Informed Consent Form

Title:	Chemoradiotherapy and Consolidation Chemotherapy with and without Oxaliplatin for Distal Rectal Cancer and *Watch & Wait (Watch & Wait)*.
Research site name:	International Research Site - Hospital Alemão Oswaldo Cruz
Address:	Rua Treze de maio, n° 1815 - Bela Vista - Bloco A - 1° subsolo - Postal code: 01327-001 - São Paulo/SP [State of São Paulo], Brazil
Contact:	+55 (11) 3549-1976/ (11) 3333-8767 roperez@haoc.com.br +55 (11) - 98303-0005 (24/7 service)
Physician in charge of this research:	Rodrigo Oliva Perez
Name of the Institution Independent Ethics Committee (IEC)	Independent Ethics Committee of Hospital Alemão Oswaldo Cruz
Address, postal code contact details of IEC and operation hours	Address: Rua: Treze de maio, n° 1815 - Bela Vista - Bloco B - 5° andar - Postal code: 01327-001 - São Paulo/SP, Brazil Operation hours: Monday to Thursday – 8 AM to 6 PM and Friday – 8 AM to 5 PM Phone: +55 (11) 3549-0862
Independent Brazilian Ethics Committee (CONEP)	Address: SRTVN - Via W 5 Norte - Lote D, Edifício PO 700, 3° andar - Ala Norte. Ala Norte - Brasília - DF - Postal code: 70,719,040
Contact information for the Independent Brazilian Ethics Committee (CONEP):	Phone: +55 (61) 3315-5878 Telefax: +55 (61) 3315-5879 Operation hours: Monday through Friday from 08:00 AM to 06:00 PM
Name of Subject:	
Subject Identification Number:	

We invite you to take part in this trial because you were diagnosed with rectal cancer very close to the anus with no signs that the disease had spread to other organs (metastasis).

Before deciding if you want to take part, it is important that you understand why this research is being performed, all the procedures involved, the possible benefits, risks and discomforts which will be described and explained below.

The purpose of this trial is to find out whether chemotherapy treatment given after radiotherapy/chemotherapy with two drugs (fluoroprimidine + oxaliplatin) leads to a greater chance of elimination of the rectal tumor near the anus compared with treatment using only one drug (fluoropirimidine).

At any time before, during and after the research, you may request further clarification about the trial, refuse to take part or withdraw from taking part or perform procedures that you do not desire. In all these cases you will not be harmed, penalized or held liable in any way. If you are under treatment, it will continue in the same way even if you do not want to take part in the trial anymore. Your contribution is important; however you should not take part against your will.

This trial was reviewed by an Independent Ethics Committee (IEC) which is a body that protects the well-being of subjects. The IEC is responsible for evaluating and monitoring the ethical aspects of all research involving human beings, in order to ensure the dignity, rights, safety and well-being of subjects.

After being introduced and clarified about the research information, if you accept to take part as a volunteer, you must place your initials on all pages and provide a signature at the end of this document, prepared in two copies. Each copy will also be initialed on all pages and signed by the responsible researcher, and one copy should remain with you, so that you can consult it whenever necessary.

After your consent, using a computer program we will proceed with a randomly (at random) and repetitive drawing process whose result does not describe a specific pattern, but follows a possibilities distribution for the proposed treatments. Furthermore, you will take a copy of this informed consent form that will be yours.

Who will take part in this trial?

Patients with rectal cancer near the anus.

What will happen to me if I take part?

You will be followed up during the whole treatment (either with 1 or 2 drugs), and it will be performed as is already done currently with an oncologist physician, in addition to a multidisciplinary team that will follow you.

The physician responsible for this study, as described on page 1, will follow you up and will be attentive to the onset of side effects from the treatment exactly as it is regularly conducted. In the event of any eventuality related to your participation, you may be admitted to a hospital with the complete commitment of the medical team that will provide assistance for any intercurrences and/or side effects.

The tests and procedures that will be performed are the same as the procedures and tests that are performed for any patient with rectal cancer as part of clinical practice. All patients will be assessed by a specialist physician with tests of:

- Magnetic Resonance Imaging: The MRI machine has a big magnet that interacts with our body. Thus, it creates high-definition images in three planes: horizontal, vertical and with the body divided into layers;
- Rectal touch: It consists of introducing the specialist physician's index finger, protected by a latex glove and lubricated, into the patient's anus;
- Endoscopic assessment: The examination consists of anal introduction of an imaging device called endoscope, which permits the visualization of rectum segments that may indicate the cancer.

STUDY TREATMENT

Possibility 1:

Treatment may be performed with radiotherapy (54Gy) for 25-30 days (except weekends) along with chemotherapy (2 tablets of capecitabine per day taken by mouth at a daily dose of 825mg/m2). When radiotherapy (along with chemotherapy) ends, the randomly selected patients will take a 1- to 2-weeks interval and the second part of the treatment will be performed with only 1 chemotherapy drug, with a dose of 1000 mg/m2 of Capecitabine twice a day for 14 days in a 21-day cycle for 4 cycles (12 weeks). Only this group of patients will receive treatment with a single drug (same tablet taken by mouth).

Possibility 2:

Treatment may be performed with radiotherapy (54Gy) for 25-30 days (except weekends) together with chemotherapy (2 tablets of capecitabine taken by mouth at a daily dose of 825 mg/m2). When radiotherapy (along with the chemotherapy) ends, the randomly selected patients will take a 1-to 2-weeks interval and the second part of the treatment will be performed with only chemotherapy using two drugs (mFOLFOX6, XELOX for 6 cycles).

In both groups, this chemotherapy-only treatment should last approximately 3 months.

When the treatment ends (3-4 months after the last date of radiotherapy), the patients will perform the same exams again (MRI, Digital Rectal and Endoscopic assessment) to verify if the tumor was eliminated or not. After this assessment, whether or not the tumor has disappeared, the treatment that will be provided afterward is entirely dependent on the decision between the patient and his/her physician and institution.

Only those patients with a partial/complete response at the time of response assessment at 12 weeks should be submitted to the response assessment at 18 weeks after the end of treatment. Patients with incomplete response (poor response) at 12 weeks will be recommended for surgery at that moment.

Will taking part in this trial help me with the rectal cancer I have?

So far, these two forms of treatment using radiotherapy and chemotherapy with one or two drugs are the most well-known forms that can lead to the elimination of the rectal tumor located near the anus and able to avoid surgery. There are no studies comparing the two forms (with one or two drugs). Despite this, published experiences with one drug and published experiences with two drugs show very similar results of tumor elimination without the need for surgery. There are other forms of treatment using radiotherapy for just 5 days (not 25-30 days) followed by chemotherapy with two drugs. However, this form of treatment has never been assessed in research regarding the tumor elimination without surgery.

Patients with rectal cancer near the anus often require delicate and time-consuming surgery to treat the disease. This surgery can result in some important consequences such as difficulties in urinating, difficulties to have sexual intercourse (in men with difficulty in penis erection) and use of a feces collection bag in the belly (colostomy/ileostomy). Despite this, in patients treated with radiotherapy and chemotherapy before this surgery, near to one in three patients have complete tumor elimination. In some specialized centers for the cancer treatment, such patients have been followed up with periodic exams, without the immediate need for surgery. In these cases, surgery would only be performed if exams show that the tumor has grown or appeared again. Several researches studied different combinations and doses of radiotherapy and chemotherapy to try increasing the chances of the tumor disappearance and, therefore, to avoid surgery in a larger number of patients. In general, the treatment is made with radiotherapy and chemotherapy combined (for approximately 6 weeks) and then a second part with only chemotherapy.

In the trial you are being invited to take part, we want to find out if in the second part of the treatment (after radiotherapy and chemotherapy combined), the combination of chemotherapy and 2 drugs leads to a greater chance of tumor disappearance than chemotherapy with only one drug. Many hospitals have used both treatment methods (with one or two drugs in this phase of treatment). But if the combination of two drugs increases the chances of tumor disappearance was not studied yet. It is also possible that the treatment with 2 drugs presents more side effects than with 1 drug.

Does taking part in this trial involve costs?

As a subject in one of the two treatments listed above, you (a) and your companion will have the right to guaranteed reimbursement for expenses such as food and transportation, without restriction only to them, under the researcher's assessment, in case the participant comes to the hospital exclusively for trial procedures. All procedures are already part of the usual clinical practice treatment, i.e., the participant will come for the clinical treatment and it is possible that it will not be necessary to come to the hospital just for the study procedures.

You will have no costs to participate in the study. You can also seek compensation for damages resulting from your participation in the study. Furthermore, in the event of any damage resulting from the research, you will receive full and immediate assistance at no cost.

What will my obligations be if I take part?

Attending the 3 program visits to the Research Site, performing the exams and procedures (MRI, Rectal Touch and Endoscopic assessment and performing the treatment in one of the selected groups).

What are the possible risks related to this trial?

As the purpose of this trial is to compare the results of chemotherapy with only one drug (capecitabine) or with two drugs (capecitabine + oxaliplatin), the most common adverse reactions related to treatment with only one chemotherapy drug (capecitabine) include: Gastrointestinal disorders such as dry mouth, excess gas, adverse reactions related to ulceration/inflammation of mucous membranes, such as inflammation of esophagus, stomach, small intestine, large intestine and gastrointestinal hemorrhage (bleeding). Cardiac disorders such as swollen legs, chest pain of cardiac origin including angina pectoris, heart muscle disease, myocardial infarction/ischemia, heart failure, sudden death, increased heart rate, cardiac arrhythmias and palpitations. Nervous system disorders such as insomnia, confusion, impairment of brain functions and cerebellar signs such as lack of motor coordination, difficulty articulating words, changes in balance and changes in coordination. Infections and infestations such as local infections, life-threatening generalized infections (including bacterial, viral and fungal origin) and sepsis (disseminated infection). Disorders of the blood and lymphatic system such as anemia and reduction of all blood cells. Skin and subcutaneous tissue disorders such as itching, localized skin detachment, skin darkening, nail disorders, light sensitivity reactions and sensitivity to radiotherapy. General disorders related to the administration site such as pain in the legs and arms and pain in the chest (non-cardiac); eye irritation; respiratory problems such as shortness of breath and coughing. Musculoskeletal disorders such as low back pain, muscle and joint pain. Psychiatric disorders: depression.

Combined treatment with two chemotherapy drugs (capecitabine + oxaliplatin) may develop some side effects related to the use of the second drug. These side effects may include swelling, increased heart rate, chest pain, redness, swelling and pain in the palms of hands or soles of feet, abdominal pain, constipation, diarrhea, loss of appetite, feeling sick, vomiting, mouth irritation, pancreas and intestine inflammation, anemia, decrease in white blood cells and blood platelets, change of liver enzymes, allergic reactions, back pain, change in sensitivity of hands and feet, cough, shortness of breath, worsening of kidney function, tiredness, fever, impaired vision and hearing.

Chemotherapy can have serious side effects that, in very rare situations, can even lead to death. Such events are possible in both groups, as with any medical treatment (clinical or surgical) for rectal cancer. In case of any eventuality related to your participation, you may be admitted to a hospital with the complete commitment of the medical team that will provide assistance for any intercurrences and/or adverse events. You can be compensated for any damages resulting from the research.

What are the possible benefits of taking part in this study?

There is a possibility of greater chance of tumor elimination with chemotherapy with 2 drugs.

Will I have access to the results of exams I perform in this trial?

You will have access to all exams performed during the follow-up period. You will also have access to the final results of the trial, which can be: chances of tumor elimination (number of patients whose tumor has disappeared), risk or tumor recurrence (when the tumor has returned after apparent initial disappearance), and risk of tumor appearance in other organs.

How is my personal data going to be used?

All information collected in this trial will be confidential (your name will never be disclosed). Only the researcher and/or research team will know your identity and we are committed to keep it confidential. The information we collect from this trial will only be used for the present research and will be regularly monitored by an independent group of expert scientists that will let us know if the trial needs to be interrupted or changed (due to clear benefit or harm). We intend to publish and present the results so that other patients can benefit from this research trial.

We will always strictly maintain patient confidentiality and all data will be kept in a very secure environment. The subjects will be anonymized (recruited but not personally identified) — they will be identified by numerical codes aiming at safeguarding their identity. The study will follow all applicable privacy and confidentiality laws to minimize such risks, as well as procedures to ensure the restrict access to electronic case report form (REDCAP database), and the secrecy and confidentiality of their information, according to the Article 5 of the General Data Protection Law – LGPD – No. 13,709, dated August 14, 2018, and CNS/MS Resolution 466/2012, ensuring the anonymization of sensitive data.

What are the agreements when you provide the informed consent form?

Your participation in this trial is voluntary. You may discontinue your participation in this trial at any time without affecting your regular treatment. If you withdraw from the trial, all information collected up to that point will be kept in the database.

If you agree to take part, you are agreeing to allow site team to:

- Collect your health card number;
- Collect your address and other contact details;
- Access your medical records (through your GP, hospital records or government health records) to assess your progress and any treatments you may have received;
- Contact you (in person, by phone or email) between 15 and 30 days after starting the trial to assess your progress;
- Contact an alternate person, which you inform us, if we cannot contact you;
- Allow people from the Independent Ethics Committee (IEC), or the Independent Brazilian Ethics Committee (CONEP) or the drug manufacturers to check if the data are accurate and that the trial was conducted according to quality standards (Good Clinical Practice [GCP]).

Information that will be collected

All information collected as part of this trial will remain confidential except as required by law. Your trial information will be securely stored in a secure electronic database located at Hospital Alemão Oswaldo Cruz.

Who should I contact if I have any doubts/concerns?

Your trial physician can answer any questions/concerns you may have about this trial and your participation. He can be contacted at any time during the trial and must be contacted immediately if you experience any injury, illness and/or medical condition. See the contact information listed on the first page of this ICF.

Questions about your rights as a participant may be addressed by the Independent Ethics Committee that reviewed/approved the study CCHOWW. See the contact information listed on the first page of this ICF.

Informed Consent Form

By signing this Informed Consent Form, you confirm that:

- I had time to read the information and think about the trial, and my questions were answered accordingly.
- I agree to take part in the trial and I understand that my participation is completely voluntary.
- I agree that my encoded personal information may be used as described in this document.
- This Informed Consent Form will be signed and initialed in two original copies by me, the trial physician and, whenever applicable, by the witness and/or legally acceptable representative.
- By signing this Informed Consent Form, the trial physician ensures the subject, on his own behalf, on behalf of the sponsoring company and on behalf of the institution, the rights herein described.
- I understand that I will receive an original copy of this Informed Consent Form.

The other original copy will be kept under the responsibility of the study physician.

We will present two options for obtaining the informed consent form, and this ICF has two copies, which must be signed at the end by the participant or by the legal representative, as well as by the responsible researcher, or by the person(s) authorized.

The signature of the legally accepted representative (as per the Brazilian Civil Code) must be included if the subject is unable to sign by himself. The relationship between the subject and the legally accepted representative must be informed. The signature of the impartial witness must be included if the subject is unable to read or write.

1 If the informed consent form is being provided by a surrogate decision-maker:

By providing your permission to Mr./Ms./Mrs. _____ to take part, you do not waive any of your legal rights. You agree that the investigator or site's team may contact _____ if possible or any of the alternative contacts for information if unable to contact _____.

You provide your permission to Mr./Ms./Mrs. _____ to take part?

Please sign below:

Legal Representative, if applicable	Legal Representative, if applicable Name: Signature: Doc. Identity card: _____ Kinship: _____	Date:_____ Time:_____

OR

2 If the informed consent form is being provided in writing

I have read, or it was read to me, the information from the study CCHOWW. I have been explained of the nature, purpose, duration and foreseeable effects and risks of the trial and what I am expected to do. I was given enough time to ask questions and decide about my participation. My questions were satisfactorily answered. I understand that the results will be kept confidential in accordance with the legislation of my country. By signing and dating this form, I agree to participate in the Study CCHOWW. I am not waiving any of my legal rights. I will also agree that the investigator or trial team may contact any of my alternative contacts for information if they are unable to contact me.

Subject	Subject Name:_____ Signature:_____	Date: _____ Time:_____

TRIAL TEAM STATEMENT

I, the undersigned, acknowledge that I have provided all information necessary for understanding the Study CCHOWW to the aforementioned subject. I certify that, to the best of my knowledge, the person signing this informed consent form understands the nature, demands, benefits and risks of taking part and that his/her signature is valid and voluntarily provided.

Researcher	Researcher who conducted the discussion of the Informed Consent Form Name: _____ Signature: _____	Date: _____ Time: _____

We ask for your indication and authorization so if we cannot contact you on your personal telephone number (if available), we may contact you on alternative telephone numbers registered below.

PARTICIPANT CONTACT INFORMATION

Name and Address:
Mobile Phone Number:
Alternative Phone Number:
E-mail:

ALTERNATIVE CONTACT INFORMATION 1

Name and Address:
Mobile Phone Number:
Alternative Phone Number:
E-mail:

ALTERNATIVE CONTACT INFORMATION 2

Name and Address:
Mobile Phone Number:
Alternative Phone Number:
E-mail:

ALTERNATIVE CONTACT INFORMATION 3

Name and Address:
Mobile Phone Number:
Alternative Phone Number
E-mail