work*. 1998. p. 41-70.

CAPDEVILLE, G. de; ALVES, A. A.; BRASIL, B. dos S. A. F. Embrapa Agroenergia's innovation and business model: strategic management integration of R&D and TT. Brasília, DF: Embrapa Agroenergia, 2017.

CAVANAGH, P. R.; ULBRECHT, J. S.; CAPUTO, G. M. New developments in the biomechanics of the diabetic foot. *Diabetes/metabolism research and reviews*, v. 16, n. S1, p. S6-S10, 2000.

CCATES – Collaborating Center of SUS Health Technology Assessment and Excellence. Health technology assessment. Brasília, DF: CCATES, 2019. Available at: http://www.ccates.org.br/areas-tematicas/avaliacao-de-tecnologias-em-saude/. Accessed on August 10, 2021.

CCATES – Collaborating Center of SUS Health Technology Assessment and Excellence. Institutional development support program for SUS. Brasília, DF: CCATES, 2019. Available at: https://www.cnj.jus.br/e-natjus/arquivo-download.php?hash=44b1c3f1d39b7b38f8aef3f687b764183fb634d2. Accessed on February 12, 2023.

CONTÓ, M.; D'AGOSTINO, C.; PETRAMALE, C. A. Medical devices in the Unified Health System (SUS) – evaluation and technological incorporation. *Electronic Journal of Health Management*, n. 4, p. 3016-3023, 2015.

CUTLER, D. M.; MCCLELLAN, M. Is technological change in medicine worth it? *Health Affairs*, v. 20, n. 5, p. 11-29, 2001.

DESANTANA, J. M. Are we really translating pain knowledge to clinical practice? *BrJP*, SciELO, v. 5, p. 89-90, 2022.

DEVITO, N. J.; BACON, S.; GOLDACRE, B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. *The Lancet*, v. 395, n. 10221, p. 361-369, 2020.

DO AMARAL, M. G.; RENAULT, T. B. The Quintuple Helix of University-Industry-Government-Society-Environment Relations. *Journal of Management, Society and Innovation*, v. 5, n. 2, p. 110-114, 2019.

DUARTE, Aldira Guimarães; ÁVILA, Carlos F. Domínguez (Orgs.). *A COVID-19 no Brasil: ciência, inovação tecnológica e políticas públicas*. 5. ed. Curitiba: Editora CRV, 2020. v. 1.

FARIAS, A. D. P. Regulatory context and practices for submission of clinical evidence in the registration of medical devices at ANVISA. Master's Thesis (Professional Master's in Clinical Research) – Hospital de Clínicas de Porto Alegre, Porto Alegre, 2022.

FELIPE, M. S. S. *et al.* A look at the Health Economic-Industrial Complex and Translational Research. *Saúde em Debate*, v. 43, p. 1181-1193, 2020.

FERNANDES, L. A. Evaluation of the VESTA organic respirator controller through mathematical modeling of COVID-19, with application of the Lyapunov Linearization Method and Routh-Hurwitz Criterion. Master's Thesis (Master's in Biomedical Engineering) – University of Brasília, Brasília, DF, 2022.

FORT, D. G. *et al.* Mapping the evolving definitions of translational research. *Journal of Clinical and Translational Science*, v. 1, n. 1, p. 60-66, 2017.

FRADE, M. A. C. *et al.* Management of diabetic skin wounds with a natural latex biomembrane. *Medicina Cutanea Ibero-Latino-Americana*, v. 32, n. 4, p. 157-162, 2004.

FREEMAN, C. The determinants of innovation: Market demand, technology, and the response to social problems. *Futures*, v. 11, n. 3, p. 206-215, 1979.

FREITAS, A. M. *et al.* Proteinuria as a risk factor for diabetic retinopathy. *Brazilian Archives of Ophthalmology*, v. 65, p. 83-87, 2002.

FUDGE, N. *et al.* Optimizing translational research opportunities: a systematic review and narrative synthesis of basic and clinical scientists' perspectives of factors which enable or hinder translational research. *PLoS One*, v. 11, n. 8, p. e0160475, 2016.

GABBAY, J.; WALLEY, T. Introducing new health interventions. *BMJ*, v. 332, n. 7533, p. 64-65, 2006.

GADELHA, C. A. G. *et al.* Health is development: the health economic-industrial complex as a national strategic option. Rio de Janeiro: Fiocruz - CEE, 2022.

GEEST, S. *et al.* Enhancing health care for the future in Switzerland: implementation science to bridge the "valley of death". *Texto & Contexto - Enfermagem*, v. 30, 2022.

GEWANDSZNAJDER, F.; ALVES-MAZZOTTI, A. J. The method in Natural and Social Sciences. São Paulo: Pioneira, 1998.

GIBBONS, M.; LIMOGES, C.; NOWOTNY, H.; SCHARTZMAN, S.; SCOTT, P.; TROW, M. The New Production of Knowledge – The Dynamics of Science and Research in Contemporary Societies. London: Sage Publication, 1994.

GOMES, R. de P. *et al*. Clinical trials in Brazil: international competitiveness and challenges. *BNDES Setorial*, n. 36, Sept. 2012, p. 45-84, 2012.

GUYATT, G. *et al*. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA*, v. 268, n. 17, p. 2420, 1992.

HADDAD, M. C. L. *et al*. Systematic evaluation of the diabetic foot. *Diabetes Clin*, v. 9, n. 3, p. 187-192, 2005.

HANNEY, S. R. *et al*. How long does biomedical research take? Studying the time taken between biomedical and health research and its translation into products, policy, and practice. *Health Research Policy and Systems*, v. 13, n. 1, p. 1-18, 2015.

HELEN, W. H. Bridging the translational gap: collaborative drug development and dispelling the stigma of commercialization. *Drug Discovery Today*, v. 21, n. 2, p. 299-305, 2016.

HESS, C. T. Wound and ulcer treatment. São Paulo: Reichmann & Affonso Ed., 2002.

HOURELD, N. N. Shedding light on a new treatment for diabetic wound healing: a review on phototherapy. *The Scientific World Journal*, v. 2014, 2014.

HUANG, X. *et al*. Hyperbaric oxygen potentiates diabetic wound healing by promoting fibroblast cell proliferation and endothelial cell angiogenesis. *Life Sciences*, v. 259, p. 118246, 2020.

INTERNATIONAL DIABETES FEDERATION. IDF Diabetes Atlas 10th edition 2021. *Int. Diabetes Fed. Diabetes Atlas*, 10th ed., 2021, p. 1-176.

KHOURY, M. J. *et al.* The emergence of Translational Epidemiology: from scientific discovery to population health impact. *American Journal of Epidemiology*, v. 172, n. 5, p. 517-523, 2010.

KRAUSS-SILVA, L. Health technology assessment: methodological and operational issues. *Public Health Notebooks*, v. 20, p. S199-S207, 2004.

LENFANT, C. Clinical research to clinical practice—lost in translation? *New England Journal of Medicine*, v. 349, n. 9, p. 868-874, 2003.

LEE, E. M.; BOYER, S. The state of medical device regulation (MDR) readiness in UK SMEs. *ISO Life Sciences*, UK, 2019.

LOPES, A. A. Evidence-based medicine: the art of applying scientific knowledge in clinical practice. *Revista da Associação Médica Brasileira*, v. 46, p. 285-288, 2000.

LUPATINI, E. de O *et al.* Medicines and translational research: stages, actors, and health policies in the Brazilian context. *Saúde em Debate*, v. 43, p. 181-199, 2020.

LUPATINI, E. de O. Translational research and medicines: elapsed time between clinical development and dispensing in SUS, and associated factors. Doctoral Thesis (Doctorate in Public Health) – University of Brasília, Brasília, DF, 2022.

MACEDO, G.; PEDROSA, H. C.; RIBEIRO, J. F. Clinical and therapeutic approach to diabetic foot. In: VILAR, L., editor. *Clinical Endocrinology*, v. 2, p. 671-685, 2001.

MANAMAYA, R.; DEVI, W. A. Assessment of risk factors and knowledge of heart disease among community people in selected area, Pokhara. *International Journal of Nursing Care*, v. 5, n. 2, p. 235, 2017.

MAZZUCATO, M. The entrepreneurial state: debunking the myth of the public vs. private sector. São Paulo: Portfolio-Penguin, 2014.

MINEIRO, A. A. C. Who are the actors of the quadruple and quintuple helix? Multiple cases in consolidated scientific and technological parks. In: *XXII SemeAd Administration Seminar*. Goiânia, GO, 2019.

MINEIRO, Andrea Ap da Costa; SOUZA, Thais Assis de; CASTRO, Cleber Carvalho de. The quadruple and quintuple helix in innovation environments (incubators and science and technology parks). *Innovation & Management Review*, v. 18, n. 3, p. 292-307, 2021. Available at: https://doi.org/10.1108/INMR-08-2019-0098. Accessed on October 28, 2024.

MORAES, H. A. B. de *et al.* Factors associated with glycemic control in a sample of individuals with diabetes mellitus from the Brazilian Adult Health Longitudinal Study, Brazil, 2008 to 2010. *Epidemiology and Health Services*, v. 29, 2020.

MOREL, C. Translational research: what is it? *Ciência Hoje*, Rio de Janeiro, v. 369, 2020. Available at: https://cienciahoje.org.br/artigo/pesquisa-translational-o-que-e-isso/. Accessed on January 20, 2023.

MRUÉ, F.; CENEVIVA, R. Replacement of the cervical esophagus by a latex biosynthetic prosthesis. *Experimental study in dogs*, 1996.

NASCIMENTO, A. F. Impact analysis of clinical evaluation on the health registration of high-risk medical devices. *Health Surveillance Debate*, v. 7, n. 2, p. 37-45, 2019.

National Health Surveillance Agency – ANVISA. Technical Note No. 004/2016/GGTPS/DIREG/ANVISA. Brasília: ANVISA, 2016. Available at: https://www.gov.br/anvisa. Accessed on October 30, 2024.

National Health Surveillance Agency – ANVISA. RDC Resolution No. 185, dated October 22, 2001. Approves the Technical Regulation for registration, modification, revalidation, and cancellation of medical products. *Official Gazette of the Union*, Brasília, DF.

National Health Surveillance Agency – ANVISA. RDC Resolution No. 10, dated February 20, 2015. Provides regulations on conducting clinical trials for medical devices. Brasília: ANVISA, 2015. Available at: https://www.in.gov.br/web/dou/-/resolucao-rdc-n-10-de-20-de-fevereiro-de-2015-16867093. Accessed on October 30, 2024.

National Health Surveillance Agency – ANVISA. RDC Resolution No. 40, dated August 26, 2015. Defines notification requirements for medical products. *Official Gazette of the Union*, Brasília, DF.

National Health Surveillance Agency – ANVISA. RDC Resolution No. 270, dated February 28, 2019. Addresses the transition from a registration system to a notification system for Class I medical devices. *Official Gazette of the Union*, Brasília, DF.

National Health Surveillance Agency – ANVISA. RDC Resolution No. 546, dated August 30, 2021. Establishes essential safety and efficacy requirements applicable to health products. *Official Gazette of the Union*, Brasília, DF.

National Health Surveillance Agency – ANVISA. RDC Resolution No. 548, dated August 30, 2021. Establishes criteria for conducting clinical trials with medical devices. Brasília: ANVISA, 2021. Available at: https://www.in.gov.br/web/dou/-/resolucao-rdc-n-548-de-30-de-agosto-de-2021-340924872. Accessed on October 30, 2024.

NEVES-JUNIOR, W. F. P. *et al.* Influence of the fabrication process on the final properties of natural-rubber latex tubes for vascular prosthesis. *Brazilian Journal of Physics*, v. 36, p. 586-591, 2006.

NUNES, G. A. M. A.; REIS M. C.; ROSA, M. F. F.; Peixoto L.; ROCHA; ROSA, S. R. F. A system for treatment of diabetic foot ulcers using led irradiation and natural latex. RESEARCH ON BIOMEDICAL ENGINEERING, v. 32, p. 3-13, 2016.

NUNES, G. A. M. de A. Characterization of latex insoles: evaluation of latex composites as a proposal for developing insoles for the treatment of patients with diabetic foot. Master's Thesis (Master's in Biomedical Engineering) – University of Brasília, Brasília, DF, 2017.

HEALTH POLICY ANALYSIS OBSERVATORY. Analysis of Health Policies in Brazil [Internet]. Available at: http://www.analisepoliticaemsaude.org. Accessed on January 20, 2023.

OLIVER, K. *et al.* A systematic review of barriers to and facilitators of the use of evidence by policymakers. *BMC Health Services Research*, v. 14, n. 1, p. 1-12, 2014.

ORTON, L. *et al.* The use of research evidence in public health decision-making processes: a systematic review. *PLoS One*, v. 6, n. 7, p. e21704, 2011.

PEDROSA, H. C. *et al.* The challenge of the Diabetic Foot Project. *Diabetes Therapy*, v. 4, n. 19, p. 1-10, 1998.

PIEDADE, A. D.; HENRIQUES, R. S. From law to reality: measuring time-to-access of CONITEC-approved drugs in the Brazilian Public Health Care System (SUS) in Paraná State. *Value in Health*, v. 18, n. 7, p. A810, 2015.

REGGI JUNIOR, S. S.; MORALES, P. H. A.; FERREIRA, S. R. G. Is there concordance in renal and retinal involvement in diabetic microangiopathy? *Brazilian Archives of Endocrinology & Metabology*, v. 45, p. 452-459, 2001.

REIS, M. do C. dos. Induction system for tissue neoformation for diabetic foot with LED light-emitting circuit and use of natural latex. Doctoral Thesis in Electrical Engineering, PGEA.TD-083/2013, Department of Electrical Engineering, University of Brasília, Brasília, DF, 163p.

ROBSON, M. C.; HILL, D.; WOODSKE, M. E.; STEED, D. L. Wound healing trajectories as predictors of the effectiveness of therapeutic agents. *Archives of Surgery*, v. 135, p. 773-777, 2000.

ROSA, M. F. F.; DOMÍNGUEZ, A. G. D.; GUIMARÃES, S. M. F. Historical context of the health sector in Brazil: an interpretation from the privatist/preventive model to current trends in public health, 2017.

ROSA, M. F. F. *et al*. Development of hard technology for diabetic foot treatment: a case study from the public health perspective. *Saúde em Debate*, v. 43, special issue 2, p. 87-100, 2020. DOI: https://doi.org/10.1590/0103-11042019s207.

ROSA, S. S. R. F. *et al*. Regeneration of diabetic foot ulcers using red LED light therapy and a natural latex biomembrane. *Annals of Biomedical Engineering*, v. 47, n. 4, p. 1153-1164, 2019. DOI: https://doi.org/10.1007/s10439-019-02220-5.

ROSA, S. S. R. F. *et al*. Investigator Brochure – Laboratory Equipment. Biomedical Engineering Laboratory, University of Brasília (UnB), Brasília, 2023.

SACKETT, D. L. *et al*. Evidence-based medicine: What it is and what it isn't. *BMJ*, v. 312, n. 7023, p. 71-72, 1996.

SAEEDI, P. *et al*. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes Research and Clinical Practice*, v. 157, p. 107843, 2019.

SANTANA, T. F. Analysis of inflammation and oxidative stress in the tissue healing process after combined use of curcumin liposomes in natural latex biomembranes and LED therapy for tissue regeneration in patients with diabetic ulcers. Master's Thesis (Master's in Biomedical Engineering) – University of Brasília, Brasília, DF, 2021.

SANTOS, V. C. C. Economic analyses in the incorporation of health technologies: reflections on the Brazilian experience. Master's Thesis (Professional Master's in Public Health) - Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, 2010.

HEALTH DEPARTMENT, S. A. Diabetic foot manual: strategies for the care of people with chronic disease. Department of Primary Care. Brasília: Ministry of Health, 2016.

SES-DF. Diabetic foot management protocol in primary and specialized health care. Brasília, 2018. Available at: http://www.saude.df.gov.br/wp-content/uploads/2018/04/PROTOCOLO-PE-DIABETICO.pdf. Accessed on January 5, 2023.

SHIMADA, A. L. B. RL1844007SE/ ALS/TECAM Report Biochemical Pharmacy Laboratories – UnB CRF-SP N 79429, 2018. Available at: http://bdtd.ibict.br/vufind/Record/UNB_fdc1848e72da98afa75c6052d352bfd8. Accessed on January 5, 2023.

SILVA, A. C. da. Rapha® device for diabetic foot healing: a translational health approach. Master's Thesis (Master's in Biomedical Engineering) – University of Brasília, Brasília, DF, 2021.

SILVA, H. P.; PETRAMALE, C. A.; ELIAS, F. T. S. Advances and challenges in the national health technology management policy. *Public Health Journal*, v. 46, suppl. 1, p. 83-90, 2012.

SILVA, M. J. S. da; OSORIO-DE-CASTRO, C. G. S. Organization and practices of pharmaceutical care in oncology within the Unified Health System. *Interface – Communication, Health, Education*, v. 23, 2019.

SINGH, N.; ARMSTRONG, D. G.; LIPSKY, B. A. Preventing foot ulcers in patients with diabetes. *JAMA*, v. 293, n. 2, p. 217-228, 2005.

SOUZA, L. P. S.; SOUZA, A. M. V.; PEREIRA, K. G.; FIGUEIREDO, T.; BRETAS, T. C. S.; MENDES, M. A. F.; SANTANA, J. M. F.; MOTA, É. C.; SILVA, C. S. O. SWOT matrix as a management tool for improving nursing care: a case study in a teaching hospital. *Health Management Journal*, Brasília, DF, v. 4, p. 1633-1643, 2013.

TAVARES, N. U. L. *et al.* Free access to medicines for chronic disease treatment in Brazil. *Public Health Journal*, v. 50, p. 7s, 2016.

TAVARES, N.; PINHEIRO, R. Pharmaceutical Assistance in SUS: advances and challenges for effective comprehensive therapeutic care. *Tempus – Collective Health Acts*, v. 8, n. 1, p. 49-56, 2014.

TRICCO, A. C. *et al.* Barriers and facilitators to uptake of systematic reviews by policymakers and healthcare managers: a scoping review. *Implementation Science*, v. 11, n. 1, p. 1-20, 2015.

VALENTE, M. Technology Readiness Level (TRL): understanding the reliability framework in NASA projects. *Certi.Insights*, Florianópolis, September 9, 2021. Available at: https://certi.org.br/blog/trl-desenvolvimento-projetos/. Accessed on January 20, 2023.

VARGAS, M. A.; ALVES, N. G.; MREJEN, M. Science, technology, and innovation in times of pandemic: COVID-19 implications. *Development Notebooks*, v. 16, p. 145-172, 2021.

VIJAY, V.; SNEHALATHA, C.; RAMACHANDRAN, A. Socio-cultural practices that may affect diabetic foot development. *IDF Bulletin*, v. 42, p. 10-13, 1997.

WAGNER, J. A.; KROETZ, D. L. Transforming translation: impact of clinical and translational science. *Clinical and Translational Science*, v. 9, n. 1, p. 3-5, 2016.

WEHLING, M. Translational medicine: can it really facilitate the transition of research "from bench to bedside"? *European Journal of Clinical Pharmacology*, v. 62, n. 2, p. 91-95, 2006.

WEBSTER, A.; GARDNER, J. Aligning technology and institutional readiness: innovation adoption. *Technology Analysis & Strategic Management*, v. 31, n. 10, p. 1229-1241, 2019.

WOOLF, S. H. The meaning of translational research and why it matters. *JAMA*, v. 299, n. 2, p. 211-213, 2008.

YAZDANPANAH, L.; NASIRI, M.; ADARVISHI, S. Literature review on diabetic foot ulcer management. *World Journal of Diabetes*, v. 6, n. 1, p. 37, 2015.

ZAVALA, A. V.; BRAVER, D. Semiotics of the foot: primary and secondary prevention of diabetic foot. *Diabetes Clinica*, v. 4, n. 2, p. 137-144, 2000.

ZEQUERA, M. L. *et al*. Study of plantar pressure distribution on the sole of the foot in normal and diabetic subjects using a hydrocell pressure sensor. In: *Proceedings of the 25th Annual International Conference of the IEEE Engineering in Medicine and Biology Society* (IEEE Cat. No. 03CH37439). IEEE, 2003. p. 1874-1877.

ZERHOUNI, E. A. *et al*. Translational and clinical science – time for a new vision. *New England Journal of Medicine*, v. 353, n. 15, p. 1621, 2005.

APPENDICES

APPENDIX 1: Proof of Online Submission to ANVISA for Phase 3

Comprovante de Protocolização Página 1 de 1

ANVISA

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA
Unidade de Atendimento e Protocolo - UNIAP
Impresso em: 02/08/2021 10:59:44

COMPROVANTE DE PROTOCOLIZAÇÃO ON-LINE

Protocolo:
25352.122205/2021-19
Expediente:
3010249219
Número de Transação:
6747332021
Tipo de Documento:
Petição
Número do Processo:
25351240835201960
Nome do Produto:
[sem nome]
Favorecido:
23.320.521/0001-21 - INOVATIE CONSULTORIA E SERVICOS EM SAUDE LTDA - ME
Assunto:
80131 - ENSAIOS CLÍNICOS - Notificação de término de ensaio clínico no Brasil - dispositivos médicos

Protocolizado On-Line via Peticionamento Eletrônico por:
071.701.408-88 - CAMILLE RODRIGUES DA SILVA em 02/08/2021 10:59:44

APPENDIX 2: Manual - Documentation Required for Obtaining ANVISA Licensing

Manual

Documentation Required for Obtaining ANVISA Licensing

This manual aims to guide researchers, developers, and manufacturers of medical devices on the regulatory requirements for obtaining ANVISA licensing. The detailed content addresses the essential documentation and mandatory processes to ensure that the medical device is approved for use in the Brazilian market, meeting the highest standards of safety, efficacy, and technical compliance.

This manual not only seeks to fulfill legal and regulatory requirements but also provides a practical tool to assist stakeholders in overcoming regulatory barriers, promoting an effective transition of the device to the market. In this way, the work contributes to the advancement of safe and innovative medical technologies aligned with both national and international regulatory guidelines.

1. Product Technical Dossier (PTD)

a) Detailed description of the device (purpose, components, materials used, functionality);
b) Technical and functional specifications;
c) User manual;
d) Manufacturing flowchart.

2. Risk Management Report

a) Identification, analysis, evaluation, and mitigation of risks associated with device use;
b) Compliance with ABNT NBR ISO 14971 standard.

3. Validation Report for Tests and Studies

a) Results of preclinical studies (biocompatibility, cytotoxicity, etc.);
b) Data from clinical trials (Phases I, II, and III), including safety and efficacy;
c) Stability studies of the device.

4. Good Manufacturing Practices (GMP) Certificate

a) Issued by ANVISA to certify that the manufacturer complies with quality requirements;
b) Compliance with RDC No. 665/2022 (or the most recent version).

5. Laboratory Test Reports

a) Performance tests of the device;

b) Electrical and mechanical safety tests;

c) Electromagnetic compatibility tests (for electronic devices).

6. Product Certification by Notified Body

a) Applicable to medium- and high-risk devices;

b) Compliance report with international standards (ISO 13485, IEC 60601, etc.).

7. Labeling Documentation

a) Labels and packaging containing usage instructions, warnings, and precautions;

b) Translations, where applicable.

8. International Regulatory Data (if applicable)

a) Registration certificates from other countries (FDA, CE Mark);

b) Studies or approvals conducted outside Brazil.

9. Post-Market Monitoring Plan

a) Strategy to monitor device performance and safety after commercialization;

b) Plans for sanitary surveillance and adverse event reporting.

10. Risk Classification Justification

a) Clear demonstration of how the device was classified (Classes I, II, III, or IV);

b) Criteria based on RDC No. 185/2001 or the most updated version.

11. Sanitary Surveillance Fee (TFVS)

a) Proof of payment of the corresponding fee.

Note: The list of documentation may vary depending on the type of medical device and its risk classification. However, this manual provides the primary documents required as a foundation for conducting the regulatory process.

Manual

Documentation Required for Obtaining ANVISA Licensing

Author's Note:

This manual was developed based on the results and discussions presented in the doctoral thesis titled **Ethical and Regulatory Dimensions of the Technological Development Process for a Portable Medical Device for Diabetic Foot Treatment: From Bench to Scale Manufacturing**, authored by **Vladimir França Nogueira**, defended within the Graduate Program in Electrical Engineering at the University of Brasília (UnB). The research aimed to investigate the translational process of medical devices in Brazil, with an emphasis on regulatory barriers and strategies to overcome them.

The knowledge acquired during the research was fundamental in structuring this manual, which seeks to serve as a practical tool for researchers, developers, and manufacturers aiming to understand and meet the regulatory requirements imposed by ANVISA. Thus, the manual reflects the commitment to translating theory into practical guidance, contributing to the promotion of safe and effective medical innovations in the Brazilian market.

I extend my gratitude to all the advisors, colleagues, and institutions that contributed to the research underpinning this work.

Vladimir França Nogueira

Brasília-DF, November 29, 2024

REFERÊNCIAS:

ANVISA. Resolution RDC No. 185, of October 22, 2001. Regulates the registration of medical products in Brazil. National Health Surveillance Agency, Brasília, 2001. Available at: https://www.in.gov.br. Accessed: Dec. 13, 2024.

ANVISA. Resolution RDC No. 665, of March 30, 2022. Establishes the requirements for good manufacturing practices for medical devices and in vitro diagnostic products. National Health Surveillance Agency, Brasília, 2022. Available at: https://www.in.gov.br. Accessed: Dec. 13, 2024.

ABNT. Brazilian Association of Technical Standards. ABNT NBR ISO 14971:2020: Medical devices - Application of risk management to medical devices. Rio de Janeiro: ABNT, 2020.

ABNT. Brazilian Association of Technical Standards. ABNT NBR ISO 13485:2016: Medical devices - Quality management systems - Requirements for regulatory purposes. Rio de Janeiro: ABNT, 2016.

IEC. International Electrotechnical Commission. IEC 60601-1: Medical electrical equipment - Part 1: General requirements for basic safety and essential performance. Geneva: IEC, 2020.

APPENDIX 3: Manual - Documentation Required for Obtaining INMETRO Certification

This manual aims to guide researchers, developers, and manufacturers of medical devices on the regulatory requirements for obtaining certification from INMETRO. The detailed content addresses the essential documentation and mandatory processes to ensure that the medical device is approved for use in the Brazilian market, meeting the highest standards of safety, efficacy, and technical compliance.

This manual not only seeks to fulfill legal and regulatory requirements but also provides a practical tool to assist stakeholders in overcoming regulatory barriers, promoting an effective transition of the device to the market. In this way, the work contributes to the advancement of safe and innovative medical technologies aligned with both national and international regulatory guidelines.

1. Formal Request

a) Official certification process request submitted to the Product Certification Body (OCP), including technical and functional specifications.

2. Technical Product Manual

a) Detailed description of the device, including its operating principle, technical specifications, and mode of operation.

3. Technical Design

a) Documentation containing drawings, diagrams, and technical specifications of the device components.

4. Test Reports

a) Laboratory test reports demonstrating the device's performance, electrical, mechanical, and electromagnetic safety.

b) Electromagnetic compatibility (EMC) tests, in compliance with IEC 60601-1 standards.

5. **Risk Management Plan**
   a) Report in accordance with ABNT NBR ISO 14971, detailing the identification, evaluation, and mitigation of risks associated with the device.

6. **Good Manufacturing Practices Certification**
   a) Document issued by ANVISA certifying the manufacturer's compliance with Good Manufacturing Practices requirements (RDC No. 665/2022).

7. **Validation Report**
   a) Results from studies demonstrating the functionality and safety of the device under real-use conditions.

8. **User Manual**
   a) Document providing guidance on device operation, warnings, and usage precautions, translated into Portuguese.

9. **Regulatory Compliance Reports**
   a) Demonstration that the device meets applicable national and international standards, such as ISO 13485 (Quality Management) and IEC 60601-1 (Medical Equipment Safety).

10. **Labeling and Packaging**
    a) Samples of labels and packaging containing mandatory information, such as manufacturer identification, batch number, and usage instructions.

11. **Declaration of Conformity**
    a) Document from the manufacturer certifying that the device was produced in compliance with applicable technical standards.

12. **Biocompatibility Test Reports (if applicable)**
    a) For devices that come into contact with tissues or body fluids, in compliance with specific ISO standards.

13. Administrative Fees

a) Proof of payment of fees associated with the certification process submitted to the Product Certification Body (OCP).

14. Audit Reports (when applicable)

a) Audits conducted at the manufacturing site to verify compliance with technical and regulatory standards.

Note: The list of documentation may vary depending on the type of medical device and its risk classification. However, this manual provides the primary documents required as a foundation for conducting the regulatory process.

Manual

Documentation Required for Obtaining INMETRO Certification

Author's Note:

This manual was developed based on the results and discussions presented in the doctoral thesis titled **Ethical and Regulatory Dimensions of the Technological Development Process for a Portable Medical Device for Diabetic Foot Treatment: From Bench to Scale Manufacturing**, authored by **Vladimir França Nogueira**, defended within the Graduate Program in Electrical Engineering at the University of Brasília (UnB). The research aimed to investigate the translational process of medical devices in Brazil, with an emphasis on regulatory barriers and strategies to overcome them.

The knowledge acquired during the research was fundamental in structuring this manual, which seeks to serve as a practical tool for researchers, developers, and manufacturers aiming to understand and meet the regulatory requirements imposed by INMETRO. Thus, the manual reflects the commitment to translating theory into practical guidance, contributing to the promotion of safe and effective medical innovations in the Brazilian market.

I extend my gratitude to all the advisors, colleagues, and institutions that contributed to the research underpinning this work.

Vladimir França Nogueira

Brasília-DF, November 29, 2024

REFERÊNCIAS:

INMETRO. Ordinance No. 54, of February 1, 2016. Technical quality regulation for equipment under INMETRO conformity assessment. Available at: https://www.inmetro.gov.br. Accessed: Dec. 13, 2024.

ABNT. Brazilian Association of Technical Standards. ABNT NBR ISO 14971:2020: Medical devices - Application of risk management to medical devices. Rio de Janeiro: ABNT, 2020.

ABNT. Brazilian Association of Technical Standards. ABNT NBR ISO 13485:2016: Medical devices - Quality management systems - Requirements for regulatory purposes. Rio de Janeiro: ABNT, 2016.

IEC. International Electrotechnical Commission. IEC 60601-1: Medical electrical equipment - Part 1: General requirements for basic safety and essential performance. Geneva: IEC, 2020.

INMETRO. Base Document for the Certification of Medical and Dental Products. Available at: https://www.inmetro.gov.br. Accessed: Dec. 13, 2024.

ANVISA. Resolution RDC No. 665, of March 30, 2022. Establishes Good Manufacturing Practices requirements for medical devices. National Health Surveillance Agency, Brasília, 2022. Available at: https://www.gov.br/anvisa. Accessed: Dec. 13, 2024.