Study title:	Efficacy and safety of transcutaneous posterior tibial nerve stimulation in relation to faecal continence in patients undergoing surgery for rectal neoplasia
NCT number:	
Date	27th August 2025
Promotor:	Althaia, Xarxa Assistencial Universitària de Manresa, Fundació Privada
Department:	General and Digestive Surgery
Centre:	Hospital Sant Joan de Déu, Xarxa Assistencial Universitària de Manresa, Althaia

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1. General information

1.1. Identification of centre/s and department/s where the study will be carried out

The study will mainly involve the General and Digestive Surgery department with the collaboration of the Physical Medicine and Rehabilitation department of la Xarxa Assistencial Universitària de Manresa, Fundació Althaia.

2. Study hypothesis

Principal hypothesis

The application of transcutaneous posterior tibial nerve stimulation in patients with post-surgical low anterior resection syndrome (LARS) improves faecal incontinence.

Secondary hypothesis

- Transcutaneous posterior tibial nerve stimulation improves sexual function
- Transcutaneous posterior tibial nerve stimulation results in improved perceived quality of life
- The use of transcutaneous posterior tibial nerve stimulation has very mild and tolerable side effects, thus presenting a good safety profile

3. Objectives

Principal objective

To evaluate the effectiveness of posterior tibial nerve stimulation in relation to faecal incontinence in patients undergoing surgery for rectal neoplasia, at 1, 6 and 12 months post-surgery.

Secondary objectives

- To evaluate the efficacy of posterior tibial nerve stimulation in relation to sexual function in patients undergoing surgery for rectal neoplasia
- To evaluate the impact of posterior tibial nerve stimulation on the quality of life of patients undergoing surgery for rectal neoplasia
- To evaluate the safety of the use of posterior tibial nerve stimulation in patients undergoing surgery for rectal neoplasia

4. Methodology

4.1. Study design

Randomized clinical trial with controlled health product and 12-month follow-up.

The study will be triple blind, since the patient, consulting physician and the researcher who will analyse the data will not know which group each patient belongs to. Only the therapeutic rehabilitation will be aware of the randomization.

4.2. Centre study

The study will be carried out at the General and Digestive Surgery System Department of the Hospital Sant Joan de Déu, Althaia.

The centre has an annual volume of colon neoplasia interventions of around 140 surgeries/year and rectal neoplasia of around 30 surgeries/year.

4.3. Target population

The reference population will be patients undergoing surgery for rectal neoplasia from the regions of Bages, Berguedà, Moianès and Solsonès..

4.4. Study subjects

All patients undergoing surgery for rectal neoplasia who meet the following inclusion and exclusion criteria.

4.4.1. Inclusion criteria

- Adult patients diagnosed with rectal neoplasia and who have undergone a high anterior rectal resection regardless of the surgical approach (open, laparoscopic, laparoscopic+TaTME or robotic+TaTME).

4.4.2. Exclusion criteria

- Patients not operated on or within active surveillance strategy programs (watch & wait)
- Patients with ostomy
- Patients with contraindications to the use of the neurostimulator:
- Pacemaker / Defibrillator / Other electronic devices
- History of heart problems
- Propensity to excessive bleeding (coagulopathies)

- Damage to the nervous system (epilepsy)
- Current pregnancy
- Infections or skin lesions
- Severe vascular disorders
- Active neoplasms.

4.5. Study groups

4.5.1. Control group

The control group will undergo a placebo (sham) neurostimulation. For placebo neurostimulation of the posterior tibial nerve, the MedFit-3 neurostimulator, with CE marking, will be used. A subtherapeutic dose of 80 Hz - 150 μs will be applied.

The main reason for performing a control is to be able to objectively determine whether there is really a benefit from the technique applied. For LARS, multiple therapeutic and hygienic-dietary options have been tested, so not doing a control group seems to us to be a suboptimal way of assessing the results obtained. In addition, in some cases, patients may show spontaneous partial improvement during post-operative recovery.

The proposed dose is the one commonly used as an analgesic dose. This allows the patient to have the perception of applying neurostimulation without reaching the optimal dose to perform neurostimulation.

Therefore, a dose commonly used in the world of physiotherapy and rehabilitation is applied for analgesic purposes. This allows the patient to activate the same physiological pathways of the mechanism of action of neurostimulation, without there being a total activation because it is a dose lower than the optimal one.

This is a widely used dose and has been shown to have no risks for the patient. In this case, it will not provide benefits either because the ideal dose for neurostimulation is not reached. But it helps us to make a more reliable double blind.

4.5.2. Intervention group

In the intervention group, the same MedFit-3 neurostimulator will be used, with CE marking; and a dose of 20 Hertz (Hz) – 200 microseconds (μs) will be applied.

For both the control group and the intervention group, the pelvic floor rehabilitator will program the neurostimulator for each case and then they will be trained on how to perform the neurostimulation.

In order to apply the therapy, the patient must sit down for the placement of the electrodes, which consists of:

- One electrode on the sole of the foot / heel (positive pole - red cable)
- The other electrode will be placed two fingers above (about 5 cm) and a little behind the internal malleolus (ankle). (negative pole - black cable)

It will be done on 2 feet at the same time.

The first session will be carried out with the rehabilitator to learn how it works and resolve doubts about its use, and later the sessions will be carried out at home.

In both groups, a session schedule will be indicated according to the following scheme:

- From the 1st to the 3rd month post-surgery: stimulation 3 times a week
- From the 4th to the 6th month post-surgery: stimulation 2 times a week
- From the 7th to the 12th month post-surgery: 1 time a week

4.6. Randomization

Stratified randomization according to surgical approach and in blocks. Patients will be randomly assigned to one of the two study groups in a 1:1 ratio. The random assignment of patients to the Control Group (CG) or the Intervention Group (IG) will be performed using a computer program for generating random sequences (http://www.randomization.com). A list of balanced blocks of variable size will be generated to ensure equitable allocation of treatments. The generation of the randomization sequence and the control of the assignment to each study group will be the responsibility of the Research, Epidemiology and Biostatistics Unit. The recruitment of patients will be the responsibility of the principal investigator. The investigator will not be aware of the patient's allocation group until the patient has signed the informed consent.

6.6.1. Subject withdrawal criteria

Patients are free to decide to end the study at any time, at any stage of it, as long as the principal investigator is notified.

The criteria for stopping therapy would be considered adverse cutaneous effects such as skin lesions, pain that makes stimulation intolerable, appearance of edema of the lower extremities due to other diseases, ... Or also in the case of refusing to continue for other personal reasons.

In any case, even if patients present adverse effects due to the use of the neurostimulation device, it would not be necessary to withdraw them from the study and only the applied therapy would be stopped. In order to be able to perform an intention-to-treat analysis of the collected data.

In case of relapse of the disease, it would be necessary to assess the need or not to stop the therapy and the possibility of performing it concomitantly with the rest of the necessary treatments.

6.6.2. Control of adverse events

Definition of adverse event (AE) and serious adverse event (SEA):

- Adverse event (AE): Any unfavourable clinical incident that occurs during the stay in Home Hospitalization, regardless of its causal relationship with the new implemented model or digital platform.
- Serious adverse event (SEA): Any incident that leads to death, life-threatening, unplanned hospital admission, significant disability or any other medically important situation.

Event Classification: AEs and SEAs will be classified according to:

- Severity: mild, moderate or severe

Neuromodulation has mainly mild local adverse effects. These may include pain, burning or more directly with the application of the therapy, skin redness, allergy to the adhesive.

- Relationship to treatment/monitoring: probable, possible or unrelated

Methods for detecting adverse events:

- Active monitoring with follow-up visits

Procedures for recording and reporting adverse events:

- All AEs and SEAs will be recorded in RedCAP and it will be assessed whether or not therapy should be suspended. Even if therapy is suspended, patients will continue with the agreed monitoring.
- SEAs will be reported to the Clinical Research Ethics Committee (CEIm) according to current regulations, within a maximum of 24 hours and to the Spanish Agency for Medicines and Health Products (AEMPS).

Procedures to assess severity and relationship with treatment:

- Clinical assessment by the healthcare team.
- Joint review with the Principal Investigator in serious or doubtful cases.

Patients may report adverse effects or doubts by emailing the principal investigator (Dr. Meritxell Font Prat of General Surgery and the Digestive System, via meritxell.fontprat@gmail.com) or by telephone with the rehabilitation specialist (Cèlia

Jané of CAP Bages ASSIR, telephone 938748828) who will be provided to them on the day the entire study and therapy in question are explained.

Follow-up of participants who experience AEs or SEAs:

- Clinical follow-up will be carried out until the event is resolved or stabilized.
- All corrective actions applied and their effectiveness will be recorded.

Confidentiality and data protection:

- Data from AEs and SEAs will be processed in strict compliance with personal data protection regulations.

4.7. Sample size

Regarding the sample size calculations, assuming an alpha error of 5%, a correlation between pre-intervention (baseline) and post-intervention (1, 6 and 12 months) LARS values of 0.5 and a standard deviation of the mean difference of 7.4, the sample size required to have 80% power to detect a 4.4-point difference in the mean difference (pre-post LARS) between the 2 groups is 40 patients per group. Assuming 5% loss to follow-up, the final sample size required for this study is 84 patients. Linear mixed-effects models and a significance level of 0.05 will be used.

4.8. Study period

The patient inclusion period is estimated to begin in September 2025 until September 2027. The patient follow-up period is 1 year, with the follow-up of the last included patient expected to end in September 2027. In any case, follow-up is expected to last until September 2028.

4.9. Description of the activities to be carried out

All patients who underwent surgery for rectal neoplasia from September 2025 to August 2027 will be recalled the first month after surgery and informed about the clinical trial.

They will be given specific information about the tests, follow-up, tibial nerve stimulation, and the corresponding informed consent.

Patients who agree to participate in the study and sign the informed consent will be assessed to see if they have LARS with the LARS questionnaire. In the event that they have a minor or major LARS, they will be randomized (1:1) to undergo the surgery and follow-up.

All patients who enter the study, regardless of the branch they belong to, will have 2 visits (baseline visits):

- General Surgery: Functionality questionnaires (LARS, Wexner) and quality of life and sexual function questionnaires (FIQLS and QLQ-CR38) will be administered during the first visit.
- Pelvic Floor Rehabilitation: to assess sphincter function and first posterior tibial nerve stimulation session (*).

Patients in the experimental group will receive stimulation of the posterior tibial nerve with a pulse amplitude of 200 μs and a frequency of 20 Hz. Patients in the control group will receive stimulation with subtherapeutic doses of a pulse amplitude of 80 Hz and a frequency of 150 μs.

All patients will have their first session with the rehabilitator to learn how it works and resolve any doubts about its use, and later the sessions will be held at home.

Both groups will be given a session schedule.

- From the 1st to the 3rd month post-surgery: stimulation 3 times a week
- From the 4th to the 6th month post-surgery: stimulation 2 times a week
- From the 7th to the 12th month post-surgery: 1 time a week

Clinical follow-up will consist of a new visit with the surgeon at 6 months (visit 1) and one year (visit 2) to complete the different questionnaires on functionality and quality of life. A second visit with the Pelvic Floor Rehabilitation Specialist will also be made at 12 months to re-evaluate sphincter function.

In patients who find it difficult to visit the follow-up surgeon due to logistical issues, they will be offered the possibility of doing a telematic follow-up (survey via REDCap). The accepted response time will be plus/minus 15 days from the day of the scheduled visit. In the event of no response, they will be called or an appointment will be made in person.

If at the end of the study the results are favourable, the control group will be offered the possibility of using the neurostimulator.

At the current time, the study does not contemplate applying it as a clinical practice (due to limited own funding), but we do consider it a good therapeutic option to implement in the future if the results are beneficial.

4.10. Description of the study determinations and measurements

At the baseline visit, data will be collected on the patient's demographic and clinical characteristics, related to the oncological process, surgical details and the immediate post-operative period through a review of the clinical history.

It will be when recruitment begins and posterior tibial nerve stimulation therapy begins, 1st, 6th and 12th months post-surgery, that the questionnaires assessing faecal incontinence, quality of life, sexual dysfunction and the impression of global improvement will begin.

6 months after the intervention has ended (18 months post-IQ), a telephone call will be made to assess that the patients have not presented any adverse events not recorded during the therapy.

	1st month post-surgery	**6th month post-surgery**	**12th month post-surgery**	**18th month post-surgery**
Surgeon visit	X	X	X	
Rehabilitator visit	X		X	
Therapy formation	X			
Collection of demographic and clinical data	X			
Questionnaire administration				
LARS	X	X	X	
Wexner	X	X	X	
FIQLS	X	X	X	
QLQ-CR38	X	X	X	
PGI-I			X	
Telephone visit				X

4.11. Description of quality control mechanisms

The trial will be conducted in accordance with the European Union (EU) Good Clinical Practices regulations.

To ensure that the data are complete, that is, that essential data or values are not missing, that they are accurate and that they do not present internal contradictions,

specialized data collection tools such as REDCap will be used. To avoid errors in manual entry, REDCap allows the definition of validation rules to detect atypical, inconsistent values, incorrect ranges or inappropriate formats.

Mechanisms will be used to ensure that personal and sensitive data are protected at all times. The collected data will be stored on an Institutional server to prevent its loss.

The REDCap platform allows for the maintenance of a detailed record of changes (log) which allows the traceability of any adjustments made to the data to be documented to maintain transparency.

4.12. Statistical analysis

Quantitative variables will be summarized with the mean and standard deviation, in case they follow a normal distribution. Otherwise with their mean, 25th percentile and 75th percentile. Categorical variables are shown in absolute values and relative frequencies.

Homogeneity analysis of patient characteristics: the Student's T test will be used for the comparison of means between independent groups with a normal distribution and the Mann-Whitney U test for the comparison of means between independent groups in the event that the variables do not follow a normal distribution. The Pearson Chi-square (X2) test will be used for the comparison of proportions between independent groups. For the comparison of proportions between independent groups for small samples, Fisher's exact statistic will be used (when the expected frequency in any of the 2x2 boxes of the contingency table is less than 5) or the exact Monte Carlo method (when the expected frequency in any of the 2xn boxes of the contingency table is less than 5).

In order to evaluate the effect of the intervention on the main and secondary dependent variables from a longitudinal perspective, generalized linear mixed effects models will be used. These models will allow the analysis of data with repeated measures over time for each patient, taking into account both intraindividual variations and differences between individuals. This statistical strategy will be particularly useful for controlling the correlation between observations of the same subject and for managing incomplete or unbalanced data over time. In addition, covariates that influence the evolution of the functional state can be included, which will contribute to increasing the robustness and precision of the estimates of the effects of the intervention.

The analysis will be performed by intention to treat. The statistical significance level used will be 5% bilateral ($p<0.05$). The IBM SPSS Statistics v.29 program and the STATA v.14 program will be used for the statistical analysis.

5. Data management

The study data will be recorded using an electronic Data Collection Notebook (eQRD) designed with the REDCap program. The REDCAP platform is hosted on the institution's own servers (Althaia, Xarxa Assistencial Universitària, Fundació Privada), and has the security measures determined by the institution. The data is stored on the local web server where the organization has installed the software. Access to this REDCap is published at https://www.althaia.cat/redcap/ To access the application, it is necessary to do so with the user's email and password. A system has been incorporated so that only the application service can send data to the backoffice, through a firewall that only allows requests from the application's IP addresses. The web server has the HTTP X-Frame-Options header configuration enabled with the value "same-origin" to prevent clickjacking attacks. The principal investigator and the Study Sponsor as owners of the data will be responsible for their custody. The data will be collected in a database specifically designed for the study in a coded form. Each patient will be assigned a numerical code. The patient's demographic, clinical and laboratory data will be entered into the database associated with this code.

In another database, the principal investigator will record the equivalence between each numerical code and the patient's clinical history number.

Only the principal investigator and study collaborators will have access to the data recorded in the project database hosted on REDCap.

6. Ethical aspects and data confidentiality

During the conduct of the study, international ethical standards for human research established in the principles defined in the Declaration of Helsinki and subsequent revisions (Helsinki, Finland, October 2024), the code of good clinical practices and national recommendations will be followed in accordance with current legislation established in:

- Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulates clinical trials with medicinal products.

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices and Royal Decree 192/2023 of 21 March, which regulates medical devices

Prior to the start of the study, authorization will be requested from the CEIm of the IRIS-CC as the reference CEIm of the participating centres. Any modification of the protocol, other than administrative changes, will require an amendment to the protocol that must be approved by this same Committee.

It is planned that once the CEIm approval is obtained, the protocol will be registered in the international Clinical Trials database.

6.1. Considerations regarding information to subjects and informed consent

The research team will explain to each patient the nature of the study, its purposes, procedures, estimated duration, potential risks and benefits related to their participation in the study, as well as any inconvenience that this may entail.

Each participant will be informed that their participation in the study is voluntary and that they can abandon it at any time, without this affecting their subsequent medical treatment, or the relationship with the doctor who treats them.

The patient will be provided with the Patient Information Sheet (attached document FIP-CI) and Appendix 1 on data protection (attached document Appendix Data Protection) and will have sufficient time to read and understand the researcher's explanations contained therein, before signing the informed consent (attached document FIP-CI). On the day of the consultation with the pelvic floor rehabilitator, they will also be provided with the explanatory document on how to apply neurostimulation therapy. A copy of these documents will be provided to the patient (attached document neurostimulation therapy and sham therapy). No patient will be included in the study without having previously given written consent.

6.2. Data confidentiality

The sponsor and the study researchers must guarantee the confidentiality of patient data and ensure that the provisions of current data protection regulations are complied with at all times.

The processing, communication and transfer of personal data of all participants will comply with Organic Law 03/2018, of December 5, on the Protection of Personal Data and the guarantee of digital rights and Regulation (EU) 2016/679 of the European Parliament and of the Council, of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data ("General Data Protection Regulation" or "GDPR"), fully applicable since May 25, 2018.

The patient data collected for the study will be identified by a code, so that no information that could identify them is included, and only the study researchers will be able to relate this data to the patient and their clinical history. The identity of the participants will not be available to any other person except in a medical emergency or legal requirement.

In addition to the rights already provided for in previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation), participants can also limit the processing of data that is incorrect, request a copy or transfer to a third party (Portability) the data they provide for the study. To exercise their rights, they must contact the principal investigator of the study or the Data Protection Delegate (DPD) of Althaia, Xarxa Assistensial Universitària de Manresa, F.P. via email dpd@althaia.cat. They also have the right to contact the Data Protection Agency if they are not satisfied.

Patient data cannot be deleted even if they leave the study, in order to guarantee the validity of the research.

Althaia, Xarxa Assistensial Universitària de Manresa, Fundació Privada /Meritxell Font will be responsible for the processing of their data and undertakes to comply with the data protection regulations in force. Information regarding the patient's identity will be considered confidential in general.

In accordance with current legislation, the patient has the right to be informed of the data relevant to their health that are obtained during the course of the study. This information will be communicated to them if they wish; in the event that they prefer not to be informed, their decision will be respected.

The researcher and the Promoter are obliged to keep the data collected by the study for at least 25 years after its completion.

7. Applicability of the study

This study is one of the first to evaluate functionality after performing surgeries as aggressive as anterior rectal resection, where for oncological and survival reasons, functionality is secondary. With this project, we want to give importance to fecal

incontinence and sexual dysfunction since it has implications for the quality of life of patients. In addition, we try to add a new therapeutic tool to mitigate its alteration.

It should be noted that this is a pilot study/small sample size, and that therefore, studies with more statistical power would be needed and certainly with the application of the more supervised neuromodulation technique (sessions always with the rehabilitator), but the results obtained are already promising.

8. Economic report

At the moment there is no funding available for the study.

The cost of the study basically lies in obtaining the neurostimulators which will be borne by the General Surgery Department.

9. Work plan (schedule of activities)

- Preparation (during April-May 2025):
    - Design of the protocol with the different associated documents (informed consent, compliance documents, commitment document, data protection annex)
    - Presentation to the CEIM
    - Registration on clinicaltrials.gov
- Launch:
    - Start inclusion of patients from September 2025 to August 2027
        - Visit with surgery and rehabilitation at the time of entry into the study (1st month post-surgery) and performance of tests
        - Follow-up visit at the 6th and 12th month post-surgery and performance of tests
    - Data collection in RedCAP
    - Recruitment closure August 2027
    - Follow-up until August 2028
- Analysis (2nd semester 2028):
    - Data analysis
    - Statistical study
- Data publication and dissemination of results 2029

10. Publication policy

The results obtained in this study, whether positive or negative, will be presented at national and/or international conferences and published in scientific journals.

A description of this clinical trial will be available at clinicaltrials.gov as required by Spanish legislation.