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Participant Information Sheet

COMBINER

The effectiveness of lithium plus quetiapine COMBination versus lithIum versus quetiapiNe monothErapy in the maintenance treatment of bipolar disordeR: the COMBINER trial

Summary of the COMBINER trial

- This trial is looking at two types of medication, lithium and quetiapine. These are used as "maintenance treatment", which means patients take them in the longer term to reduce the risk of having major periods of depression or feeling elated. We are investigating whether these drugs taken together or on their own are better at reducing the chances that a person will experience these episodes in the longer term.
- We know both medications work, but we don't know which is better, or if combining the two could be best.
- Joining the trial is voluntary. Before you decide if you would like to take part, we would like to give you information about why we are doing the research and what it will involve. If you decide not to take part, your usual care will not be affected in any way.
- Please take the time to read this information sheet fully. Feel free to talk to others about the trial if you wish.
- You will have the opportunity to discuss the trial with a member of the research team and there will be time to ask any questions you may have.
- Please read on or visit our online information for more information:

<tba>

Why have I been invited?

We are inviting you to take part because you have a diagnosis of bipolar. This means you may be eligible to take part in the **COMBINER** trial and receive your treatment as part of the trial.

Do I have to take part?

No, this is up to you. Taking part is voluntary. You do not have to take part if you do not want to, and this will not affect the care you receive. We are giving you this information so you can consider it carefully before you choose. Feel free to discuss it with friends and family, and if there is anything that is not clear, please do speak to a member of the care or research team.

Why are we doing this research?

Bipolar is a serious mood disorder which affects about one in 50 people in the UK. Complications include mood episodes of mania and depression, which can lead to hospitalisation as well as work and relationship problems.

Long-term treatment reduces the number of mood episodes that someone experiences. We call this maintenance treatment. It is very important for controlling bipolar long term. Maintenance treatment usually means a mood stabiliser, such as lithium, or an antipsychotic, such as quetiapine.

In the **COMBINER** trial we are looking at whether taking lithium and quetiapine together is better than either one taken alone. Both are already used to treat bipolar, but we're not sure if either one or both taken together is better at helping reduce mood episodes. We also don't know if using both together is acceptable to people in terms of other bipolar symptoms, side effects, and convenience.

What is randomisation?

When we don't know which treatment option is best, we need to compare them. To make a fair comparison we use 'randomisation'. Most large trials use randomisation. This means everyone taking part is randomly allocated to the treatment choices in the trial. This is to avoid bias – like personal preferences affecting how people are treated or assessed.

If the groups of participants receiving each treatment are similar, then any differences in the overall results should be because of the treatment. Randomisation makes results more reliable.

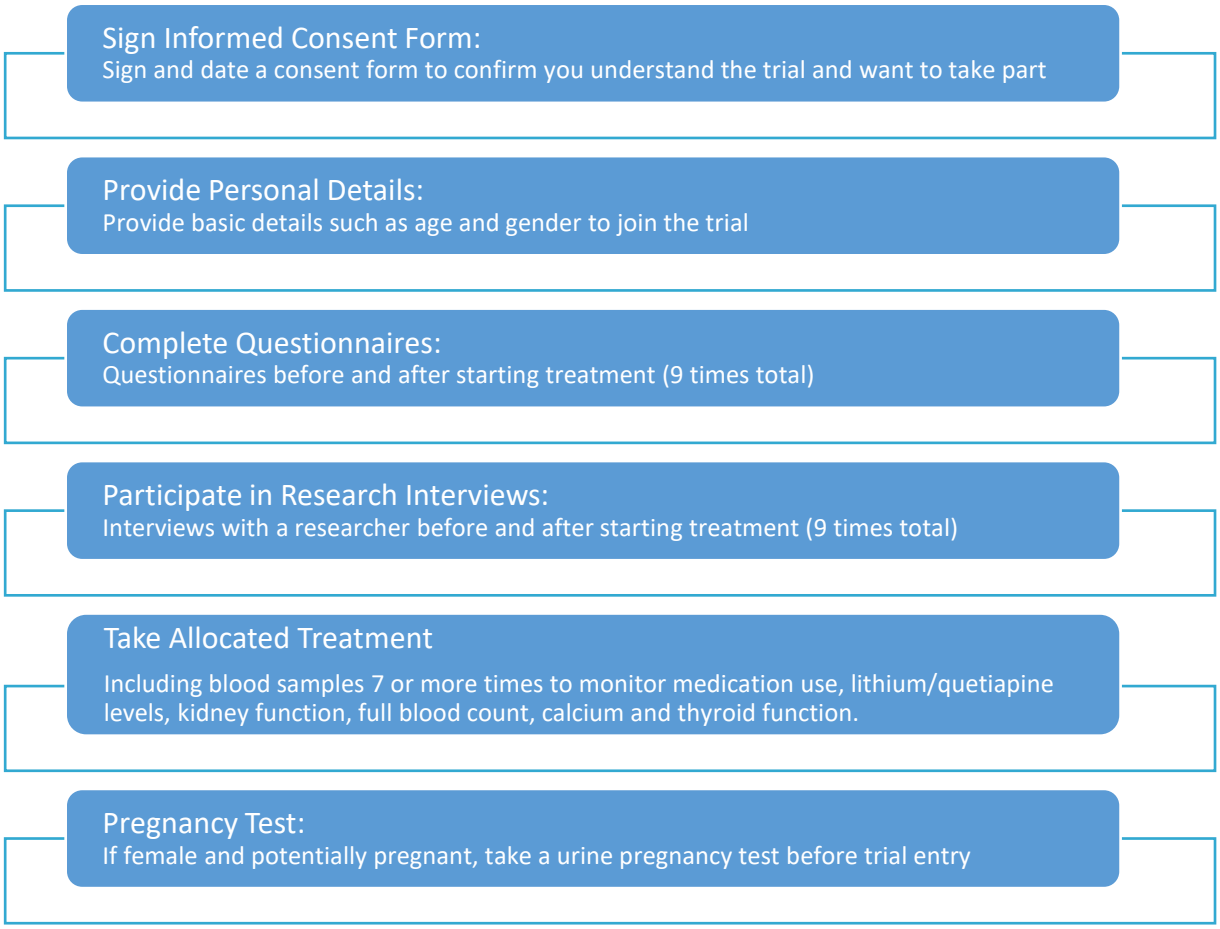
In the COMBINER trial, there is an equal chance of being allocated to one of three groups:

- **Lithium**
- **Quetiapine**
- **Lithium *and* quetiapine**

Neither you nor your care team will choose which group you will be allocated to. The rest of your care will continue as normal. You will be told your allocation when you enter the trial. Your trial treatment will then be prescribed and managed by a doctor from your Trust approved for the trial.

What would taking part involve?

If you decide to take part, we will ask you to do the following over the next 24 months:



There is a researcher with lived experience of bipolar on the team. They are available to help you with decisions about trial entry, if you want to know anything about the trial during it, and if you start the trial and then decide you don't want to take part anymore.

What will I be asked to do if I agree to participate in the trial?

This first visit will take place in clinic where you will meet a member of the local research team. This visit will last about two hours. Other trial visits can be done by phone or video call if it suits you better.

FIRST VISIT

At this visit you can ask any questions. You will be given time to think about if you would like to take part. If you decide you would like to take part, you will be asked to sign and date the online consent form. The doctor will also sign this and email you a copy (you can have a paper copy if you prefer).

During this visit you will be asked some questions about your medical history. Your blood pressure, waist, height and weight will be measured. You may be asked to give up to four blood samples depending on when the last one was taken. All samples will be about four millilitres, about the same as a teaspoon. These are to measure your blood sugar levels, kidney function and full blood count and will not be stored. An electrocardiogram (ECG) may also be taken, depending on when you last had one. An electrocardiogram is a quick, painless test that measures the electrical activity of your heart, such as your heartbeat. Small sticky pads, called electrodes, will be placed on your arms, legs and chest. The electrodes are connected by wires to the ECG machine which picks up the electrical signals that make your heartbeat.

We will ask you to complete a set of questionnaires on a tablet. These questionnaires will include questions related to your mental health, education, employment and general health and wellbeing. Your researcher will also ask you questions in the form of a research interview, which is how we assess symptoms and side effects in bipolar related research.

Once the assessments have been done and your doctor has confirmed you are eligible, you will be randomly allocated to lithium, quetiapine, or both together. This will be done using an online system. You will be told which treatment you have been allocated to and the doctor will prescribe it for you to collect as you would any other prescription.

TREATMENT

Your trial treatment can be taken at home as advised by your doctor.

If you are allocated to start lithium, you will be given a lithium treatment pack to record your treatment details. You will need to attend for a weekly blood test whilst the lithium is slowly increased. This is so the blood level of the medicine is within the range we know is best for maintenance treatment. Once it is at the right level, you will have blood tests every 3-6 months to check it stays at this level, and if you change dose.

If you are allocated to both lithium and quetiapine, you will start one treatment before the other. You should not start both treatments at the same time. You can discuss with you doctor which treatment is best to start first. You will continue taking you first treatment for a period of 4 weeks before the second treatment is commenced.

Table 1: Summary of the visits and how long they should take

What happens at each visit?	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
Have online research interview (about 30 minutes)	✓	✓	✓		✓	✓	✓	
Have a full online research interview (about 90 minutes)				✓				✓
Complete questionnaires (about 15 minutes)		✓		✓		✓		✓
Blood tests for kidneys, blood sugar, etc. (15 minutes, local team)	✓	✓	✓	✓				✓
Blood tests for medication (15 minutes, local team)	✓	✓	✓	✓		✓		✓

Physical checks: Blood pressure, height and weight, pulse (15 minutes, local team)		✓		✓		✓		✓
Electrocardiogram (15 minutes, local team)				✓				✓

FOLLOW UP VISITS – 3, 6, 9, 15, 18 and 21 months

After you have been allocated a treatment, we will follow you up every three months for two years so we can monitor how you are doing and find out which treatment is better long term.

We will send you a link to complete trial questionnaires on your personal device. These should take about 15 minutes. These will ask you about treatment and any side effects you may have had. You can have help with these on the phone if you don't have access to a phone or computer to complete them on.

We will also repeat some of the research interviews to find out how you have been doing with your bipolar. These can be done via telephone or video call. This should take about 30 minutes.

The research interviews will be done by a researcher based at a different hospital in the trial. This researcher will not know your allocated treatment. Keeping a treatment hidden is known as 'blinding' and means the researcher won't be biased about it when they assess you. It is really important that you don't share which treatment you are taking with the other researcher.

At follow up visits 6 and 18 months, you will be invited to your normal clinic to measure your blood pressure, and your height, weight and waist if this hasn't been done recently.

BLOOD TESTS

If taking lithium, we will measure the lithium in your blood to get it to the right level, then every 3 months in the first year and 6 monthly after that. This is needed when taking lithium to make sure the lithium in your blood is at the right level to work effectively. In routine care, lithium is monitored by regular blood tests. However, in this trial we are also taking blood samples for everybody to monitor if participants have been taking medication as prescribed, and record why not if there are changes.

If taking quetiapine, we will check your blood for the amount of quetiapine in it every 3 months in the first year and 6 monthly after that. The blood samples to measure the levels of medication in your blood will be about 5 millilitres (the same as a teaspoon). If you are taking quetiapine, the sample will be sent from your Trust to a laboratory at University Hospitals Birmingham NHS Foundation Trust if your hospital can't do this test. After the sample has been measured it will be destroyed. No samples will be stored or returned to your own Trust.

You will also be asked to give blood samples to monitor your kidneys etc, similar to those taken at your first visit, every 3 months in the first year and 6 monthly after that. After these samples have been measured they will be destroyed.

12 MONTH VISIT

At the 12 months visit you will be asked to complete the full set of questionnaires again and have a full research interview remotely (i.e. telephone or video call). These will be the same questionnaires and

assessments as the very first visit. We may also invite you to the clinic where you joined the trial to measure your blood pressure and your height, weight and waist and perform an electrocardiogram if this hasn't been done recently.

FINAL VISIT

During this visit you will be asked to complete all the questionnaires a final time and have a final research interview remotely. We will also invite you to your normal clinic to measure your blood pressure, height, weight and waist and perform and electrocardiogram if this hasn't been done recently. You will leave the trial after your 24 month visit.

RECORDING INTERVIEWS

If you allow it, some of your online research interviews may be audio recorded. The trial researchers will meet regularly during the trial to listen back to randomly selected recordings and independently review them. This is to check that everyone doing the assessments is doing them to the same standard. The recordings will be stored until the trial results have been published and then deleted. **If you don't want your interview to be recorded, you can let the research team know.**

What are the possible benefits of taking part?

This trial will help us find out if taking lithium and quetiapine together – or either alone – best helps to reduce symptoms of bipolar and extend the time to the next mood episode. Although there may be no immediate benefits to you, the aim is to help other patients who have suffered for years with recurring bipolar mood episodes.

What are the possible disadvantages and risks of taking part?

We don't know whether taking a combination of lithium and quetiapine or taking either treatment alone will best improve your symptoms, which is why we are doing the trial. Both lithium and quetiapine can have side effects (see below), but the medical and research teams will monitor you and your health closely. If you have any concerns during the trial, please contact the research team. This can include the research team member with lived experience of bipolar disorder.

Taking quetiapine and lithium together can increase the risk of lithium neurotoxicity, although this is very rare. Symptoms include confusion, nausea and vomiting and an irregular heart rhythm, so the medical and research team will monitor your blood levels closely to minimise this risk. Blood tests to monitor for neurotoxicity will be taken at least three monthly for the first year and six monthly the following year. An ECG will be taken before you start your trial treatment and then again at 12 and 24 months to monitor your heart activity and rhythm.

If you are already taking lithium or quetiapine before signing consent, you will be asked if you are willing to switch treatments if you are randomised to an alternative drug. Your healthcare team will explain the procedure for 'weaning off' your current medication, which will likely be over a 4–8-week period. Weaning off any treatment carries the risk of side effects, but your medication will be reduced slowly so that a small amount remains in your system and minimises this chance.

Some of the questionnaires you will be asked to complete contain questions of a sensitive nature. Your research team will be on hand to support you through completion of these questionnaires should you feel

you need this. The system used to complete these questionnaires will allow you time to pause and resume completion when you feel ready however we do ask that you fully complete each questionnaire.

If you become unwell during your treatment, seek medical help and please let the research team know. If at any time we are concerned that you may be at potential risk of harm to yourself local safeguarding procedures will be followed and we will inform your clinical care team, and also inform you of the acute care services available to help. We will need to breach confidentiality to inform your healthcare team.

Will my travel expenses be reimbursed?

Yes, we will reimburse your travel expenses for trial visits to the hospital. We will reimburse you for your time with £25 for completing assessments at the first visit, £50 for completing assessments at 12 months, and £75 for completing assessments at 24 months. This includes an additional £5 to account for mobile data costs for the remote assessments. Please speak to your research team about this.

Is the treatment safe?

Along with their useful effects, most treatments can cause unwanted side effects, although not everyone experiences them. Before starting treatment, you should read the manufacturer's printed information leaflet provided inside the box. The leaflet will give you more information about the treatment and a full list of side-effects which can be experienced, but we have a summary below.

Lithium (mood stabiliser)

Lithium is widely used to treat bipolar in adults. It comes as tablets or a liquid. Which you receive will depend on your needs and local NHS practice. You will start on a low dose and your doctor will increase it until there is a certain level in your blood. It can take a few weeks or months to get to this level, and it can take a while before the lithium starts to work. Usually lithium is taken once a day before bed but it can be taken in other ways and your prescriber will discuss this with you.

To start, you'll need regular blood tests to get the levels of lithium in your blood right. It needs to be a certain level to treat your bipolar symptoms. However, if it is too high, it can damage your kidneys, so these blood tests are very important. People taking lithium long term should still have a blood test every three months.

Once you're on the right dose right, you may not have noticeable side effects. However, some people may still find that lithium slows down their thinking or makes them feel a bit "numb".

Lithium can have some quite common side effects. More than one in ten people may experience:

- feeling thirsty
- needing to urinate more often
- feeling tired
- feeling nauseous or having mild stomach problems
- putting on weight
- hand tremors

The unwanted side-effects often improve as your body adjusts to the medicine, but speak with your doctor if any side effects continue or become troublesome.

Some side effects are more serious. You should tell your care team straight away if you experience:

- dizziness or feeling faint
- strong twitches especially in your legs or jaw
- confusion or your mind feels mixed up and you find it hard to think
- slurred speech
- feeling unsteady on your feet or clumsy
- a fit or seizure

Quetiapine (antipsychotic medication)

Quetiapine is widely used to treat mental health conditions, including bipolar and schizophrenia.

Quetiapine can have some quite common side effects. More than one in ten people may experience:

- feeling sleepy during the day
- problems with your movement
- headache
- feeling dizzy
- putting on weight
- constipation
- swollen breasts, pain in your breasts or leaking breast milk
- irregular periods or stopped periods
- fast heartbeat
- dry mouth
- increased risk of diabetes if you have a family history of diabetes

Some side effects are more serious. You should tell your care team straight away if you experience:

- high temperature and stiffness
- shaky movements in face, mouth, arms and legs
- sweating and loss of senses

Quetiapine comes as tablets or a liquid. Which you receive will depend on your needs and local NHS practice. You'll start off on a low dose which will be increased if needed. It can take a few weeks to get the right dose to start improving your symptoms.

Side effects should improve and should be manageable, but if you find they are not, speak to your doctor.

Pregnancy

Taking lithium is not recommended in pregnancy due to its association with foetal abnormalities, especially in the first trimester. Taking quetiapine in pregnancy may make it more likely that you develop gestational diabetes, which might require blood sugar levels to be checked. We will check these regularly throughout the trial.

Female participants of childbearing potential (i.e. who could potentially get pregnant) will be asked to provide a urine pregnancy test at their first visit and won't be able to take part if they are pregnant or planning to get pregnant. Urine pregnancy samples will be destroyed after analysis and will not be stored.

Female participants of childbearing potential will be requested to use effective contraception whilst on trial treatment and until thirty days after trial treatment has finished. At each three month follow up visit you will be asked by the researcher to confirm you are currently taking effective contraception. If you have stopped taking or missed any of your contraception since the last follow up you may be asked to take a pregnancy test.

If you become pregnant during the trial, please inform a member of the research team. Your research team may need to stop your treatment on the trial and your doctor will advise on further medical care should this be necessary. You will still be followed up in the trial and be asked to complete the interviews with the researcher as your information will still be useful.

PART 2 – ABOUT HOW WE CONDUCT RESEARCH

Who is organising and funding the research?

This trial is sponsored by the University of Birmingham, which means the University has certain legal and ethical responsibilities for the trial. It is being run by Birmingham Clinical Trials Unit and is funded by the government through the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (ref:158667). The Chief Investigator for the trial is Professor Steven Marwaha, a consultant psychiatrist.

How have patients and the public been involved in this trial?

The COMBINER trial has been developed with patient and public involvement (PPI) representatives who have lived experience of bipolar. Members of the Lived Experience Advisory Panel (LEAP) with experience of bipolar have been involved in reviewing this Patient Information Sheet and developing the questions measuring how acceptable participants find their treatment. The LEAP members will also be involved in making patients and medical staff aware of the trial results.

The conduct of the trial is entirely in the hands of very experienced researchers and no PPI group or lay person has any access to your personal healthcare records or is able to influence your treatment.

Who has reviewed the trial?

All research which takes place in the NHS is looked at by an independent group of people who protect patient interests. This group is called a Research Ethics Committee. Before we asked any patients to join, the trial was reviewed and approved by North West - Haydock Research Ethics Committee.

What happens if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, a member of the research team will tell you and discuss whether you should continue in the trial. We may ask you to re-sign a consent form if you do.

What if I no longer want to take part?

If you decide not to take part in the trial any longer (withdraw from the trial early) please contact your research team. A member of the research team will arrange for your standard clinical care to continue. If you decide not to take the trial treatment any longer, your information is still very useful to us if you are happy to still provide it.

If you have concerns about continuing in the trial, our lived experience research assistant is available to discuss these with you, if you think it would be helpful.

What if I am already taking a bipolar treatment?

If you are already taking bipolar medication such as lithium or quetiapine your doctor may ask if you are willing to stop this if you are randomly allocated to the lithium only or quetiapine only trial arm. This will include a 'weaning' off period where your medication is stopped gradually over 4-8 weeks and the new medication started to avoid you becoming unwell during this period or having any unwanted side effects.

How long will I be followed up for?

Once the trial has finished, we may want to get information about your progress from national health registries, for example to check for use of treatment or other services for up to 10 years after the end of the trial. If you consent to it, the central research team may, in the future, access electronic data from your central NHS records, such as NHS Digital or Hospital Episode Statistics. This would give us information routinely collected during your visits to your GP and hospital and lets us find out about your health and use of NHS services after the trial has ended without contacting you again. To do this, we would send your name, gender, date of birth and NHS number with any request for information. You may withdraw your consent for researchers to access electronic data from your central NHS records at any time without giving a reason by speaking with your researcher.

How will we use information about you?

We will need to use information from you and your medical records for this research project. This will include:

When	What data will be collected
First visit (baseline)	• Full date of birth, sex at birth, gender, NHS number • Contact details: email address and/or mobile phone number • Relevant medical history • Current and past medications • Questionnaires completed during this visit
Follow-up visits 3, 9, 15 and 21 months	• Questionnaires completed online and during interviews • Review of electronic records for any emergency medication or acute service use
Follow up visits at 6, 12, 18 and 24 months	• Questionnaires completed during this visit • Current medication use

	• Review of electronic records for any emergency medication or acute service use

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

As sponsor of this research, University of Birmingham is responsible for looking after your information. We will keep all information about you safe and secure:

- All information collected from you will be securely stored and kept strictly confidential according to the Data Protection Act 2018 in the same way as your usual medical records.
- Information for this trial will be recorded and stored on our secure University of Birmingham servers.
- Appropriate firewalls, antivirus software, restricted access and security controls are built into the database
- University of Birmingham staff receive regular data protection training
- Your data will not be shared outside the UK.

If you choose to receive links to follow up questionnaires via text message, your mobile telephone number will be shared with a UK-based, GDPR compliant third-party SMS platform. Text messages will be sent by the provider for the purpose of providing a link to the COMBINER questionnaires only. Your data will not be used by the third-party for any other purpose.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records and your hospital or GP notes. If you do not want this to happen, tell us and we will stop.
- You have the right to ask us to access, remove, change or delete data we hold about you for the purposes of the study. You can also object to our processing of your data. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this.

How will we use information about you after the trial ends?

We will keep your trial data for a maximum of around 3 years after the trial end. The trial data will then be fully anonymised and securely archived. After 25 years it will be destroyed.

Where can I find out more about how my information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- in the leaflet available from www.hra.nhs.uk/patientdataandresearch

- by asking one of the research team
- by contacting the University of Birmingham Data Protection Office:

The Data Protection Office, Legal Services, The University of Birmingham, Edgbaston, Birmingham B15 2TT. Email: dataprotection@contacts.bham.ac.uk. Telephone: 0121 414 3916

What if something goes wrong?

We do not expect any problems as a result of your participation in the trial. However, all patients are covered for negligent harm according to NHS indemnity guidelines. If you have a concern about any part of this trial, you should ask to speak to a member of the research team who will do their best to answer your questions. If you prefer, in the first instance, to speak to the member of the research team with lived experience of bipolar, this will be possible. The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants. In the event that something does go wrong and you are harmed during the trial there are no special compensation arrangements. If you are harmed then you may have grounds for legal action but you may have to pay your legal costs.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility remains with the NHS organisation responsible for the clinical site and is therefore indemnified through NHS Resolution. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation. The NHS have a duty of care to participants whether or not the participant is taking part in a clinical trial and the normal NHS complaints mechanisms will still be available to you.

If you wish to complain about any aspect of the way you have been approached or treated during this trial, the normal NHS complaints mechanisms will be available to you. If you wish to complain about how you have been treated during this trial please feel free to speak with our lived experience research assistant and also contact the Patient Advice and Liaison Service (PALS) or the Complaints Team at your local hospital. The contact details can be found on the end of this Information Sheet.

What if I do not want to take part?

Participation in the trial is entirely voluntary and if you decide not to take part you do not have to give a reason. If you do choose to enter the trial you are free to change your mind and withdraw at any point.

The standard of care provided to you by your doctor will not be affected in anyway should you decide not to participate or withdraw from the trial.

What happens at the end of the trial?

At the end of the trial your doctor will continue to look after you and your treatment. Your doctor will discuss with you the option of continuing or stopping the treatment allocated to you during the trial.

Involvement of your GP

If you take part, we will tell your GP that you are taking part in the trial.

What will happen to the results of the trial?

Once the trial is completed and the data is analysed, we will publish results from the trial in medical journals, to help other doctors to learn and for patients to benefit. This will be in an anonymous way so you cannot be identified. Names and other identifiable information will not be included in the results.

Do you have any further questions?

You will have some time to think about the trial and make your decision. You may wish to discuss it with your family or friends. If you take part, you will receive a copy of this information sheet and a copy of the signed consent form. If, at any time, you have any questions about the trial you should contact your trial doctor or research nurse using the details below.

Thank you for taking the time to read this information sheet.

Please visit our online information tool for more information: *tbc*

Contact Information

If you would like to speak to someone about the trial please contact:

< Contact Name > <Job Title>

<Telephone and/or E-mail>

Support can also be found through *<NHS Patient Advisory and Liaison Service (PALS); or local equivalent>*

Tel: *<insert local PALS contact number(s)>* Email: *<insert local PALS email address>*

Alternatively, you can contact the COMBINER trial team:

COMBINER trial office
Birmingham Clinical Trials Unit
Public Health Building
University of Birmingham
B15 2TT
Email: combiner@trials.bham.ac.uk

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