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Randomised treatment of Acute Pancreatitis with Infliximab: Double-blind multi-centre trial (RAPID-I)

Professional Legal Representative Information Sheet

Contents

Your patient is invited to take part in RAPID-I

RAPID-I is a study testing a medicine called infliximab to treat acute pancreatitis (a disease of your patient's pancreas).

This information sheet has been given to you because your patient may be eligible to take part in this study, however they are lacking capacity to make this decision for themselves and there is no suitable relative or friend available to act as their personal representative. You are eligible to act as your patient's professional representative, if you wish, to give consent on your patient's behalf.

Your patient does not have to take part in this study and you are free to decide whether or not you wish to make this decision on behalf of your patient. You are being asked to consider what your patient would want if they could make this decision themselves; please set aside your own personal views when making this decision.

Before you decide if your patient would wish to take part, it is important for you to understand why the research is being done and what it will involve for your patient.

When your patient regains capacity, they will be given an information sheet similar to this one and they will be asked if they would like to consent to their continued participation in this study or not. You will be informed of this.

Before you decide whether you would like your patient to take part it is important for you to understand why the research is being done and what it will involve for your patient.

Please ask a member of the research team if there is anything that is not clear, or if you would like more information.

Thank you for taking the time to read this information sheet. We hope you will find it helpful.

Important things to know

In this study we will test a medicine called infliximab to treat acute pancreatitis. We will compare two different doses of infliximab (in a solution of salt water) with a placebo (salt water containing no infliximab) to find out if infliximab is effective and safe for acute pancreatitis. We also wish to see how genes (which your patient was born with) work in acute pancreatitis, and if there is a link

between the way genes work and the way infliximab works.

If you choose for your patient to take part, they will be put into one of three groups. These three groups are:

- 5 milligrams of infliximab per kilogram body weight
- 10 milligrams of infliximab per kilogram body weight
- Placebo (saline)

The study medicine will be given through a tube into one of your patient's veins.

The study is for adults aged from 18-85.

Why are we doing the RAPID-I study?

Acute pancreatitis is a common and serious disease that needs emergency admission to hospital, but there are no medicines to cure the illness or speed up recovery. Acute pancreatitis causes severe pain in the stomach area, loss of hunger, sickness and vomiting. In one out of every three or four patients part of the pancreas may die and become infected. Usually infection has to be drained away through the skin or by endoscopy (camera passed through the mouth) or by surgery.

In one out of every ten patients the lungs, heart or kidneys may stop working well and if this happens patients may need to spend time on the intensive care ward. Patients with very bad acute pancreatitis may need to stay in hospital for three months or more and a number of patients die from acute pancreatitis (three to five out of every one hundred patients).

Infliximab is a medicine that may help patients with acute pancreatitis by stopping swelling and soreness (inflammation) in the pancreas and other parts of the body. If infliximab is given early it is possible that infliximab may stop more serious acute pancreatitis with all its problems and may help patients with acute pancreatitis get home and back to normal more quickly. On the other hand, infliximab may have no effect on acute pancreatitis, so we wish to test it to find out if it works or not. Several million people in the world have been treated with infliximab and medicines like it for bowel and joint disease, but it has not been tried in acute pancreatitis. This study is called RAPID-I because it will test the medicine as soon as possible (rapidly) after patients have come to hospital with acute pancreatitis, and because it is the first study (number one) to do so.

The results of this study will be used to develop new treatments for patients with acute pancreatitis.

Why has your patient been asked to take part?

We are inviting your patient to take part in this study because they have been diagnosed with acute pancreatitis at one of the hospitals in the study.

The study aims to recruit 290 patients.

What will your patient have to do if they take part?

If you decide your patient would wish to take part, you will be asked to sign a consent form on behalf of your patient to confirm you want them to take part in the study. You will be given a copy of the consent form and the information sheet to keep.

After you have given consent on behalf of your patient, they will be put into one of the three groups. The study medicine will be given within 36 hours from onset of their abdominal pain. The study medicine needs to be given quickly to give it the best chance of working. They will also be given antibiotics into a vein. Patients treated with infliximab have a slightly increased risk of developing infection so antibiotics are given to reduce the risk of infection.

While your patient is in the study, the research team will record details about them that are part of standard care:

- How bad their pain is
- How their heart, lungs and kidneys are working
- The ward they are on (normal or intensive care)
- Blood, urine and other tests they have
- The cause of their acute pancreatitis
- Any treatment they have

We wish to collect blood samples during the study. The study blood samples will be used to find out if infliximab is helping to treat acute pancreatitis or not. For this we will measure a protein in the blood that is linked with acute pancreatitis, up to 28 days after the study medicine has been given. Whenever possible blood with be taken

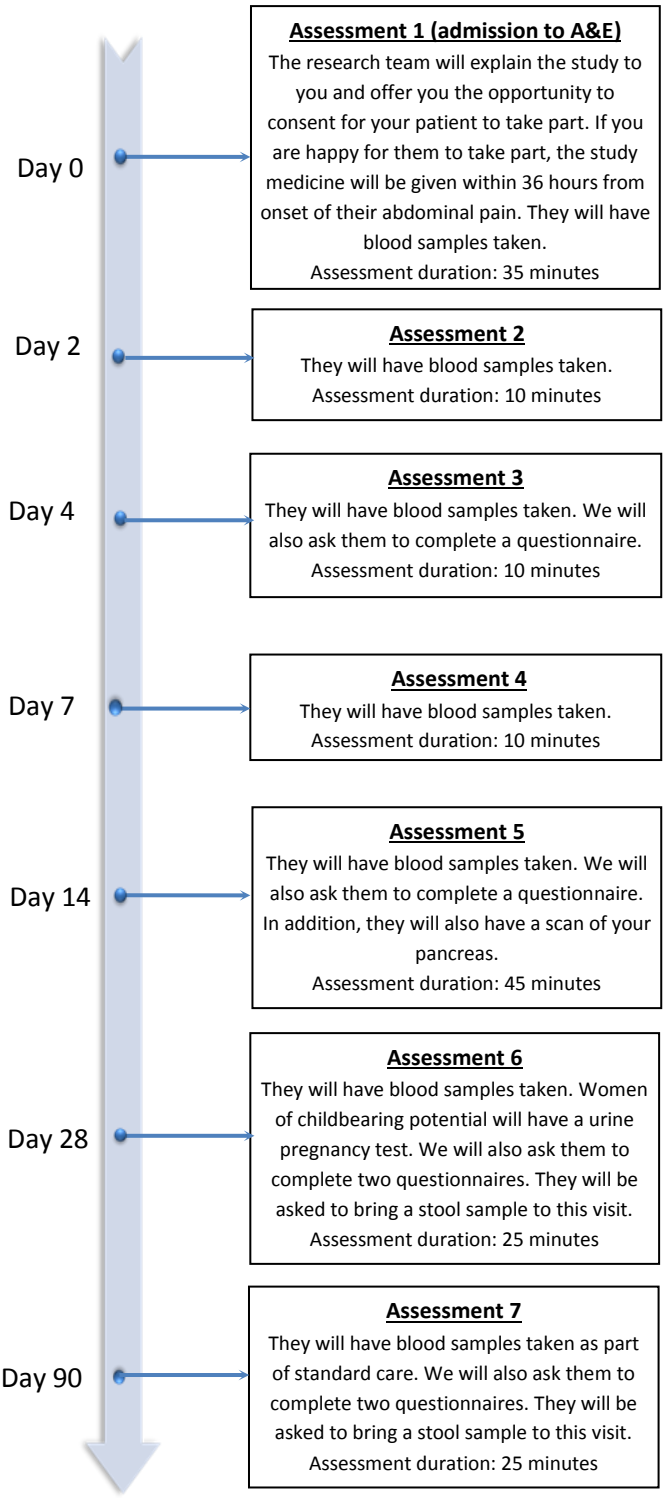
at the same time that routine samples are taken. When blood samples are taken for the study, the amount taken will be about 1 ½ tablespoons of blood. We will also check whether your patient may have hepatitis B virus before starting the study. If they are not known to have hepatitis B before starting the study, this will not stop them taking part, but if they are found to have hepatitis B they might need treatment for it. The study blood samples will also be used to check the levels of study drug in their blood, to check if they develop resistance to infliximab, to see how acute pancreatitis has affected your patient's immune system (parts of the body that fight infection) and to see if there are any links between the way genes work in acute pancreatitis and the way infliximab works. On two occasions we will ask your patient to provide stool samples to help tell us how well their pancreas is working.

On one occasion in the study your patient will have a CT scan of their pancreas, which is something patients may have as part of standard care for acute pancreatitis.

Your patient will be asked to complete questionnaires about how they are, and what treatment they have (up to a maximum of 6 questionnaires over 90 days).

The study will run for 90 days from when your patient is given the study medicine. If they are sent home from hospital while they are in the study they will be asked to come back to the hospital for the study assessments. They would usually have to attend hospital once more than normal in standard care (Assessment 5 at Day 14). If they are still in hospital at the time of the study assessments, they will have these in hospital.

Timeline of assessments



How will I know which treatment my patient is going to have?

In research we often split patients up into groups to study how different treatments work. Patients in one group get a different treatment from patients in another group. In the RAPID-I study there are three groups:

- 5 milligrams of infliximab per kilogram body weight
- 10 milligrams of infliximab per kilogram body weight
- Placebo (saline with no infliximab)

It is very important that each group in the RAPID-I study has a similar mix of patients, so we know that if one group of patients does better than the others, it is very likely because of the treatment and not because this group has a different mix of patients. A single injection of hydrocortisone and chlorpheniramine will be given to reduce the chance of any reaction from infliximab, as well as a course of antibiotics to reduce the chance of infection. These extra medicines will also be given to your patient if they receive placebo so we can be sure that any difference in outcome between infliximab and placebo is due to infliximab and not the extra medicines.

We use a computer programme that puts patients 'at random' into one of the groups – you might hear this described as 'randomisation' or 'random allocation', but they all mean the same thing. Neither you nor your patient choose what group your patient will be in.

In the RAPID-I study, patients will be randomised equally to each of the three groups, so this means that your patient has the same chance of being put into each group.

This study is also a "blinded trial", which means that neither you, your patient nor the research team will know which treatment your patient will be given. The pharmacist who prepares the study medicine will know which group your patient is in and this information will be available to the research team if needed in an emergency.

What are the benefits and risks of taking part?

By taking part in this study your patient's symptoms of acute pancreatitis may get better although it is also possible that infliximab may have little or no effect. Infliximab helps in bowel and joint disease and early research shows that infliximab may help patients with acute pancreatitis but we do not know, so we wish to find out by doing this study.

The results of this study may help others with acute pancreatitis and will be valuable in developing new medicines to treat acute pancreatitis.

Millions of patients in the world have been treated with infliximab for various diseases. Infliximab is a safe medicine and usually very well tolerated. Side effects from infliximab are uncommon. Most side effects occur when infliximab is given more than once, unlike in this study that tests a single dose of infliximab.

The two side effects that could occur with a single dose of infliximab, although unlikely, are allergic reactions (also known as infusion reactions) and infections.

Some patients (fewer than 5%) develop an infusion reaction while the medicine is given. This may cause headache, muscle ache, dizziness, low or high blood pressure, itching, fever, rash, flushing, sneezing, shortness of breath, stomach problems with nausea and vomiting, chest tightness, redness of the skin, sweating, shivers, light-headedness, sleepiness or racing of the heart. These side effects are usually mild to moderate and can usually be treated with drugs. All patients in the RAPID-I study will receive a single injection of hydrocortisone and chlorpheniramine before the trial medicine is given, to reduce the chance of an infusion reaction. If the side effects are serious, you or your patient's research doctor may consider stopping the study treatment. Infusion reactions occur in up to one in 20 patients having their first infliximab infusion. No deaths have been reported.

Another rare event that may occur one to 14 days after the infusion is a reaction that takes a while to develop (known as a delayed hypersensitivity reaction). This may cause fever, rash, headache, sore throat, muscle or joint pain, hand and face swelling or difficulty swallowing.

Infliximab is a medicine made of proteins from humans and mice. It is possible that your patient's body could react against the medicine. Then if they have other medicines in the future that contain mouse proteins their body might react again. Your patient should tell doctors in the future that they may have been treated with mouse proteins in this study. With your consent, your patient's GP will be told by letter they are taking part in this study. The letter will contain details of the study medicine your patient may have.

Some patients given infliximab have simple infections such as the common cold, while other patients get more severe infections such as pneumonia or infection of the

blood. About one in 100 patients treated with infliximab could develop a serious infection, so all patients in the RAPID-I study will be given antibiotics to help stop infection as well as medicines to reduce reactions. You should let the research team know if your patient has a history of infection (if known). If your patient develops an infection during the study, you or your patient should discuss this immediately with the research team.

Some patients have had tuberculosis (also called TB, a lung infection) during a course of infliximab, and a few have died from this. Although the risk from one dose is unknown, it is possible that your patient may have more of a chance to get tuberculosis if they receive infliximab. If your patient or any of their close family members have had tuberculosis, you should inform your research team (if known), so they do not enter the study, to prevent tuberculosis. If you have any reason to suspect that your patient may have been exposed to tuberculosis in the past, you should inform the research team so they do not enter the study.

Other side effects after a single dose are rare. Side effects such as skin, joint and heart problems usually occur after infliximab has been given more than once.

Patients who are pregnant or breastfeeding cannot take part in the study. If your patient is a woman who could become pregnant they will be asked to have a pregnancy test before and during the study and must use contraception throughout the study and for a short time afterwards (until 6 months after receiving the study medicine). If your patient becomes pregnant while they are in the study they should immediately tell the research team. Women who become pregnant during the study will be closely monitored and expected to return for all study visits. Medical information about any pregnancies or breastfeeding during the study will be collected.

As part of the study your patient will have one CT scan 14 days after coming into hospital. Your patient's doctors will be able to use this CT scan for your patient's standard care, and may request that they have further CT scans for their standard care if their illness is more severe. The radiation from a single CT scan is low, but with repeated CT scans a small increase in the risk of cancer has been found. By taking part in this study it is estimated that over your patient's lifetime the increase in their risk of cancer is roughly 1 in 1100.

The research team will ask your patient about any side effects they have had at every assessment and will record them for the study. If your patient suffers from any of the side effects, or any other problems that you/they feel are not normal during the study, you/they should let the research team know at once.

What are the alternatives for treatment?

There is no other medicine to stop damage in the pancreas and other parts of the body, or to help patients with acute pancreatitis get home and back to normal more quickly. There is no other medicine to stop more serious acute pancreatitis. Feeding may have to be given in cartons of liquid (supplements) or through a tube in your patient's nose or into a vein. If parts of the pancreas die and become infected then removal by endoscopy (camera passed through the mouth) or surgery may be needed. If the lungs, heart or kidneys stop working well, then your patient may need to go to intensive care.

Does your patient have to take part?

No, taking part is voluntary. It is up to you to decide whether or not your patient would object to taking part. If you decide your patient would wish to take part you can also choose to stop their participation at any time without giving a reason, for the duration of time they are deemed to be lacking capacity. The standard of care your patient will receive now or in the future will be the same whether they take part or not.

What happens if I change my mind?

If at any point you decide to stop your patient from taking part in the study, they will receive the treatment and follow up usually offered by their hospital. If you do decide to stop your patient from taking part we will ask you if you think your patient would wish to:

- Complete the follow up visits for the study
  OR
- Stop taking part with no more study visits

The research team may be required to collect some limited information about any side effects your patient

may have as a result of taking part in this study. This will only be collected if required by the regulatory authorities.

Will my patient's participation be kept confidential?

Yes. All information collected about your patient during the study will be handled according to all applicable ethical and legal requirements.

Their NHS hospital will collect information from them and their medical records for this research study, in accordance with our instructions.

Your patient's NHS hospital will use their name, NHS number and contact details to contact them about the research study, and make sure that relevant information about the study is recorded for their care, and to oversee the quality of the study. Individuals from the University of Liverpool (the research team and representatives of the study Sponsor) and regulatory organisations may look at their medical and research records to check the accuracy of the research study. Your patient's NHS hospital will pass these details to the University of Liverpool along with the information collected from your patient and their medical records. The only people in the University of Liverpool who will have access to information that identifies your patient will be people who need to contact them and/or audit the data collection process. The people who analyse the information will not be able to identify your patient and will not be able to find out their name, NHS number or contact details. Your patient's NHS hospital will keep identifiable information about your patient from this study for up to a maximum of 25 years after the study has finished.

Your patient will be given a study number, which will be used on each paper form that records details about their care and participation in the RAPID-I study. Both you and your patient's full name will be included on their consent form and a copy of this will be sent to the coordinating centre for the study, the Clinical Trials Research Centre (CTRC), which is part of the University of Liverpool. Every effort will be made to remove your patients name from any further information about them that leaves the hospital, so that they cannot be recognised from it. Your patients name will usually be removed by one of the study team at their hospital, but may be removed by the CTRC upon receipt.

When you agree for your patient to take part in a research study, the information about your patient's health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your patient's information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your patient's information could be used for research in any aspect of health or care, and could be combined with information about them from other sources held by researchers, the NHS or government. Where this information could identify your patient, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact your patient about future opportunities to participate in research. It will not be used to make decisions about future services available to your patient, such as insurance. Where there is a risk that your patient can be identified their data will only be used in research that has been independently reviewed by an ethics committee.

Details about the use of health services (health economics) will be collected in this study. The study team will retrieve information from your patient's electronic hospitalisation records held by their hospital finance department. The collected data will only have their RAPID-I study number attached to it and no other personal identifiable information. Researchers at Bangor University, who are part of the RAPID-I research team, will use these data to calculate the overall costs of care. The data will be securely transferred from the hospital to the CTRC, then from the CTRC to Health Economics researchers at Bangor University using an encrypted electronic transfer system. These data will be collected for the period that your patient is in the study only, and stored securely for no longer than 12 months at Bangor University following the completion of the RAPID-I study, it will then be returned to the University of Liverpool for

long-term storage. Bangor University will act as a joint data controller, with the University of Liverpool.

Safety and pregnancy information will be provided confidentially and securely to the company who supply infliximab (Merck, Sharp and Dohme). Information on patients who are breastfeeding will also be provided confidentially and securely to the company.

What will happen to my patient's blood samples?

All samples will have personal details removed and will be sent to the National Institute for Health Research (NIHR) National Biosample Centre in Milton Keynes for processing and storage. A unique study number will be the only way of identifying their samples. Only the research team will be able to link this unique study number to your patient.

During the study the samples will be transported from the NIHR Biosample Centre to Liverpool Clinical Laboratories, and other UK laboratories approved by the University of Liverpool, for analysis of the results of the study.

Once the samples for this study have been analysed, there may be some sample remaining. Optionally, and with your consent, we wish to keep this for use in future research studies to advance the care and treatment of patients with acute pancreatitis, including for future studies we undertake with researchers in other countries. Any future research will be handled according to all applicable ethical and legal requirements of the UK. The samples will be labelled using your patient's unique study number and securely held for an unlimited time by the NIHR National Biosample Centre.

Limited data collected from this study will be given to the researchers to help them study the samples, including data on your patient's genes. Your patient will not be identified and your patient's clinical information will not be transported or stored in the same place as the samples. Your patient's inherited genes are your patient's and belong to no one else, so if your patient or anyone else made public your patient's inherited genes then it could be possible for your patient to be identified from samples obtained in this study. We will not share your patient's identity with any other researchers and we will remove all links to your patient's identity from any data on your patient's genes we share with other researchers, making it very unlikely that your patient could be identified by taking part in this study.

Any results from future research will not be added to their notes and we will not be able to tell your patient the results of future studies carried out on these samples.

What will happen to the results of the study?

The results of the study will be presented at medical conferences and published in medical journals so that we can explain what the results show. The results of the study will also be made available to participants. Confidentiality will be ensured at all times and your patient will not be identified in any publication.

What if there is a problem?

If you have any concerns about this study, you should ask to speak with one of your patient's 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 your patient's treating hospital.

Every care will be taken in the course of this research study. In the unlikely event that your patient is injured as a result of the organisation (University of Liverpool) managing the trial, compensation may be available, but your patient may have to pay their own legal costs. Your patient's treating hospital has a duty of care to your patient whether or not you agree to their participation in the trial and the University of Liverpool accepts no liability for negligence on the part of your patient's hospital's employees. If your patient is harmed and this is due to someone's negligence, then your patient may have grounds for a legal action for compensation against the NHS Trust where your patient is being treated, but your patient may have to pay for their legal costs in connection with this matter.

Additional information

The University of Liverpool is the sponsor for this study in the United Kingdom. We will be using information from your patient and their medical records in order to undertake this study and will act as a joint data controller

for this study, with Bangor University. This means that we are responsible for looking after your patient's information and using it properly. The University of Liverpool will keep identifiable information about your patient for up to 25 years after the study has finished. Your patient's rights to access, change or move their information are limited, as we need to manage their information in specific ways in order for the research to be reliable and accurate. If your patient withdraws from the study, we will keep the information about them that we have already obtained. To safeguard your patient's rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your patient's information at www.rapid-one.org.uk.

The University of Liverpool is responsible for managing this study; the University of Liverpool has asked that the day-to-day running of the study is carried out by the Clinical Trials Research Centre (CTRC), which is part of the University of Liverpool.

The RAPID-I study has been reviewed for scientific content by the Medicines and Healthcare Products Regulatory Agency (MHRA), the Health Research Authority (HRA) and the National Research Ethics Service Committee. The South Central - Oxford C Research Ethics Committee has reviewed the study and given approval for it to take place.

This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership.

MRC Medical Research Council

NHS National Institute for Health Research

Thank you for reading this information sheet

Contacts for further information

If you would like more information or have any questions about the RAPID-I study please talk to:
Principal Investigator: **<PI NAME>**
Research Nurse: **<RN NAME>**
Telephone: **<number>**

Or visit the website: www.rapid-one.org.uk
If you wish to talk about the study with someone who is not part of the research team you can contact the local NHS Patient Advice and Liaison Service (PALS) or equivalent on: <telephone number>

RAPID-I

Randomised treatment of Acute Pancreatitis with Infliximab: Double-blind multi-centre trial

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Patient's Professional Representative Consent Form

To be completed by the Researcher:

Centre Name:		Patient Initials:			

Once you have read and understood each statement please initial each box	Initial
Example: I confirm that I have read and understand the Patient's Professional Representative Information Sheet.	JS
1. I have read and understood the information sheet for this study. I have had the opportunity to ask questions and have had these answered satisfactorily.	☐
2. I understand that my patient's participation is voluntary and that if at any time I consider that my patient would object to being included, I am free to withdraw them from the study at any time, without giving a reason, and without their care or legal rights being affected. I understand that in some cases further information about any unwanted effects of their treatment may need to be collected by the study team.	☐
3. I understand that my patient's data will be held securely for a maximum of 25 years at site by the Clinical Trials Research Centre (CTRC) of the University of Liverpool and that they will be stored in a confidential manner.	☐
4. I give permission for a copy of this consent form, which will include both my name and my patient's name, to be sent to the CTRC (where it will be kept in a secure location), to allow confirmation that my consent was given, on behalf of my patient.	☐
5. I understand that relevant sections of my patient's medical notes and any data collected during the study may be looked at by authorised individuals from the research team and those listed in 'Will my patient's participation be kept confidential' (above, including NHS Trust and Regulatory Authorities). I give permission for these individuals to have access to my patient's records.	☐
6. I give permission for blood and faecal samples to be collected from my patient and analysed for the study including analysis of my patient's genes.	☐
7. I understand that my patient's safety, pregnancy and lactation data (if applicable) will be sent to Merck Sharp and Dohme.	☐
8. I agree to my patient's health economics (overall cost of care) data being securely transferred from my hospital to the CTRC, who will then securely transfer this to the research team at the University of Bangor for analysis.	☐
9. I agree to my patient's GP being informed of their participation in the study.	☐
10. In my opinion, my patient would not object to taking part in the above study.	☐
For women of childbearing potential only: N/A *(Please tick if not applicable)* ☐ 11. I understand that my relative/friend should use adequate contraception for 6 months after they have received the trial medicine.	☐
Below are optional statements:	
12. I agree to allow my patient's information or results arising from this study to be used in future healthcare and/or medical research.	☐
13. In my opinion, my patient would not object to gifting any of their remaining samples and required data to the University of Liverpool (to be stored at the NIHR National Biosample Centre) for use in any future ethically approved research for acute pancreatitis.	☐

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Patient's Professional Representative Consent Form

To be completed by the Researcher:

Centre Name:		Patient Initials:	

Patient's **full** name (please print):	

To be completed by the patient's professional representative (independent of the study):

Professional representative **full** name (please print):			
Professional representative signature:		Date:	dd / mm / yyyy

To be completed by the Researcher:

Researcher **full** name (please print):			
Researcher signature:		Date:	dd / mm / yyyy