EURO POWER

Postoperative Outcomes Within an Enhanced Recovery After Surgery Protocol

Colorectal Surgery

Short Title	EuroPOWER
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Chief Investigator Agreement

The clinical study as detailed within this research protocol (version 1.0, 04/2018), or any subsequent amendments will be conducted in accordance with the (Note for guidance on Good Clinical Practice, CPMP / ICH / 135/95) defined as an international standard of scientific and ethical quality aimed at designing, recording and writing reports on clinical trials involving human subjects. These standards publicly guarantee the protection of the rights, safety and well-being of the subjects participating in the study and ensure the integrity and credibility of the data obtained in a clinical trial; in accordance with the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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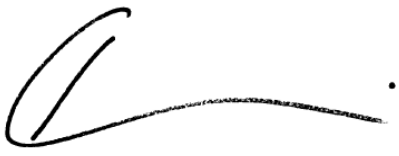

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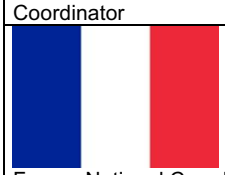 France National Coordinator	**Samir Jaber** Department of Anesthesiology and Intensive Care Centre Hospitalier Universitaire de Montpellier, Montpellier s-jaber@chu-montpellier.fr	**Karem Slim** Service de Chirurgie Digestive & Unité de Chirurgie Ambulatoire & Président de GRACE (Groupe francophone de Réhabilitation Améliorée après Chirurgie) kslim@chu-clermontferrand.fr
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GLOSSARY OF TERMS AND ABBREVIATIONS

AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
ASA	American Society of Anesthesiologists
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EPCO	European Perioperative Clinical Outcome
ERAS	Enhanced recovery after surgery
ESA	European Society of Anesthesiology
ESICM	European Society of Intensive Care Medicine
IQR	Interquartile range
LOS	Length of stay
MAR	Missing at random
MCAR	Missing completely at random
MINS	Miocardial injury after non-cardiac surgery
PE	Pulmonary embolism
PONV	Post-operative nausea and vomiting
TSC	Trial Steering Commitee

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1. SUMMARY

Short title	EuroPOWER
Methods	30 days European Multicentre observational cohort study of postoperative complications following elective colorectal surgery within any compliance of an ERAS protocol (including patients with 0 compliance) in a participating hospital during the 30-day cohort period with a planned overnight stay.
Research sites	Hospitals across Europe with an elective colorrectal surgical service
Objective	To provide detailed data describing post-operative complications and associated mortality To provide detailed data describing adherence to ERAS protocol and its association to morbidity and length of stay. To provide detailed information on the influence of the volume of patients undergoing surgery on each center and postoperative complications censured at 30 days after surgery.
Inclusion criteria	All adult patients (aged ≥18 years) undergoing elective colorectal surgery during the 30-day study period.
Statistical analysis	Number of patients: All eligible patients undergoing elective colorectal surgery during the study month in European participating hospitals. Univariate analysis will be used to test factors (patient, surgical, and ERAS related) associated with surgical complications, length of stay (LOS) and in-hospital death. Single and multi-level logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. A stepwise approach will be used to enter new terms. A single final analysis is planned at the end of the study.

	Summary statistics with post hoc Bonferroni corrections will be used to assess possible dose–response dependence in percentage of patients with postoperative complications and LOS.
Proposed Start Date	A 30 day period in 2019
Proposed End Date	2019
Study Duration	4 months

2. INTRODUCTION

Over 312 million major surgical procedures are performed globally each year(1) and despite advances in surgical and anaesthetic care, morbidity after abdominal surgery is still high. Colorectal surgery is associated with a high risk of morbidity and mortality in comparison to other general surgery subspecialties.

Overall mortality rates following colorectal surgery range from 1 to 16.4%(2-4) with morbidity rates as high as 35%(2,3,5). The concept of fast-track surgery, also called enhanced recovery after surgery (ERAS) or multimodal surgery involves using various perioperative strategies to facilitate better conditions for surgery and recovery in an effort to achieve faster discharge from hospital and more rapid resumption of normal activities after surgery through reducing postoperative stress and improving clinical practice by incorporating evidence-based medicine into patient management. ERAS protocols have repeatedly been shown to reduce length of stay(6-8) without influencing complication or readmission rates(8,9).

Although individual components may vary, most of the ERAS programs include avoidance of fasting, preoperative optimization of health, preoperative carbohydrate loading, avoidance of bowel preparation, goal-directed hemodynamic therapy, multimodal analgesia with avoidance of opiates, avoidance/early removal of tubes (nasogastric tube, Foley catheter, and drains), support of gastrointestinal function, and early convalescence(10).

The development and widespread application of ERAS, in combination with laparoscopic surgery, represent a paradigm shift in perioperative care. Furthermore, the association between laparoscopic approach and ERAS perioperative management has recently proposed as the best option for patients undergoing segmental colectomy for colon cancer(9).

Our aim is to conduct a European 30-day cohort study of adults undergoing elective colorectal surgery within any compliance of an ERAS protocol (11-12) (including patients with 0 compliance) to provide detailed data describing post-operative predefined (13) complications and associated mortality.

3. OBJECTIVE AND PURPOSE OF THE ASSAY

To assess the incidence of 30-day postoperative predefined complications following elective colorectal surgery within any compliance of an ERAS protocol (including patients with 0 compliance) in European centres.

3.1 Specific aims

Post-operative complications following major abdominal surgery are common. The inclusion of enhanced recovery protocols has shown that by applying a series of perioperative measures, postoperative complications can be reduced as well as hospital stay. Current knowledge is based on small, prospective single centre studies or retrospective databases. However, there are no long-term prospective data analysing compliance with these items and their relationship to postoperative complications. Compliance with these protocols is very variable across centres and countries; the decrease in postoperative complications seems to be directly related to the complete compliance of the protocols.

To solve this problem we need concrete data in which these protocols are carried out with a high level of compliance and by the analysis of complications in a predefined way according to the European recommendations proposed by the ESA(10). Therefore, we propose a prospective observational study of one month of duration throughout Europe, analysing predefined postoperative complications within 30 days after surgery. The feasibility of this study is supported by the wide participation in observational studies carried out by the ESA, and by the wide participation in ongoing observational studies carried out by our research team. (NCT03012802). Our hypothesis is that the number of patients who develop predefined postoperative complications within 30 days of surgery decreases as there is greater compliance with the predefined ERAS protocol items. The results of this study will allow to identify, on the one hand, the type of patients presenting postoperative complications and, on the other hand, to identify those items of the ERAS protocols that are independently associated with a reduction in postoperative complications and hospital stay, which will allow to focus the perioperative efforts in those items that actually improve the postoperative outcomes.

- Aim 1 will establish the number of patients developing predefined postoperative complications within 30 days of surgery in adult patients undergoing elective colorectal surgery with any compliance of an ERAS protocol (including patients with 0 compliance). This will allow us to determine the actual impact of these protocols.

- Aim 2 will allow us to know the type of predefined complication presented by the patients included in the ERAS protocols and in patients undergoing colorectal surgery; This will allow, on the one hand, to have a starting point for future clinical trials, and, on the other hand, to focus efforts to avoid these complications.

- Aim 3 will allow us to identify those perioperative items of ERAS protocols that are actually associated with a decrease in postoperative complications.

The proposed study will establish a real view of the number of patients presenting postoperative complications that will overcome the limitations of available retrospective studies and provide greater insight into the items of the protocols that are associated with decreased complications; on the other hand, our hypothesis is that the number of patients who develop predefined postoperative complications within 30 days of surgery decreases as there is greater compliance with the predefined ERAS protocol items.

4. STUDY DESIGN

4.1 Inclusion/Exclusion Criteria

Inclusion Criteria

All adult patients (aged ≥18 years) undergoing primary elective colorectal surgery and by any approach (Includes surgery with laparoscopic, assisted laparoscopic approach or open approach) in a participating hospital during the 30-day cohort period with a planned overnight stay.

Exclusion Criteria

- Patients submitted for emergency surgery
- Patients with complex cancer who required resection of organs other than bowel. (i.e. kidney, gastric resection, ovarian)

- Patients treated with endoscopic techniques using the hybrid TaTME technique (Transanal Total Mesorectal Excision)
- Bowel transit reconstruction surgery
- Patients who refuse to participate

4.2. Outcome Measures

Primary outcome measure

All predefined mild-moderate-severe postoperative complications within 30 days of surgery (See Appendix I).

Secondary outcome measures

- In-hospital all-cause mortality (censored at 30 days after surgery)
- Compliance with ERAS items (within 30 days after surgery). See Appendix II for a description of ERAS items.
- Duration of hospital stay (duration of primary hospital stay after surgery)

Rationale

Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine were published by the EPCO definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures in 2015(10). We believe it is the best way to evaluate postoperative complications. The European Society of Anesthesiology recommends its use. In addition, these definitions of complications have already been used in large observational studies. Besides, Clavien-Dindo classification of surgical complications will be included.

4.3 Schedule of Assessment

	Pre-assessment clinic	Day of operation	Post-op day 1	Post-op day 2	Post-op day 3	Day of discharge	4 weeks	90 days
Baseline CRF	**X**	**X**						
Treatment CRF		**X**						
Discharge CRF						**X**		
30 day CRF							**X**	
90 day CRF								**X**

4.4 Methods against Bias

To avoid the confusion generated by the application of the ERAS protocols or their particular items, compliance with these will be collected individually, as well as their overall compliance in each patient and centre (see Appendix II).

4.5 Study data

The study data collection will comply with the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679). Data will be collected on all eligible patients who undergo elective colorectal surgery within any compliance of an ERAS protocol during the study month. Only routine clinical data will be included and where this is unavailable the domain will be left blank e.g. patients who do not require blood tests. It is possible that national groups may supplement their core data set with a very limited number of additional variables if these can be accommodated within the case record form (CRF) and they comply with regulations applied to this study.

The researchers must complete the CRF provided by the Promoter and send the data as indicated at the beginning of the study. The researcher's file must be conserved in a safe place, which contains all the relevant documentation of the study. The data of the patients collected CRFs during the trial, should be documented anonymously and

dissociated, linking to a code (patient trial identification number), so that only the researcher can associate such data with an identified or identifiable person.

The researcher will keep the original clinical documents of each patient of the study, which consist of all medical and demographic information including laboratory data, electrocardiograms, etc., and a copy of the signed informed consent form, for at least 25 years after completion or suspension of the study.

By signing the protocol, the researcher agrees to follow the procedures for document preservation.

4.5.1 Data collection

Complications will be evaluated through the patient's medical records.
Data will be collected in individual hospitals on a paper CRF for each patient recruited. Paper CRFs will be stored within a locked office in each centre. This will include identifiable patient data in order to allow follow-up of clinical outcomes. Data will then be pseudo-anonymised by generating a unique numeric code and transcribed by local investigators onto an internet based electronic CRF (eCRF). Each patient will only be identified on the electronic CRF by their numeric code. Thus the co-ordinating study team cannot trace data back to an individual patient without contact with the local team. A patient list will be used in each centre to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points (See Appendix V).

4.6 Audit organisation

EuroPOWER will be led by the study management group who will be responsible for study administration, communication between project partners, data collation and data management. National coordinators will lead the project in each European country and:

- Identify local coordinators in participating hospitals
- Assist with translation of study paperwork as required

- Ensure distribution of study paperwork and other materials
- Ensure necessary regulatory approvals are in place prior to the start date
- Ensure good communication with the participating sites in his/her nation

Local coordinators in individual institutions will have the following responsibilities:

- Provide leadership for the study in their institution
- Ensure all relevant regulatory approvals are in place for their institution
- Ensure adequate training of all relevant staff prior to data collection
- Supervise daily data collection and assist with problem solving
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of eCRFs by supervising local data entry
- Communicate with the relevant national co-ordinator

4.7 End of Study Definition

The end of the study is defined as the end of the 30-day follow-up for the last patient included. Data analysis shall follow this.

4.8 Ethics and informed consent

We anticipate that patient consent will not be required in EuroPOWER on the basis that the dataset will only include variables documented as part of routine clinical care and that identifiable patient data will not leave the hospital where each individual patient is treated. The need for informed consent will depend on each participating country. However, the Direction of EuroPOWER will provide informed consent for all participating countries. Unless written informed patient consent is provided, only anonymised or coded data will be provided to the EuroPOWER.

Informed consent will be provided through standard writing, in language easily understandable to the participant. The patient must write his name and that of the informant doctor in his own handwriting and, date and sign the informed consent, as well as receive a copy of the signed document.

If the subject cannot read or sign the documents, an oral presentation can be made or the signature of the authorized legal representative of the subject can be obtained, whenever a witness not involved in the study witnesses it and is mentioned in the same document and / or clinical history.

It is expected that different countries have different regulatory requirements regarding patient consenting. Where required, the EuroPOWER study protocol will include country specific appendices to describe specific procedures regarding the use of identifiable patient data and the procedures involved and regulatory approvals required. Where individual patient consent is given for participation, it is recognised that this may provide the opportunity to link EuroPOWER data to national registry data on survival and other healthcare information. Plans for supplementary data collection in individual nations will also be detailed in a country specific appendix to this protocol.

4.9 Safety considerations

There are no safety considerations relating to the EuroPOWER. There is no risk of harm to either patients or investigators.

4.10 Data handling and record keeping

All identifiable data collected, processed and stored for the purposes of the project will remain confidential at all times and comply with Good Clinical Practice for research (GCP) guidelines; the principles of the Data Protection Act 1998 (UK), and The General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679). Data will only be handled by the 'direct care team'. This means only the normal doctors and nurses etc see the data.

The data collection platform used will be Castor EDC https://www.castoredc.com/. Castor EDC complies with all applicable laws and regulations: Good Clinical Practice (GCP), 21 CFR Part 11, EU Annex 11, and the European Data Protection Directive.

Each centre will maintain a trial file including a protocol, local investigator delegation log, documentation of the relevant regulatory approvals and patient list. EuroPOWER data collection sheets will be stored securely in a locked cupboard and handled only by clinical staff familiar will handling personal data and with Good Clinical Practice for research. Data will be anonymised prior to transfer to the EuroPOWER Audit management group except where the patient has given written informed consent to allow transfer of identifiable data. Access to the data entry system will be protected by username and password, delivered during the registration process for individual local investigators. All electronic data transfer between participating centres and the coordinating centre will be encrypted using the SSL 3.0 protocol (HTTPS). Desktop and laptop security will be maintained through user names and passwords. All local investigators will be asked to undergo training in accordance with the Research Governance Framework. The study master files will be stored in an approved repository for 25 years following the end of the study.

The data collection platform that will be used allows for a security system that:

- Each user has their own individual account; sharing of passwords is not permitted and we enforce strong password choices when creating or changing passwords.
- Customers log in through SSL/TLS1.2.
- The authorisation to access data is determined per person per institute and is always maintained by the study administrator, thereby excluding the possibility of unauthorised access to data by other researchers or institutes.
- The application code has been written in such a way that the risk of SQL injection and related attacks is kept at as low as possible.
- Continuous Penetration Tests ensure that the application and infrastructure security is always state-of-the-art.
- The application servers are hosted at True; True has been certified by the Lloyd's Register Quality Assurance (LRQA) according to the international information security norm ISO 27001:2013. True provides its services in accordance with the Dutch NEN7510 norm for information security in healthcare.
- The application servers are located at Overamstel, Amsterdam, The Netherlands.
- The data center is managed 24/7 and has round-the-clock physical security.
- Unauthorized access to the data center is not possible.
- The data center is protected by digital surveillance equipment

- All data is stored on servers in the Netherlands, and backups are stored at another geographical location to ensure maximum security and continuity, in line with the EU Data Protection Directive.
- Castor EDC runs on fully managed virtual private servers. All servers are continually and pro-actively monitored, and in the event of any emerging problems or loss of availability action is immediately taken according to our standard operating procedures.
- Backups are made four times a day and are moved to another geographical location on a daily basis.
- Intrusion detection systems and other systems continuously check for errors and prevent hackers from accessing the system.
- The application runs on a protected server with only strictly necessary services and ports open to the outside world.
- A hardware firewall ensures that no unwanted connections can be made to any of the Castor servers.

4.11 Safety reporting

The trial involves negligible risks to patients and investigators. Adverse events will not be monitored or reported.

4.12 Monitoring and audit

The Data monitoring and ethics committee will routinely monitor data collection in individual hospitals or conduct source data verification.

5. STATISTICAL ANALYSIS

5.1 Objectives

The primary objective of the study is to measure the incidence of predefined postoperative complications within 30 days following elective colorectal surgery with

any compliance of an ERAS protocol (including patients with 0 compliance), including complications that occurred before hospital discharge and those that happened after discharge and required ambulatory or in-hospital care. The complications that will be analysed in this study are: infections, cardiovascular complications and other complications such as bleeding and acute kidney injury (please refer to EPCO definitions)(13). The secondary objectives of this study include measuring the 30-day mortality and LOS associated with these complications and describing the incidence of complications for different adherence to the ERAS protocol. EuroPOWER will address the need to describe the frequency, severity and nature of complications following surgery and the associated short-term mortality.

Primary outcome measure

All predefined postoperative complications within 30 days after surgery, including complications that occurred before hospital discharge and those that happened after discharge and required in-hospital care. Complications will be evaluated through the patient's medical records. Postoperative complications are defined according standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine (EPCO)(13).

Secondary outcome measures

- In-hospital all-cause mortality (censored at 30 days following surgery)
- Compliance with ERAS items (within 30 days following surgery). See Appendix II for a description of ERAS items. Compliance of an individual component will be presented as a binary relationship yes / no. While overall compliance will be reported as a percentage: number of interventions fulfilled/total number of perioperative interventions evaluated.
- Duration of hospital stay (duration of primary hospital stay after surgery)

5.2 Sample size calculation

Our plan is to recruit as many centres as possible on an international basis and ask them to include all eligible patients in the study. Only centres including 10 valid patients will be included in the data analysis. We do not have a specific sample size and statistical models will be adapted to the event rate provided by the sample recruited.

5.3 Initial descriptive analysis

5.3.1 Participants

All participating hospitals have been asked to keep a log of the data that is collected. Data included in the study, missing data and completeness of follow up will be illustrated using a STROBE flow diagram. The inclusion criteria are all adult patients (age≥18 years) undergoing elective colorectal surgery within any compliance of an ERAS protocol (including patients with 0 compliance) in a participating hospital during the 30-day study period. Patients undergoing emergency surgery are excluded. Only hospitals returning valid data describing 10 or more patients will be included in the study. All eligible patients' data should be uploaded to the online e-CRF. A thorough data cleaning procedure will be implemented as follows:

- A robust e-CRF is designed to ensure data entry errors are minimised. The e-CRF provides a warning message and asks the user to confirm the value of any data entered which lie outside the pre-determined validity range.
- Checking for outliers. If there are extreme outliers, the data points will be excluded from the analysis. A secondary analysis will be conducted with all data included to gauge the difference in results.
- Duplicates will be checked for and removed using the software package SPSS Statistics 22.
- Handling of missing data is outlined in section 6.0.

5.3.2 Baseline characteristics

To give a broader understanding of the patients enrolled in the study, baseline characteristics of all the patients will be presented. Numbers (%) or means (SD) and medians (IQR) will be given for each group as appropriate.

- Demographic: Age, sex, smoking status and American Society of Anesthesiologists (ASA) Physical Status grade, weight, height, preoperative transfusion.

- Nutrition related: body mass index, unplanned weight loss> 10% in the past 6 months, Albumin <3; preoperative (oral) nutritional supplements, preoperative oral carbohydrate load (Type and amount).
- Frailty related (see Appendix III)
- Prehabilitation related (see Appendix IV)
- Anaemia related: preoperative anaemia treatment, preoperative iron treatment (dose, route).
- Surgery related: Surgical procedure, surgical approach, cancer surgery, conversion to open (defined as: the inability to complete the dissection laparoscopically, including the vascular ligation, and usually, but not always, requiring an incision larger than that required to remove the specimen), duration of surgery, drains, stomas, fluids administered (types and amount), intraoperative diuresis, anaesthesia (epidural, spinal, wall block)
- Comorbidities: Presence of Hypertension, Diabetes Mellitus, Coronary Artery Disease, Heart failure (ejection fraction), Cirrhosis (portal Hypertension), Metastasis cancer, Stroke or Transient Ischaemic Attack, COPD/Asthma, Chronic kidney disease
- Preoperative blood test results: haemoglobin, albumin, and creatinine.
- Postoperative variables: haemoglobin, creatinine, Postoperative (oral or intravenous) nutritional supplements, postoperative transfusion, gum chewing after surgery, Intravenous fluids discontinued in the early postoperative period after recovery room discharge; time to mobilization, time to oral intake, postoperative anaemia treatment, postoperative iron treatment (dose, route), re intervention, readmission.

5.3.3 Primary analysis

The primary outcome measure of this study is the percentage of patients with predefined postoperative complications within 30 days after surgery. LOS, the number of deaths and the overall of complications within 30 days after surgery will be reported. The primary effect estimate will be the odds ratio of 30-day, percentage of patients with

postoperative complications, reported with 95% confidence intervals and p-value. The significance level will be set at $p<0.05$.

A multivariable logistic regression analysis will be used to develop a generic model in which all biologically plausible predictor variables will be entered. With the expected large sample size, a large number of predictors can be included in the model without over fitting, thus predictors will be selected based on clinical suitability and assessment of correlated variables. The model will be adjusted for the following covariates: age, sex, smoking status, surgical procedure category, ASA grade, presence of co-morbidities, anaesthetic technique, laparoscopic surgery, cancer surgery, baseline blood test results (namely haemoglobin, albumin and creatinine) and those described in point 5.3.2. For the purpose of this analysis will be grouped with upper gastrointestinal surgery and lower gastrointestinal surgery. All predictors will be entered into the model using forced simultaneous entry. To assess the reliability of our models, bootstrapping will be undertaken. To account for variations within countries, hospitals and patient groups and their influence on outcome, a three-level hierarchical generalised linear mixed model will be used. Patients will be entered in the first level, hospitals in the second level and countries in the third level. This model will take into account the differences between countries and hospitals (e.g. among countries and hospitals) in relation to differences within those levels (e.g. among patients within hospitals). If this model fails to converge, a two level hierarchical model will be constructed with patients in the first level and countries in the second level. The results of the regression models will be reported with adjusted odds ratios, 95% confidence intervals and associated p-values. Unadjusted odds ratios will also be presented for comparison. To characterise the differences across hospitals, median odds ratio will also be reported for 30 days complications and mortality.

Residuals will be examined to ensure the assumptions for regression analyses are met. Goodness-of- fit for the models will be performed using the Hosmer-Lemeshow test. For multivariable regression analysis, multi-collinearity (correlations among predictor variables) is expected. Multi-collinearity will be assessed using the Variance Inflation Factor (VIF). This measures the extent to which the variance of the model coefficient will be inflated (due to correlation of the variable with the other predictor variables) if that variable is included in the model. A $VIF>10$ will be considered to be collinear and will be excluded from the analysis.

Overall compliance will be calculated as the average of all pre- and intraoperative ERAS adapted elements, as specified in the ERAS society colon and rectal guidelines ERAS patients' guideline compliance will be categorised into quartiles. The sample will be divided into four quartiles in dependence on the median and the intercuartilic range of the registered ERP compliance. Summary statistics with post hoc Bonferroni corrections will be used to assess possible dose–response dependence in a percentage of patients with postoperative complications and LOS.

The data set will be analyzed using the percentage of patients with postoperative complications and LOS the main and secondary outcome variables. The influence of the following factors will be assessed: sex, age, ASA status, BMI, nutrition, frailty and prehabilitation variables (when recorded) preoperative haemoglobin, comorbidity, including hypertension, diabetes mellitus, coronary arterial disease, chronic obstructive pulmonary disease, and chronic renal disease; surgical approach (open, laparoscopic), duration of surgery, intraoperative fluid administration; and individual components of the ERAS protocol. Univariate analysis will be initially undertaken to assess the relationship between each factor and the outcome variables. Comparisons will be made using the $\chi 2$ test for all categorical variables and the t test and Kruskall-Wallis test will be used to evaluate differences between continuous normally and non-normally distributed variables, respectively. Owing to its non-normal distribution, LOS was analyzed by log-normal transformation and independent t tests with back exponentiation. Multivariate analysis, using binary logistic regression for development of complications and linear regression of log transformed length of LOS, will be then performed for all variables in the univariate analysis with a significant or near-significant difference ($P < 0.1$). $P < 0.05$ will be considered statistically significant. Differences in LOS between the ERAS compliance groups will be also analyzed using Kaplan–Meier curves and log-rank tests as LOS was censored if the patient will decease.

5.3.4 Secondary analyses

5.3.4.1 Postoperative mortality

The number and percentage of deaths within 30 days of surgery will be reported for each surgical category A logistic regression model with mortality as an outcome will be developed. The variable selection procedure will follow that of the primary analysis.

The results will be reported as odds ratios with 95% confidence intervals and associated p-values.

5.3.4.2 All complications

The 30-day in-hospital complications that will be recorded in the e-CRF are: infectious complications, cardiovascular complications and other types of complications. Each complication will be graded as mild, moderate or severe. The overall incidence of each type and severity of complication and associated mortality rate will be reported. Association between hospital mortality, complications and mortality after major complications will be analysed according to the method previously described by Ghaferi and colleagues. For this analysis, hospitals will be ranked anonymously according to their risk adjusted mortality rate and divided into five quintiles. For hospitals in each quintile, the incidence of overall and major complications and the rate of death among patients with major complications will be compared and reported.

5.3.4.3 Postoperative hospital stay

The median hospital length of stay (LOS) following the start of surgery, overall, by survival status and by complication status will be reported. Post-operative LOS is the duration in days from the date of the end of surgery to the date of discharge from hospital.

5.3.5 Nation Specific analysis

Data will be collected all countries. The number of participating sites and total number of patients for each country will be reported. Number and percentage of patients experiencing mortality and surgical complications within 30 days of surgery will be reported for each region. This will help to provide an understanding of post-surgical care in different European countries. Post-operative complications and mortality will be documented for each region, but will not be published since the multivariable regression used in the primary analysis will adjust for country-level differences.

5.3.6 Handling of missing data

5.3.6.1 Data missing from database

A thorough approach will be undertaken by investigators to ensure completeness of data collection and data uploading. However, if data are still missing, then the following data handling technique will be used. If data are missing completely at random (MCAR), then case-wise deletion will be used to exclude the subjects from the analysis. Little's test will be used to investigate the patterns of the missing data.15 It tests whether data is MCAR or missing at random (MAR). If ≤5% of data is missing at random, then a complete case analysis will be conducted by excluding patients with missing data. If ≥5% of data is missing at random, then multiple imputation will be used. Multiple imputation substitutes a predicted value on the basis of other variables that are available for each subject. If data for any particular site are completely missing, then the site will be excluded from the analysis.

5.3.6.2 Sensitivity Analysis

A sensitivity approach will be taken if some data seem unrealistic. The primary analysis will be repeated excluding these patients. If relevant outcome data are missing, such as complications, the primary analysis will be repeated once, assuming that all patients with missing outcome data had no complications. The analysis will then be repeated again with the opposite outcome. This will provide an understanding of how the findings may be affected if the data were complete.

6. FUNDING AND INSURANCE

The EuroPOWER will be funded by RedGERM (Spain).

No commercial funding for conducting this study is expected.

7. DISSEMINATION OF RESEARCH FINDINGS

Results from this study will be presented in a peer-reviewed journal. Authorship will follow international guidelines (See Appendix IV).

8. EUROPOWER COMMITTEES

Trial management group

Day-to-day trial management will be coordinated by a trial management group consisting of the Chief investigator, his/her support staff and members of the RedGERM.

Trial Steering Committee

The trial Steering Committee will oversee the trial and will consist of several independent clinicians and trialists, lay representation, co-investigators, and an independent Chair. Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- Approving the final trial protocol
- Major decisions such as need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMEC
- Informing and advising on all aspects of the trial

Data monitoring and ethics committee

The Data Monitoring and Ethics Committee (DMEC) is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The committee will agree conduct and remit, which will include the early termination process. During the period of recruitment into the trial the DMEC will monitor safety data and routinely meet to assess safety analyses. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by reviewing adverse events.

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APPENDIX I. DEFINITION OF POSTOPERATIVE COMPLICATIONS

Pre-defined mild-moderate-severe postoperative complications. This includes complications that occurred before hospital discharge and those that happened after discharge and required ambulatory or in-hospital care. Postoperative complications are defined according standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine (EPCO)(13).

- **Acute Kidney Injury[8]**

Severity grading:

- *Mild:* Serum creatinine Increase of 1.5-1.9 times baseline value within 7 days or ≥0.3mg/dL (30 µmol/L) within 48 hours. Urine output ≤0.5ml/kg/h for 6-12 hours
- *Moderate:* Serum creatinine Increase of 2.0-2.9 times baseline value within 7 days. Urine output ≤0.5 ml/kg/h for 12 hours.
- *Severe:* Serum creatinine Increase of 3.0 times baseline within 7 days or increase in serum creatinine to ≥4.0 mg/dL (≥350 µmol/L) with an acute rise of >0.5 mg/dL (>50 µmol/L) or initiation of renal replacement therapy. Urine output ≤0.3 ml/kg/h for 24 hours or Anuria for 12 hours.

- **Acute Respiratory Distress Syndrome (ARDS)**

Respiratory failure, or new or worsening respiratory symptoms, commencing within one week of surgery; and a chest radiograph or computed tomography scan which demonstrates bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; and respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present.

Severity grading:

- *Mild:* PaO_2:FiO_2 between 200 and 300 mmHg with PEEP or CPAP ≥5 cmH_2O
- *Moderate*: PaO_2:FiO_2 between 100 and 200 mmHg with PEEP ≥5 cmH_2O
- *Severe*: PaO_2:FiO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

- **Anastomotic leak**

Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure. The escape of luminal contents from the site

of the anastomosis into an adjacent localised area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a sub-clinical leak.

Severity grading* *(This severity rating is valid for all complications that are marked with an asterisk)*

- *Mild:* Results in only temporary harm and would not usually require specific clinical treatment.
- *Moderate:* More serious complication but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment.
- *Severe*: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.

- **Arrhythmia***

Electrocardiograph (ECG) evidence of cardiac rhythm disturbance.

- **Cardiac arrest**

The cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. ECG changes may corroborate the incidence of cardiac arrest.
Severity grading: None

- **Pulmonary oedema***

Evidence of fluid accumulation in the alveoli due to poor cardiac function.

- **Gastro-intestinal bleeding***

Unambiguous clinical or endoscopic evidence of blood in the gastro-intestinal tract. Upper gastrointestinal bleeding is that originates from the oesophagus, stomach and duodenum. Lower gastro-intestinal bleeding originates from the small bowel and colon.

- **Bloodstream infection***

An infection which is not related to infection at another site and which meets either of the following criteria:

1)Patient has a recognised pathogen cultured from blood cultures which is not related to an infection at another site
2)Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following:

a) Common skin contaminant cultured from two or more blood cultures drawn on separate occasions

b) Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and a physician starts antimicrobial therapy

c) Positive blood antigen test

- **Myocardial infarction***

Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:

- Symptoms of ischaemia
- New or presumed new ST-segment or T-wave ECG changes or new left bundle branch block
- Development of pathological Q-waves on ECG
- Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intra-coronary thrombus at angiography or autopsy

- **Pneumonia***

Chest radiographs with new or progressive and persistent infiltrates, or consolidation, or cavitation, and at least one of the following:

a)Fever (>38°C) with no other recognized cause

b)Leucopaenia (<4,000 white blood cells/mm3) or leucocytosis (>12,000 white blood cells/mm3)

c)For adults >70 years old, altered mental status with no other recognised cause

…and at least two of the following:

- New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
- New onset or worsening cough, or dyspnoea, or tachypnoea
- Râles or bronchial breath sounds
- Worsening gas exchange (hypoxia, increased oxygen or ventilator demand)

- **Post-operative haemorrhage***

Blood loss occurring within 72 hours after the end of surgery which would normally result in transfusion of blood. Gastro-intestinal bleeding is defined above.

- **Pulmonary embolism (PE)***

A new blood clot or thrombus within the pulmonary arterial system.

Guidance: Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D- dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery.

- **Stroke***

Embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

- **Surgical site infection (superficial)***

Infection involving only superficial surgical incision which meets the following criteria:

1)Infection occurs within 30 days after surgery and

2)Involves only skin and sub-cutaneous tissues of the incision and

3)The patient has at least one of the following:

a) Purulent drainage from the superficial incision

b) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision and at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, or superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture- negative finding does not meet this criterion.

c) Diagnosis of a incisional surgical site infection by a surgeon or attending physician

- **Surgical site infection (deep)***

An infection which involves both superficial and deep parts of surgical incision and meets the following criteria:

1) Infection occurs within 30 days after surgery if no surgical implant is left in place or one year if an implant is in place and

2) The infection appears to be related to the surgical procedure and involves deep soft tissues of the incision (e.g. fascial and muscle layers) and

3) The patient has at least one of the following:

a) Purulent drainage from the deep incision but not from the organ/space component of the surgical site

b) A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or no cultures were taken whilst the patient has at least one of the following signs or symptoms of infection: fever (>38°C) or localized pain or tenderness. A culture-negative finding does not meet this criterion.

c) An abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathologic or radiologic examination

d) Diagnosis of a deep incisional surgical site infection by a surgeon or attending physician

- **Surgical site infection (organ/space)***

An infection which involves any part of the body excluding the fascia or muscle layers and meets the following criteria:

1) Infection occurs within 30 days after surgery and

2) The infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and

3) The patient has at least one of the following:

a) Purulent drainage from a drain that is placed through a stab wound into the organ/space

b) Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space

c) An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination

d) Diagnosis of an organ/space surgical site infection by a surgeon or attending physician

- **Urinary tract infection***

An infection associated with at least one of the following signs or symptoms which should be identified within a 24 hour period: Fever (>38 °C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other

recognised cause and a positive urine culture of ≥105 colony forming units/mL with no more than two species of microorganisms

- **Paralytic ileus***

Failure to tolerate solid food or defecate for three or more days after surgery.

- **Delirium**

Delirium may be identified using the Intensive Care Delirium Screening Checklist.
Patients are first evaluated for an altered level of consciousness. Those with a response to mild or moderate stimulation, an exaggerated response to stimulation or normal wakefulness are evaluated fully. Patients receive one point for each of the following criteria: inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance or symptom fluctuation. Severity grading: Integrated into definition

APPENDIX II. ERAS ITEMS

1. Data on prior income, education and counselling[11-12]

It will be considered a completed item if dedicated advice and preoperative information by a surgeon or an anesthetist about the process is given to the patient.

2. Preoperative Optimization

It will be considered a completed item if the smoker patient stops smoking 4 weeks before the intervention; and/or the alcohol abuser patient ceases the consumption of alcohol 4 weeks before surgery. In those cases in which patients do not smoke or drink alcohol, this component will not be taken into account.

3. Mechanical Bowel Preparation

It will be considered a completed if no mechanical bowel preparation is used.

The administration of oral antibiotics will also be considered in cases where mechanical bowel preparation is performed.

4. Preoperative fasting

It will be considered a completed item if preoperative fasting is limited to two hours for clear liquids (water, coffee, juice without pulp); and 6 hours for solids.

5. Preoperative Administration of carbohydrate drinks

It will be considered a completed component if a carbohydrate drink is administered preoperatively (400 cc of 12.5% maltrodextrinae carbohydrate drink 2-3 hours before surgery).

6. Avoid sedative drugs before intervention

It will be considered a completed item if medium or long-acting sedatives are not administered. The administration of short-acting or ultra-short-acting sedatives to perform loco-regional anaesthesia or spinal or epidural anaesthesia is permitted. The following are considered as short-acting or ultrashort-acting sedatives: Lorazepam, Midazolam, Methohexital, Dexmedetomidine, Ketamine.

7. Thromboprophylaxis

It will be considered a completed item if patients receive compression stockings, intermittent pneumatic compression stockings, and receive antithrombotic prophylaxis

with low molecular weight heparin in the postoperative period, which should be extended to 28 days after surgery.

8. Antibiotic prophylaxis

It will be considered a completed item if routine prophylaxis with intravenous antibiotics is given 30 to 60 minutes before starting surgery. Additional doses should be administered for prolonged procedures in accordance with the half-life of the drug used. The antibiotic is not docketed.

9. Prevention of postoperative nausea and vomiting (PONV)

It will be considered a completed item if patients receive PONV prophylaxis according to their risk based on a multimodal approach.

10. Laparoscopy or minimal incisions

It will be considered a completed item if laparoscopy is performed. Although this item will be regarded as positive in cases where despite open approach, small incisions are used.

11. Nasogastric intubation

It will be considered a completed item if nasogastric intubation is not used, neither intraoperatively nor postoperatively.

12. Prevention of intraoperative hypothermia

It will be considered a completed item if fluid heaters and / or thermal blanket during surgery are used.

13. Perioperative management of fluids.

It will be considered a completed item if restrictive fluid therapy (defined as maintenance fluid therapy <2 ml / kg / h) along with goal-directed hemodynamic therapy that includes stroke volume, stroke volume variation or cardiac output as a goal are used.

14. Drains

It will be considered a completed item if drains in abdominal cavity are avoided (pelvic drain is permitted in rectal surgery with low anastomosis).

15. Urinary catheter

It will be considered a completed item if the urinary catheterisation is removed 24-48 hours after surgery.

16. Prevention of Postoperative ileus

It will be considered a completed item if intraoperative fluid balance is less than 2000cc. The intraoperative balance will be calculated according to: Total intraoperative fluid administered (Crystalloid + colloid + blood products) - (estimated blood loss - diuresis - insensitive losses). Insensitive losses will be considered as 1.5 ml / kg / h in all cases. This calculation, and the fulfilment of this point, will be carried out based on eCRF variables (weight, total intraoperative fluid administered, diuresis, estimated blood loss).

17. Postoperative Nutrition

It will be considered a completed item if patients with preoperative malnutrition (defined as weight loss> 10% in 6 months or BMI <18) receive nutritional supplementation. The fulfilment of this point, will be carried out based on eCRD variables. In those cases in which there were no preoperative nutritional alterations, this component will not be evaluated

18. Postoperative glycaemic control

It will be considered a completed item if that patients receive glycaemic control within 24 hours from the end of surgery, with a blood glucose target of <180mg / dl.

20. Early mobilization

It will be considered a completed item when the patient moves at least into an armchair in the first 12 hours after surgery (alone or helped by others).

21. Early Oral Intake

It will be considered a completed item if there is oral intake in the first 6 hours after surgery.

22. Strategies to spare opioid consumption

It will be considered a completed item if more than two drugs and/or analgesic strategies are used to spare opioid consumption.

APPENDIX III: FRAILTY. ROCKWOOD SCORE

Clinical Frailty Scale

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

APPENDIX IV: PREHABILITATION VARIABLES DEFINITIONS FOR EUROPOWER

Cardiopulmonary exercise testing (CPET)[14, 15]

Provides a global assessment of the integrated response of the pulmonary, cardio-vascular, metabolic, and haematological systems. Key is the integration of respired gas analysis (O2 and CO2 concentrations) with ventilatory flow measurements, thereby enabling calculation of O2 uptake (V_ O2) and CO2 output (V_ CO2), typically on a breath-by-breath basis, under conditions of progressively increasing physiological stress imposed by a defined profile of external work rate (WR).

Cardiopulmonary exercise testing variables registered in EuroPOWER

$\dot{V}O_2peak$	Absolute ml/min	ml/kg/min	% of predicted
Anaerobic threshold	Absolute ml/min	ml/kg/min	

V_ O2peak

V_ O2peak is a metabolic rate defined as the highest oxygen uptake (V_ O2) attained on a rapid incremental test at end-exercise.

As such, it is reflective of the patient's 'best effort' but it may not reflect what was potentially achievable for that patient (i.e. it is not necessarily a physiologically maximal end-point). The highest V_ O2 that could be attained by a patient is defined as the maximum V_ O2 'the oxygen uptake during an exercise intensity at which actual oxygen uptake reaches a maximum beyond which no increase in effort can raise it' (a physiological end point). It is a metabolic rate defined as the highest V_ O2 attained on a rapid incremental test at end-exercise.

Anaerobic Threshold (AT)

The AT provides an index of submaximal, sustainable exercise capacity, and if present cannot be volitionally influenced by the patient. Importantly, it predicts postoperative complications and mortality in a wide range of surgical populations with more precision than other CPET variables. The AT is a metabolic rate defined as the V_ O2 above which arterial [lactate] first begins to increase systematically during incremental exercise.

The AT is a metabolic rate expressed in ml kg^1 min^1 or ml min^1. It is defined as the V_ O2 above which arterial (lactate) first begins to increase systematically during incremental exercise reflecting increased glycolysis

Functional Walk Tests

Simple walk tests utilize an activity that patients are familiar with, are inexpensive, require little equipment and are easy to administer. They can be used to assess functional capacity and provide an alternative when the more comprehensive gold standard CPET is not available. The most widely employed and investigated of these are the 6-minute walk test (6MWT) and the incremental shuttle walk test (ISWT).

6MWT

Measures how far subjects can walk along a flat corridor, turning around cones at each end, at normal pace, in 6 minutes. Median distances are 500–600 m in healthy subjects. Units: metres

Prehabilitation

A group of interventions, integrated into the clinical pathway before a surgical procedure and aimed at both reducing imminent patient risk and promoting lasting beneficial effects on perioperative recovery and outcome.

Exercise programmes for surgery

When prescribing any exercise training programme, consideration should be given to the frequency, intensity, time, type, volume and progression (FITT-VP) principles.

- Frequency

Describes how many times per day, per week or per month exercise training takes place. For the EuroPOWER study: How many times/week.

- Intensity

Describes, in relative or absolute terms, the effort associated with the exercise.
“Moderate intensity” is used to describe exercise performed at either 46 to <64 % of VO2max, 64 to <76 % HRmax, or 12 to 13 on Borg’s 6 to 20 RPE scale.
“Vigorous intensity” defines exercise completed at 64 to <91 % of VO2max, 76 to <96 % of HRmax, or an RPE of 14 to 17.

“Maximal” exercise performed at ≥91 % of VO2max, ≥96 % of HRmax, or at an RPE ≥18. In the EuroPOWER study High Intensity trainining is considered as a maximal exercise.

- Time

Describes the duration of the exercise session, in terms of hours.

- Type

Refers to the mode of exercise being undertaken (e.g. walking, running, cycling, dancing and resistance training).

- Volume

Is the product of the frequency, intensity and time principles of exercise and therefore describes the total amount of exercise performed.
(Self calculated in EuroPOWER CRF)

Anxiety reduction

Defined as: patients scheduled for a visit with a trained psychologist focusing on providing anxiety reduction techniques such as relaxation exercises and breathing exercises.

Abbreviations

6MWT: 6-minute walk test
CPET: cardiopulmonary exercise test
ISWT: incremental shuttle walk test
FITT-VP: frequency, intensity, time, type, volume and progression
HIT: high-intensity interval training
HRmax: maximal heart rate
RPE: ratings of perceived exertion
VO2max: maximal oxygen uptake

APPENDIX V: CONFIDENTIAL PATIENT LOG SHEET

CONFIDENTIAL Patient log sheet				
Study	**EuroPOWER**			
Local Principal Investigator's Name :		**Centre / Institution Name :**		**Centre Number :**
Patient study subject ID	**Patient Name**	**Patient Date of Discharge**	**30 days Follow-up**	
			Planned date	**Actual date**

APPENDIX VI: AUTHORSHIP POLICY

This publication charter is based on recommendations of the International Committee of Medical Editors (http://www.icmje.org/icmje-recommendations.pdf).

1. Group Authorship

The principal EuroPOWER paper will be published on behalf of all contributors. The author will be listed as 'The EuroPOWER Study Group' and a footnote will carry the names and affiliations of contributors. Individual contributors will be included in this list if they registered as local investigators on the EuroPOWER data entry website and have a certificate of participation, or they are a member of the core study management team. Where an author takes responsibility for preparing a manuscript on behalf of the study group, this would be listed as 'John Smith and the EuroPOWER Study Group'. Where an author takes responsibility for preparing the manuscript and for the content of the paper, the study group would be acknowledged and the author listed as 'John Smith for the EuroPOWER Study Group.'

2. Individual Authorship

Reports of sub-studies using EuroPOWER data may qualify for individual authorship. A contributor claiming authorship should meet the following criteria:

- Substantial contribution to the work: conception or design or data collection or analysis or data interpretation AND
- Contributed to drafting or revising the manuscript AND
- Approved the final version of the manuscript AND
- Agreement to be accountable for all aspects of the work and agree that all questions regarding accuracy and integrity of the data are investigated and resolved.

Authors should be listed on any secondary study analysis plans that are submitted for review by the steering committee.

3. Acknowledgements

The trial funders must be acknowledged in all publications.

4. Arbitration

In the event of a dispute, the steering committee will make a ruling. In the event disagreement within the steering committee, the Chief Investigator will be the final arbiter.

5. Standard Operating Procedure – publications

Any investigator wishing to publish any data derived from EuroPOWER, including national or local data should follow the following procedure.

6. Secondary study proposal

The EuroPOWER trial steering committee encourages high quality secondary analyses of the trial data and supports the wider principle of data sharing. EuroPOWER investigators will be given priority to lead secondary analyses. Participation and authorship opportunities will be based on contribution to the primary study. No publications are allowed before the primary publication, however, if the primary manuscript has not been accepted for publication within twelve months following the completion or termination of the clinical trial at all sites, a co-ordinating investigator may publish clinical methods and data from their own site. Where necessary, a prior written agreement will set out the terms of such collaborations. Investigators should submit a secondary study proposal for review by the steering committee. The steering committee will consider the scientific validity and the possible effect on the anonymity of participating centres prior to approval of secondary study proposals. 'Cleaned' data from the international dataset will only be released after the statistical analysis plan for the secondary study has been approved. Any data sharing requests/proposals must be approved by the Data Sharing Committee at the coordinating centre and will require a Data Sharing Agreement. Any analysis incorporating EuroPOWER data from one or more study sites will be considered a secondary analysis and subject to these rules

7. Confidentiality and anonymity

The identity of study participants must be protected. Before data is released, patient-identifying information will be removed. However, it remains the responsibility of the authors to ensure that individual patients cannot be identified as a result of publication.

8. Responsibilities of the lead author

• Writing the statistical analysis plan and submitting this to the steering committee for peer review

• Co-ordinating the data analysis

• Co-ordinating the writing of the paper

• Circulating drafts

• Ensuring that all authors listed meet the authorship criteria

• Ensuring quality assurance of the data and analysis

• Submitting the manuscript for internal peer review by the EuroPOWER trial steering committee

• Informing the EuroPOWER study group when the paper has been submitted to a journal and when it has been approved for publication.

9. Internal peer-review

Publications using data derived from EuroPOWER have the potential to impact the reputation of the study. Before any manuscript is submitted to a journal it must be reviewed and approved by the trial steering committee or nominated deputies. This process will occur in a timely manner. If a manuscript is rejected, constructive feedback will be given to help the authors improve the paper.

10. Funders Peer Review

The trial funders must be afforded the opportunity to review any proposed publication in accordance with the relevant contracts.

11. Publications without approval

The EuroPOWER Study Group is supportive of access to EuroPOWER data by local contributors. The EuroPOWER trial steering committee is responsible for protecting the reputation of the EuroPOWER Study Group and ensuring that publications derived from EuroPOWER are of high quality, accurate and representative of the data collected. If data derived from EuroPOWER is published without internal peer-review and approval outlined above, the EuroPOWER trial steering committee reserves the right to contact the publisher to report a breach of the publication charter. We expect that this would result in either the retraction of the paper or refusal to publish the work.

Submission of a secondary study proposal

Secondary study proposals and data sharing requests should be submitted to the data management team

12. References

Defining the role of authors and contributors. International Committee of Medical Journal Editors.

http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining- the-role-of-authors-and-contributors.htm

APPENDIX VII: WMA DECLARATION OF HELSINKI - ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and individuals with the

appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in

which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's

decision to withdraw from the study must never adversely affect the patient- physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.