To be printed on hospital headed paper

PARTICIPANT INFORMATION SHEET

MILI: A clinical trial investigating the use of a drug called metformin as a way of reducing the cancer risk in people with Li Fraumeni Syndrome (LFS)

We'd like to invite you to take part in our research trial. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with family and friends. If there is anything that is not clear, or if you would like more information, please ask us.

What is the purpose of the trial?

- This trial is to determine whether a medication called metformin will reduce the chance of developing cancer in people with Li Fraumeni syndrome (LFS). A person with LFS carries a pathogenic variant* within their *TP53* gene and this is associated with an increased risk of cancer. Scientists have shown that among other things *TP53* controls metabolism within the cell, in other words it decides how the cell turns nutrients into energy. In people carrying a *TP53* pathogenic variant, their metabolism is turned up. There is evidence that metformin can "turn down" metabolism in people with LFS and this may reduce their chances of getting cancer.
- In this trial, adults with LFS who agree to take part will be randomly allocated either to i) have cancer surveillance alone or ii) have cancer surveillance and take metformin every day for up to 5 years. By comparing results from the two groups, we will be able to tell whether metformin can reduce the risk of developing cancer and/or delay the emergence of cancer.
  Metformin is a very commonly used drug that is licensed to treat diabetes. However, it is not licensed as a cancer prevention for people with Li Fraumeni Syndrome (LFS).

Why have I been invited?

- You have been invited to take part in MILI because you carry a pathogenic variant in *TP53* and have a diagnosis of LFS. You may have initially contacted us yourself or been identified by your regional genetics centre as someone who may be eligible to take part.
- The trial intends to recruit 224 adults with LFS.

Do I have to take part?

- No. Taking part in this trial is entirely voluntary. If you decide to take part but change your mind, you can withdraw without giving a reason. Withdrawal from MILI will not affect your clinical care.

What will happen if I decide to take part?

The trial is being conducted in hospitals in the UK. If you decide to take part in MILI, your local genetics team will make a referral and send your contact details, NHS number and medical information such as your age, gender, genetic mutation type, relevant past medical history (plus if required, family history) and a recent whole-body MRI

**Many different terms are used to describe cancer causing genetic variants. "Mutation," "disease causing alteration or variant," "pathogenic mutation," or "pathogenic variant" are all terms you may come across. We will use the term "pathogenic variant" to describe a variant in a gene which is known to increase the chance of developing cancer.*

scan, if done locally to a recruiting centre; this will usually be the nearest to where you live. Your local genetics team may also be one of the recruiting centres and therefore will already have this information.

- **Initial Trial Visit to Main Genetics Recruitment Centre**: Once you have been referred by your local genetics team, you will then receive a letter or a phone call from our research team at one of the recruitment centres, to arrange for an initial trial visit. You will have the opportunity to discuss the trial in more detail and to ask any questions. If you still want to enter the trial, you will be invited to sign a consent form. Any research activities and assessments will be done after the informed consent form has been signed by you.

- We will need to check that you are eligible to take part in the trial; to do this you will have a fasting blood test. We are not able to provide meals or meal expenses therefore, you may wish to bring a snack with you to take once you have had your fasting blood tests. If you are able to become pregnant you will have a pregnancy test (either urine or a blood test). We will check your height and weight to calculate your Body Mass Index (BMI) and take your blood pressure. The doctor will discuss your medical history and will ask if you have noticed any changes to your skin.

- **Welcome email:** Straight after the visit, you should receive an automated welcome email from the MILI team at the University of Oxford (please see the section below on contacting you). You will be asked to confirm which hospital you visited for the trial so that we can to check that we have your correct email address. If you don't think you've received the email, please check your junk mail or contact us at the recruiting centre.

- **Quality of Life questionnaires:** After the visit**,** you will also be asked to complete some quality of life questionnaires which will be sent to you via an automated email from the MILI team. The quality of life questionnaires are designed to help us learn more about how LFS affects your everyday life, such as your mental and physical wellbeing.

- **Randomisation process:** After your initial visit, if the test results from the visit show you are eligible, we will enter you into the randomisation process. This means you will be randomly allocated by computer to either the intervention arm which is yearly Standard of Care MRI surveillance and metformin or, to the control arm which is yearly Standard of Care MRI surveillance alone and no metformin. As the randomisation is 1:1, there is a 50% chance you will be assigned to get metformin. We will notify you in writing and may also phone you to check that you know what arm of the trial you have been randomised to. We will also send you a trial participation card with our contact details.

- **Initial telemed call:** Once you have been randomised, a member of the research nurse team based at the Oxford University Hospitals NHS Foundation Trust will telephone you. They will explain to you how the telemed calls will work, talk to you about the randomisation outcome and, if you have been allocated to take metformin, they will explain the starting dose of metformin to take.

- **Taking metformin:** If you are randomised to receive metformin, you will receive a supply of metformin tablets to your home by post from our hospital pharmacy. You will need to wait for a phone call from the telemed team before you can start taking the tablets. During your first two months on the trial the metformin dose will be gradually increased every 2 weeks and this will be managed by a member of the telemed team. This gradual increase in metformin is recommended for anyone taking metformin for the first time. You will therefore start on a lower dose of 500mg (1 tablet) of metformin each day and this will be increased until you reach a maximum dose of 1000mg (2 tablets) taken twice daily. You will then remain at the metformin dose you tolerate the best for up to 5 years.

- **Telemed calls**: The trial has been designed so that you can be followed up without coming into hospital regularly. The majority of the telemed calls will be carried out by a research nurse based at Oxford University Hospitals NHS Foundation Trust.

- **Telemed calls (surveillance + metformin arm):** Once you have started the metformin, a member of the telemed team will contact you by phone every 2 weeks during the first two months of the trial to help you manage the metformin dose increase. After each phone call, you will receive an automated email confirming the dose of metformin to take for the next 2 weeks. If you have any queries during this initial period of taking metformin and wish to speak to someone, please call us at the recruiting centre.

- The telemed team at Oxford will then call you every 6 months until you complete the trial. During these calls they will check on how you are, ask you about any side effects from taking the metformin and whether you are managing to take your metformin as prescribed. They will also ask for an update on any recent medical investigations e.g., outcome of scans, other medications, including vitamins and supplements that you are currently taking.

- **Telemed calls (surveillance alone arm)**: After you have started the trial, a member of the telemed team will contact you by phone during your first week in the trial and then every 6 months until you complete the trial. During these calls we will check on how you are and ask for an update on any recent medical investigations e.g., outcome of scans, other medications, including vitamins and supplements that you are currently taking.

- **Annual visits to Recruiting Centre:** While you are on the trial, you will be invited to return to see our research team at the recruitment centre where you consented to take part for a yearly check-up appointment.

- At these visits, a fasting blood test will be taken which means you will not be able to eat beforehand. We are not able to provide meals or meal expenses therefore, you may wish to bring a snack with you to take once you have had your fasting blood tests. We will check your weight to calculate your Body Mass Index (BMI). The doctor will ask if you have noticed any changes to your skin.

- **Quality of Life questionnaires**: At the time of these visits, the MILI team at Oxford University will send you an automated email with a link in it and if you are able, will ask you to complete some quality of life questionnaires.

- **Please refer to the table in Appendix 1 which shows the visit schedule.**

Completing the trial

- You will remain on the trial for up to 5 years unless you decide to stop your participation or need to be withdrawn from the trial by the research team.

Contacting you during the trial

- In addition to the telemed calls, our research team at the recruiting site where you consented to take part, may also need to communicate with you at various points during the trial. We will also provide you with a contact information card so that you can contact us too.

- The MILI team based at Oxford University will also contact you via an automated email with a welcome message once you have consented to take part in the trial. They will also contact you via the automated email to send

you a link to the quality of life questionnaires that they would like you to complete each year. These questionnaires are to be completed around the time of your visit to our recruiting site.

- For those randomised to receive metformin, the MILI team will send you an automated email asking you to confirm receipt of your delivery of metformin tablets. You may also get a phone call from our hospital pharmacy if they need to confirm your contact details for sending you the metformin tablets or if there has been an issue with receipt of the metformin tablets. During the first 2 months of taking metformin, after each phone call with the central telemed team, you will receive an automated email confirming the dose of metformin to take for the next 2 weeks.

- We will also need you to update our research team if your contact details change. More information about how we will store your contact details is described under the section **"**Will my taking part in the trial be kept confidential?"

What should I consider?

At your initial visit to our research team at the recruiting centre, we will check that you are eligible to take part in the trial. Prior to the initial visit there are a few things to consider:

- If you are pregnant, you will not be eligible to be enrolled (please see below for further information).
- If you are on treatment for diabetes or you are already taking metformin for any reason, we will not be able to enrol you into the trial.
- The trial is collecting your Standard of Care surveillance MRI result; therefore, you should be able to undergo MRI scanning.
- Taking part in the MILI trial does not prevent you from taking part in other research studies. However, a discussion should take place with our research team before taking part in other studies that involve medication.

Can I continue to take other medications during the trial?

As part of the trial, we will ask you about what regular prescribed and over-the-counter medications you are taking. Most medications are safe to continue if you have been allocated to take metformin. However, some need to be used with caution such as medications that affect your kidneys including diuretics (like acetazolamide and methazolamide), anti-epileptic medications like topiramate (Topamax) and zonisamide (Zonegran) and regular pain relief medications such as aspirin, ibuprofen, naproxen and indomethacin. Please note, low-dose aspirin (75mg) is safe for use. If you are concerned about any medications you are currently taking or planning to take, please discuss this with your geneticist, GP or a member of our team.

What if I am pregnant or wish to become pregnant during the trial?

Pregnancy is one of the exclusion criteria for the trial and you will not be able to enter the trial if you are pregnant at screening. You can contact us again about taking part after your pregnancy. We will therefore ask that all women of childbearing potential to have a pregnancy test prior to enrolment.

If you become pregnant during the trial and are allocated to take metformin, you can decide if you wish to continue taking the metformin or not. Additional pregnancy information is provided in appendix 2 of this information sheet which provides you with more information about these options. The pregnancy information also explains that we will need to follow-up your pregnancy even if you decide to withdraw from participating in the trial.

Effect of Metformin on female and male fertility

There is no evidence that metformin affects the fertility of women or men taking it.

Contraception

You are not required to change your contraceptive use in order to participate in the MILI trial.

Possible side-effects from metformin:
If you are allocated to the metformin arm, then you may experience some side-effects from the treatment. Metformin is most commonly used for the treatment of Type 2 diabetes and Polycystic Ovary Syndrome (PCOS) and is taken regularly by an estimated 3 million people in the UK. The majority of people who take metformin tolerate it well but about 30% experience side effects such as mild diarrhoea, nausea or vomiting, or other side effects listed in the table below.

Table showing side effects of metformin:

Very common side effects (more than 1 in 10 people)
• Digestive problems e.g. feeling sick (nausea), being sick (vomiting) • Diarrhoea • Belly ache (abdominal pain) • Loss of appetite
Common side effects (up to 1 in 10 people)
• Change in taste • Decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin).
Very rare side effects (fewer than 1 in 10,000 people)
• Lactic acidosis (see below) • Abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). • Skin reactions such as redness of the skin (erythema), itching or an itchy rash such (hives)

Very common side effects from metformin tend to occur soon after starting treatment and are less likely to occur if metformin is started at its lowest dose and gradually increased (as we will be doing in this trial). Other side effects resolve spontaneously or if the dose is reduced.

Lactic acidosis:
The most serious side effect is lactic acidosis. Lactic acidosis is a build-up of acid in the bloodstream but it is very rare and affects fewer than 1/10,000 people taking metformin. It is most commonly observed in people whose kidneys are not working properly. For this reason, the kidney function of all participants will be checked during the initial visit and then every year during the trial. If there is any evidence that your kidney function is becoming affected, we will contact you to discuss reducing the dose of metformin or discontinuing your participation in the trial.

The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical conditions in which part of the body has a reduced supply of oxygen (e.g., severe heart disease). Symptoms of lactic acidosis include difficult or laboured breathing, abdominal pain, muscle cramps, weakness and hypothermia (fall in body temperature) followed by coma. In case of suspected symptoms, you should stop taking metformin and seek immediate medical attention.

Will metformin be made available to me after the trial has ended?

Currently, metformin is not licenced or approved for LFS; the results from the MILI trial will be used to inform a licencing decision. If the study results support the use of metformin, the findings will be discussed with the

regulatory bodies MHRA/NICE and you and your GP will be informed. The trial will be unable to provide compassionate access to metformin.

What are the possible benefits of taking part?

- Although there is evidence from mice with LFS that metformin delays cancer, this is the first trial to test this in people with LFS. We do not know what the outcome will be and this is why we are conducting this trial. The information obtained from this trial will be used to support a future licencing decision for metformin as a cancer prevention agent for people with LFS.
- All participants will have yearly skin check-up and yearly blood tests to look for any signs of cancer.
- The trial will help to understand how cancers form in LFS and how metformin affects this process.
- The trial will help to understand the impact that having LFS has on your quality of life.

Are there any possible disadvantages or risks from taking part?

The side effects of metformin are detailed above. Other risks of taking part in this trial are low. We will be asking you to provide some blood samples during the trial that will be collected from a vein in your hand or arm and may cause bruising and/or fainting.

You will undergo screening assessments and annual visits at a recruiting site. This site may be different from your local genetic centre and you may be required to travel further for the annual visits.

What happens if I get cancer while I am participating in this trial?

If any of the tests conducted during this trial show you have a cancer or any abnormal finding that indicates cancer, we will immediately contact you and your local genetics team. Your local genetics team will arrange further investigations and/or treatment at your local hospital. We will also inform your GP.

If your tests confirm you have cancer, we will discuss whether you should stay on the trial or not. It is likely, if you are to have lengthy treatment, such as chemotherapy, that we will advise you to stop participating in the trial.

Further information about assessments in MILI

Whole Body and Brain MRI Scanning:

The MILI trial will collect the results of your annual standard of care whole-body MRI scan during your participation in the trial. The trial will also collect the results of your brain and breast MRI scans that you may already receive as standard of care. If you have not had surveillance scans before, please speak to your local genetics team.

Sample collection:

The MILI trial will be collecting and analysing samples for the purpose of monitoring the safety and side effects of metformin. In addition to this, the trial will be collecting samples for further research into LFS. You will be asked to give consent for the research sample collection.

Blood samples:

We would like to collect blood samples from you during screening and, once you are in the trial, every year at your annual visit to our research team at the recruiting centre.

The amount of blood taken at your initial and year 1 visits will be up to 60mls, which is the equivalent of 4 tablespoons of blood. For the years 2-5 visits, we would like to collect up to 30mls, which is the equivalent of 2 tablespoons of blood. We will ask for your consent to collect blood samples.

Some of the blood samples will be analysed at our recruiting centre where they will be tested and reported to us as per the hospital laboratory procedure. Other blood samples will be sent to a central lab based at the University

of Oxford for processing. They will then be sent onto other labs within and also outside of Oxford University for analysis in order to understand more about LFS (described below).

Blood samples collected at the first visit to the recruiting hospital from participants who are found to be ineligible for the trial will be discarded.

Tumour tissue samples:

If you develop an abnormal lesion (e.g., a mole or lump) or a cancer during the trial and have a biopsy or an operation to remove it at your local hospital, we will ask your local hospital to send a portion of this tissue to a central laboratory based at Oxford University. This is so that further research can be carried out into LFS. We will ask for your consent to collect tissue samples.

What will happen to any samples I give?

We are collecting samples in the trial in order to test them for the following:

- To understand why people with LFS are more likely to get cancer.
- To help understand how metformin works in the cells of people with LFS.
- To identify biomarkers or circulating proteins that could, in the future, be used to detect cancer in people with LFS.
- To investigate whether certain TP53 pathogenic variants are more linked to certain cancers than others.

As explained above, tissue samples and some of your blood samples will be transferred to a central laboratory based at the University of Oxford. The samples sent to the central laboratory will be identified by your trial number, date of birth and initials.

The tissue samples will be analysed in laboratories based at Oxford University. Some of the blood samples will be sent on to other laboratories both inside and outside of the University of Oxford for certain analyses for the trial. These will include specialist or commercial laboratories in the UK and worldwide, including outside of the European Economic Area. Before leaving the central laboratory, the samples will have been 'de-identified' and assigned a trial code which means you cannot be directly identified from these samples.

On completion of the trial, any remaining blood or tissue samples not used in the analyses by labs at Oxford University will be stored in an Oxford University biobank for future studies. Any samples that were sent abroad and not used will be destroyed. These future studies may take place in the UK or worldwide, including outside of the European Economic Area. We will ask for your consent to store remaining samples in the biobank; otherwise, any remaining samples will be destroyed. A copy of your consent form will be sent to the biobank. This is because it will be necessary for the biobank to retain a copy of your consent form until the sample has been depleted or destroyed, in order to meet the traceability requirements of the Human Tissue Act.

What if we find something unexpected during the trial?

- Should the telemed team be concerned by any symptoms that you report during a telemed call, they will contact us, the research team at the recruiting centre. The research team at the recruiting site will contact you and advise you on next steps; this may be to visit your GP, your local hospital or the recruiting centre.
- All of your whole-body MRI scans will be checked and reported by a Radiology Consultant at the recruiting centre. As per Standard of Care, if any abnormalities are detected on your scan, our research team at the recruiting centre will make arrangements to inform you, your local genetics team and your GP. Your GP would be contacted directly and recommended that you have additional hospital (NHS) investigations conducted. All information about you is kept strictly confidential.
- The analyses from the research samples are not expected to change your medical care. However, in the event that a finding might be of clinical use, your local genetics team and your GP will be contacted. They will inform

you if they think the finding is medically important or interesting to your current or future health care.

Will my General Practitioner/family doctor (GP) be informed of my participation?

Your GP will receive a letter and the trial information sheet so he/she is aware you have entered the MILI trial. We will ask for your consent before we notify your GP that you are participating in the trial.

There may also be instances where your GP will be contacted to follow up incidental findings that may be of clinical significance, for example if you become unwell during the trial.

Will I be reimbursed for taking part?

Participation in this trial is voluntary and you will not be reimbursed for your participation. However, the trial will be able to reimburse reasonable travel expenses for all trial participants on the production of receipts or a mileage claim.

Will my taking part in the trial be kept confidential?

Yes. The trial will follow ethical and legal practice and all information about you will be handled in confidence.

- **How you will be identified in the trial:** Information collected about you during the trial will be kept in a secure password protected clinical trial database managed by the University of Oxford. Your information will be strictly confidential. In the clinical trial database, you will be identified by a trial number. Your personal identity will not be identifiable from this number.
- **Who will see my trial data?** As explained above, for the majority of data collected about you, it will be collected in such a way that you will only be identified by your trial number. However, in order to contact you during the trial we will need to collect data that identifies you such as your contact details and date of birth.
- The following teams will also need to see both the trial data that does not identify you and the trial data that does identify you in order to run the trial: our research team at the recruitment site (including pharmacy staff and the courier company if they are delivering your metformin), the telemed team at Oxford University Hospitals NHS Foundation Trust and the MILI trial team at the University Oxford will need to see the trial data collected about you including data which can identify you in order to run the trial. In addition, responsible members of the University of Oxford, regulatory bodies and NHS Trust personnel may also be given access to your data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations.
- Any identifiable (personal) information will be held securely in the clinical trial database which is managed by Oxford University and it will only be made available to those team members who need access to run the trial.
- **Blood and tissue samples:** Samples collected for the trial will be identified by your initials, date of birth and a unique trial number to ensure accurate logging of your samples. Your full name and address will not be kept with the samples and will not be shared with the researchers.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the sponsor for this trial and the data controller and is responsible for looking after your information and using it properly.

- Your local genetics team will need to pass on your report of diagnosis of LFS TP53 variant and your details (name, NHS number, home address, phone number and email address) on to our research team at the recruiting centre in order for us to manage your assessments during the trial. Our research team at the recruiting centre will use your name, NHS number and contact details (home address, phone number, email address), to contact you about the trial, to manage your treatment on the trial and to oversee the quality of

the trial. We will keep identifiable information about you such as Consent forms from this trial for a minimum of 5 years after the trial has finished, as per local NHS Trust policies.

Use of third-party service providers:

- We may disclose your personal data to our third-party service providers to carry out activities specifically for the purpose of this research and as explained in this information sheet. Any third-party service providers are required to take appropriate security measures to protect your personal data in line with University of Oxford policies. We do not allow our third-party service providers to use your personal data for their own purposes, but rather to only process your personal data for specified purposes and in accordance with our instructions. Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights. You can find out more about how we use your information by contacting the study team at the end of this letter.
- The telemed team based at Oxford University Hospitals NHS Foundation Trust will be using information which has been collected during the trial from you to manage your participation in the trial. They will use the minimum amount of personally-identifiable information possible.
- If you are allocated to the metformin arm, the pharmacy team at the recruiting site hospital will need to use your contact details (name and address, phone number and email address), in order to post the metformin tablets to your home address. They may also need to pass your contact details onto a third-party courier company if required.
- At your initial visit we will enter your contact details (your name and contact details) into the clinical trial database this is so the MILI trial team based at Oxford University can send you an automated email containing Quality of Life questionnaires. Please ensure you check your junk email folder. As described above, you will be asked to complete the Quality of Life questionnaires just after your initial visit to our research team and then close to the time of each annual visit to our research team at the recruiting centre. The information from the completed questionnaires will be stored in the clinical trial database which means that we will also be able to access to the answers you provide.
- The University of Oxford will hold identifiable information about you (your name and contact details) in the clinical trial database if you consent to be contacted about future research. We will hold this information beyond the end of the trial which could be a minimum of 5 years (in compliance with legislation).
- In order for a biobank at the University of Oxford to store your samples for future research, it will also be necessary for them to retain a copy of your consent form (which includes your name and signature) until the sample has been depleted or destroyed. This is in order to meet the traceability requirements of the Human Tissue Act. The consent form will be stored separately from your samples. It will not be possible to directly identify you from the samples.
- At the end of this trial, the MILI trial team intends to share data from this trial with researchers in other countries in order to pool together research into LFS and to support other research in future. It will not be possible to identify you from this data. This data will only be released to researchers for specific projects that have received the appropriate approvals (i.e., ethical and regulatory).
- The MILI trial would like to carry out an audit of MRI images during the trial in order to assess the quality of your treatment. De-identified copies of your MRI scans will be uploaded by our research team and stored in a database hosted by the University of Oxford, Oxford University Hospitals NHS Trust and other collaborators. As part of the audit, your MRI scans may be reviewed by a group of radiologists who will monitor the quality of imaging being delivered in the trial. The MRI scans may also be used in future for education, research and training with other radiologists and commercial companies once the trial has ended. The MRI scans will be stored on a database for this purpose and it will not be possible to identify you from the scan data.

- Information about you, or derived from your samples, will not be shared with any outside agency such as the police, insurance companies or your employer unless you give your specific instruction for us to do so, or we are compelled to release the information under common law.

- Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at: https://compliance.web.ox.ac.uk/individual-rights

You can find out more about how we use your information by contacting the **MILI trial office** via email: **octo-MILI@oncology.ox.ac.uk**

What will happen if I don't want to carry on with the trial?

You are free to withdraw at any time and without having to give a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the care you receive from any service. The research team will respect your decision and we will happily answer any questions you might have at the time. Below are the different withdrawal options in MILI should you decide to withdraw.

- **Discontinue metformin only (metformin arm):** metformin is a safe and well-tolerated treatment, however a small number of participants allocated to this treatment may find that they are unable to tolerate the metformin, or that they wish to stop taking it. If this is the case, you can stop taking the metformin and continue to remain in the trial and have the trial assessments. It will not affect your participation in the trial.

- **Temporary pause from active trial participation:** If you have an illness that requires you to have treatment that is predicted to last less than 12 months, you may wish to temporarily pause active participation in the trial; this will include stopping taking metformin if you are allocated to this arm. Our team at the recruiting centre will keep in touch with you to find out how are you are getting on. Once you feel ready to re-join the trial, our team may need to check whether there have been any changes to your medications you are taking or a change in health status. Please note that any participant who temporarily pauses active trial participation and later re-joins will not be re-randomised; you will return to the trial arm that you were originally randomised to.

- **Permanent withdrawal from active trial participation:** Alternatively, there could be a number of reasons why you may choose to completely withdraw from active participation in the trial. These reasons could include a diagnosis of cancer that requires treatment other than surgical resection (such as chemotherapy or radiotherapy), development of another illness that takes priority, or a personal decision to discontinue the trial. Once you have had a discussion about withdrawal with one our consultants at the recruiting centre, your local genetics team will then take over your care. Please note, participants who withdraw from the trial cannot re-enter the trial at a later date.

- **Withdrawal and safety follow-up:**

  If you experienced any unwanted effects from the trial treatment and as a result were withdrawn from the trial, it is a requirement that we collect further information about these effects from your medical records after you have withdrawn from the trial until the trial ends.

  Health status follow-up:

- If a decision is taken to permanently withdraw you early from active trial participation, we would like to continue to follow-up your health status via your medical records for up to 5 years or until the end of the trial (whichever comes first). We will ask for your permission to do this. You do not need to do anything. Our research team at the recruiting centre will ask your local genetics team to share information about your health status. This information will be entered onto the clinical trial database.

  No wish for health status follow-up:

- However, you can also decide that you do not wish your health status to be followed up by our team (we still need to follow you up for safety reasons as explained above). This is what we call "consent withdrawal". Our research team will talk through the withdrawal options with you during the withdrawal discussion.

Your trial data and samples

- If it is decided that you will withdraw from the trial early, the research team would like to keep any data and samples we have already collected from you prior to withdrawing. This is because LFS is a rare disease and the data and samples will be used to help our understanding of this disease. If any of your samples are transferred into a biobank at the end of the trial, we would also like to keep them for future research. However, you are free to request that your samples (blood and tissue) are destroyed at any time during and after the trial, unless they have already been analysed at the time of your request, in which case it will not be possible to destroy them.

What if there is a problem?

- The University of Oxford, as Sponsor, will provide compensation for any injury caused by taking part in this trial. We will pay 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 wish 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 or where the protocol wasn't followed by sites. In these cases, NHS indemnity will apply.
- If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this trial, you should contact the **MILI trial office** by emailing **octo-MILI@oncology.ox.ac.uk** or, you may contact the University of Oxford Research Governance, Ethics & Assurance (RGEA) office on 01865 616480, or the head of RGEA, email rgea.complaints@admin.ox.ac.uk.
- The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research trial. If you wish to contact the PALS team please contact <please insert relevant local NHS site phone number and email from the PALS website or http://www.ouh.nhs.uk/patient-guide/pals.aspx.

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

The MILI trial team has worked closely with the George Pantziarka TP53 Trust, the UK's largest LFS advocacy and support organisation, to develop the MILI trial concept and design, this document as well as the trial protocol. Aspects of the trial, such as its "open-label" design where no placebo arm is used were chosen by the Trust's members. We are involving families with lived experience of LFS in disseminating information about the trial, presenting findings online and on social media and in participating in the committees that oversee the trial. If you are interested in getting involved behind the scenes of MILI, please contact http://www.tp53.co.uk. For more information about getting involved in clinical research, please see www.crn.nihr.ac.uk/can-help/patients-carers-public/how-to-take-part-in-a-trial/

What will happen to the results of this trial?

We will provide you with a summary of the results. The MILI trial team will also present the results of this trial to the LFS community on websites, social media and through the George Pantziarka TP53 Trust. The MILI trial team will also be presenting the findings at conferences and in publications. In parallel with MILI, a similar trial will be run in Germany, USA and possibly also Canada. The MILI trial team hopes to pool the results from these studies in one larger dataset that will also be presented to the LFS community, in publications and at conferences. Please be assured that you will not be personally identified from any report or publication placed in the public domain.

Who is organising and funding the trial?

The MILI trial is sponsored by the University of Oxford via the Oxford Cancer Trials Office (OCTO). It is funded by the National Institute for Health and Care Research (NIHR), part of the Department of Health with an additional grant from Cancer Research UK for samples research. The George Pantziarka TP53 Trust is contributing towards the cost of travel expenses. The recruiting centres taking part in this research will receive payment for the trial assessments but this trial is not run for profit.

Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This trial has been reviewed and given favourable opinion by West of Scotland REC 1 Research Ethics Committee.

Further information and contact details:

Please contact <insert local site details for recruiting centre> Tel. xxx or by email xxx

Thank you for considering taking part in MILI.

APPENDIX 1 MILI TRIAL VISIT SCHEDULE

Timing / Procedure	-28 days to 0 (Screening)	Week 1 Day 1	Week3 Day 15	Week5 Day 29	Week7 Day 43	Week 9 Day 57	Month 6	Month 12 (Year 1)	Month 18	Month 24 (Year 2)	Month 30	Month 36 (Year 3)	Month 42	Month 48 (Year 4)	Month 54	Last visit Month 60 (Year 5)	Cancer Diagnosis/ withdrawal (if applicable)
Informed Consent	x																
Medical History & medication checks	x																
Dermatological (skin) check-up	x							x		x		x		x		x	
Your details (personal and family history) & contact details	x																
Pregnancy test	x																
Blood pressure, height	x																
Weight to calculate Body Mass Index (BMI)	x							x		x		x		x		x	
Fasting blood sample collection	x							x		x		x		x		x	
Collection of Standard of Care Whole Body MRI result	x							x		x		x		x		x	
Allocation of trial arm	x																
Quality of Life questionnaires	x							x		x		x		x		x	
Telemed call (Metformin arm) (Includes collection of brain (and breast) scan results)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Telemed call (Control arm) (Includes collection of brain (and breast) scan results)		x					x	x	x	x	x	x	x	x	x	x	
Collection of tumour tissue (if cancer diagnosed during trial)																	x
Administration of metformin		Metformin to be taken daily for the duration of the trial (metformin arm only)															

Key:	
	Screening assessments at recruitment site
	Questionnaires for you to complete. Sent via email from OCTO MILI.
	Trial assessments at yearly visit to recruitment site
	Data collected by the central telemedicine team
	Metformin dose increase phase & metformin dosing phase for trial

APPENDIX 2:

FOR PERSONS OF CHILD BEARING POTENTIAL

Participant Pregnancy Information

MILI: A clinical trial investigating the use of a drug called metformin as a way of reducing the cancer risk in people with Li Fraumeni Syndrome (LFS)

Introduction

This information is for participants who are considering taking part in the MILI trial or who are taking part in the MILI trial and who wish to/may become pregnant during the trial. The purpose of this information is to:

- provide more information about pregnancy and participation in the MILI trial.
- to explain would happen if you were to become pregnant and why we would like to follow up the progress of your pregnancy (if you are allocated to the metformin arm).

As explained in the Participant Information Sheet, you are not required to change your contraceptive use in order to participate in the MILI trial. However, if you become pregnant or plan to become pregnant whilst on the MILI trial, it's important that you understand what your options are with regards to participation in the trial. Please take the time to read this information carefully, and discuss it with family, friends and your genetics team if you wish. Please ask if there is anything that is not clear, or if you would like more information.

MRI scans and pregnancy

As explained in the Participant Information Sheet, if you take part in MILI, the trial will need to collect your annual standard of care whole-body MRI scan result for trial entry and then annually. In addition, the trial will collect the results of the annual brain and breast scans that you may receive locally. Whilst there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning during pregnancy unless there is a clinical benefit. Therefore, standard of care whole-body MRI scans will not be conducted whilst you are pregnant.

You can still continue to participate in the MILI trial and receive 6 monthly telemed calls but you will not be required to attend annual visits to the recruitment centre during pregnancy.

If you have brain and breast MRI scans done locally, please speak to your local genetics team if you have any questions about these scans during pregnancy.

Metformin and pregnancy

If you become pregnant or plan to become pregnant during your participation in the MILI trial (and are allocated to the metformin arm) you can choose whether or not you wish to continue metformin during your pregnancy. Although metformin crosses the placenta into the baby's bloodstream, there is no evidence that metformin is harmful to the mother or baby during pregnancy. Metformin is commonly used to treat women with diabetes or those who develop diabetes during their pregnancy. Studies have shown that children born from mothers who were taking metformin whilst pregnant had normal motor and social development up to four years of age. However, longer term studies looking at the effects of metformin in children over four years of age have not yet been conducted.

You may decide to pause metformin during your pregnancy, either because of personal choice or after discussing with your healthcare team – such as your midwife, your GP and your genetics team. If you decide to stop taking metformin during your pregnancy, you can continue to participate in the MILI trial and receive 6 monthly telemed calls but you will not be required to attend annual visits to the recruitment centre during your pregnancy.

Once you have given birth, we would recommend that you restart metformin within 4 weeks unless there are medical reasons contraindicating it, or you wish to not take metformin while breastfeeding.

Metformin and breast feeding

Metformin passes into breast milk in tiny amounts and has not been linked to side-effects in healthy breastfed babies. However, we would advise mothers on the metformin arm of the trial who are breastfeeding premature babies or babies with kidney problems to stop taking metformin and seek advice from their GP or specialist as to when it is safe to restart it.

If you decide to stop taking metformin when you are breastfeeding, you can continue to participate in the MILI trial. You will also be able to resume attending the annual visit to the recruitment centre for MRI scans and assessments.

Once you have completed breastfeeding, we would recommend that you restart metformin within 4 weeks unless there are medical reasons contraindicating it.

If I become pregnant whilst on the trial, who do I contact?

If you become pregnant whilst you are participating in the MILI trial then it is important to let your consultant at the recruiting centre know about your pregnancy. They will talk to you more about participation in the trial during pregnancy, answer any queries about metformin and pregnancy if you have been allocated to take it.

If you are due to have a call with the telemed team, please also let them know about your pregnancy and they will ask a member of our trial team at the recruiting site to contact you if we have not already done so.

Why we would like to collect information on your pregnancy (metformin arm)

If you are allocated to the metformin arm and became pregnant while enrolled in this trial, our trial team will follow up your pregnancy to collect some information on you and your baby. This will help the trial to understand more about the trial treatment metformin. Information collected from you will help understanding of the effects and safety of the trial treatment.

What Information will I need to supply?

Our research team at the recruiting centre will collect information from you on your pregnancy. This may be throughout your pregnancy, once your baby is born and for some time (up to 28 days) after the birth. Our research team will record specific information about the pregnancy for example; the expected delivery date. Information on the progress and outcome of the pregnancy will be recorded by our research team at a later date. We will only collect information from routine assessments of yourself and your baby.

Will my information be kept confidential?

Yes, your information will be kept confidential and your child's name will not be collected. For more information about how your information will be used, please refer to the confidentiality section of the MILI trial Participant Information Sheet.

What will happen to my data?

The data about your pregnancy will be held securely in the trial database with the other trial data collected about you. For more information about what will happen to your data, please refer to the Participant Information Sheet.

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