PROTOCOL NAME - Procalcitonin for Early Diagnosis of Anastomotic Leakage in Esophagogastric Surgery (PEDALES study)

PROTOCOL IDENTIFYING NUMBER – v2.2016

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Glossary of abbreviations

IEC	Indipendent ethics committee
ICH/ GCP	International Conference on Harmonisation (ICH) /Good Clinical Practice standard
MoH	Ministry of Health

INDEX

1 Summary

Title	Procalcitonin for Early Diagnosis of Anastomotic Leakage in Esophagogastric Surgery (PEDALES study)
Study coordinator	Dr. Ferdinando Carlo Maria Cananzi
Protocol identifying number	v1.2016
Protocol version date	26.05.2016
Background and rationale	Anastomotic leakage (AL) represents one of the most serious complications after esophageal and gastric surgery for cancer with a dramatic impact on post-operative course, functional and oncologic outcomes. AL has been reported to occur in 1% to 15% of patients underwent gastrectomy and in up to 35% of patients who underwent esophagectomy. A prompt diagnosis and treatment of AL may increase both short- and long-term outcomes and it may reduce the hospital stay, readmission rate and medical costs. An accurate and early diagnostic marker of AL could drive the decision-making process of the surgeon finally improving the management of patient. Procalcitonin (ProCT) is the precursor for the hormone calcitonin, which is mainly produced by the neuroendocrine cells in the thyroid gland and in the lungs. It is a 116 amino-acids protein which have been found to circulate at very low concentrations in serum of healthy subjects (less than 10 pg·mL-1). However, in sepsis, systemic infection and severe inflammations such as pancreatitis, appendicitis, burns, heat stroke, multitrauma and extensive surgery the serum levels of ProCT usually increase markedly, attaining values of tens, to hundreds, to thousands-fold that of normal levels. Interestingly, ProCT has been reported as potential early predictive marker for the clinical outcome of septic complications after abdominal surgery.
Population and patient selection criteria	Patients older than 18 years scheduled for esophageal (group A) and gastric (group B) resection with curative intent for cancer with both open and minimally invasive approach. Exclusion criteria: patients undergoing surgery without an anastomosis being performed; ongoing infection at surgery; emergency procedures; ASA score > 3; other synchronous cancer. Expected sample size: 500 patients (approximately 200 patients in group A and 300 patients in group B).
Study design and study duration	This is a prospective multicentric observational study including all patients undergoing esophageal and gastric surgery for cancer in elective setting. For all included patients, demographic, clinic, surgical and pathologic data, postoperative complications (within 30 days after surgery or during the same hospitalization) and their

management, length of hospital stay and readmission are recorded. In all cases white blood count, ProCT and C-reactive protein (CRP) levels are measured before surgery and during the first seven postoperative day (POD).
Expected study duration: 2-3 years.

Objectives

The primary aim of this study is to define whether ProCT might be an early and reliable predictor of AL after oesophageal and gastric resection for cancer. In addition, a comparison of the use of C-reactive protein (CRP) and ProCT for early diagnosis of post-operative complications (both surgical and general complications) will be performed.

Statistical methods, data analysis

From literature we can expect around 10% of AL, so the expected sample size is at least 500 patients (approximately 200 patients in group A and 300 patients in group B). However, giving the high variability of AL reported in Literature, a preliminary analysis will be performed after 1 year in order to evaluate the actual AL rate and to better define the sample size, and consequently the accrual time.

Ethical considerations

Blood tests are commonly performed during the post-operative stay of esophago-gastric surgery. Therefore no additional risks are expected for patients included in the study.

Study time table

Project starting date: 1 month after Ethical Committee approval
Project completion of data collection: 31.05.2019
Project data analysis: 30.06.2019
Project presentation of scientific report: 31.07.2019

2 Background and introduction

Overall, esophagogastric cancers have a poor prognosis, even in patients with localized disease. Treatment of locoregional disease is generally by surgical resection with or without neoadjuvant or adjuvant chemo- or radiotherapy. Despite recent improvements associated with centralization of services, perioperative optimization, surgical technique and postoperative care, esophagogastric surgery remains one of the most demanding surgeries and is associated with major morbidity which may impact long-term quality of life and survival.

Anastomotic leakage (AL) represents one of the most serious complications after esophageal and gastric surgery for cancer with a dramatic impact on post-operative course, functional and oncologic outcomes [1]. AL has been reported to occur in 1% to 15% of patients underwent gastrectomy and in up to 35% of patients underwent esophagectomy. In Literature, the median time to AL is 7 days after surgery [2-9].

Biomarkers such as C-reactive protein (CRP) and interleukin 6 (IL-6) have been considered as an interesting tool to early diagnose postoperative complications in other surgical fields [10].

Procalcitonin (ProCT) is the precursor for the hormone calcitonin, which is mainly produced by the neuroendocrine cells in the thyroid gland and in the lungs. It is a 116 amino-acids protein which have been found to circulate at very low concentrations in serum of healthy subjects (less than 10 pg·mL-1). However, in sepsis, systemic infection and severe inflammations such as pancreatitis, appendicitis, burns, heat stroke, multitrauma and extensive surgery the serum levels of ProCT usually increase markedly, attaining values of tens, to hundreds, to thousands-fold that of normal levels. Interestingly, ProCT has been reported as potential early predictive marker for the clinical outcome of septic complications after abdominal surgery [11-13].

In 2015, a small study published by Hoeboer and colleagues suggested that elevated ProCT levels may timely precede combined surgical/infectious complications mainly associated with anastomotic leakage after esophagectomy [14]. ProCT has also revealed as early predictor of septic complications after sleeve gastrectomy [15]. In addition, a recent large prospective study has demonstrated that ProCT may be a helpful marker of anastomotic dehiscence after colorectal surgery with a good negative predictive value [16].

3 Rationale of the study

A prompt diagnosis and treatment of AL may increase both short- and long-term outcomes and it may reduce the hospital stay, readmission rate and medical costs. An accurate and early diagnostic marker of AL could drive the decision-making process of the surgeon finally improving the management of patient. ProCT could be an easy-to-use and affordable marker to early detect AL and others surgical post-operative complications. Moreover, this biomarker might be evaluated as criteria of discharge aiming to reduce the length of stay after esophagogastric surgery.

4 Objectives of the study

4.1 General objectives

The primary aim of this study is to define whether ProCT might be an early and reliable predictor of AL after esophageal and gastric surgery for cancer.

In addition, a comparison of the use of C-reactive protein (CRP) and ProCT for early diagnosis of post-operative complications (both surgical and non-surgical) will be performed.

4.2 End-points

4.2.1 Primary endpoint

Discrimination achieved by CRP or ProCT will be compared by area under the ROC curves (ROC-AUC).

4.2.2 Secondary endpoint

Sensitivity, Specificity, Positive and Negative Predictive Values (PPV and NPV), positive and negative Likelihood Ratio (LR+ and LR-) will also be computed.

4.2.3 Explorative endpoint

In order to find out the optimal cut-off for diagnostic tests, the decision level plot will be created, where the X and Y variables will be respectively CRP (or ProCT) concentration and Youden index (sensitivity + specificity – 1). The best cut-off will be chosen according to both clinical and statistical criteria.

5 Patient selection criteria

5.1 Inclusion criteria

- All patients older than 18 years scheduled for esophageal and/or gastric resection for cancer with both open and minimally invasive approach in elective setting.
- Full availability of laboratory data
- Ability to give informed consent

5.2 Exclusion criteria

- Surgery without an anastomosis being performed
- Emergency procedures
- ASA score > 3
- Other synchronous tumor
- Ongoing infection at surgery (bacterial, viral, parasitic)
- Ongoing noninfectious systemic inflammations at surgery (inhalational injury; pulmonary aspiration; pancreatitis; mesenteric infarction; heat stroke)
- Trauma (mechanical injury; burns)

6 Study Design

6.1 General design

This is a prospective multicenter observational study.

The study involve all patients undergoing surgical resection for esophageal (group A) or gastric (group B) cancer.

For all patients the following clinic-pathologic data will be recorded: age, sex, gender, performance status, comorbidities according to the Charlson Comorbidity Index [17], ASA score, preoperative oncologic treatment, type of operation, surgical approach (open or minimally invasive), extent of lymphadenectomy, tumor location, tumor stage, postoperative complications (within 30 days after surgery or during the same hospitalization) and their management classified according to the Dindo-Clavien classification and to the Comprehensive Complication Index [18,19], length of post-

operative hospital stay and 30-day unplanned readmission. As regards laboratory data, in all cases white blood count, ProCT and CRP levels will be recorded as shown in the study scheme.

The expected duration of the study is 2-3 years depending on the actual patients accrual and the complications rate.

7 Statistical considerations

7.1 Sample size

From literature we can expect around 10% of AL, so the expected sample size is at least 500 patients (approximately 200 patients in group A and 300 patients in group B). However, giving the high variability of AL reported in Literature, a preliminary analysis will be performed after 1 year in order to evaluate the actual AL rate and to better define the sample size, and consequently the accrual time.

Esophageal cancer

A sample of 200 patients (20 with AL and 180 without) achieve 79.9% power to detect a difference of 0.175 between a diagnostic test (CRP) with an area under the ROC curve (AUC) of 0.675 and another diagnostic test (ProCT) with an AUC of 0.85 using a two-sided z-test at a significance level of 0.0500. The data are continuous responses. The AUC is computed between false positive rates of 0.000 and 1.000. The ratio of the standard deviation of the responses in the negative group to the standard deviation of the responses in the positive group for diagnostic test 1 is 1 and for diagnostic test 2 is 1. The correlation between the two diagnostic tests is assumed to be 0.600 for the positive group and 0.600 for the negative group.

Gastric cancer

A sample of 300 patients (30 with AL and 270 without) achieve 83.3% power to detect a difference of 0.15 between a diagnostic test (CRP) with an area under the ROC curve (AUC) of 0.675 and another diagnostic test (ProCT) with an AUC of 0.825 using a two-sided z-test at a significance level of 0.0500. The data are continuous responses. The AUC is computed between false positive rates of 0.000 and 1.000. The ratio of the standard deviation of the responses in the negative group to the standard deviation of the responses in the positive group for diagnostic test 1 is 1 and for diagnostic test 2 is 1. The correlation between the two diagnostic tests is assumed to be 0.600 for the positive group and 0.600 for the negative group.

7.2 Analysis

All values will be recorded as absolute values and percentages, means and standard deviation, medians and range, as appropriate. Wilcoxon test will be used to compare biomarkers' distribution between different groups. Receiver operating characteristic (ROC) curves and the corresponding area under curve (AUC) will be used in order to evaluate biomarkers as predictors of AL and post-operative complications. A 95% confidence interval (95% CI) will be employed to calculate specificity (Sp), sensitivity (Se), positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio positive and negative (LR+ and LR-).

8 Forms and procedures for collecting data and data managing

Data elements will be collected in a excel file, equal for all the centers. All patients will be identified with a unique code

9 Ethical considerations

9.1 Patient protection

The study will be conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments).

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice

The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

9.2 Subject identification – Personal Data protection

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and will be included on all case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must will accompany the informed consent administered to the patient.

9.3 Informed consent

All patients will be informed of the aims of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. The form of the patient informed consent statement is given as an appendix to this protocol.

10 Conflict of Interest

Investigator and research staff members declare they have no conflict of interest with this study.

11 Data ownership

The study coordinator is the owner of the data resulting therefrom. All centers and investigators participating are invited not to disseminate information or data without the study coordinator's prior express consent.

12 Publication Policy

After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator for coordination and homogeneity purposes.

13 Study time table

Project starting date: 1 month after Ethical Committee approval

Project completion of data collection: 31.05.2019

Project data analysis: 30.06.2019

Project presentation of scientific report: 31.07.2019

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ANNEX A - CRF

Age at the time of surgery: _____ (years)

Sex: M F

ECOG Performance status: _____ (grade)

Charlson Comorbidity Index (see table below): _____ (score)

American Society of Anaesthesiologists' (ASA) classification: _____ (grade)

Pre-operative chemo- and/or radiotherapy: Yes No

Tumor location: Esophagus Esophagogastric junction Stomach

Type of surgery: _____ (brief description of the operation)

Histology: squamous cell carcinoma adenocarcinoma (diffuse intestinal mixed)

Grading: G1 G2 G3 G4

TNM/UICC pathologic stage (8th edition): I II III IV

30-day morbidity

- brief description / day of occurrence: _____ / _____
- Clavien-Dindo classification: I II IIIa IIIb IV V
- Comprehensive Complication Index[a]: _____ (score)

Length of post-operative stay: _____ (days)

30-day unplanned readmission: Yes No

Laboratory data (as reported in study scheme)

a: http://www.assessurgery.com/calculator_single/

Table. Charlson risk index

Condition	Assigned weights for diseases
Myocardial infarct	1
Heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6
Weighted comorbidity classes	
Low	0 points
Medium	1 to 2 points
High	3 to 4 points
Very high	≥5 points

ANNEX B - Declaration of Helsinki

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

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 minimizes 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 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 minimize 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 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 authorized 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 authorized 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 authorized 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 authorized 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 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 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.

ANNEX C - Informed consent

Studio clinico

"*Procalcitonina per l'identificazione precoce delle deiscenze anastomotiche in chirurgia esofagogastrica*"

Foglio informativo per il paziente

Egregio Signor/Gentile Signora _____

Lei è affetto da neoplasia esofago-gastrica.
Le neoplasie esofago-gastriche rappresentano una patologia complessa il cui trattamento negli stadi loco-regionali prevede, in genere, la resezione chirurgica eventualmente associata a trattamenti complementari chemio e/o radioterapici peri-operatori. Nonostante i significativi miglioramenti in termini di tecnica chirurgica, assistenza peri-operatoria, centralizzazione dei servizi in Istituti specializzati, la chirurgia esofago-gastrica resta una chirurgia articolata associata, in alcuni casi, allo sviluppo di complicanze post-operatorie. La deiscenza anastomotica, in particolare, costituisce una delle principali problematiche dopo questo tipo di chirurgia che può influenzare significativamente il decorso post-operatorio e un suo tempestivo riconoscimento può agevolarne sensibilmente la gestione. La Procalcitonina è un precursore ormonale normalmente presente nel sangue d'individui sani a concentrazioni bassissime. Un suo innalzamento è stato rilevato in diverse condizioni cliniche tra cui infezioni severe, traumi e gravi ustioni. Alcuni studi hanno documentato che la Procalcitonina può essere un marcatore rapido e precoce di complicanze dopo chirurgia addominale. Il dosaggio della Procalcitonina viene effettuato su campioni ematici ottenuti da un normale prelievo di sangue. Scopo di questo studio è verificare l'utilità del dosaggio della Procalcitonina nel precoce riconoscimento della deiscenza anastomotica. Lo studio prevede, quindi, il dosaggio di tale sostanza nei giorni successivi all'intervento nel contesto dei routinari accertamenti postoperatori che verranno effettuati. Non vi saranno variazioni rispetto al routinario trattamento previsto per l'intervento cui sarà sottoposto.

Privacy
Tutti i Suoi dati personali saranno trattati in conformità alla legge 196/03 in materia di privacy. Il suo consenso per il trattamento dei Suoi dati relativi allo studio in oggetto verrà raccolto a mezzo di idonea informativa.

Diritti del soggetto
La Sua partecipazione a questo studio è volontaria. Non dovrà partecipare a questo studio se non lo desidera. Ha il diritto di cambiare idea e di lasciare in qualunque momento lo studio senza dare alcuna motivazione. Se desidera lasciare lo studio, basterà semplicemente dirlo a uno dei membri del gruppo di ricerca. La Sua decisione di non partecipare non avrà alcuna conseguenza sulla qualità delle cure che le verranno successivamente prestate. Tutte le nuove informazioni concernenti questo studio che saranno disponibili dopo che lo studio sarà avviato e che potrebbero annullare la Sua disponibilità Le saranno comunicate.
Il medico sperimentatore potrà escluderLa dallo studio senza il Suo consenso se deciderà di non sottoporsi ai test di verifica di eleggibilità o se non seguirà le procedure richieste dallo studio, o se lo studio si rivelasse dannoso per la Sua salute
Se ha domande circa i suoi diritti come soggetto di ricerca, o qualunque domande circa questo studio, potrà rivolgersi al medico responsabile del progetto, il Prof/Dr. _____.
Avrà naturalmente una copia firmata di questo modulo di consenso da conservare.

Studio clinico
"*Procalcitonina per l'identificazione precoce delle deiscenze anastomotiche in chirurgia esofagogastrica*"

Consenso informato

Io sottoscritto/a .....
sono stato esaurientemente informato dalla lettura del Foglio Informativo per il paziente e dal medico ricercatore riguardo allo studio.
Dichiaro inoltre che sono state date risposte esaustive e comprensibili alle domande da me formulate sempre riguardo a tutti i momenti della procedura medica in esame.

Sono conscio del fatto che mi verrà fornito apposito modulo di consenso e l'informativa privacy per la raccolta dei miei dati sensibili relativi allo studio in oggetto.

Io sottoscritto confermo, firmando questo modulo, di essere d'accordo a partecipare a questo studio e di aver ricevuto copia di questo modulo di Consenso Informato

_____ _____

Firma del paziente Data

_____ _____

Firma del medico Data

ANNEX D - Study scheme

Before surgery	Post-operative day									
	0	1	2	3	4	5	6	7	.	30
WBC ProCT CRP	Surgery	WBC ProCT CRP	WBC ProCT CRP	WBC ProCT CRP	WBC ProCT CRP	WBC ProCT CRP	WBC ProCT CRP	WBC ProCT CRP		
Patient registration		Observation period (data collection)								Final evaluation

WBC: white blood cell; ProCT: Procalcitonin; CRP: C-Reactive Protein.