Official title of the trial Preoperative adaptive radiotherapy concurrent with chemotherapy for rectal adenocarcinoma (Adaptive Rectal Cancer Trial 02). Interventional study.
Official title of the trial in more patient-friendly terms Preoperative adaptive radiotherapy concurrent with chemotherapy for rectal adenocarcinoma
Facility where the trial will be conducted At San Raffaele Hospital, you are being asked to participate in a study aimed at improving a radiotherapy technique already widely used in our Radiotherapy Department since 2009 to treat patients suffering from the same disease as you. This technique may be more effective than the one currently used.
Trial Coordinating Center Radiation Therapy Department, San Raffaele Hospital
Registry in which the trial is registered or will be registered (if applicable) and any identification code, if available Identification code _____ Registry: Clinicaltrials.gov
Principal Investigator at the Center Name: Dr. Paolo Passoni Operating Unit: Radiotherapy Service
Sponsor/Promoter Prof. Nadia Di Muzio
Local Ethics Committee responsible **Comitato Etico CET Lombardia 1**

Dear Madam/Sir, The information contained in this information sheet is very detailed. We ask that you agree to participate in the trial ONLY after carefully reading this information sheet and having had a THOROUGH INTERVIEW with a member of the trial team. This INTERVIEW must take the NECESSARY TIME to fully understand the proposed treatment.

A. INTRODUCTION

Dear Madam/Sir,

We are proposing that you participate in the clinical trial, which we will explain below.

You have the right to be informed about the purpose and characteristics of the trial so that you can freely and informedly decide whether to participate.

This document aims to inform you about the nature of the trial, its purpose, and what participation will entail for you, including your rights and responsibilities.

Please read the following carefully. The researchers involved in this project, some of whom are listed at the beginning of this document, are available to answer your questions. No question you may have is trivial: don't be afraid to ask it!

In addition to us, you can discuss the proposal contained in this document with your family doctor, your family members, and other trusted people. Take all the time you need to decide. You can take an unsigned copy of this document home to think about it or discuss it with others before making a decision.

If you decide not to participate in the trial, you will still receive the best possible care for patients with your condition/disease. Your refusal will in no way be interpreted as a lack of trust.

Once you have read this entire information notice, received answers to any questions you may have, and decided to participate in the trial, you will be asked to sign a consent form, of which you will receive a paper copy.

B. INFORMATION SECTION. OVERVIEW OF THE TRIAL: KEY INFORMATION

Standard therapy for operable rectal adenocarcinoma consists of radiotherapy concurrent with chemotherapy, followed by restaging—repeating all initial tests—and surgery. The pathologist then examines the surgical specimen and defines the pathological stage. When the pathologist finds no further evidence of disease, even microscopic, he or she defines this situation as a "pathological complete response" to preoperative treatment. The primary goal of this study is to increase the rate of pathological complete responses (pCR) from the current 41% to 70%. We plan to achieve this by increasing the radiotherapy dose to the residual tumor still visible on MRI images performed midway through the radiotherapy treatment, improving patient selection with the use of a radiobiological index called ERI_TCP, and better identifying the target, based on intermediate MRI, for which to increase the dose.

pCR is an important goal because it is a strong positive prognostic factor: patients who achieve a pCR have a prognosis comparable to that of patients with stage I (very early, early stage) disease. Furthermore, patients who achieve a pCR automatically have a clinical complete response (cCR) to pre-surgical restaging. These patients may even be offered a postponement of surgery if rectal disease recurs.

- Why am I being asked to participate in this trial?

You have been included among those being asked to participate in this trial because you have certain clinical characteristics that will be further detailed in Section C of this information document.

- What are the objectives of the trial? How many centers and patients will participate?

The research we are presenting here aims to obtain data to confirm or deny our goal of a significant increase in pathological complete responses, as described in the introduction.

The trial is expected to be conducted only at our center and will enroll a total of 33 patients.

- What is the routine care approach for treating the disease?

Preoperative radiotherapy (RT), concurrent with chemotherapy, is standard therapy for stage T3-4N0 or node-positive rectal adenocarcinoma. For over 20 years, our medical oncology department has administered concurrent chemotherapy consisting of three cycles of oxaliplatin—the first administered alone 14 days before the start of RT, the second concurrently with the start of RT, and the third 14 days later—and capecitabine, tablets that patients take from the first day of oxaliplatin until the end of RT. Since 2009, our Radiotherapy department has focused on adaptive preoperative radiotherapy. Patients undergo a CT scan and a magnetic resonance imaging (MRI) prior to radiotherapy. These two tests help prepare the radiotherapy treatment plan. A target volume corresponding to the rectal disease, the adipose tissue around the rectum, and the pelvic lymph nodes is identified. A dose of 41.4 Gy is

prescribed for this volume in 18 fractions, a dose biologically equivalent to the dose considered standard by international guidelines, i.e., 50.4 Gy in 28 fractions. Halfway through the RT treatment (i.e., after 9 fractions of RT and two cycles of oxaliplatin), a small-area MRI is repeated. These images identify the residual rectal disease, which receives an increased dose (boost) of 3.1 Gy in the last 6 fractions of RT for a total dose of 46.2 Gy in 18 fractions. Using this technique and doses, biologically equivalent to the standard, we treated 152 patients from 2009 to 2023. The rate of pathological complete remissions was 29% in patients who received the full dose of both treatments. 98% of patients received the full dose of radiotherapy and 89% received all 3 cycles of chemotherapy. The main toxicities were diarrhea and rectal inflammation, grade 3 (number of bowel movements >7 or requiring abundant hydration for diarrhea, and frequent false urges to evacuate that interfere with daily routines in the case of rectal inflammation) in 6.5% and 5% of patients, respectively. No grade 4 (life-threatening) or 5 (death) toxicities were observed. These results are consistent with the best results available in the medical literature.

The new study follows the same framework with three differences: 1) the increased dose (boost) to residual disease will be even higher (4 Gy) in the last six fractions; 2) the most responsive patients, for whom increasing the dose is worthwhile, will be identified using a radiobiological index called ERI_TCP, which takes into account the initial volume of the rectal lesion and the volume still visible on the MRI performed midway through RT treatment; 3) the MRI scheduled midway through treatment will be with contrast medium. This will make it much easier to identify the residual lesion.

Is it my choice whether or not to participate?

You can freely choose whether or not to participate in the trial. Even after accepting, you can change your mind at any time. In this case, you will still receive the standard therapies for your disease, which are those listed above, but which also have potential risks and benefits.

If I decide not to consent to participating in the trial, what choices do I have?

If you decide not to participate in the trial, you will still be followed by the clinical center treating you and will be treated using the best approved (non-experimental) therapeutic methods for your disease. You may also participate in another ongoing trial.

What happens if I decide to participate in the trial?

The study will last exactly as long as the standard therapy: after the radiochemotherapy, there will be a break of approximately six weeks, after which you will undergo a repeat proctoscopy, a chest and abdominal CT scan with contrast, and another MRI with contrast to re-stage the disease. This is followed by surgery and histological examination of the surgical specimen, which will determine the final degree of response to the treatment—in other words, whether the disease has completely disappeared even

under microscopic examination (complete pathological response) or whether residual disease remains, which will have been completely removed. Based on the histological examination, the oncology colleagues will decide whether to administer further chemotherapy as a precaution. Finally, you will be monitored periodically with instrumental tests for at least 5 years. Everything expected after chemoradiotherapy is standard.

The full schedule of visits and tests planned during the trial is outlined in the next section: Section C, Point 3, "What tests, exams, and procedures are included in the trial?"

What are the risks and benefits of participating in the trial?

Participation in this trial may involve both risks and benefits. It is important to carefully evaluate them before making a decision.

Expected Benefits

The following benefits are expected from participation in this study: as stated in Section B (General Information), achieving a complete pathological response is an important positive prognostic factor. Furthermore, something not covered by this protocol but permitted, is the possibility of postponing surgery in the event of complete resolution of the disease on pre-surgical restaging tests.

Potential Risks

Participation in the study may involve some risks related to the higher dose delivered to the residual rectal lesion. This increased dose will undoubtedly increase the likelihood of proctitis, or inflammation of the rectum. The clinical manifestation of proctitis is a false urge to evacuate. The urge may be so intense, combined with abdominal cramps, that it requires an urgent evacuation. Typically, the subsequent evacuation consists of the expulsion of small amounts of feces or mucus. Proctitis always occurs during radiochemotherapy for rectal lesions, however, in our previous experience, it reaches such an intensity and frequency that it causes incontinence, thus compromising normal daily activities in approximately 5% of cases. Other side effects, such as frank diarrhea, nausea, vomiting, and weakness, may occur, but these are attributable to the treatment as a whole and not to the increased dose to the residual disease, which is the focus of the study. Specific remedies will be prescribed for all these side effects during medical checkups during treatment. However, they are generally self-limiting, typically disappearing within a couple to three weeks.

- Is consent final? Can I decide to withdraw from the clinical trial (voluntary withdrawal)?

You can withdraw from the trial at any time and for any reason, without having to provide a reason.

If you decide to no longer participate, please let one of the trial physicians know as soon as possible: it is important to discontinue treatment safely. Your doctor may consider a final follow-up visit/exam.

Your doctor will keep you informed of any changes in the trial that may affect your willingness to participate.

- Are there any reasons why the trial might be terminated involuntarily (early termination)?

Yes, the investigator may decide to terminate your participation in the trial if:

- Your health changes and participation in the trial is potentially harmful

- New information becomes available and the trial is no longer in your best interests

- You do not follow the agreed-upon rules for participation in the trial

- For women: You become pregnant during the trial

- The trial was interrupted by the competent authorities or by the Sponsor

Will I be able to access the trial results?

The investigators and the Sponsor undertake to make the trial results available to the scientific community. You may ask the investigator to communicate the general results of the trial to you.

C. INFORMATION SECTION. FURTHER INFORMATION

1. What is the aim of the trial?

To increase the probability of pathological complete response.

2. Which patient groups are being compared? What is the experimental intervention?

Only one group of 33 patients will be recruited. As already mentioned, the new study follows the same design as the preoperative radiochemotherapy treatment, with three differences: 1) the boosted dose to residual disease will be even higher (4 Gy) in the last six fractions; 2) the most responsive patients, for whom increasing the dose is worthwhile, will be identified using a radiobiological index called ERI_TCP, which takes into account the initial volume of the rectal lesion and the volume still visible on the MRI performed midway through the RT treatment; 3) the MRI scheduled midway through the

treatment will be with contrast. This will greatly facilitate the identification of the residual lesion. Here are the inclusion criteria, common to all prophylactic treatments:

Initial stage (standard stage)

Histological confirmation of rectal adenocarcinoma
Microsatellite status: stable
Clinical stage T2N0 in the lower rectum, eligible for surgical intersphincteric resection or rectal amputation with permanent colostomy.
Clinical stage T3-T4N0 or any T with positive lymph nodes
Lower margin of the rectal lesion no more than 12 cm from the anal verge

Exclusion criteria
Presence of disease localization in other organs, previous history of oncology within the last 5 years, prior chemotherapy, prior pelvic radiation therapy, active rectal ulcerative colitis, inadequate spinal cord, liver, or kidney function (for concomitant chemotherapy), pregnancy, or breastfeeding.

The workflow is as follows:

1) The patient undergoes a CT scan and MRI for centering.

2) The radiation oncologist prepares the radiation treatment. Simultaneously, the medical oncologist requests tests to verify the feasibility of concomitant treatment.

The overall treatment plan is as follows:

Day	Day	Day
-14°	0	+14°
1st cycle OXA	2nd cycle OXA	3rd cycle OXA

Capecitabine----------Stop

RT (18 fractions)----------Stop

The first cycle of oxaliplatin (the first chemotherapy drug) begins 14 days before the start of radiotherapy. The medical oncologists will give you capecitabine tablets (the second concomitant drug)

at personalized doses based on your weight, height, and enzyme status. These tablets are to be taken from the first day of chemotherapy (day -14) until the end of radiotherapy, excluding weekends. Two weeks later, the second cycle of oxaliplatin begins (day 0). After another two weeks, the third and final cycle of oxaliplatin begins (day +14). Radiotherapy begins concurrently with the second cycle of oxaliplatin and will consist of 18 fractions in total, 5 per week from Monday to Friday.

3) Between the 9th and 11th fraction of radiotherapy, you will repeat the MRI scan.

The second phase of radiotherapy treatment will be prepared using this MRI image and the ERI_TCP will be calculated. This value will determine eligibility for the new protocol:

- For ERI_TCP values ≥32.6, the patient is not eligible and will be treated with RT at the doses used until now.

- For ERI_TCP values <32.6, the patient is potentially eligible for the new protocol,
  if these other inclusion criteria are met:

- Lower margin of the lesion at least 10 mm away from the theoretical surgical resection line.

- Good general health (ECOG Performance Status ≤ 2)

- Age between 18 and 80 years

- Signed informed consent form

Patients who meet these conditions will be recruited and will receive a dose boost (4 Gy instead of the usual 3.1 Gy) on residual disease identified on the mid-field MRI.

Why recruit patients with ERI-TCP <32.6? Because this subgroup of patients has the best chance of pathological complete response, 41% with the current treatment compared to a very low percentage in the subgroup with ERI-TCP ≥32.6. Therefore, for the former, it may be reasonable to accept a risk of increased toxicity, considering that the dose increase is intended to increase this probability to 70%.

3. What tests, tests, and procedures are planned if I participate in the trial?

There are no tests not included in standard treatments; the only experimental procedure will consist of an increase in the radiotherapy dose. All other blood tests, number of visits (weekly), and the duration of visits are the same as those expected during standard radiochemotherapy treatment.

4. What risks might I face if I participate in the trial? (Section no longer than 4 pages)

As already mentioned, the increased dose to the residual disease will certainly increase the likelihood of proctitis, i.e., inflammation of the rectum.

We believe that the new treatment may affect your disease better than the currently available treatments, however, its efficacy is the subject of this study. We can reasonably rule out worse results.

Radiation treatment to the pelvis, the anatomical site of the rectum, bladder, and female reproductive organs, is incompatible with pregnancy. If you are a fertile woman, you must absolutely eliminate the risk of pregnancy during the treatment period. Furthermore, since the ovaries are defunctionalized by radiation at doses much lower than those delivered, there is a risk of permanent premature menopause. If subsequent pregnancies are desired, the patient must inform the radiation oncologist. This will allow for prompt egg collection procedures.

Since chemotherapy will be administered during this time, breastfeeding is absolutely not recommended.

Even standard radiochemotherapy may temporarily limit a patient's work, social, and sexual life, given the aforementioned side effects, which are not serious but potentially disturbing.

<u>Risk frequency categories.</u>

The table below presents the toxicity data from our previous experience with adaptive radiotherapy concurrent with chemotherapy.

Expected toxicity (data from our experience with adaptive radiotherapy, 152 pts.)			
Hematological toxicity	**Any grade**	**G1-2**	**G3-4**
Neutropenia	27 (14.5%)	24 (12.9%)	3 (1.6%)
Anemia	20 (10.7%)	19 (10.2%)	1 (0.5%)
Thrombocytopenia	26 (14%)	26 (14%)	0 (0%)
Non-hematological toxicity	**Any grade**	**G1-2**	**G3-4**
Astenia	24 (12.9%)	22 (11.8%)	2 (1.1%)
Diarrea	99 (53.2%)	82 (44.1%)	17 (9.1%)
Tenesmo	41 (22%)	39 (21%)	2 (1.1%)
Sanguinamento rettale	18 (9.7%)	17 (9.1%)	1 (0.5%)
Proctite	95 (51%)	86 (46.2%)	9 (4.8%)
Nausea	40 (21.5%)	39 (21%)	1 (0.5%)
Vomito	8 (4.3%)	7 (3.8%)	1 (0.5%)
Tossicità genitourinaria	36 (19.3%)	34 (18.3%)	2 (1.1%)
Tossicità cutanea	38 (20.4%)	32 (17.2%)	6 (3.2%)
Neuropatia periferica	30 (16.1%)	29 (15.6%)	1 (0.5%)
Stomatite	4 (2.1%)	4 (2.1%)	0 (0%)
Post-operative complications			
Overall		79 (42.5%)	
Anastomotic leak		14 (7.5%)	
Infection		20 (10.7%)	
Fistula		19 (10.2%)	
Intestinal obstruction		12 (6.4%)	

Vascular events	8 (4.3%)
Other	20 (10.7%)

5. How will I be informed of any unexpected results following further diagnostic tests?
No further diagnostic tests beyond those indicated are planned unless clinically necessary.

6. Is it useful/necessary to inform my family doctor?
Yes, for our professional integrity and for continuity of care. You will be given a letter written specifically for him or her.

What will be my commitments and responsibilities if I decide to participate?

• Strictly follow the instructions and requests of the healthcare staff following the trial and ensure attendance at appointments.
• Inform the doctor following the trial:
o of all medications you are taking, including non-conventional medicine,
o of any side effects that arise during the trial,
o of any hospital visits or admissions to facilities other than the trial center,
o of current or previous participation in other clinical trials.

• Avoid pregnancy or breastfeeding during the trial. A preliminary pregnancy test is highly recommended.
• For men: Avoid fathering a child during the trial.
• Inform your doctor promptly if you or your partner are considering becoming pregnant during the trial or within (insert period in months/years) after the last dose of the investigational drug (indicate which).

7. Will I incur costs for participating in the trial? Will I be reimbursed for any expenses? Will I receive compensation?

There are no costs to you arising from participation in the trial, as these are fully covered by the Sponsor/Promoter. Furthermore, no financial compensation is provided for participation in the trial.

8. What happens if I suffer harm as a result of participating in the trial?

Participation in a clinical trial may involve inconveniences and risks that cannot be determined in advance. For this reason, the clinical trial provides insurance coverage to protect your participation.
In compliance with applicable laws, insurance is provided to cover any harm suffered as a result of participation in the trial, for the entire duration of the trial, covering the civil liability of the investigator and the Sponsor.

Any risks arising from the trial will be covered by OSR's third-party liability insurance.

It should be noted that, according to the Ministerial Decree of July 14, 2009, the insurance policy does not cover any value exceeding the maximum limit and is effective only for damages for which a claim for compensation is submitted no later than the period specified in the policy. This limitation does not, however, affect your right to obtain compensation from the person responsible for any damage (protecting the trial subject).

9. How will my health data, including identifying information, be processed during the trial, and who will have access to it?

Your data, particularly personal and health data, and only to the extent necessary for the trial's objectives and for pharmacovigilance purposes, will be processed in compliance with EU Regulation 2016/679, known as the GDPR (General Data Protection Regulation), and Legislative Decree No. 101 of 10 August 2018. In practical terms, participant documents will be kept in a secure location and will not contain your name, known only to researchers, but an identification code.
The anonymized data may be subject to review by regulatory bodies and used for scientific publications (journals, conferences).
Your clinical data collected for the trial, as well as the results of the tests performed, will be retained for the periods required by law and subsequently destroyed. They will not be destroyed unless a) it is no longer possible to trace them back to your identity because they were anonymized during the trial itself; or b) you have given your specific informed consent.
If personal data is transferred to a third country or an international organization, all the safeguards required by Article 46 of GDPR 679/2016 regarding the transfer will be implemented.
Further information is included in the attached data processing authorization form.

10. How will my biological samples collected for the trial be processed, and who will have access to them?

The study does not involve the collection of biological samples.

11. How can I access the trial results?

Once the trial is concluded and all the resulting data has been collected, they will be analyzed to draw conclusions. The investigators and the Sponsor undertake to make them available to the scientific community. The regulation provides for participants to have access to the trial results.
Therefore, you may ask the investigator to communicate the general results of the trial to you.

12. Has the trial been approved by the Ethics Committee?
The trial protocol proposed to you has been reviewed and approved by the Lombardy Ethics Committee (CET L1). The Ethics Committee verified, among other things, that the trial complies with the Standards of Good Clinical Practice and the ethical principles expressed in the Declaration of Helsinki, and that your safety, rights, and well-being have been protected.

13. Who can I contact for more information about the clinical trial in which I am invited to participate?

DR. PAOLO PASSONI, DR. NAJLA SLIM

14. If I participate in the trial, who can I contact if I need assistance?

For any questions or unplanned or unscheduled events during the trial (doubts regarding ongoing treatment, side effects, decision to abandon the trial, etc.), please contact:
Radiation therapy for all patients is performed by radiology technicians. When a patient experiences a clinical problem outside of scheduled follow-up visits, he or she reports it to the technicians, who then notifies the radiation oncologist on duty.
If you deem it appropriate to report events or facts related to the trial in which you participated or to individuals not directly involved in the trial itself, you may contact the Ethics Committee that approved the trial, the Health Management of the Radiotherapy Service Trial Center at San Raffaele Hospital, and the competent authority.

Attachments
• Consent form for the processing of personal data

Additional documents:
• Letter for the family doctor

B. CONSENT SECTION

(Note: 1 copy for the participant, 1 copy for the trial director)

Trial Title: _____

Protocol Code: Adaptive Rectal Cancer Trial 02

Trial Sponsor: Prof. Nadia Di Muzio, Radiotherapy Department, San Raffaele Hospital, Milan.

Principal Investigator: PAOLO PASSONI, RADIOTHERAPY SERVICE, SAN RAFFAELE HOSPITAL, MILAN

_____

I, the undersigned _____

born _____ on __/__/_____

I DECLARE

☐ that I have received from Dr. _____ comprehensive explanations regarding the request to participate in the research in question, as reported in the information section of this consent form, a copy of which was delivered to me on _____ at _____ (indicate date and time of delivery);

☐ that the nature, purposes, procedures, expected benefits, possible risks and drawbacks, and alternative treatment modalities compared to the proposed clinical trial have been clearly explained to me and that I understand them;

☐ that I have had the opportunity to ask the study investigator any questions I might have and that I have received satisfactory answers;

☐ that I have had sufficient time to reflect on the information received;

☐ that I have had sufficient time to discuss it with third parties;

☐ that I have been informed that the trial protocol and all forms used have received a favorable review from the relevant Ethics Committee;

☐ that I am aware that the research may be interrupted at any time, at the discretion of the research director;

☐ that I have been informed that I will be kept informed of any new data that may compromise the safety of the research and that, for any problems or further questions, I can contact the doctors who are treating me;

☐ that, for the best protection of my health, I am aware of the importance (and my responsibility) of informing my family doctor of the trial in which I agree to participate. I am aware of the importance of providing all information (medications, side effects, etc.) concerning myself to the investigator;

☐ that I have been informed that the results will be disclosed to the scientific community, protecting my identity in accordance with current privacy legislation;

☐ that I am aware that any choice expressed in this consent form may be revoked at any time and without justification;

☐ that I have received a copy of this consent form.

I therefore DECLARE that

☐ I want to participate in the trial

☐ I want ☐ I do NOT want to be informed of any unexpected information relating to my current or future health that may incidentally emerge from the investigations involved in the trial, including genetic information, when this could lead to possible benefits.

☐ I want ☐ I do NOT want to be informed of unexpected information relating to my current or future health only when this could be useful for my healthcare or to enable me to make informed reproductive choices.

☐ I want ☐ I do NOT want to be contacted after the trial ends to provide information on my health status (applies only to contacts not foreseen as follow-up by the study protocol).

If applicable:

☐ I accept ☐ I do NOT accept the use of contraceptive drugs.

_____ ___/___/_____ _____ _____

Full name of the adult patient Date Time Signature

(N.B. If the patient is unable to (If the informed consent form is read or signed personally, a witness independent of the Investigator and the Sponsor must be present throughout the entire informed consent discussion. The witness must personally sign and date the informed consent form after the form and any other written information have been read and explained to the subject and the subject has given verbal consent to participate in the study.)

In this case:

I, the undersigned..... testify that Dr.

.....has thoroughly explained to

Mr./Ms.....
.....

the characteristics of the study in question, as reported in the attached information sheet, and that the subject, having had the opportunity to ask all the questions he/she deemed necessary, has freely agreed to participate in the study.

Printed name and surname of independent witness .....

Date..... Signature of independent witness .....

STATEMENT OF THE PHYSICIAN WHO COLLECTED CONSENT

(Patient's name and surname, place and date of birth)

Title of the trial: _____

Protocol Code: Adaptive Rectal Cancer Trial 02

Trial Promoter/Sponsor: _____

Principal Investigator (Name, Affiliation, References): _____

_____

I, the undersigned, Prof./Dr. (Name and Surname) _____ in my capacity as Principal Investigator (or the Principal Investigator's delegate)

DECLARES

that the Patient has voluntarily consented to participate in the trial.

I also declare that:

☐ I have provided the Patient with comprehensive explanations regarding the purposes of the trial, the procedures, the possible risks and benefits, and the possible alternatives;

☐ having verified that the patient has sufficiently understood the information provided

☐ having given the patient the necessary time and opportunity to ask questions about the trial

☐ having clearly explained the possibility of withdrawing from the trial at any time or changing the choices made

☐ having not exercised any coercion or undue influence in requesting this consent

☐ having provided the patient with information on how the trial results will be communicated to him/her

_____ _____

Place and date Time

_____ _____

First name Surname (print) of the physician Signature (and stamp)

who provided the information and obtained the consent

This form is an integral part of the consent and must be kept together with

the previous informed consent information sheet