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Original Article

Development and application of the Rapha® device for the treatment of diabetic foot ulcers

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Abstract: Introduction: Transforming medical research into real-world healthcare solutions is a complex endeavor that may benefit from the synergy between academic research, governmental support, and industry innovation. Objectives: In this article we delve into the framework of Translational Medical Research (TMR) in Brazil, elucidating the possible interplay between public universities and other pivotal stakeholders in the translational journey. Methods: Our focal point is the Rapha® device, an innovative medical technology, as we explore its ethical and regulatory journey. We seek to understand the environment that shapes healthcare technology development through a mixed-methods research design, combining policy analysis with stakeholder interviews. Results: The research begins by examining public policies, aiming to carve out a socially inclusive and advantageous ecosystem. We then highlight the pivotal components-steps, milestones, stakeholders, and policies that underpin the TMR process. Our findings reveal that while TMR frequently culminates in patents and technology transfer agreements, specific regulatory and production challenges exist, particularly during transitioning from the T3 (clinical trials) to T4 (public health practice) phase. We provide insights into its translational progression by tracing the developmental stages from foundational research (T0) to clinical trials (T3) for the Rapha® device. Conclusion: Ultimately, this study underscores TMR's vital role in advancing healthcare access and posits that academic institutions can significantly influence the creation of ethically robust, regulated, and impactful medical innovations, contributing meaningfully to global healthcare.

Keywords: TMR, diabetic foot, Rapha® device, Brazil's unified health system, health policy and technology readiness level

Introduction

Among chronic diseases, diabetes mellitus (DM) stands out as one of the most widespread conditions affecting modern society, with its prevalence and consequences becoming increasingly concerning [1]. According to the International Diabetes Federation (IFD), the estimated number of patients diagnosed with this condition is expected to surge from 537 million in 2021 to 783 million by 2045 among individuals aged 20 to 79 [2]. This metabolic disorder, characterized by disruptions in glucose and other metabolic processes, brings a host of complications.

One of the most concerning complications of DM is the diabetic foot. It not only affects the patient's quality of life but can also have dire physical implications. Diabetic foot ulcers, which arise primarily from a combination of neuropathy and vascular pathologies, can progress to severe infections requiring amputations, impacting not just the digits but, in severe cases, entire limbs [3]. Moreover, biomechanical alterations in diabetic patients often lead to foot deformities, increasing their vulnerability to infections.

The treatment for diabetic foot varies based on the degree of limb involvement, considering the presence and/or severity of ischemia, infection, or both. Currently, multiple treatment options are available for managing lesions, such as dressings with various types of available coverings, debridement of devitalized tissues, revascularization procedures, local application of growth factors, hyperbaric oxygen therapy, and

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various procedures aimed at skin replacement. Amputation remains the most frequently employed last-resort treatment [4].

This article presents the promising results of the Rapha® project technology, which integrates a latex biomembrane derived from Hevea brasiliensis in conjunction with a light-emitting diode (LED). This combination promotes the reduction of free radicals in injured tissue, angiogenesis, and other benefits [5]. Accordingly, it accelerates wound healing, closing lesions faster than conventional treatments [6-9]. We analyzed the outcomes of this case study using translational research to assess the knowledge generated from basic research and its clinical application until its market availability [10, 11].

Coined initially as "from bench to bedside," translational research aims to integrate various stages of research and knowledge, striving for practical applications that benefit society [12, 13]. While similar terms like "Translational Medicine" and "Translational Science" are sometimes used interchangeably, nuances distinguish each [14]. Historically, translational research was viewed linearly, consisting primarily of two main stages: basic and applied research. However, contemporary perspectives encompass a more holistic and bidirectional approach. This expanded model now includes evidence synthesis, knowledge translation, technology implementation, evaluation, and the broader impact on health systems, ensuring research reaches clinical application and effectively integrates within health care practices [13, 15].

Introducing a new technology into the health system is a multi-faceted journey. It encompasses various stages, from research to implementation, and involves several stakeholders attending to ethical, regulatory, scientific, and financial concerns. Given the complexity and rigor of these processes, it's unsurprising that the path from initial research to actual use can be long, resource-intensive, and fraught with challenges [16, 17].

In the beginning, innovations are rooted in basic research, with potential solutions subjected to meticulous testing. Only after proving their merit in these preliminary stages they advance to clinical research. Throughout this progression, continuous data collection is paramount, and it's not uncommon for some clinical trials to be halted until they align with stringent regulatory standards. Ethical imperatives mandate that results from these trials be disseminated to the broader community. Yet, concerning as it may be, less than half of these findings see publication within a year of a study's conclusion [18].

The importance of publishing scientific outcomes cannot be overstated; they play a pivotal role in clinical and managerial decision-making. Nevertheless, even when these results are made public, obstacles persist. The healthcare community often grapples with challenges related to accessing, interpreting, and applying this research in tangible, patient-centric ways [19-21].

Throughout these extensive processes, integrating and optimizing stages are crucial, ensuring that benefits from innovative inventions, such as the Rapha® device, are available and accessible to society. Identifying the stages, entities, and regulations within the Brazilian context is justified, as gathering such information can pinpoint gaps and opportunities for improvement in Research and Development (R&D), ethics, and regulatory processes. This aids decision-making and supports the implementation of new ideas, services, and products encompassed within the framework of translational management competencies.

Material and methods

Translational models, such as the Translational Medical Research (TMR) approach, strive to depict the nuanced complexities of research through empirical evidence. This comprehension enables the delineation and characterization of stages, calculation of average durations, and recognition of primary contributors. This knowledge illuminates the mechanisms of knowledge creation and its subsequent applications for societal gain. The translational procedure comprises various phases, called T-time periods (T0 to T4). These phases streamline the process of converting research into tangible health advantages, as showcased by the National Institutes of Health (NIH) Roadmap, which is a relevant theoretical framework, detailing the "epidemiology and phases of knowledge translation and synthesis - from discovery to population health impact", illustrated in **Figure 1** and consistent with the Rapha® translation [11].

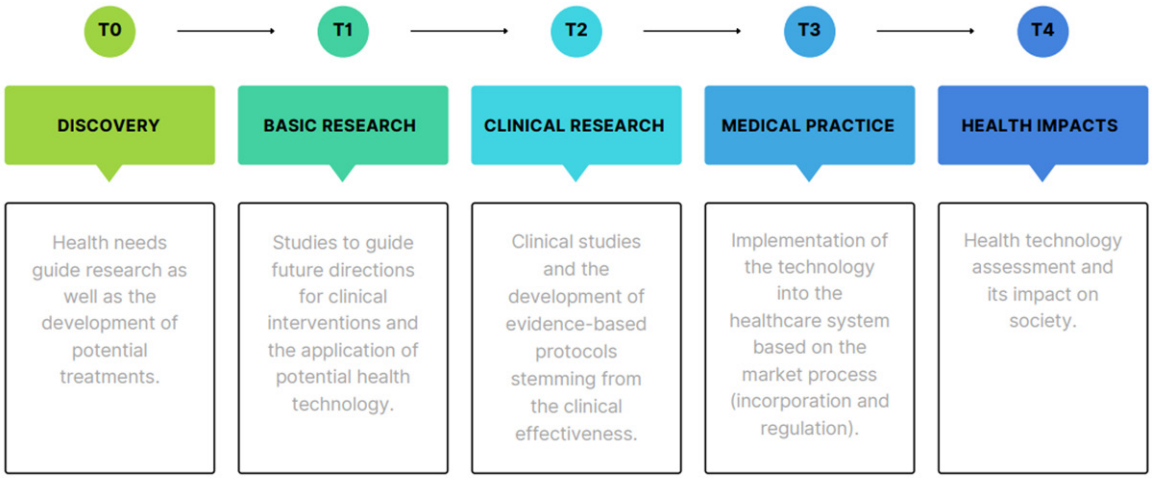

Figure 1. Translational model depicting the phases of translation from T0 to T4 for the Rapha® device. It should be noted that this model does not suggest a linear progression in research. Adapted from [13] for the Rapha® device.

Data was collected through the acquisition process, encompassing both academic and scientific product information for a qualitative approach. This collection process involved both document analysis and fieldwork. For data processing, we employed content analysis techniques, focusing on distinct themes to underscore elements pertinent to the translational research of the Rapha® device. Key elements identified during data collection were assigned values, enabling a comparative analysis of translational research outcomes across phases T0 to T4. Specifically, data was gathered on the product Concept, Animal Ethics Committee, patents, Technological Transfer, Brazilian Institute of Metrology, Quality, and Technology (INMETRO) registration, and Brazilian Health Surveillance Agency (Anvisa) authorization for the eventual release in the Brazilian market. This data facilitated content analysis using a simple thematic approach, suggesting the single case study reached a particular level of maturation and translation. The timeframe for this analysis covered the period from March 2011 to March 2023, focusing on the R&D of the Rapha® device.

Regarding ethical and regulatory considerations, it was crucial to pinpoint normative acts and policies pertinent to translational research for technology registration and validation within the Brazilian context. This identification was facilitated through extensive searches on the Ministry of Health's Health Legislation System website (MH), the Anvisa portal, the Official Gazette of the Union, and the Brazilian Legislation Portal. Additionally, the normative acts repository of the Health Policy Analysis Observatory and Anvisa's Collegiate Board Resolutions (CBR) technical regulations were referenced.

The document analysis revealed the macro and subprocesses with considerable specificities. Notably, these processes occur non-linearly but tend to follow this pattern over time. Additionally, fieldwork signposts these processes and their respective outcomes. Thus, the time stages T0, T1, T2, T3, and T4 were identified as results of the translation of Rapha® device over time.

Initially, investigations and tests involving human participants were conducted before evaluation and approval by the Research Ethics Committee/National Brazilian Research Ethics Committee to protect study participants in line with research ethics. Subsequently, data were collected to translate the T0 phase, detailing device descriptions and findings to present health outcome standards for specific locations, times, and research participants. This procedure also encompasses device design and description.

The T1 phase encompassed pre-clinical analysis, detailing the tests conducted and subsequent findings during health applications. The objective was to characterize discoveries and assess potential health applications through

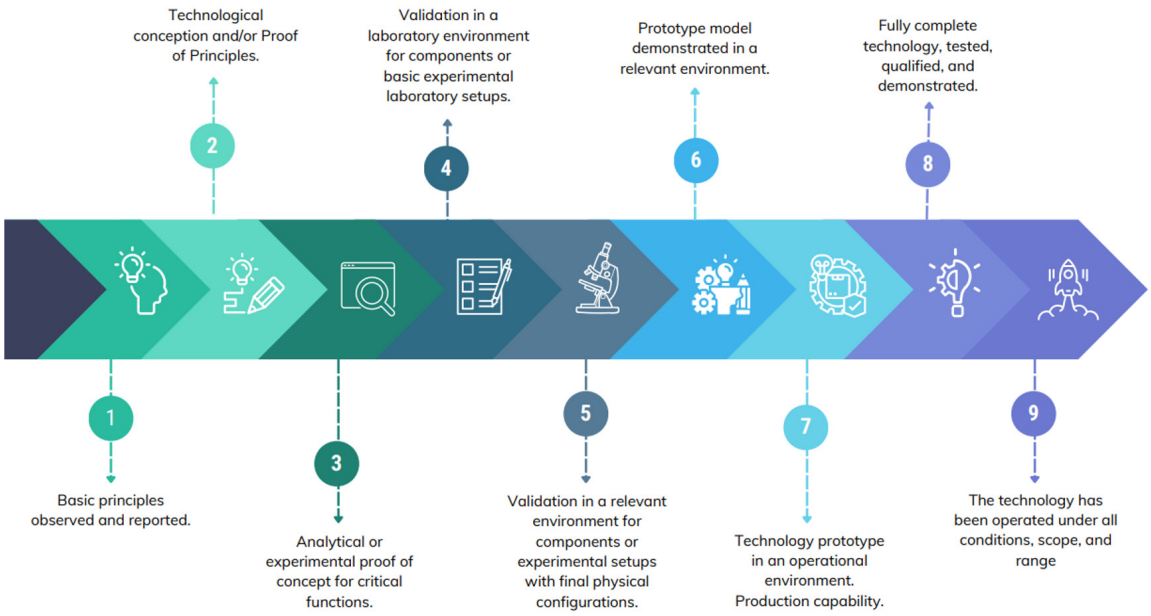

Figure 2. The nine levels of technological readiness. Adapted from [23].

animal clinical studies. Restrictions for the Rapha® device's initial use were also observed. This phase spanned basic and pre-clinical research, from discovery to development. Here, basic research refers to experimental studies that exclude human subjects and other non-clinical investigations.

The T2 phase focused on clinical analysis through health applications and main evidence guidelines. This analysis included the evaluation of the effectiveness of interventions to enhance patient health and prevent the progression of diabetic foot ulcers using observational and experimental studies. The device was tested on diabetic foot patients to preliminarily assess the latex blade's safety, tolerability, and outcomes from continuous device usage.

The T3 phase charted approval for technology market insertion, adhering to guidelines, standards, and regulations set by Anvisa and INMETRO based in Brazil, and those from the US Food and Drug Administration (FDA) or European Union (EU). This stage was critical for the medical device's validation. Upon fulfilling the requirements of competent agencies, the sanitary registration of technology was granted. INMETRO also evaluated and granted certification for the LED device for human use.

In the T4 phase, the device's launch and influence in the Brazilian market are anticipated, accompanied by routine practice monitoring. However, this stage has not been achieved yet, as the T3 regulatory approval phase has just been completed.

For the analysis of the Rapha® device, the Technology Readiness Levels/Manufacturing Readiness Levels (TRL/MRL) analysis tool was employed to address the technology's competitive intelligence process geared towards the market. The TRL scale [22], aims to standardize technological companies' innovation processes with a technological maturity scale. This procedure also allows for a detailed monitoring of the technological asset during the research, development, and validation processes, and facilitates direct comparisons between different products.

The National Aeronautics and Space Administration (NASA) developed the TRL scale in the 1970s to assess a technology's maturity level [23]. Various research and technological development institutions have widely adopted and used it internationally. Thus, it is essential to identify stakeholders in technology management through nine levels of the technology lifecycle as illustrated in **Figure 2**. Accordingly, the Rapha® technology is evaluated based on its maturation from the translation.

Results

Initial phase of the technology (T0) - description and discovery

Location, people, facts, events, and frequencies: The research herein described employed document analysis and a conceptual approach for the Rapha® device's transfer. This device received approval from the Ethics Research Committee of the Foundation for Education and Research in Health Sciences of the State Health Department of the Federal District (SHD/FD), under protocol number 052/2012, and the Ethics Research Committee of the Faculty of Health Sciences at the University of Brasília (UnB) with the proof number 085906/2018 and Certificate of Presentation of Ethical Review nº 94910718.5.0000.0030 in 2019. A multi-disciplinary team affiliated with the Graduate Program in Biomedical Engineering conducted the study under the guidance of Prof. Dr. S.R.F. Rosa and Prof. Dr. A. F. da Rocha. They collaborated with the outpatient clinics for Diabetic Foot associated with the following hospitals: Gama Regional Hospital (GHR), North Wing Regional Hospital (NWRH), and Taguatinga Regional Hospital (TRH), all in Brasília, Brazil, while also making daily follow-ups at the patients' residences.

The device comprises of a healing insole and an electronic circuit for tissue regeneration. The healing insole is crafted from the natural latex of the rubber tree Hevea brasiliensis. It is customized to match each patient's specific characteristics and dimensions. Subsequently, adhesive latex sheets were used for better application in patients. Consequently, the healing of diabetic foot ulcers was achieved through the combined and simultaneous action of latex biomaterial and low-intensity LED irradiation, promoting tissue regeneration and neoformation.

In its multidisciplinary mission, the research group, focused on Research, Development, and Innovation (R&D&I) to address diabetic foot cases. Despite a strong connection with the UnB, the team incorporated independent professionals from various sectors, highlighting interdisciplinary collaboration. This alliance was crucial in advancing the T0 phase of Rapha®'s translational research, where the union of multiple expertise shaped technology. The results led to a series of publications, acknowledging the impact and contribution of the technology to the Brazilian Unified Health System (UHS).

Rapha® device - technical concept of the technology: The Rapha® device, a portable tool, integrates a mobile electronic system designed for tissue neoformation using phototherapy principles, to enhance wound healing by expediting the scarring process. Its light-emitting circuit comprises: a control module and an LED matrix module. Currently, low-power LED phototherapy has proven effective in managing various diseases. In this context, the Rapha® device is seen as a novel phototherapy modality, noteworthy for its low cost and ease of use. Furthermore, the Rapha® device is portable and user-friendly; the LED beam is emitted for a predetermined time of approximately 35 minutes.

The latex derived from the Brazilian rubber tree, Hevea Brasiliensis, is a milky substance composed of 50% water, 30-45% rubber particles (cis-1,4-polyisoprene), and 4-5% of other constituents like proteins, lipids, and carbohydrates [23]. Its biocompatibility enables it to promote angiogenesis, formation of extracellular matrices, cell adhesion, and tissue repair [24]. This study explored this latex biomembrane as an innovative dressing for skin ulcers (**Figure 3**). Its cost-effectiveness, ease of handling, and efficiency in accelerating healing, especially in diabetic patients, are remarkable, owing to its debriding and neoangiogenic potential [25].

Rapha® is an innovative phototherapy device focused on healing diabetic foot ulcers. It is composed of a panel embedded with 30 red LEDs. The device employs a timed circuit regulating light emission (**Figure 4**). Additionally, a green LED serves as a time-count indicator, and an auditory alert is activated after a preset period. All technology is encased in an ABS PA757 plastic shell, powered by 9V alkaline batteries. The device is conveniently secured to the patient using self-adhesive elastic bandages.

Patent application: Securing a patent is often an inaugural stride in the translational journey. With this in mind, the cross-disciplinary team, drawing expertise from engineering, health,

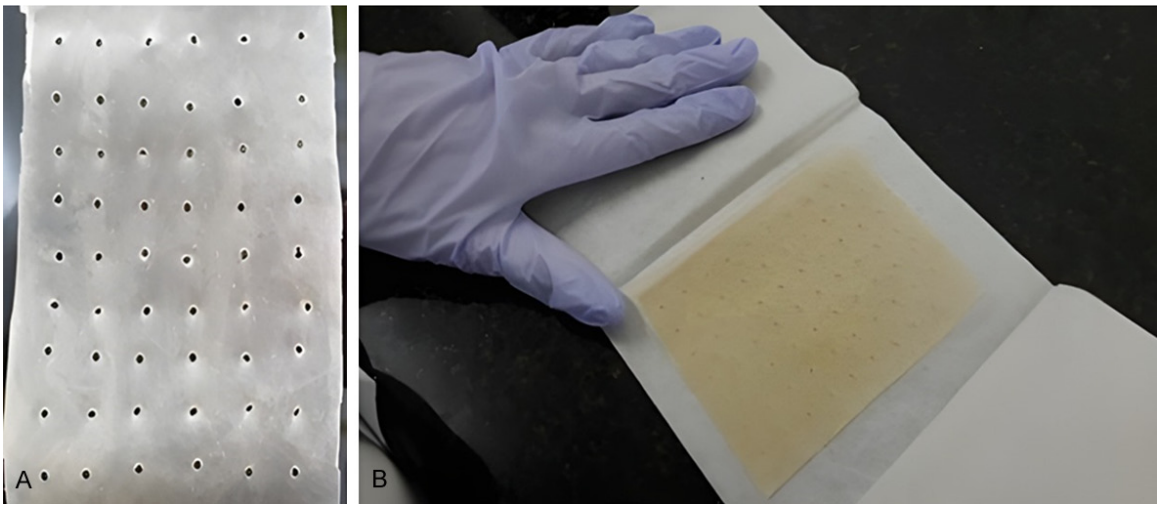

Figure 3. Perforated membrane displayed on parchment paper [6].

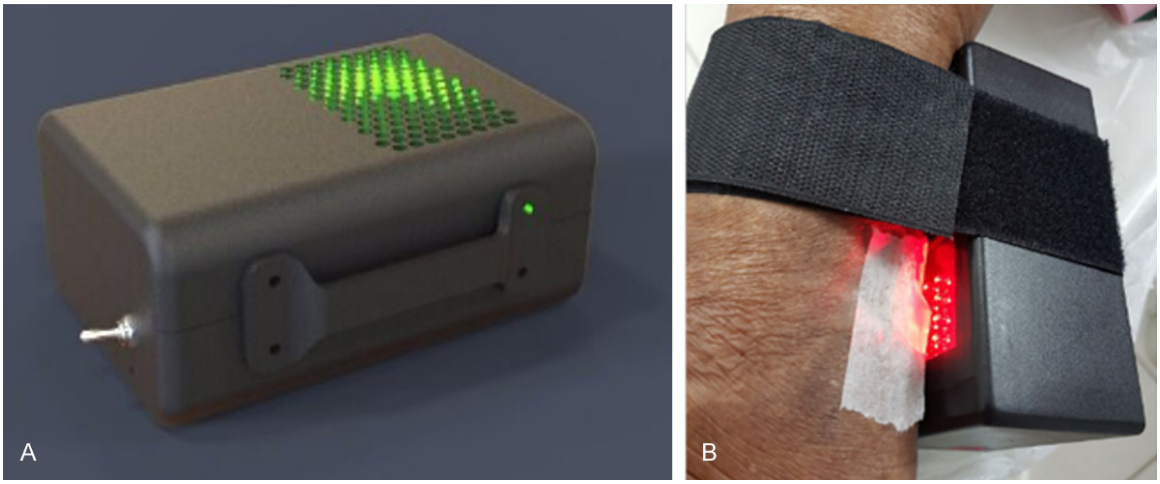

Figure 4. Perspective view of the Rapha® equipment and its mode of use [10].

and biology, crystallized the concepts that underscore the T0 phase. The identified patents were cataloged by attributes such as protection number, patent date, title, overseeing institution, inventors/authors, academic departments, type of protection, group classification, and subgroup, as presented in **Table 1**. This table displays the various innovations stemming from the Rapha® device, which has driven knowledge and advancement across various fields from 2011 to the present day. One can observe the validation of phase T0, initiated by the patent's first draft in 2011 based on Reis' doctoral thesis [26], and several subsequent contributions and enhancements of the device over time. This sequence underscores the nonlinear nature of translational research. Furthermore, the work emphasizes the interdisciplinary collaboration of biomedical engineering, healthcare and biology, encompassing various processes and stages to achieve patent registration. Thus, the nonlinear progression in research phases aiming at translation is underscored by stages like T2 and T3, the former concerning clinical research, and the latter addressing regulatory aspects and technology transfer. Both of these stages are contingent upon ethical approval and patent filing. Activities linked to T2 and T3 were previously incorporated by T0, following clinical protocol actions and patent filing, in line with this nonlinearity over time.

Table 1. Patents related to the specific features of the Rapha® device

Protection Number	Filing Date	Title	Managing Institution	Academic Unit	Type of Protection	Classification	Subgroup Classification
PI 1103692 3	18/7/2011	Cushioning insole for diabetic feet	University of Brasilia Foundation	Faculty of Technology - UnB Gama Faculty - UnB	Invention Patent	Health	Medical and hospital devices
PI 1103691 5	18/7/2011	Sensorized insole for diabetic feet	University of Brasilia Foundation	Faculty of Technology - UnB Gama Faculty - UnB Faculty of Technology - UnB	Invention Patent	Health	Medical and hospital devices
PI 1103690 7	18/7/2011	Healing insole for diabetic feet	University of Brasilia Foundation	Faculty of Technology - UnB Gama Faculty - UnB Faculty of Technology - UnB	Invention Patent	Health	Medical and hospital devices
BR 10 2016 019963 8	29/8/2016	Microperforated adhesive made from latex, associated with LED light sources for direct application to internal and external human inflammatory processes	University of Brasilia Foundation	Gama Faculty - UnB Faculty of Technology - UnB	Invention Patent	Health	Biomaterials and biomolecules
BR 10 2017 014239 6	29/6/2017	Constructive arrangement applied to foot prosthesis manufactured with elastic and damping characteristics, and its method for quantifying mechanical energy to be reused	University of Brasilia Foundation	Gama Faculty - UnB	Invention Patent	Health	Assistive technology
BR 13 2021 001944 0	2/2/2021	Latex-based biomembranes (Hevea brasiliensis) containing liposomes with curcumin (Curcuma longa) and papain (Carica papaya) and their use associated with led therapy for the treatment of chronic ulcers and diabetic wounds	University of Brasilia Foundation	Planaltina Faculty - UnB Gama Faculty - UnB Institute of Biological Sciences - UnB	Certificate of Addition	Health	Biomaterials and biomolecules
BR 10 2022 007175 6	13/4/2022	Portable Photodynamic Therapy Transducer for Use on Infected Diabetic Foot Wounds	University of Brasilia Foundation	Gama Faculty - UnB Faculty of Technology - UnB	Invention Patent	Health	Medical and hospital devices
BR 51 2022 001637 0	1/7/2022	Ulcer classification according to artificial intelligence	University of Brasilia Foundation	Gama Faculty - UnB	Computer program	Health	Diagnosis

Second phase of technology (T1) - pre-clinical or non-clinical tests

Pre-clinical tests involved both in vitro and in vivo sample testing. Below are the tests detailed by topic.

Biocompatibility tests: Biocompatibility assessments were carried out using natural latex blades. The LED device will not directly contact the patient's skin during treatment, as a latex membrane always separates them. Consequently, the device was exempt from these tests.

Cytotoxicity potential evaluation - in vitro: The cytotoxicity of natural latex blades was assessed on V-79 cell lines. These fibroblasts were cultivated on culture plates and subjected to varying extraction medium concentrations (100%, 50%, 25%, and 12.5%) over 24 hours. Following this period, an MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) at a concentration of 1 mg/ml was added, and samples were incubated for an additional 2 hours, followed by isopropanol addition. Absorbance analysis was conducted at 570 nm, using 650 nm as a reference. Results indicated a cell viability reduction exceeding 30% compared with the negative control, at concentrations of 12.5%, 25%, and 50% of latex blades. However, at 100% concentration, a cell viability reduction was also noted, surpassing 30% when compared to the negative control. It's inferred that natural latex blades are non-toxic for V-79 cells up to 50% concentration but show cytotoxicity at 100%.

Intracutaneous reactivity toxicological assay in rabbits: An Intracutaneous Reactivity Toxicological Assay in Rabbits was performed to assess the cutaneous reactivity of natural latex blades using intradermal injections in rabbits (Oryctolagus cuniculus). After shaving the dorsal region near the spine, a sample was prepared, using a ratio of 0.1 g latex diluted in 1.0 ml of sterile saline. This solution was then subjected to a water bath at 37°C for 72 hours. Each of the three rabbits received five injections of the sample solution on the left side with the sample and five 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 noticed in both the sample and control areas, subsiding after 24 hours. Systemic toxicity was not identified. The resulting score, comparing the sample's reaction to the control, was 0.0. It was concluded that the natural latex blades exhibited no intracutaneous reactivity in the tested rabbits.

Guinea pig cutaneous sensitization test - Buehler Method: Using this method, the study aimed to assess the potential sensitizing effects of natural latex blades on guinea pigs (Cavia porcellus). For this purpose, animals were divided into two groups: experimental, consisting of 10 guinea pigs, and control, consisting of 5. The latex sample was applied to the left flank of the Experimental Group (EG), while the Control Group (CG) received gauze dressings. These 6-hour applications were repeated thrice weekly for three weeks on the same spot. On the 28th day, following an 11-day break, a challenge application was placed on the right flank. Observations made 24 and 48 hours post-application removal, in line with Organization for Economic Cooperation and Development (OECD) Test Guideline 406 (Guidelines for Testing of Chemicals: Skin Sensitization), showed no signs of irritation, erythema, or edema. Hence, the natural latex sample was determined as non-sensitizing for guinea pig skin under this test's conditions.

Repeated dose dermal toxicity test (28 days) in rats: In a study sanctioned by the ALS Laboratories Ltda Animal Ethics Committee, the systemic toxic effects of dermal exposure to latex blades in Wistar rats over 28 days were investigated, following the guidelines of ISO10993:11. In the study, 20 rats underwent dermal applications and were observed for nearly a month. Results revealed no mortality or clinical toxicity signs, with minor alterations in specific parameters in females. Histopathological evaluations also confirmed the absence of lesions related to exposure. Thus, it was concluded that the latex blade does not induce systemic toxic effects, supporting their classification as non-toxic.

Third phase of technology (T2) - clinical tests in humans

This clinical study is part of the Rapha® project, which sought to clinically evaluate ulcer healing progression in two distinct groups: the EG and CG. The former utilized the Rapha® technology

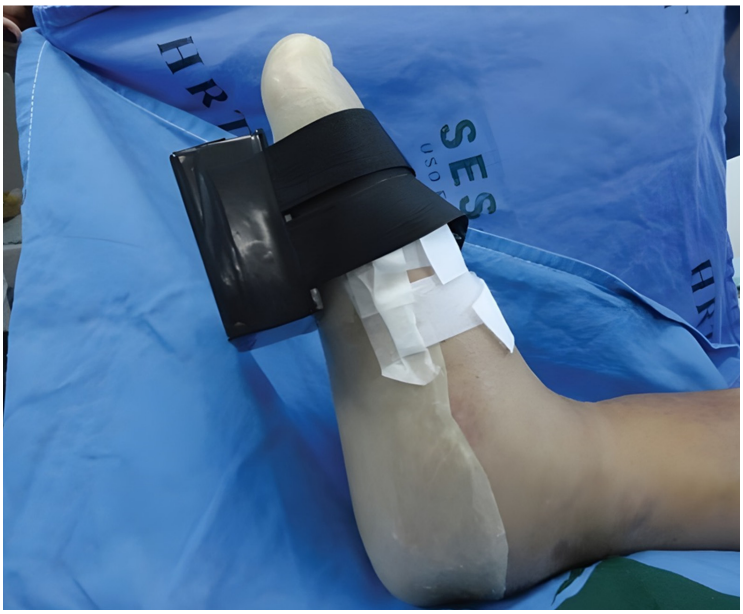

Figure 5. Participant using Rapha® for tissue regeneration [26].

daily at home, with in-person assistance once a week from the research team and remote daily support, in addition to bi-weekly outpatient evaluations. Meanwhile, the latter group, the CG received treatment per the Brazilian UHS protocol, wherein weekly dressings are administered or as required, under the responsibility of outpatient nurses.

Regulatory aspects for clinical phases and private sector participation in T2 translational phase: Clinical studies play a pivotal role in the regulatory approval of medical products and healthcare devices, ensuring their safety and efficacy. Ethical and regulatory approval from Anvisa, aligned with guidelines from Technical Note No. 004/2016 and regulations such as CBR 10/2015 and 548/2021, is paramount to conducting such trials in Brazil. This approval process involves several requirements, including submitting Special Notifications based on the product's risk classification. Moreover, a well-defined protocol detailing the study design and methodology is essential. Collaboration with the private sector in the T2 phase can streamline the transition, ensuring healthcare device manufacturing adheres to Good Manufacturing Practices. An exemplar of this process is the development of the Rapha® device, which benefited from guidance and cooperation from private companies in clinical trials to meet regulatory and ethical standards.

Clinical trials: Three clinical studies were conducted to evaluate the safety and efficacy potential of the Rapha® device. These studies are described in the subsequent sections.

Preliminary clinical trial of Rapha®: safety and efficacy: At the Reginal Hospital of Taguatinga (RHT), in the Federal District in Brazil, a pioneering clinical trial was carried out for the preliminary version of Rapha®, aiming to evaluate its safety and efficacy [26]. Adhering to Resolution 196/96 of the National Health Council, the study, under protocol number 052/2012-SHD/FD, occurred between August and December of 2013, involving six participants who collectively presented with 11 ulcers. Each ulcer was categorized into a CG, treated with the standard UHS protocol using silver alginate-releasing foam dressings, and an EG treated with Rapha®. The analysis revealed superiority in the EG, positioning Rapha® as a potential advancement in the treatment of foot ulcers in hospital and home settings. Rapha®'s versatility was demonstrated by its home application after detailed instructions, starting with creating a customized insole. **Figure 5** showcases the use of this novel approach.

Medical staff consistently instructed participants from both groups to adhere to the following guidelines: glycemia control, use of adapted footwear or offloading shoes or wheelchairs (depending on the wound location), ample rest, self-care for the wounds, such as keeping them dry during showers and refraining from wearing unsuitable footwear. Adhering to these guidelines is vital for ulcer healing.

For enhancing treatment efficiency, membranes should be placed on the wound so that it's entirely covered, with the Rapha® device positioned directly on top, in contact with the membrane. The surface of the LED panel should, ideally, completely cover the wound. If this is not possible, it is suggested to segment the treatment, applying it successively to each section of the wound.

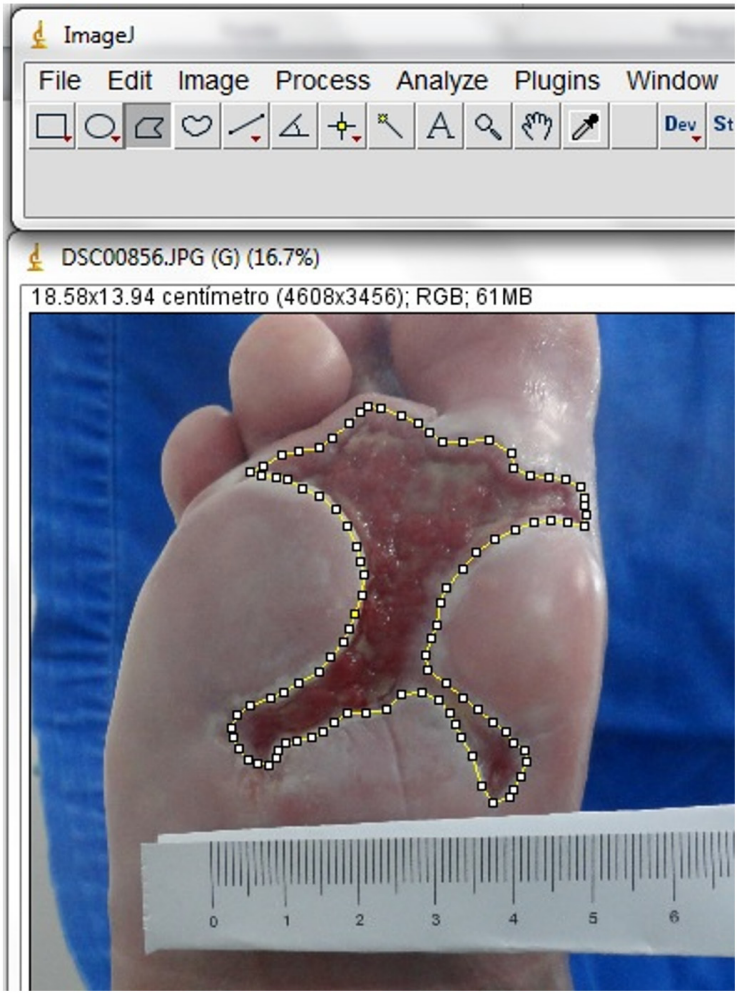

Figure 6. Ulcer border delineation using ImageJ® software [26].

All study participants were subject to weekly evaluations, which included in-person visits and data collection involving the treatment team. The CG and the EG underwent periodic assessments that did not exceed 7 days.

Digital images acquired were analyzed using the ImageJ® software to quantify the total ulcer area. **Figure 6** displays an image acquisition process.

After measuring the total ulcer area, the Ulcer Healing Index (UHI) was calculated using Equation (1):

$$UHI = \frac{(A_i - A_f)}{A_i} \quad (1)$$

Where, UHI - Ulcer Healing Index; Ai - Initial Area; Af - Final Area.

The UHI, is interpreted as follows [27]: UHI = 1: indicates complete re-epithelialization (total healing); UHI = 0: no signs of re-epithelialization; UHI > 0: reduction in ulcer area; UHI < 0: increase in ulcer area.

The contraction of the ulcers was also evaluated in percentage terms using the formula, as shown in Equation (2) below [28]:

$$CRU = \frac{(A_i - A_f)}{A_i} \times 100 \quad (2)$$

Where, CRU - Contraction Relative Ulcer; Ai - Initial Area; Af - Final Area.

Generally, most participants adhered to healing recommendations, such as rest, wearing offloading or appropriate footwear, and self-care of the ulcer. No side effects were reported or observed with the tissue neoformation induction system throughout the study period. The only inconvenience mentioned by participants was a faint odor. This scent is attributed to the natural smell of rubber (latex) and the body's perspiration.

Medical experts deemed the outcomes achieved with the Rapha® system to be highly satisfactory. Consequently, a collective analysis of the findings suggests that the tissue neoformation induction system presents as an effective treatment option for diabetic foot ulcers due to its application convenience, affordability, and potent wound-healing induction.

Figure 7 provides an overview of wound progression from the initial state and after 2 and 4 weeks. It also highlights that the treatment with the EG was more effective than in the CG. Statistical tests demonstrated that the differences between the outcomes of the two treatments were statistically significant ($P < 0.001$). For further details, please refer to the cited literature. Thus, these findings serve as the initial evidence related to the safety and efficacy of Rapha®.

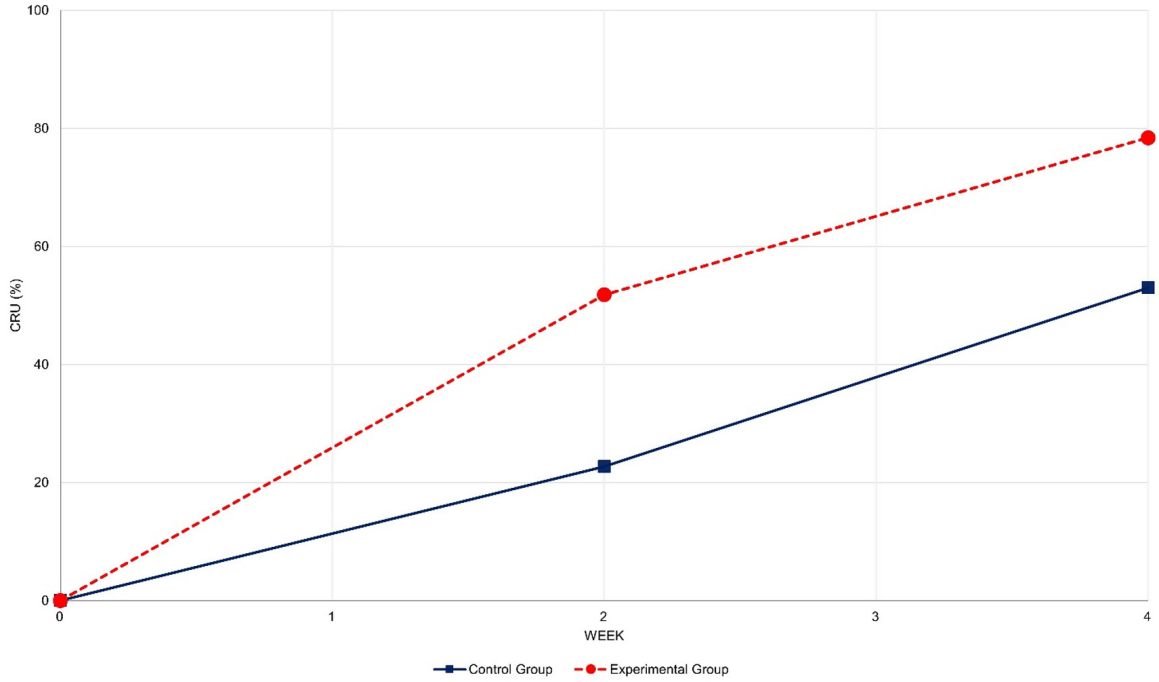

Figure 7. Ulcer border delineation using the ImageJ® software [5].

Clinical trial on the treatment of neuropathic ulcers using the Rapha® system: A randomized, double-blind clinical trial was conducted under the supervision of the Human Research Ethics Committee and carried out in outpatient clinics of the NWRH and GHR and in the homes of the 94 patients involved. These individuals, afflicted by neuropathic ulcers of the diabetic foot, had injuries on the lower limbs and showed no hypersensitivity to latex.

Participants were grouped as follows:

- GI: Underwent daily Rapha® treatment at home, monitored bi-weekly by nurses and evaluated fortnightly at GHR and NWRH.

- GII (Control): Received standard UHS treatment with calcium alginate or silver foam dressings applied bi-weekly at the outpatient clinic.

- GIII: Applied Rapha® daily at home after training. Clinical evaluation was done fortnightly at GHR and NWRH. Clinical aspects of injuries and quality of life were assessed using specific scales such as Texas Brodsky and SF-6D Brazil.

Of the sample, 60.18% were men and 39.82% women, averaging 60 years of age. The assessment of the lesions revealed that 60% were superficial, 26.7% affected tendons, and 13.3% were infected. Ankles and feet were the most affected areas. The lesions persisted for an average of 25 months. The most notable impairments in quality of life involved functional capacity, social aspects, general limitations, and pain. Furthermore, 46.7% of participants had undergone amputations due to ulcers, persisting for about five years. It was observed that 60% reported dependency on mobility. All ulcers included in the study were neuropathic. **Figures 8**-**10** illustrate the healing progress under the intervention of Rapha®.

The latex biomembrane demonstrated strong adherence, facilitating the proliferation of keratinocytes and subsequent tendon and dermal reconstruction. Throughout the study, 33% of participants across groups (GI, GII, and GIII) developed new ulcers. This phenomenon can be attributed to the complex causes of diabetic ulcers. Notably, patients treated by UHS exhibited hemodynamic and metabolic imbalances, making them more susceptible to the emergence of new lesions. Additional observed causes included micro-traumas, prolonged static posture, and inappropriate footwear.

Photobiomodulation show systemic effects, including a marked elevation in T lymphocyte cellular proliferation, albeit short-lived. In pa-

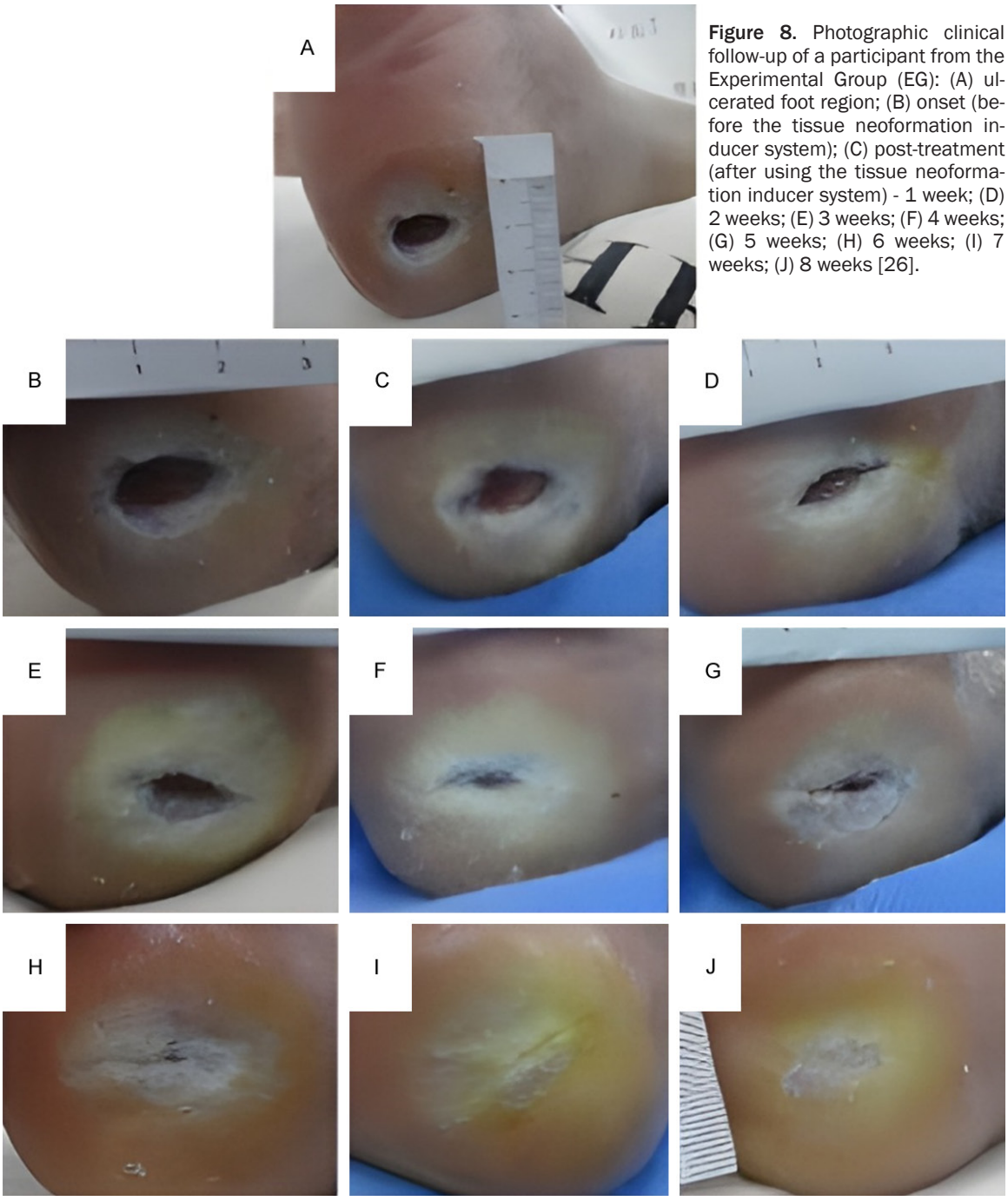

Figure 8. Photographic clinical follow-up of a participant from the Experimental Group (EG): (A) ulcerated foot region; (B) onset (before the tissue neoformation inducer system); (C) post-treatment (after using the tissue neoformation inducer system) - 1 week; (D) 2 weeks; (E) 3 weeks; (F) 4 weeks; (G) 5 weeks; (H) 6 weeks; (I) 7 weeks; (J) 8 weeks [26].

tients treated with the Rapha® device (GI and GIII), there was a continuous decrease in non-viable tissues. In contrast, GII patients who used conventional dressings showed an increase in these tissues, reaching 74.7%, while GI and GIII groups recorded only 4.9% and 23.1%, respectively, after six weeks of therapy, as illustrated in **Figure 11**.

The Granulation Red Index (GRI) evaluated the quality of granulation tissue. As per **Figure 12**, there was an increase in GRI in all groups after a week of treatment. However, after 4 weeks, only the Rapha® treated groups (GI and GIII) maintained improvement in the GRI. In contrast, the group undergoing conventional treatment (GII) recorded a significant

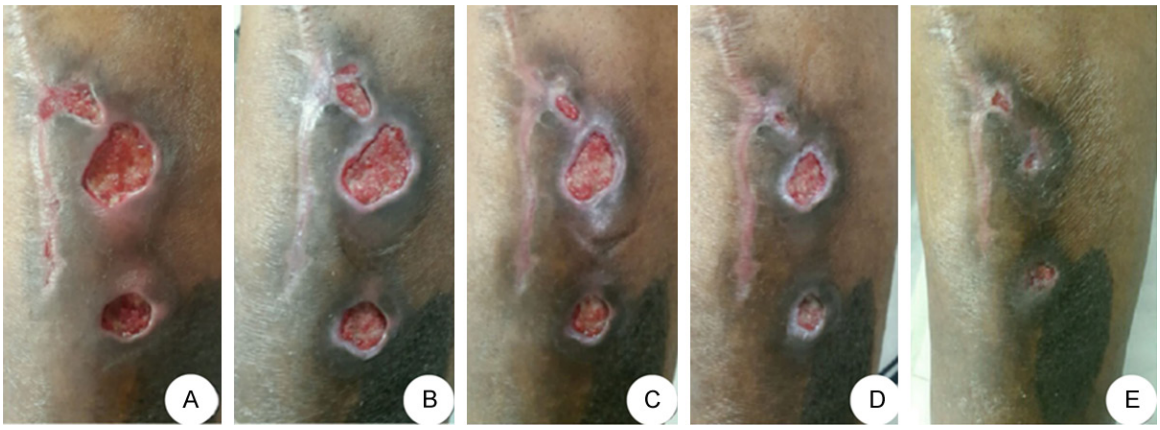

Figure 9. Photographic documentation of the healing process - P(15.4) from GIII: (A) Before treatment; (B) 1 week after treatment initiation; (C) 2 weeks; (D) 4 weeks; (E) 6 weeks, Advent Period of the Wound [26].

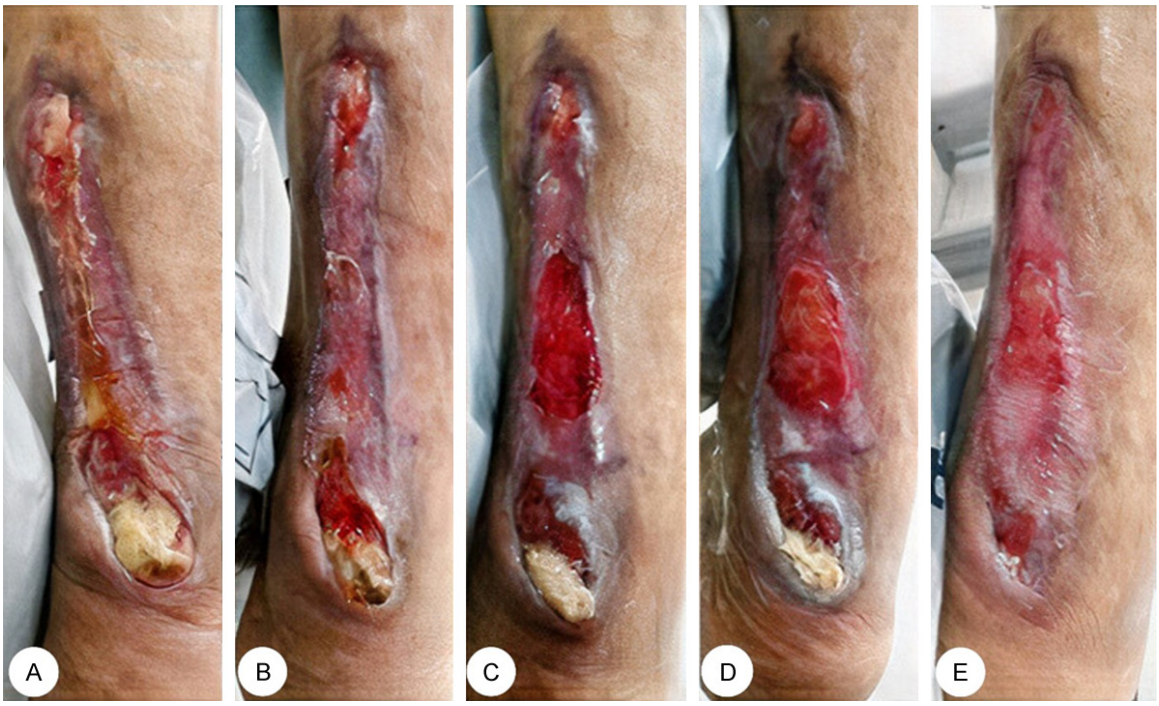

Figure 10. Photographic documentation of the healing process - GIII: (A) Before treatment; (B) 1 week after treatment initiation; (C) 2 weeks; (D) 4 weeks; (E) 6 weeks [26].

decrease in this index, with values of 28.3, significantly lower than the values recorded in the GI (49.4 $P < 0.05$) and GIII (32.1 $P < 0.05$) groups.

Six weeks after the start of the treatment, there's a noticeable reduction in ulcer area across all groups. **Figure 13** illustrates the average CRU (healing rate) of the ulcers for each group during weeks 0, 2, 4, and 6, highlighting the progression of the healing process over the course of the treatment.

The Mann-Whitney test was employed to discern statistical differences between initial and final ulcer areas across treatment groups. Participants or the EG treated with the Rapha® system (GI and GIII) showed a statistically significant difference ($P = 0.017$ and $P = 0.050$, respectively). In contrast, the group undergoing conventional treatment (GII) exhibited any statistical significance ($P = 0.421$).

These data underscore the superiority of the Rapha® system in accelerating the healing

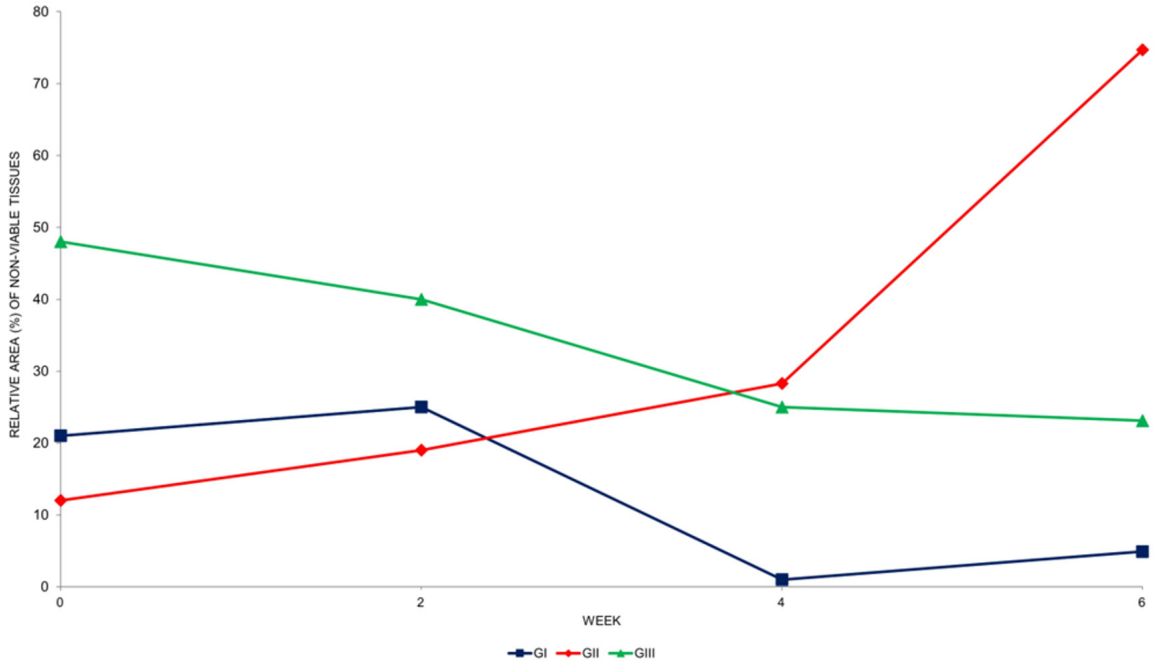

Figure 11. Relative areas (%) of non-viable tissues on the wound surfaces of diabetic participants undergoing clinical trial, after 2, 4, and 6 weeks.

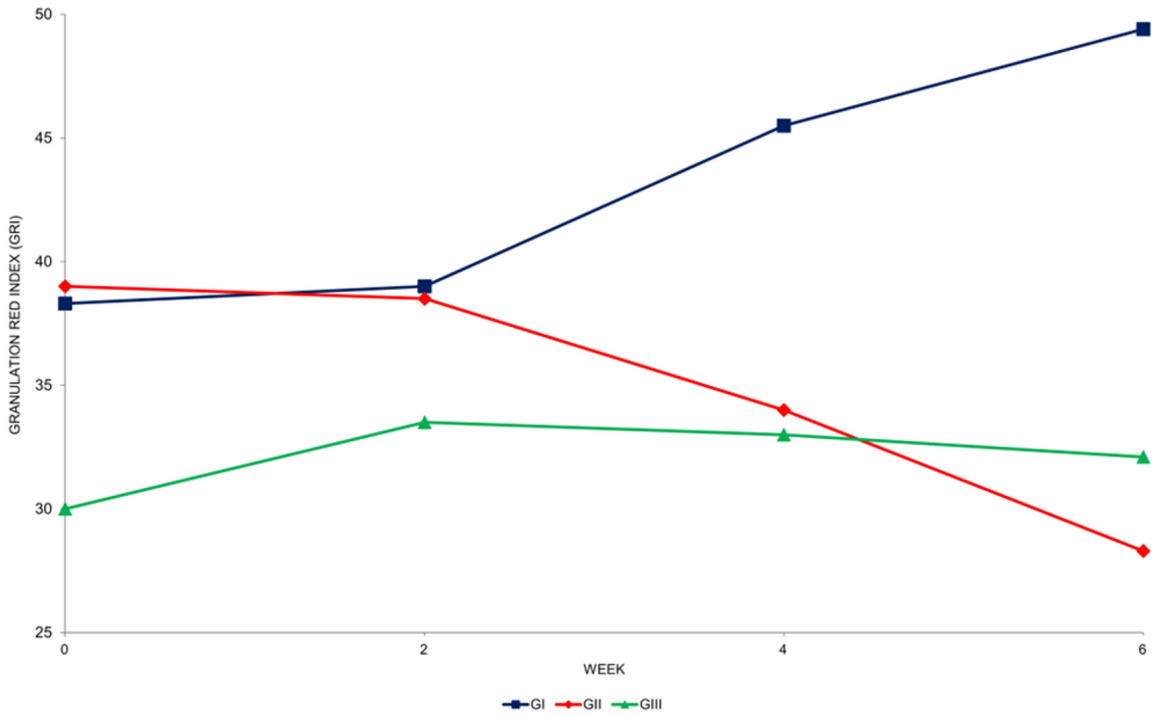

Figure 12. Evolution of the Granulation Red Index (GRI) of ulcers in participants undergoing the clinical trial over a 6-week period.

of diabetic foot ulcers compared to the standard UHS protocol adopted at NWRH and GHR hospitals. It's crucial to note that the Rapha® device consistently met operational standards defined by national quality norms.

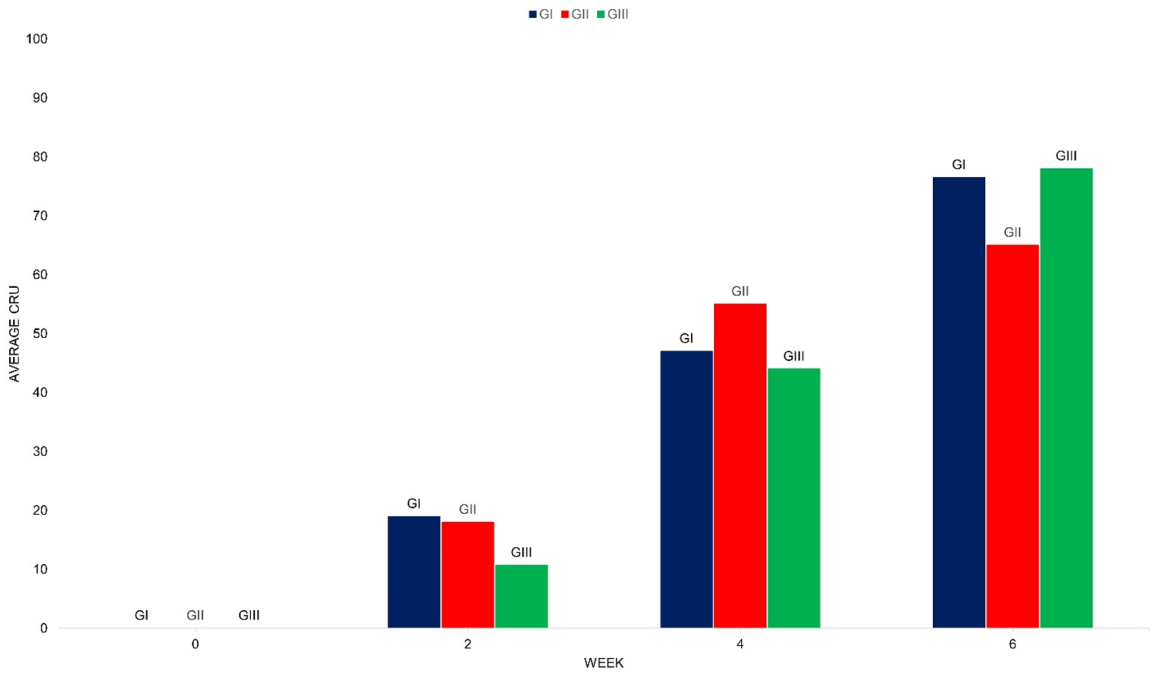

Figure 13. Recovery index of the ulcer healing process for the same treatment weeks.

The advantages of the Rapha® system become even more apparent when comparing the progress of GI and GIII groups with GII. The former two groups experienced significant advances in all healing phases: granulation tissue formation, reduction of non-viable tissues, contraction, and wound edge approximation.

The Ethics Committees approved this Phase III efficacy and safety study, and Anvisa was notified of its execution. Upon completion of the study, along with the necessary technical information regarding the Rapha® product, submissions are being made to ANVISA for the registration of this new health product in the country.

Fourth phase of technology (T3) - technological transfer, INMETRO certification, Anvisa registration, and technology incorporation

The Rapha® device research is not yet in full compliance with the translational process and is currently undergoing the submission phase with Anvisa, the Brazilian regulatory agency. The T3 phase of the Rapha® device translational process can be assessed from four perspectives: first, the transfer of technology to a qualified private company meeting the minimum requirements; second, the INMETRO certification process; third, the Anvisa registration process for commercial medical device use; and fourth, the incorporation of Anvisa approved technology into either public or private healthcare systems.

Notably only a private entity's tax identification number is eligible to submit the technology for Anvisa's analysis. In the Rapha® device case, universities lack this prerogative. This restriction is common among universities due to the absence of accredited and qualified labs or facilities to manufacture and market the technology. Universities undoubtedly have the technical and scientific expertise for research and development. However, mass industrial production must adhere to manufacturing regulatory standards, typically the private sector's domain. Exceptions exist, such as public research centers like the Oswaldo Cruz Foundation, Butantan Institute, and the recent Scientific, Technological, and Innovation Institution. These exemplify a structured R&D ecosystem throughout the productive chain until ANVISA approval.

To obtain Anvisa registration, both the INMETRO Conformity Certificate and the "Investigator Brochure," detailing the technology from its conception to its manufacturing, ensuring safe-

ty and efficacy within the health system, are paramount. This process integrates research and development with regulatory, ethical, and statistical aspects (from the university) and the scaled production regulatory process (from the private sector). After Anvisa and the INMETRO Conformity Certificate validate the Investigator Brochure and private sector documents is received, the technology earns the Anvisa registration seal.

The integration of technology into the healthcare system primarily occurs through its registration, followed by its distribution to hospitals, medical centers, and occasionally, pharmacies, based on the type of the device. This signifies the technology's integration into the private health system. MH can also incorporate the technology via the UHS, aiming it to distribute to municipal and state health departments following existing standards, regulations, and legislation. This national incorporation by the Brazilian Commission for Incorporation of Technologies in the UHS, an entity associated with the MH, is the ultimate goal for the Rapha® device research. Thus, the private sector plays a pivotal role in the T3 phase, ushering the technology's integration into the health system after the technological transfer from the university to the company and ANVISA registration.

Rapha® device's technological maturity assessment

The Rapha® system's technological maturity evaluation follows the TRL scale. The system underwent several phases, from proof of concept to prototype development and scaling for market availability. Furthermore, the technology has led to patents, scientific articles, and awards and is undergoing the licensing and/or technological transfer process.

The research determined that the Rapha® system reached TRL level 8, signifying a qualified and finalized system. These results were achieved after successfully completing preclinical and clinical tests and the device is now awaiting regulatory approval by Anvisa. The technology is also set for scaled implementation and integration into the healthcare system, with the licensed company overseeing the INMETRO certification and Anvisa registration.

Discussion

For the successful implementation of research, essential components include organizational resources, a moderate degree of user trust and motivation, and the presence of a guiding leader or facilitator. Additionally, forging collaborations between healthcare professionals and researchers stands out as a valuable approach, harmoniously blending researchers' theoretical insights with practitioners' practical expertise.

Challenges to effective knowledge translation arise from technological shortcomings, surging healthcare demands, and a lack of sustained support and resources. To address these hurdles, engaging local facilitators, fostering collaborative research, and prioritizing sustainability planning from the beginning is advisable.

This study evaluates the TMR process used in developing the Rapha® medical device. Spearheaded by an interdisciplinary team from the University of Brasília and its partners, the research traversed the TMR cycle - from research and development to clinical and commercial phases. The investigation affirmed the effectiveness of the university's translational approach in introducing Rapha® to the Brazilian market, navigating from phases T0 through T3. The progression to the T2 phase currently hinges on ANVISA's approval, which, once obtained, shall culminate in the T3 phase and transition to T4.

The study underscores TMR's intricate and nonlinear nature, illustrating how subsequent phases can influence and depend on earlier stages. The engagement of private companies presents a double-edged sword: it's an avenue of potential, yet it also introduces risks, especially during the technology transfer phase (T3).

In conclusion, the research posits TMR as a potent blueprint for transforming academic research into tangible medical solutions. Such a model serves the dual purpose of elevating the Brazilian healthcare sector and bolstering the national economy. Importantly, this research fills a crucial void, illuminating the pathway for Brazilian public universities to seamlessly transition their medical innovations from

academia to the marketplace and broader healthcare ecosystem.

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All procedures involving human participants were undertaken with the express informed consent of the subjects.

Disclosure of conflict of interest

The authors affirm that there are no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. The authors further confirm that they have not entered into any agreements that interfered with their ability to complete the research as planned, and they have not been constrained by any form of personal or professional circumstances that could be perceived as constituting a conflict of interest.

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