

Treating phantom limb pain following amputation

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VALORISATION

INTRODUCTION

In 2005 the Dutch Ministry of Science defined knowledge transfer and utilization as the third primary task of universities besides research and education.¹ The ministry was the first to use the term 'valorisation' in this context, which refers to the transfer of research knowledge to create societal and/or economic benefits or impact. Comparable terms used in other countries include, amongst others, knowledge exchange, social impact or third mission.²

The official definition of 'valorisation' used by the Dutch government refers to 'the process of creating value from knowledge by making it suitable and/or available for economic and/or societal use and translating it into competitive products, services, processes and entrepreneurial activity'.³

Thereby, valorisation focuses on activities that use novel research knowledge to create additional value on a societal, technical and/or economic level. These different levels are not separated but intertwined. One example is the transfer of novel digital health applications into clinical practice: The technology has to be mature and stable enough to be successfully implemented in clinical practice and/or the society but a reasonable business model is at the same time required to foster its marketing and implementation by different stakeholders to generate economic impact. The valorisation topic is also becoming increasingly important for universities with regard to research grant applications, which is reflected, e.g. in the knowledge utilization paragraph issued by the Dutch Organization for Scientific Research (NWO).³

This valorisation chapter outlines a dissemination roadmap, that describes how the results of this PhD-project already have been used and might be used in the future to create societal and economic value. First, the relevance of the clinical problem will be defined, followed by the target group and potential stakeholders for whom the results of this thesis might be relevant. Then, several activities that have been undertaken so far or further need to be undertaken to disseminate the insights and knowledge generated by this project will be described. Finally, innovative aspects and the potential societal and economic value of the research presented in this dissertation will be addressed. As two novel interventions were developed and evaluated in this PhD-thesis, this paragraph will discuss the socio-economic impact of both the clinical framework for (face-to-face) mirror therapy and the telerehabilitation platform ('teletreatment').

RELEVANCE OF THE CLINICAL PROBLEM

The global incidence of all types of lower extremity amputations varies between 6 to 31 per 100.000 in the total population.⁴ Germany ranks in the highest quarter with a total of 56.000 amputations of the lower limb performed in 2011⁵ of which around two-thirds were related to

Diabetes.⁶ Reliable data for the incidence of minor and major upper limb amputations in Germany is lacking, but it is estimated that about 6 amputations per 100.000 persons are performed annually in the general population.⁷ Up to 80% of all upper and lower limb amputees suffer from phantom limb pain^{8,9} that occurs during the first weeks following amputation and persists over many years in the majority of patients. According to a recent study¹⁰ including a mixed sample of upper and lower limb amputees with an average time since amputation of 33 years, 63% of patients was still suffering from phantom limb pain, which limited their daily routines, functioning, employment and quality of life.¹¹⁻¹³ The majority of patients receives conventional pharmacological interventions including strong pain medication such as opioids that often results in adverse events, and evidence regarding its long-term efficacy is low.¹⁴ In this context, non-pharmacological interventions such as mirror therapy that can be used by patients themselves, should also be considered in the treatment of phantom limb pain. Given the chronic nature of this condition, mirror therapy should be delivered on a regular basis over several weeks to months. However, the following clinical problems regarding the delivery of mirror therapy in patients with phantom limb pain can be identified: (1) the evidence for effects of mirror therapy to reduce phantom limb pain is insufficient; (2) little is known about important clinical aspects of the intervention; (3) a standardized evidence-based treatment protocol is lacking; (4) personal resources are often insufficient to provide face-to-face therapy with sufficient dose and (5) adherence to self-delivered exercises is generally poor.

The use of information and communication technology such as telerehabilitation has been proposed to facilitate self-delivered exercises to enhance training intensity. However, little is known about potential benefits of using telerehabilitation in patients with phantom limb pain, and controlled clinical trials investigating effects are lacking.

The findings from this dissertation might help to solve some of the clinical problems described above as they (1) contribute to the evidence and insight into important clinical aspects of mirror therapy; (2) present a clinical framework that can be used by healthcare professionals to personalize mirror therapy in daily care and (3) increase the knowledge about the potential of telerehabilitation to create a personalized blended care intervention for patients with phantom limb pain.

TARGET GROUP AND OTHER STAKEHOLDERS

The findings of this PhD-thesis might be relevant for several stakeholders as described below.

Patients and their relatives

The two novel interventions that were developed and described in this dissertation put patients with phantom limb pain following amputation in the center of the treatment. They aim to empower patients to actively self-manage their phantom limb pain, as an alternative to standard

pain medication. Patients often need to perform self-delivered mirror therapy on a regular basis in addition to face-to-face sessions with the personal therapist. The clinical framework for mirror therapy presented in this PhD-thesis serves as the foundation to develop a personalized exercise program for these face-to-face sessions and self-delivered exercises of patients. In addition, the teletreatment might be used by eligible patients as an additional tool to support self-delivered exercises and to enhance training intensity. Furthermore, patients who are in general not able to visit the therapist several times in person, might use the teletreatment to enable remote self-management of phantom limb pain. In many cases, relatives and other informal caregivers support patients regarding the self-delivery of mirror therapy at home (e.g. through the application of sensory stimuli) or the use of the teletreatment (e.g. technical support). It has been suggested that family-mediated exercises are a useful addition to face-to-face sessions.¹⁵ Therefore, the clinical framework for mirror therapy, including a patient log and leaflet to support and monitor self-delivered exercises, and the teletreatment including a manual to facilitate its self-directed use are also relevant for the patient's relatives. Finally, the framework for mirror therapy and the teletreatment might also be used by patients with other pain conditions such as complex regional pain syndrome or neuropathic pain following peripheral nerve injury or stroke patients as the theoretical rationale behind the intervention is similar.¹⁶

Health care professionals and institutions

Many different care professionals are involved in the rehabilitation of patients following amputation. In addition to physical and occupational therapists who are involved in stump care, training of motor skills and daily activities, other professionals such as physiatrists, psychologists and prosthetists also play an important role in this interprofessional care process. As such, these professionals are in many cases also confronted with the clinical problem of phantom limb pain and strive to offer patients potential solutions using structured (evidence based) treatment protocols. There is a strong demand from professionals working in routine care regarding clinical frameworks or protocols that support health care professionals in the structured delivery of the intervention. This can be seen in the frequent downloads of the open access publications of our clinical framework for mirror therapy in patients with stroke and phantom limb pain, that reached more than 45.000 reads by health care professionals around the world five years after their publication. Hence, the knowledge regarding important patient characteristics and the potential of the clinical framework and the teletreatment in treating phantom limb pain should be disseminated to all professionals involved in the rehabilitation of amputees. This might increase the knowledge and awareness with respect to non-pharmacological treatment options to treat phantom limb pain and might support coordination and structured delivery of these interventions by different disciplines. The clinical framework and teletreatment including a structured manual might also guide (future) professionals with

less experience in how to select eligible patients and how to deliver the intervention. Given the limited resources (time and/or personnel) in clinical practice, health care institutions might consider to use the teletreatment to complement guided therapy and facilitate self-delivery of exercises depending on patient characteristics such as age and computer literacy, preferences and needs.

Students and health care education

Many universities educating future professionals involved in amputee care (e.g. physical and occupational therapists) have not yet systematically integrated the treatment of phantom limb pain into their curricula. Thus, universities might use the results of this thesis to provide students with knowledge and skills regarding non-pharmacological treatment options to treat phantom limb pain. The clinical framework for mirror therapy and the teletreatment could serve as a guideline how to structure the intervention and to deliver a personalized blended treatment based on patient preferences. Lecturers might use the clinical framework as an example for clinical decision-making according to the different phases in methodical intervention defined by the Royal Dutch Society for Physical Therapy.

Regarding the teletreatment that was developed and evaluated in this dissertation, positive and negative experiences about its use in routine care should be shared with students and teachers from different disciplines. This would provide important insights and knowledge about the challenges of implementing digital health interventions in clinical practice, which in turn would facilitate further development, implementation and upscaling of digital health.

Finally, lecturers might use the user centered design process of the teletreatment as an example to illustrate the importance of interprofessional co-creation when designing novel user-friendly digital health interventions. Students and lecturers from different faculties beyond health such as communication and multimedia design, computer sciences or business administration should join forces to create engaging user-friendly solutions and appropriate business models.

Researchers

Several future research questions emerged from the different studies performed in this PhD-thesis that might be addressed by upcoming studies. One example is the result from our randomized trial suggesting that three subgroups might benefit more from mirror therapy than others. These subgroups might be validated in future studies to identify responders and to develop a more personalized treatment. Furthermore, our clinical framework might serve as guideline for designing an intervention protocol for mirror therapy for future trials investigating potential effects. The illustration of the user-centered design process of the teletreatment and the detailed process evaluation

of its use in clinical practice might inform future digital health studies about important aspects that need to be considered in the design of the study such as sufficient stakeholder involvement, training and support. The studies from this dissertation further illustrate the value of combining different qualitative and quantitative methods during the design and evaluation of the interventions in clinical practice. In addition, the results from this dissertation suggest that alternative research designs to the traditional randomized controlled trial paradigm should be considered when developing future studies investigating the impact and effects of digital health applications. Non-pharmacological interventions, in particular digital health applications, are developing fast. However, adherence of the end-users to these novel interventions is generally low. Improving adherence and uptake of digital health warrants personalized interventions and close collaboration between different stakeholders from industry, clinical practice and science¹⁷ as was the case in the PACT project. Finally, the findings from this PhD-thesis contribute to the general body of knowledge and evidence regarding mirror therapy and teletreatments for patients with phantom limb pain.

Prosthetic manufacturers and other industries

In the past years, traditional manufacturers of prosthetics are facing increased market competition through smaller enterprises and recent technological advancements such as 3D printers, disrupting traditional business models. Therefore, these corporates are seeking new business models or try to expand their existing business model by e.g., offering clients additional products or services that create unique selling points or long-term relationships. This might create new collaborations between traditional (bigger) corporates and smaller, in many cases more agile enterprises (e.g. digital health developers). Beyond this, these companies have in many cases their own physical or occupational therapists who also treat patients from other countries, in which the (para)medical infrastructure is less elaborated. However, these multinational companies need to ensure high-quality care of amputees in all markets in which they are active. The teletreatment presented in this dissertation and digital health applications in general might therefore be interesting to these companies to create a long-term relationship with their (international) clients and to deliver remote training and care. To this end, the teletreatment might be complemented with additional, more prosthetic-specific content such as prosthetic training and care.

The insights generated from the process evaluation regarding the teletreatment presented in this dissertation might help the software developer to improve the current version of the application and/or might inform the development of future applications. Software needs continuous updates and maintenance as operating systems and hardware are also rapidly evolving. These software updates should ideally be improved by novel insights, ideas and requirements from its use in routine care. This warrants close cooperation between software

companies, care professionals, end-users and research institutions. Furthermore, the end-users and their relatives need sufficient training and support regarding the use of the technology, to enable successful implementation in routine care.

Health insurance companies

The majority of amputees suffers from phantom limb pain for many years and the average annual costs per patient associated with the standard pharmacological treatment are estimated at around 1.000 Euro (unpublished data German health insurance company). Additional costs associated with phantom limb pain that are covered by health insurances are caused by medical products such as residual limb liners made from electromagnetic shielding fabric, (para)medical treatment or disability payment in case of absence from work. The two novel interventions presented in this PhD-thesis that aim to support self-management of patients with phantom limb pain might therefore also be interesting to health insurance companies to reduce costs and empower patients to actively manage their condition. Self-management approaches play an increasingly important role in the management of chronic pain.¹⁸

DISSEMINATION OF FINDINGS

The consortium of the PACT project consisted of many different partners from patient associations, clinical practice, education, research, and the industry. As such, constant knowledge exchange occurred on many different levels between the different partners through various activities such as the user-centered design process of the clinical framework and the teletreatment, project meetings or student projects. In the following paragraph the activities that already have been performed as well as future activities to disseminate the findings from this PhD-thesis are described. In addition to these activities, several products and services are presented into which the research findings have been or will be translated.

Activities performed so far

The findings from the different phases of the PACT project have already been distributed through various channels to different stakeholders such as patients, health care professionals, students and researchers as shown in table 1.

Table 1. Overview of dissemination activities that have been performed in the PACT project

Knowledge transfer to patients and society	
Activities	Description
Online blog	During the PACT project news and interesting facts have continuously been posted in a blog (http://telereha.net/) including a newsletter
TV and radio appearances	The project and its (preliminary) results have been presented in three German National TV reports (WDR Servicezeit 'Hightech in der Medizin': https://www.youtube.com/watch?v=cY7ui-nbuHw&t=41s , Medical Travel RTL 4: https://multimavision.nl/medicaltravel/ , ZDF Infokanal: der elektrische Reporter: https://www.youtube.com/playlist?list=PL4195823E4A32DBC2) and one German radio post: https://www.deutschlandfunkkultur.de/sendungsuberblick-virtueller-korpertausch-do-it-yourself.1264.de.html?dram:article_id=405201
Interview, video recording and presentations at medical fairs	The project has been presented several times to the public at a booth of the world's biggest medical fair MEDICA in Düsseldorf and the 'IT Trends' in Essen. In addition, an interview and video recording including the patient representative of the PACT project took place: https://www.youtube.com/watch?v=9rA8smDfkG8&t=14s
Newspaper report	A plain language report about the PACT project was published in the German newspaper 'Hamburger Abendblatt': https://www.abendblatt.de/ratgeber/wissen/article206579861/Zukunftstrends-Die-digitalen-Arztshelfer-kommen.html
Online articles in plain language	Several online articles e.g. on the website of the biggest patient association for amputees in Germany have been published: https://www.bmab.de/news118/ , http://rehanews24.de/das-bein-ist-weg-der-schmerz-bleibt/ , https://egesundheit.nrw.de/projekt/telereha-phantomschmerz/
Public debates	Several panel discussions about the PACT project took place (e.g. Dutch eHealth week 2016, Dutch-German Innovation Days on Digitalization in Healthcare, Creative health conference)

Activities	Description
Dissemination through patient representative	A patient representative was actively involved during all phases of the PACT project and various dissemination activities. For example, a public stand-up paddling event for amputees was organized together with the patient representative: https://www.youtube.com/watch?v=zmBDhHdbH1M
Knowledge transfer to health care professionals and clinical practice	
Publications in national professional journals	Three articles regarding the practical use of the framework and teletreatment have been published in the German national journal for physical therapists, prosthetists and general practitioners.
Presentation, workshop and debates at national conferences	The PACT project has also been presented at the Annual conference of the German Association for Hand therapy in Düsseldorf 2013, where also a workshop about mirror therapy took place for physical and occupational therapists. In addition, an online presentation was given at the 15th National physical therapy congress in Cambodia.
Implementation in routine care through practical workshops for health care professionals and online register	Several practical workshops about the clinical framework for mirror therapy and the teletreatment were organized for education and training centers and rehabilitation clinics in Germany and the Netherlands. At the moment, several German health care institutions and prosthetists use the clinical framework for mirror therapy and the teletreatment in routine care. These practitioners are listed in an online mirror therapy register: http://spiegeltherapie.com/therapeutenverzeichnis/
Open access publication clinical framework for mirror therapy in patients with phantom limb pain and stroke	The two clinical frameworks on the use of mirror therapy in stroke and phantom limb pain have been published open access on ResearchGate. They have reached more than 45.000 reads by health care professionals, researchers and educators around the world.

Knowledge transfer to education	
Practical workshops	Several practical workshops about the clinical framework for mirror therapy and the teletreatment were organized for physical therapy students of Zuyd University Heerlen (regular Bachelor and German EPEPE program) and rehabilitation management students of the University of the German Social Accident Insurance.
Web lecture	A web lecture about the theoretical foundation of mirror therapy (e.g. evidence and neurophysiological mechanisms) in patients with phantom limb pain was developed for physical therapy students of Zuyd University, Heerlen and embedded into the curriculum.
Inclusion of students in graduation projects	Physical therapy students of Zuyd University were involved in the user-centered design process of the teletreatment in the context of their bachelor thesis.
Knowledge transfer to research community	
Publication in peer-reviewed journals	All six articles included in this thesis have been published in international, peer-reviewed journals.
Presentations at (inter)national scientific conferences	The PACT project and its results have also been presented and discussed at (inter)national conferences focusing on pain research (e.g. 7th World Congress of World Institute of Pain Maastricht 2014, German Pain Congress Hamburg 2014, Myosens Symposium Göttingen 2015).
Knowledge transfer to industry and health insurances	
Collaboration with software company	The development and evaluation of the teletreatment occurred in close collaboration with a software company (Kaasa health, Germany).
Release of iOS and Android App	At the end of the PACT project a revised version of the teletreatment was released in the App Store®: https://itunes.apple.com/de/app/routine/id1152443756?mt=8 In the meanwhile, a modified version of the App has also been released for patients with

Activities	Description
	chronic pain of the upper limb: https://itunes.apple.com/de/app/routine-health/id1446256495/?platform=ipad
Providing research results to industry and health insurance companies	The publications from the PACT project have been disseminated to several health insurances and industry partners involved in the project.
Negotiations with health insurance companies and prosthetic manufacturers	During the PACT trial, negotiations with several German health insurance companies and prosthetic manufacturers about potential reimbursement and business models for the teletreatment took place. Two months after funding of the project ended, the first reimbursement was achieved. At the moment, the blended care program combining face-to-face mirror therapy and the teletreatment is reimbursed by several health insurances in Germany and is used by a variety of health care institutions in routine care.

Future dissemination and implementation activities

The following paragraph describes several future dissemination activities to further upscale the implementation and use of knowledge that was gathered in the PACT project.

Knowledge transfer to patients and society

The results of this PhD-thesis will further be disseminated to the public by press releases of Maastricht University and Zuyd University. Furthermore, the most important results will also be posted on the PACT blog (<http://telereha.net/>) and the mirror therapy website (<http://spiegeltherapie.com>). The PhD-thesis will be accessible worldwide via the research portal repository of Maastricht University (<https://cris.maastrichtuniversity.nl/portal/>). In addition, the thesis including a plain language summary will be disseminated to various partners from the PACT consortium, including the funding institution and the biggest patient association in Germany.

Knowledge transfer to health care professionals and clinical practice

Successful implementation and upscaling of digital health applications in clinical practice should be initiated by smaller regional digital health ecosystems consisting of 'early adopter' health care institutions in collaboration with their most important health insurance companies and other cooperating institutions. Therefore, additional health care professionals in Germany and the Netherlands will be trained regarding the delivery of the clinical framework and the teletreatment to foster their use and implementation in clinical practice. Communities of practice amongst health care professionals using the teletreatment will be set up to exchange experiences concerning its use in routine care. In addition, an online register of practitioners using the teletreatment will be created, so that different stakeholders are informed about whom they can contact for more information about the intervention and set up potential collaborations.

The software company that currently commercializes the teletreatment, strives to achieve additional contracts with health insurance companies, so that a wider group of patients and health care professionals in Germany, the Netherlands and beyond are able to make use of the teletreatment. Furthermore, a national article about the PACT project will be published at the end of 2019 in the Journal of Physiotherapy of the Royal Dutch Society for Physical Therapy. Thereby, a wide range of physical therapists in the Netherlands will be informed about the results of this project. Finally, this PhD-thesis will be distributed to clinical partners from the PACT consortium and allied Dutch rehabilitation centers (e.g. Adelante Centre of Expertise in Pain and Rehabilitation).

Knowledge transfer to education

A web lecture and workshop about the clinical framework for mirror therapy and the teletreatment have already been developed and performed for physical therapy students at Zuyd University Heerlen. They will also be embedded in the curriculum in the next years. Furthermore, experiences gathered through the user-centered design process of the teletreatment will be used as an example within a master class about design thinking. A workshop series is currently being developed at Zuyd University for lecturers and researchers of Maastricht University and Zuyd University. In the future, other stakeholders and clients might also enroll in this masterclass.

Knowledge transfer to the research community

Upcoming press releases of Maastricht University and Zuyd University will also inform the research community about the results of this dissertation. In 2020, a presentation about the PACT project will take place at the Orthopedic Technology (OT) World Conference in Leipzig, Germany. Several researchers and professionals from the field of prosthetics and orthotics will join the conference. Furthermore, a fact sheet

providing an overview of the PACT project and its results will be published open access to inform researchers worldwide about the knowledge gathered in this PhD-thesis.

Knowledge transfer to industry and health insurances

Multi-stakeholder business models incorporating health insurances, industry, health care institutions and the end-users should be considered in further implementation of the teletreatment in routine care. The ultimate goal is to create smaller regional digital health ecosystems with the relevant stakeholders from clinical practice, industry and research. Therefore, the results from this dissertation will be disseminated to additional German and Dutch health insurance companies in order to discuss potential reimbursement models regarding the teletreatment. Prosthetic manufacturers and orthopaedic technicians collaborating with health care institutions treating amputees will also be informed about the results of this PhD-thesis. The experiences from the delivery of the interventions in routine care should be shared with all stakeholders involved to further improve and upscale the clinical framework and the teletreatment.

INNOVATIVE ASPECTS

The following paragraph discusses several innovative aspects of the results presented in this thesis in relation to existing activities, services and products.

The clinical framework for mirror therapy in patients with phantom limb pain was developed based on the best available evidence, clinical experiences of therapists and patient preferences. It is to our knowledge the first framework in the treatment of chronic pain patients that was developed using an evidence-based approach according to the different phases in methodical intervention. This structure of the framework supports clinical decision making and can directly be integrated into the daily work of physical and occupational therapists which is embraced by many professionals. What clinical frameworks distinguishes from more rigid protocols is their flexibility to tailor the intervention to the characteristics and needs of individual patients seen in routine care. However, not many clinical frameworks have been developed and evaluated in clinical trials so far. Two other frameworks have been published regarding the application of motor learning and mental practice in neurological rehabilitation.^{19, 20}

Successful development of digital health applications needs the composition of unconventional teams, trans-institutional initiatives and

crossing conventional barriers between disciplines and funding sources.¹⁷ However, in many digital health projects co-creation together with the end-users and other stakeholders is not self-evident. The novel teletreatment presented in this dissertation was developed in close co-creation with different stakeholders including a patient representative, who were involved in all phases of the project. This close collaboration with different stakeholders ensured commitment to the project and continuous feedback on the design of the teletreatment. A novel 'product' that was developed and applied during the design process of the teletreatment is an innovative multi-stakeholder decision matrix that enables structured prioritization of user requirements. The novel aspect of this matrix is in our opinion, that the perspectives of different stakeholders within such a digital health project are taken into account. One example is the technical complexity of each requirement in terms of time and/or money needed which is rated by the software developer. Furthermore, the lessons learned from the teletreatment development phase of the PACT project point out some important and novel aspects (e.g., early process evaluations and sufficient experience of professionals) that should be considered by future digital health projects to improve novel technology-driven interventions and the outcomes of studies investigating their impact.

In the digital health sector, there is currently a clear trend towards mobile health applications. Tablets and smartphones are more and more becoming the preferred devices for interactions between health care professionals and the end-users. The teletreatment presented in this dissertation is to our knowledge at present the only mobile health application for patients with phantom limb pain that is reimbursed by health insurance companies and already partly implemented in routine care.

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