

To be Printed on Hospital Letterhead

PROTOCOL 101.1.C.004 - Patient Information Sheet

STUDY TITLE: A MULTINATIONAL-MULTICENTRE, DOUBLE-BLIND, RANDOMISED, PARALLEL GROUP STUDY TO COMPARE THE SAFETY AND EFFICACY OF 200 mg PAR-101 TAKEN q12H WITH 125 mg VANCOMYCIN TAKEN q6H FOR TEN DAYS IN SUBJECTS WITH *CLOSTRIDIUM DIFFICILE*-ASSOCIATED DIARRHEA

Protocol: PAR 101 (OPT-80) Amendment 4 Dated 13 Apr 2009

NRES Ref: 06/MRE12/87

Sponsor: Optimer Pharmaceuticals, Inc
Principal Investigator: _____
Research Centre: _____
Address: _____
City, Postcode: _____
Phone: _____
After Office Hours: _____

1. Introduction

You are being asked to be part of a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. This form will tell you what you have to do during the study and the potential risks and benefits of taking part. Please take the time to read the following information carefully. Talk to others about the study if you wish.

This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or procedures that you do not understand and ask as many questions as needed. Do not sign this form unless you are satisfied with the answers to your questions and decide that you want to be part of this study. Your participation is voluntary.

Part 1 tells you the purpose of this study and what will happen to you if you take part

Part 2 gives you more detailed information about the conduct of the study.

2. What Is The Purpose Of The Study?

Clostridium difficile-associated diarrhoea (CDAD) is a significant problem in hospitals and in the community. *Clostridium difficile* (*C. difficile*) is a bacterium that causes infection of the large bowel or intestines in people who have usually been treated with other antibiotics. *C. difficile* produces toxins (chemicals) that cause diarrhoea, stomach pain, fever, vomiting and dehydration.

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As your doctor or the site staff has explained to you, the cause of your diarrhoea may be the result of an infection caused by *C. difficile*. Your voluntary participation in this research study will help compare the effectiveness and safety of a drug called PAR 101 (OPT-80) (which has not yet been approved for this use) with another drug called vancomycin (which is approved), in the treatment of CDAD. Approximately 664 men and women with CDAD at approximately 100 sites in North America and Europe will participate in this study.

3. Why Have I Been Chosen?

You have been invited to take part in this study because you have developed diarrhoea, associated with *C. difficile* infection that in the opinion of your doctor needs to be treated with antibiotics. The study doctor who is helping to run this study has decided you may be suitable to take part.

4. Do I Have To Take Part?

It is up to you to decide if you want to take part. If you decide to take part you will be given this information sheet to keep and you will be asked to sign a consent form.

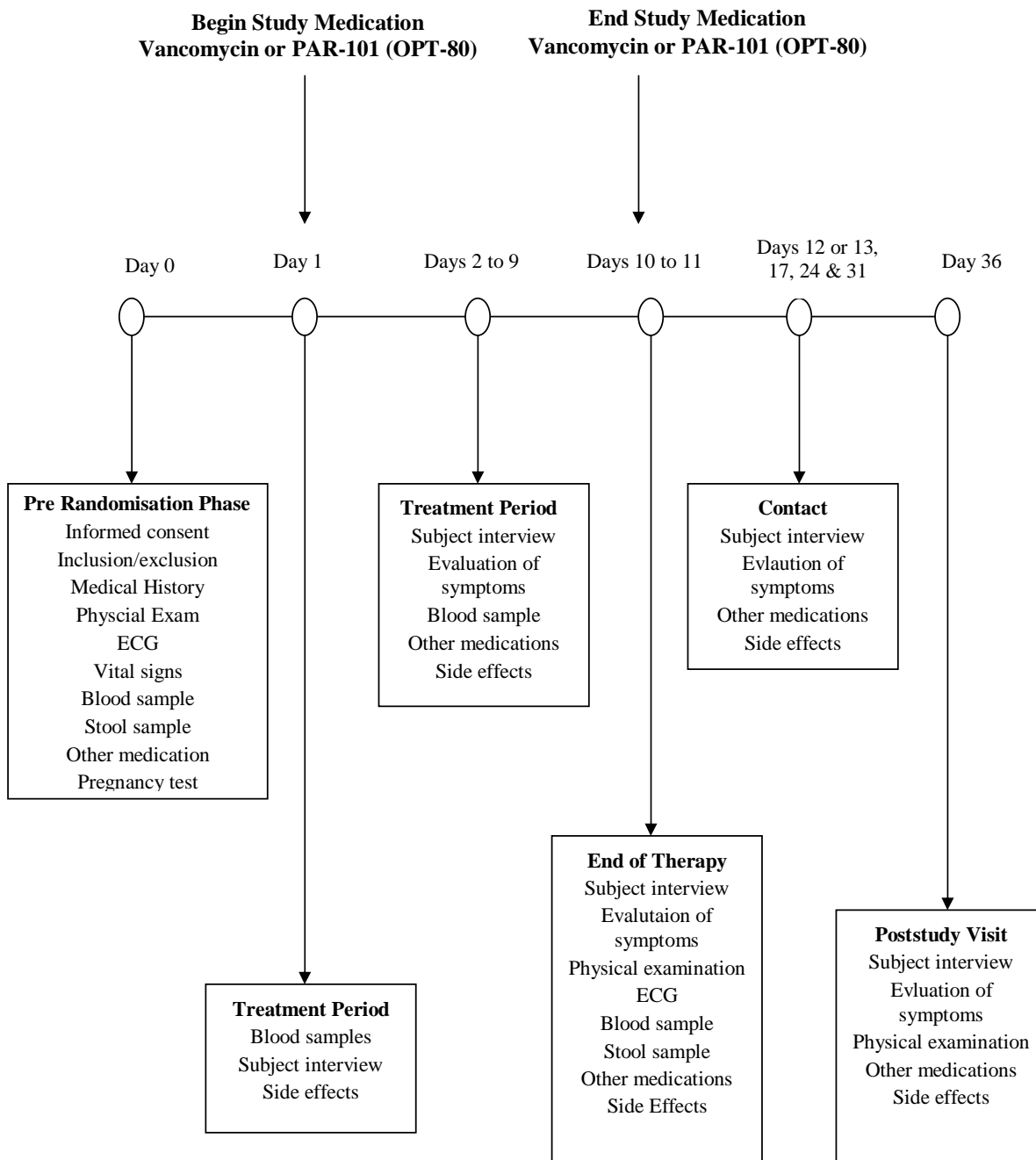
If you decide not to join the study, your medical care will not be affected. If you do decide to participate you are free to leave the study at any time without giving a reason, just tell the study doctor or staff. This will not affect the quality of care that you receive from your study doctor or other staff. If you do decide to leave the study after starting the medication you will be asked to attend, for your safety, a final visit.

Your study doctor can withdraw you from the study, without your agreement for medical reasons or because the Sponsor finds it necessary to limit or terminate this clinical study.

5. What Will Happen To Me If I Take Part?

The duration of the study is approximately 6 weeks and will include 3 visits to see your study doctor. If you are hospitalised, a study nurse or doctor will visit you (see diagram on next page)

Flowchart of Visits and Study Procedures



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If you agree to take part in this study, you will undergo a screening process to determine whether you can participate. The screening process includes the following:

- you will be asked about your signs and symptoms of CDAD
- you will be asked about your medical history (including any medications you are currently taking)
- you will have a brief physical examination by a study doctor
- your vital signs will be checked (blood pressure, pulse, temperature, weight, and height)
- some blood samples (15 ml or about 1 tablespoon) will be collected for laboratory blood tests and to check that you are able to safely enter the study
- an ECG will be performed (a test to measure your heart beat and how your heart is working)
- a urinary pregnancy test will be performed if applicable
- a sample of your diarrhea/stool will be collected for laboratory testing to look at the toxins associated with CDAD and the amount of drug present.

After completion of the screening process, the study doctor or site staff will determine whether you qualify to participate in the study. If you qualify to be in the study and still wish to participate, you will be randomly assigned (by chance, like flipping a coin) to receive one of the two study drugs. Half of the research study subjects will receive PAR 101 (OPT-80) and the other half will receive the other drug called vancomycin. Vancomycin is known to work against CDAD. The doctor will ask you to take a pill 4 times a day for 10 days. If you are randomised to receive vancomycin, each of the four pills will contain vancomycin. If you are randomised to receive PAR 101 (OPT-80), two of the four pills will contain PAR 101 (OPT-80), the other two will be a placebo. A placebo is a pill that looks like the genuine medicine but which has no active substance in it. Whether you take vancomycin or PAR 101 (OPT-80) you will be receiving the dose that is believed to be correct for treating your CDAD. The placebo pills are to make sure that neither you, nor your study doctor, will know which of the two study drugs you have been given during the study, though your study doctor can find out if they need to.

The study doctor or one of their staff will visit you or contact you every day you are on the study medication to discuss how you are feeling. Based on how you are feeling, you may be asked to provide additional blood samples and an ECG test during this time.

Once you have finished your study medication, you will again be asked about your symptoms and a physical examination, a check of vital signs (blood pressure, pulse, temperature, weight and height), laboratory blood tests, and an ECG test will be performed. You will be asked to provide a stool sample for laboratory testing.

Once a week for four weeks after the end of study drug treatment, the study doctor or his staff will contact you either in person or by telephone to discuss if you are still having symptoms. At the end of the study you will be asked to return see your study doctor to discuss if you are still having symptoms, have a physical examination and they will check your vital signs (blood pressure, pulse, and temperature).

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If the symptoms return within the four week period after stopping the study medication, you will be asked to visit the study doctor to have your vital signs checked and provide a stool sample for laboratory testing. If there is a return of your symptoms, you may be placed on additional antibiotic therapy for CDAD by your study doctor.

If at any time during your study participation your study doctor feels that it is in your best interest to receive other CDAD treatment, you will be withdrawn from the study and you will be treated for your CDAD with treatment that is considered standard of care. PAR 101 (OPT-80) or vancomycin treatment will also be stopped if severe side effects occur, if you or your study doctor wishes to discontinue treatment, or if Optimer Pharmaceuticals, Inc. (the Sponsor of the study) find it necessary to limit or terminate this study. You will continue to be monitored for four weeks after you finish taking your study medication.

Expenses And Payments

You will not receive money or any other form of compensation for taking part in this trial. The visits to the study clinic, the examinations and the study medication will be at no cost to you. Reasonable travel expenses may be reimbursed depending on your circumstances.

6. What Do I Have To Do?

If you choose to take part in this study, you will have to participate in the daily assessments of symptoms during the ten day treatment period and take all your medication every day. If you are an outpatient, you will have to visit the hospital three times and participate in telephone calls with the study doctor or nurse in between visits. Study worksheets can be provided to you to record your symptoms of CDAD. You do not have to do this but these are available as a memory aid if you may find this useful.

You should tell the study doctor or nurse if you have had any problems or started or stopped any medication. You should not take part in any other clinical trials whilst you are involved in this study.

If you are pregnant or breast-feeding, you will not be allowed to participate in the study. If you are a woman able to have children, you must use an effective method of contraception for the duration of the treatment and for four weeks after the study treatment. Should you become pregnant during the study, you must tell your doctor immediately. If you are a male you must agree to use a condom to avoid conception.

You should consult the study doctor if you are asked to take any other antibiotics than the study medication.

7. What Is The Drug Being Tested?

PAR 101 (OPT-80) is an antibiotic that targets *C. difficile* in particular and does not have any effect on most of the other bacteria found in the gut. It has been tested on animals,

and in three previous trials in humans. PAR 101 (OPT-80) is a 200 mg capsule that must be taken by mouth twice daily.

8. What Are The Alternative Treatments?

If you do not wish to participate, there are medications, which are not experimental, that are available to treat your illness as alternatives to participating in the study. They include, but may not be limited to, vancomycin and metronidazole. You may decide to receive these other available treatments. Your doctor will discuss these options with you.

9. What Are The Side Effects Of The Treatment Received When Taking Part?

All medications have the potential to cause some side effects or other reactions.

In a recently completed Phase 2B/3 trial, 302 subjects received PAR 101 (OPT-80). Of these 302 subjects, 187 reported side effects or other reactions. The following side effects were found to occur in greater than 2% of the subjects in this trial:

Nausea, hypokalaemia (low potassium), headache, vomiting, pyrexia (fever), oedema peripheral (build-up of excess fluid in the body tissues), urinary tract infection, dizziness, dyspnea (shortness of breath), anaemia (low protein in the blood), constipation, diarrhea, abdominal pain, hyperkalaemia (high potassium), rash, hypoglycaemia (low blood sugar), hyponatraemia (low sodium in the blood), hypotension (abnormally low blood pressure), dehydration, pneumonia, fatigue, pain, fall, arthralgia (joint pain), renal failure (kidney failure).

Of the side effects reported for subjects receiving PAR 101 (OPT-80), 29 were considered by the study investigators to be drug-related.

Of the 302 subjects that received PAR 101 (OPT-80) in the completed Phase 2B/3 trial, 75 subjects reported serious side effects. The following serious side effects were seen in 3 or more subjects: Cardiac failure congestive, gastrointestinal haemorrhage, anemia, pneumonia, renal failure acute, clostridium difficile colitis, sepsis, atrial fibrillation, blood uric acid increase, hypoglycemia, hypophosphataemia (low concentrations of phosphates in the blood).

In animal studies, some dogs had side effects after receiving an injection of PAR 101 (OPT-80) and another substance used to dissolve the drug in liquid. (If you get PAR 101 (OPT-80) in this study, you will not get the additional substance.) The additional substance may have caused these side effects, and researchers do not know whether these side effects can happen in people who take the capsule form PAR 101 (OPT-80). Researchers don't know if the side effects that happened to dogs can also happen to people. Ask the study doctor for more information about this.

With vancomycin taken orally some side effects may occur: Indigestion or stomach ache may occur. Also, dizziness, difficulty hearing, fever or chills. In the unlikely event you have a serious allergic reaction to this drug, seek immediate medical attention. Symptoms of a serious allergic reaction include: rash, itching, swelling, severe dizziness, breathing trouble. Under rare conditions, kidney failure has occurred in patients that receive high dosages of vancomycin over long periods of time.

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In addition another very rare reaction known as red-man syndrome, which appears as a rash usually in the face, neck, and body and is accompanied with itching, muscle aches, rapid heart rate, low blood pressure and hives may be seen.

10. What Are The Other Possible Disadvantages Of Taking Part?

As with many drugs, there is a small possibility of having serious complications or death from a number of causes such as heart, lungs, liver, kidney, intestines, other digestive organ problems, urinary tract, vascular problems and other coexisting conditions and illnesses. Most of these side effects or allergic reactions are reversible once the medication is stopped.

There is a slight risk of side effects from the routine blood tests that will be required throughout the study. These may include bruising at the site where you will have blood taken from, as well as possible inflammation (swelling, pain, redness) of the vein or an infection at this site. Of course, care will be taken to avoid these complications.

There may also be side effects and discomforts that are not known at this time. Additionally, there may be risks to the unborn child that are not known at this time. However, you will be informed of any significant new findings about the study medication to which you are randomly assigned for this study, which may or may not affect your willingness to continue your participation.

11. What Are The Possible Benefits Of Taking Part?

If the study medication is effective, you may benefit by having some relief of your symptoms. If your symptoms do not improve you will be transferred to a standard therapy for CDAD recommended by your doctor. It is possible, however, that no therapeutic or other direct health benefits may result during or following completion of this study. Information from this study may help researchers understand the diagnosis and treatment of this disease.

12. What If There Is A Problem?

Any complaint you may have about the way you have been dealt with during this study or any harm you might suffer will be addressed. The detailed information about this will be found in Part 2.

13. Will My Taking Part In The Study Be Kept Confidential?

Yes, all the information about your participation in the study will be kept confidential. The details are included in Part 2.

14. Contact Details

If you have any questions, please contact: << name of site contact (PI) and telephone number>>

15. What if I have any concerns?

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If you have any questions about your rights as a research patient, or concerns or any other questions about this study or the way it has been conducted, you should contact <<investigator name>> or you may wish to contact <<PALS details [where applicable]>>.

This completes Part 1 of the information sheet.

If the information in part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

16. What If Relevant New Information Becomes Available?

Sometimes during the course of a clinical trial, new information becomes available about the drug being studied. If this happens, your study doctor will tell you about it and discuss whether you should, or want to, carry on with the trial. If you, or your study doctor, decide you should not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue, you may be asked to sign an updated consent form.

17. What Will Happen To Me If I Don't Want To Carry On With The Study?

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

You have the right to cancel this consent at any time. If you cancel this consent, then <<site name>> and <<investigator name>> will no longer use or disclose your medical information, unless it is necessary to do so to preserve the scientific integrity of the study. However, cancelling this consent will not affect previous uses and disclosures and your medical information would not be removed from the study records.

If you fail to give your consent by signing this consent form, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any study treatment. Unless and until you do cancel the consent, it will remain valid and effective.

18. What If There Is A Problem?

Complaints:

Your NHS hospital is responsible for your care during the study. All NHS hospitals have procedures for dealing with complaints or any concerns about any aspect of the way you have been approached or treated during the course of the study. If you have a concern about any aspect of this study, you should ask to speak with the study doctor or a member of their research team who will do their best to answer your questions. If you remain

unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Harm:

If you are harmed as a result of participation in this study and it is not due to negligence or in the event of a study-related injury and if you experience an adverse reaction (side effect) <<name(s)>> can be reached at <<phone number(s)>> at any time.

Tell the study doctor if you think that being a subject in this study has caused you to be harmed. The study doctor will tell you if you can get medical care for your problem and how to receive it.

Optimer Pharmaceuticals, Inc (the Sponsor of this study) is covered by insurance, which protects you in case of any problems caused by the study. We will provide compensation for any injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).

We will provide compensation where the injury probably resulted from:

- A drug being tested or administered as part of the trial protocol
- Any test or procedure you received as part of the trial.

Any payment would be without legal commitment: (please ask if you want more information on this).

We would not be bound by these guidelines to pay compensation where:

- The injury resulted from a drug or procedure outside the trial protocol
- The protocol was not followed

You can get a copy of these guidelines should you wish. Please ask your study doctor for details.

19. Will My Taking Part In This Study Be Kept Confidential?

For purposes of this study, <<site name>> and <<investigator name>> will use medical information collected or created as part of the study, such as medical records and test results, which identifies you by name or in another way. Your consent to participate in the study means you agree that <<site name>> and <<investigator name>> may obtain your medical information that they request for study purposes from your study doctors and your other health care providers. You are also agreeing that <<site name>> and <<investigator name>> may use and share this information with the parties described below. Data collected during the study may be sent to countries, as described below, where the laws do not protect your privacy to the same extent as the Data Protection Act in the UK but all reasonable steps to protect your privacy will be taken by the companies involved. In addition, you agree that, during the study, you may not have access to some of your medical information obtained or created as part of this study. You will be allowed to access this information once the study is finished.

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Unless required by law, <<site name>> and <<investigator name>> will share this medical information only with other doctors and healthcare workers taking part in this study, Optimer Pharmaceuticals, Inc (the study Sponsor) and their authorised agents, INC Research and the U.S. Food and Drug Administration (FDA) for US, and the European Agency for the Evaluation of Medicinal Products (EMA) for Europe, governmental agencies in other countries where the study drug may be considered for approval, and the Independent Ethics Committee. The purpose for using and sharing this information with these parties is to perform the study and to ensure the accuracy of the study information. Your permission to use or give out your health information for the purposes of this study does not stop automatically. It continues indefinitely.

The results and other information from this study may be submitted to the FDA and European and other governmental agencies in other countries where PAR 101 (OPT-80) may be considered for approval.

If you agree to take part in this study, then your information will be passed on to researchers and regulatory authorities in countries that do not provide the same protection as in the UK.

With your permission your GP will be notified of your participation in the study. In addition, other medical practitioners not involved in the study may also need to be notified. We will ask your permission that these parties can be informed (please see the consent form).

20. What Will Happen To Samples I Give?

Some of the blood and stool samples collected during the study will be used to measure the amount of the study drug (PAR 101 (OPT-80)) in your blood and stools and also to try and identify the strain of *C. difficile* that you are infected with. For this purpose, the samples will be transported to a laboratory in Switzerland. All your samples will be identified only by your subject number and study number. After the study is complete, they will be destroyed.

21. What Will Happen To The Results Of The Clinical Trial?

The results of the trial may be presented at scientific meetings or published in scientific journals or books. In no case will you be identified in any presentation or publication.

22. Who is Organising and Funding the research?

The Trial is being funded by Optimer Pharmaceuticals, Inc of California. It is being organised by INC Research of North Carolina in North America, and INC Research in Europe.

The Sponsors of this study will pay (name of hospital NHS Trust) for including you in this study.

23. Who has Reviewed this Study?

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This study was given a favourable ethical opinion for conduct in the NHS by the Berkshire Research Ethics Committee.

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CONSENT FORM

Title of Project: PAR 101 (OPT-80) versus vancomycin in the treatment of *Clostridium Difficile*-associated diarrhoea

Name of Researcher: <<investigator name>>.....

PLEASE INITIAL BOX

1. I confirm that I have read and understood the information sheet dated 6 May 2009 (version 6) for the above study and have had the opportunity to ask questions.
2. I confirm that I have read and understood this document in English, and that I do not need the information I have received to be translated into another language.
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from Optimer Pharmaceuticals, Inc or companies acting on their behalf (INC Research), or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
5. I agree that my GP and other medically qualified people who may assist in my care during the study may be notified of my participation in the study.
6. I agree that data about me relating to this study may be sent to countries that do not have data protection laws that are similar to those in the UK.
7. I agree to take part in the above study.

☐☐☐☐☐☐☐

Name of Patient

Date

Signature

Name of Legal Guardian

Date

Signature

Name of Person taking consent

Date

Signature

1 for patient / legal Guardian; 1 for researcher; 1 to be kept with hospital notes

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CONSENT FORM FOR YOUNG PEOPLE (aged 16 to 18)

Young person to circle all they agree with, please:

Have you read about this project? Yes/No

Has somebody explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked the questions you want? Yes/No

Have you had your questions answered in a way you understand? Yes/No

Do you understand it is OK to stop taking part at any time? Yes/No

Are you happy to take part? Yes/No

If any answers are “no” or you **do not** want to take part, **do not** sign your name!

If you do want to take part, please write your name and today’s date:

Your name: _____

Date: _____

Your parent or guardian must write their name here too if they are happy for you to take part in this project

Print name: _____

Sign: _____

Date: _____

The doctor who explained this project to you needs to sign too:

Print name: _____

Sign: _____

Date: _____