

Report on the Originality and Feasibility of the Doctoral Dissertation

English translation of the original research document submitted for academic and ethics review. Section numbering and substantive content follow the Greek original; the original English study title and bibliography are retained. This translation is not a revised or retrospectively amended protocol.

Section 1. Study identification

1.1. Title in Greek (translated): Effectiveness of a perioperative physiotherapy programme as part of Enhanced Recovery After Surgery (ERAS) protocols.

1.1.a. Original English title: The effect of perioperative physiotherapy according to the Recovery Optimization Protocol after Surgery (ERAS) in patients after abdominal surgery

1.2. Identification of the doctoral candidate and advisory committee.

1.3. Name, capacity and signature of the candidate: Georgia–Maria Kamparoudi, Physiotherapist, Academic Fellow, Department of Physiotherapy, School of Health Sciences, International Hellenic University.

1.4. Name, capacity and signature of the supervisor: Konstantinos Ballas, Professor of Surgery, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki.

1.5. Name, capacity and signature of a member of the three-member committee: Alexandra Christara–Papadopoulou, Professor, Department of Physiotherapy, School of Health Sciences, International Hellenic University.

1.6. Name, capacity and signature of a member of the three-member committee: Ilias Kallistratos, Professor, Department of Physiotherapy, School of Health Sciences, International Hellenic University.

Section 2. Research hypothesis and scientific rationale

2.1. Hypothesis/hypotheses to be tested.

The effect of perioperative physiotherapy within Enhanced Recovery After Surgery (ERAS) protocols in patients undergoing abdominal surgery on length of hospital stay, incidence of postoperative infections and time to return to normal activity; and evaluation of complications, readmission rates, mortality rates, hospitalization costs and the feasibility of implementing such protocols.

2.2. Scientific rationale for the proposed dissertation.

2.2.a. Analysis of concepts relevant to the hypothesis to be tested. The description should be sufficiently extensive to be understood by scientists and researchers familiar with the scientific field, without necessarily having specialized knowledge of the specific research topic.

Perioperative physiotherapy: The preoperative and postoperative implementation of physiotherapy programmes, specifically the controlled programme and that usually delivered in everyday practice.

Length of hospital stay: The preoperative and, especially, postoperative duration of a patient's stay in hospital.

Postoperative infections: Infections occurring in the immediate postoperative period and associated with the length of hospitalization and the degree of patient mobilization.

Time to return to normal activity: The time required for the patient's functional recovery and social reintegration.

2.2.b. Originality. Evidence supporting the originality of the topic nationally and internationally (literature-based justification). Is this the first study on this topic? If not, how does it differ from previous studies?

INNOVATION

To date, research has mainly focused on the benefits of postoperative physiotherapy without including preoperative physiotherapy in accordance with ERAS principles. Research has also focused mainly on orthopaedic surgery, thoracic surgery or patients admitted to intensive care units. A review of the literature indicates a need to examine a holistic intervention consistent with ERAS principles, involving both preoperative and postoperative physiotherapy in patients undergoing abdominal surgery and using tools that assess their functional recovery.

2.2.c. Significance. What is the importance of accepting or rejecting the research hypothesis (with literature support)? How will the knowledge gain from the dissertation advance existing knowledge and future research in this field?

ERAS protocols promote rapid recovery to reduce postoperative stress and its consequences. They therefore follow planned, evidence-based perioperative care, including early feeding, early mobilization, adequate postoperative analgesia, prevention of postoperative nausea and vomiting, wound care and prevention of postoperative infections. Future research should focus on establishing a standardized rehabilitation programme informed by ERAS principles that can be delivered by specialist physiotherapists in inpatient and outpatient settings. Prospective studies are needed to determine the long-term effects of early mobilization and exercise-based interventions. How functional recovery can be achieved and measured should be central to future research.

Section 3. Methodology

3.1. Type of study (e.g. observational, interventional, case-control, randomized; see the source reference in the original).

The purpose of this study is to determine the extent to which early mobilization can accelerate functional recovery and reduce the incidence of postoperative pulmonary and other infections. The primary aim is to examine whether moderate-to-vigorous physical

exercise delivered shortly before surgery, together with early postoperative mobilization, reduces overall morbidity and mortality in patients undergoing abdominal surgery. This is therefore a randomized clinical and laboratory study in which patients will be randomly allocated to an intervention group or a control group after providing written informed consent.

3.2. Justification for the choice of study design, including its limitations.

Each study design has inherent advantages and disadvantages. How do these combine to justify the selected design for the research hypothesis?

Enhanced Recovery After Surgery (ERAS) programmes were introduced in the late 1990s, initially for colorectal surgery and subsequently for liver, pancreatic and upper gastrointestinal surgery. These programmes are based on the understanding that many adverse effects of surgery (e.g. loss of muscle mass and body weight and reduced resistance to infection) can be reduced through preoperative preparation [Kehlet H, 2000] and minimization of postoperative organ dysfunction to support and accelerate recovery [Kehlet, 2008]. ERAS is a multimodal approach in which physiotherapy plays an important role both before and after surgery. Preoperative physiotherapy has been shown to prepare the musculoskeletal and respiratory systems for impending physiological stress (Carli et al., 2010) and promote rapid functional recovery after surgery (Hoogeboom et al., 2014). Postoperative exercise programmes are also recommended in ERAS guidelines to support muscle recovery and return of function after major surgery (ERAS Society, 2017).

3.3. Study setting. If required, has permission been requested and obtained, or is there a collaboration protocol?

Fifth Surgical Department, Hippokration Hospital. The study may also be extended to patients at other, primarily university-affiliated, surgical departments in Thessaloniki if required by the needs of the study.

3.4. Study team. Principal investigator and additional researchers.

Principal investigator: Georgia–Maria Kamparoudi. Scientific input and advice will also be provided by the members of the three-member advisory committee: Konstantinos Ballas, Professor of Surgery, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki; Alexandra Christara–Papadopoulou, Professor, Department of Physiotherapy, School of Health Sciences, International Hellenic University; and Ilias Kallistratos, Professor, Department of Physiotherapy, School of Health Sciences, International Hellenic University.

3.5. What will be the candidate's contribution to the dissertation?

The candidate will be responsible for implementing the entire protocol programme, specifically:

- preparation of the research protocol;
- obtaining bioethics and ethics approval;

- selection of patients through randomized, blinded sampling from the Fifth Surgical Department of Hippokration University General Hospital of Thessaloniki;
- delivery of the physiotherapy programme;
- data collection;
- statistical analysis;
- concluding;
- writing the doctoral dissertation;
- dissemination of findings in accordance with the relevant regulations.

3.6. Brief description of the study design.

PATIENTS. Patients scheduled to undergo surgery (ERAS) at the Fifth Surgical Department of Hippokration University General Hospital of Thessaloniki will be randomly allocated to the intervention or control group after providing written informed consent. The control group will receive the usual inpatient postoperative physiotherapy programme; the intervention group will receive a specific preoperative and postoperative physiotherapy programme described in section 3.8.

3.7. Criteria for selecting the study population. Study groups (e.g. patients and controls); precise inclusion and exclusion criteria for each group.

Inclusion criteria: age >18–75 years [age range reproduced as written in the original]; male and female patients.

Exclusion criteria: a Functional Independence Measure score below 15 in the mobility/transfers and locomotion domains; severe pulmonary or cardiac disease preventing physical exercise; language or psychological disorders preventing comprehension of and adherence to the programme; refusal to provide written informed consent.

3.8. Description of the intervention (for intervention studies) and measured variables.

Participating patients will first be assessed by a physiotherapist in hospital as follows:

1. Completion of a study-specific questionnaire describing their current health status.
2. Completion of the Functional Independence Measure (FIM).
3. Pain measurement: 3.1 algometer; 3.2 Visual Analogue Scale (VAS).
4. Range-of-motion measurement using a goniometer.
5. Indicators of quality of inpatient care: 5.1 length of hospital stay (admission/discharge dates); 5.2 incidence of postoperative infections; 5.3 time to return to normal activity (initial and final FIM scores).

GROUPS. Patients and the assessor will not know to which group the patients belong. The study will include 180 patients divided equally between two groups. Each group will

be randomly divided into subgroups according to whether neurological problems are reported.

A. CONTROL GROUP. The usual 15-minute inpatient programme will be followed.

1. Preoperative physiotherapy: not included in the inpatient programme.

2. Postoperative physiotherapy:

2.1 Respiratory physiotherapy: 2.1.1 bronchial drainage; 2.1.2 elicitation of coughing; 2.1.3 use of Triflo.

2.2 Upper- and lower-limb therapeutic exercise.

2.3 Moving from supine to sitting and then to standing.

2.4 Walking.

B. INTERVENTION GROUP. A 45-minute preoperative physiotherapy programme will be delivered, comprising:

1.1 Completion of questionnaire information.

1.2 Preoperative education: 1.2.1 explanation of postoperative complications (pain, respiratory dysfunction and reduced mobility); 1.2.2 explanation of the postoperative physiotherapy programme.

1.3 Assessment of muscle strength using the Oxford scale.

1.4 Assessment of joint range of motion using a goniometer.

1.5 Pain assessment (algometer and VAS).

1.6 Assessment of breathing pattern.

1.7 Assessment of cough.

1.8 Assessment of functional independence using the FIM scale.

1.8 [number repeated in the original] Preoperative respiratory physiotherapy: 1.8.1 teaching diaphragmatic, thoracic and synchronized breathing, 10 repetitions; 1.8.2 thoracic expansion combined with upper-limb exercises.

1.9 Therapeutic exercise: 1.9.1 exercises to maintain joint range of motion; 1.9.2 strengthening exercises for the upper limbs, lower limbs and trunk.

1.10 Training in functional activities (changing position in bed, sitting up, standing up and walking).

1.11 Training in the use of assistive devices (elastic abdominal binder and walking aids if considered necessary).

1.12 Education of the patient and accompanying person in the preoperative and postoperative programmes; the programme will be repeated twice more before surgery.

A 45-minute postoperative physiotherapy programme will comprise:

2.1 Assessment of breathing pattern.

- 2.2 Assessment of respiratory muscles (Oxford scale).
- 2.3 Assessment of cough.
- 2.4 Assessment of the muscular system using the Oxford scale.
- 2.5 Assessment of joint range of motion with a goniometer.
- 2.6 Measurement using an algometer and VAS.
- 2.7 Respiratory physiotherapy: 2.7.1 diaphragmatic, thoracic and synchronized breathing, 10 repetitions; 2.7.2 thoracic expansion with upper-limb exercises.
- 2.8 Bronchial drainage.
- 2.9 Elicitation of coughing; use of Triflo.
- 2.10 Therapeutic exercise: 2.10.1 exercises to maintain joint range of motion; 2.10.2 strengthening exercises for the upper limbs, lower limbs and trunk.
- 2.11 Training in functional activities (changing position in bed, sitting up, standing up and walking).
- 2.12 Training in the use of assistive devices (elastic abdominal binder and walking aids if necessary).
- 2.13 Education and information for accompanying persons; postoperative programme delivered twice daily.

Measurements will be taken one day before scheduled surgery, on postoperative day 1, on postoperative day 5 and at four weeks after surgery (follow-up/retention of effects).

3.9. Description of the measurement methods and/or questionnaires to be used and whether the questionnaires are validated for the Greek population.

- Questionnaire: information on the patient's current health status.
- Functional Independence Measure (FIM).
- Goniometer.
- Algometer.
- Visual Analogue Scale (VAS).
- Indicators of quality of inpatient care.

3.10. Outcome measures: primary and secondary.

The primary outcome is the effect of the physiotherapy protocol on indicators of quality of inpatient care, namely length of hospital stay, incidence of postoperative infections and time to return to normal activity. Secondary outcomes are complications, readmission rate, mortality rate, hospitalization costs and the feasibility of implementing such protocols.

3.11. Planned subgroup analysis. Has it been decided at the outset to subdivide either study group according to specified characteristics?

Both the control group and the intervention group will be subdivided into patients with and without reported neurological problems.

3.12. How and by whom will the data be recorded?

By the doctoral candidate, in electronic spreadsheets.

3.13. Has approval been obtained from the Bioethics Committee? [No answer entered in the original document at this item.]

3.14. Statistical methods planned for assessment of primary and secondary outcomes.

Data collected for each outcome will be analysed according to their type. Continuous data will be summarized, depending on their distribution, using either mean and standard deviation or median and interquartile range. Categorical data will be summarized using relative frequencies. Comparisons of continuous data will follow a normality assessment: normally distributed variables will be compared using Student's t-test and non-normally distributed variables using the Mann-Whitney test. Categorical data will be analysed using the chi-squared test or Fisher's exact test, according to expected frequencies. Multivariable analysis will be attempted for the principal outcomes to assess the effects of multiple factors. The significance level is set at 5%.

3.15. Justification of the appropriateness of the statistical tests.

The statistical tests will correspond to the type of data analysed and the research questions posed. The statistical framework for evaluation will be classical (frequentist) statistics. Tests will be based on hypothesis testing, involving a null and an alternative hypothesis, calculation of the relevant test statistic and p-value, and comparison of the p-value with the 5% significance threshold to determine whether to reject the null hypothesis. Hypothesis-testing methods are widely used in biomedical data relevant to clinical practice. A 5% significance level is generally accepted for data of this scale and is considered adequate for drawing reliable conclusions.

3.16. Statistical sample-size calculation.

With 80% power and a 5% significance level, 24 patients per group are estimated to be required to detect a clinically meaningful difference in length of hospital stay (using Student's t-test and based on the current literature). With the same parameters, 81 patients per group are estimated to be required to detect a 50% reduction in postoperative complications. Taking these calculations into account, together with the possibility of approximately 10% loss to follow-up, 180 patients will be included, allocated 1:1 between the two groups.

Section 4. Feasibility

4. Feasibility of carrying out the proposed dissertation.

4.1. Expected duration of the dissertation, based on the available number of cases: at least three years, in accordance with the new doctoral dissertation regulations.

4.2. Detailed timetable for completion: an initial literature search in international sources has already begun and will continue. Recruitment of the first cases is expected to begin soon (during 2021), together with collection of laboratory data. Qualitative and quantitative evaluation and statistical analysis will follow, then literature-based interpretation of the data and conclusions.

4.3. Funding required and source: own resources.

Section 5. Publication strategy and bibliography

5.1. Publications expected from the research: one review and at least two clinical trials are planned for publication before the dissertation defence.

5.2. Bibliography (Vancouver format). The references below reproduce the original document, including its original bibliographic formatting and spelling.

A F O'Doherty 1, M West, S Jack, M P W Grocott Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review 2013 May;110(5):679- 89. doi: 10.1093/bja/aes514. Epub 2013 Feb 7.

Amelia Williamson 1, Barbara Hoggart Pain: a review of three commonly used pain rating scales J Clin Nurs. 2005 Aug;14(7):798-804. doi: 10.1111/j.1365-2702.2005.01121.x.

Apfelbaum J.L., Connis R.T. & Nickinovich D.G. (2012). American Society of Anesthesiologists Task Force on preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Tasks Force on preanesthesia evaluation. Anesthesiology 116(3):522-538.

Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg 2018;267:50–6. CrossrefPubMedGoogle Scholar

Burden ST, Hill J, Shaffer JL, Todd C. Nutritional status of preoperative colorectal cancer patients. J Hum Nutr Diet 2010;23:402–7. PubMedCrossrefGoogle Scholar

Erik H J Hulzebos 1, Paul J M Helders, Nine J Favié, Rob A De Bie, Aart Brutel de la Riviere, Nico L U Van Meeteren Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial JAMA. 2006 Oct 18;296(15):1851-7. doi: 10.1001/jama.296.15.1851.

ERAS Society (2017). ERAS Society Guidelines. Available from: <http://erassociety.org/guidelines/list-of-guidelines/>. [Accessed August 7 2017].

Hare G.M., Baker J.E. & Pavenski K. (2011). Assessment and treatment of preoperative anemia: Continuing Professional Development. Canadian Journal of Anesthesia 58:569-81.

Heger P, Probst P, Wiskemann J, Steindorf K, Diener MK, Mihaljevic AL. A systematic review and meta-analysis of physical exercise prehabilitation in major abdominal surgery

(PROSPERO 2017 CRD42017080366). J Gastrointest Surg 2019 [Epub ahead of print]. PubMedGoogle Scholar

Henriksen M.G., Hessel I., Dela F., Hansen H.V., Haraldsted V. & Rodt S.A. (2003). Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition, and muscle function in abdominal surgery. *Acta Anaesthesiologica Scandinavica* 47:191-199.

Hoogbeem TJ, Donkers JJ, Hulzebos EH et al. (2014) Merits of exercise therapy before and after major surgery. *Curr Opin Anaesthesiol*, 27(2):161-166.

Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation before major abdominal surgery: a systematic review and meta- analysis. *World J Surg* 2019;43:1661–8. CrossrefPubMedGoogle Scholar

Isabel Yáñez-Brage, Salvador Pita-Fernández, Alberto Juffé-Stein, Ursicino Martínez-González, Sonia Pérttega-Díaz & Ángeles Mauleón-García Respiratory physiotherapy and incidence of pulmonary complications in off-pump coronary artery bypass graft surgery: an observational follow-up study *BMC Pulmonary Medicine* volume 9, Article number: 36 (2009)

Kehlet H. Manipulation of the metabolic response in clinical practice. *World J Surg* 2000;24:690–5. PubMedCrossrefGoogle Scholar

Kehlet H, Joshi GP. Enhanced recovery after surgery: current controversies and concerns. *Anesth Analg* 2017;125:2154–5. CrossrefPubMedGoogle Scholar

Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008;248:189–98. CrossrefPubMedGoogle Scholar

Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005;242:32–3. Google Scholar

Lawrence VA, Hazuda HP, Cornell JE, Pederson T, Bradshaw PT, Mulrow CD, et al. Functional independence after major abdominal surgery in the elderly. *J Am Coll Surg* 2004;199:762–72. CrossrefPubMedGoogle Scholar

Lee T.H., Marcantonio E.R., Mangione C.M., Thomas E.J., Polanczyk C.A., Cook E.F., Sugarbaker D.J., Donaldson M.C., Poss R., Ho K.K., Ludwig L.E., Pedan A. & Goldman L. (1999). Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 100:1043-9. Liezel Schweltnus, Ronel Roos, 1 and Vaneshveri Naidoo1 Physiotherapy management of patients undergoing thoracotomy procedure: A survey of current practice in Gauteng S Afr J Physiother. 2017; 73(1): 344.

Liu Z, Qiu T, Pei L, Zhang Y, Xu L, Cui Y, et al. Two-week multimodal prehabilitation program improves perioperative functional capability in patients undergoing thoracoscopic lobectomy for lung cancer: a randomized controlled trial. *Anesth Analg* 2019 [Epub ahead of print]. PubMedGoogle Scholar

Maltby J.R. (2006). Fasting from midnight- the history behind the dogma. Best practice and research. Clinical Anesthesiology 20:363-78.

Michele Cournan DNP RN CRRN ANP-BCs Use of the Functional Independence Measure for Outcomes Measurement in Acute Inpatient Rehabilitation Rehabilitation Nursing Volume 36, Issue3 May-June 2011 Pages 111-117

Miller K.R., Wischmeyer P.E., Taylor B. & McClave S.A. (2013). An evidence- based approach to perioperative nutrition support in the elective surgery patient. JPEN Journal of parenteral and enteral Nutrition 37:39-50.

Minnella EM, Bousquet-Dion G, Awasthi R, Scheede-Bergdahl C, Carli F. Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. Acta Oncol 2017;56: 295– 300. CrossrefGoogle Scholar

Moghissi E.S., Korytkowski M.T., DiNardo M., Einhorn D., Hellman R., Hirsch I., Inzucchi S., Ismail-Beigi F., Kirkman M.S. & Umpierrez G.E. (2009). American Association of clinical Endocrinologists, American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 32:1119-31.

PanelK.J.HainesaE.H.SkinnerbS.BerneyaThe Austin Health POST Study Investigators1Association of postoperative pulmonary complications with delayed mobilisation following major abdominal surgery: an observational cohort study Physiotherapy Volume 99, Issue 2, June 2013, Pages 119-125

Pearse R.M., Harrison D.A., James P., Watson D., Hinds C., Rhodes A., Grounds R.M. & Bennett E.D. (2006). Identification and characterization of the high- risk surgical population in the UK. Critical Care 10:81.

Phillip ABrasher 1Kirstin HMc Clelland1 Linda Denehy12Ian Story2 Does removal of deep breathing exercises from a physiotherapy program including pre-operative education and early mobilisation after cardiac surgery alter patient outcomes? Australian Journal of Physiotherapy Volume 49, Issue 3, 2003, Pages 165-173

Qaseem A., Snow V., Fitterman N., Hornbake E.R., Lawrence V.A., Smetana G.W., Weiss K., Owens D.K., Aronson M., Barry P., Casey D.E.Jr., Cross J.T.Jr., Fitterman N., Sherif K.D. & Weiss K.B. (2006). Clinical Efficacy Assessment Subcommittee of American College of Pulmonary Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: A guideline from the American college of Physicians. Annals of Internal Medicine 144:575-80.

Smith I., Kranke P., Murat I., Smith A., O'Sullivan G., Soreide E. & Spies C. for the European Society of Anaesthesiology (2011). Perioperative fasting in adults and children: guidelines from the European Society of Anesthesiology. European Journal Anesthesiology 28(8):556-569.

Sorensen L.T., Karlsark T. & Gottrup F. (2003). Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Annals of Surgery 238:1- 5.

Yee Sien Ng,¹ MBBS, MRCP, FAMS, Heeyoune Jung,¹ MD, FAAPMR, San San Tay,¹ MBBS, MMed, MRCP, Chek Wai Bok,¹ MBBS, MMed, MRCP, Yi Chiong,¹ MBBS, MRCP, Peter AC Lim,^{1,2} MBBS, FAAPMR, FAM Results From a Prospective Acute Inpatient Rehabilitation Database: Clinical Characteristics and Functional Outcomes using the Functional Independence Measure *Ann Acad Med Singapore* 2007;36:3-10

Walker K.J. & Smith A.F. (2009). Premedication for anxiety in adult day surgery. *Cochrane Database Systematic Review* 4:CD 002192. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19821294>. [Accessed 13 Noe 2017].

West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, et al. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. *Br J Surg* 2016;103:744–52. PubMedCrossrefGoogle Scholar

Wilson RJ, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010;105:297–303. PubMedCrossrefGoogle Scholar