To be printed on local headed paper

Repurposed drugs to improve haematological responses in Myelodysplastic Syndromes (REPAIR-MDS)

Participant Information Leaflet

Site Name:	
Investigator's name:	

This Participant Information Leaflet (PIL) describes a research study which is available at your hospital and being coordinated by the University of Warwick's Clinical Trials Unit. The study is called 'REPAIR-MDS' and is comparing two different types of treatment in people who have been diagnosed with Myelodysplastic Syndromes (MDS). The study is taking place throughout the UK and is funded by Blood Cancer UK. It will be open in around 30 hospitals and aims to recruit 120 patients.

You are being invited to take part in this research study

- Before you decide, you need to understand why the research is being done, and what it will involve for you, should you choose to take part.
- Please take the time to read this information carefully and discuss it with others if you wish. Please let us know if you would like any further information.
- It is important that you take the time to decide whether you would like to participate in this study. If you decide not to take part, this will not affect the standard of care you receive from your doctors in any way.
- If you agree to take part, you are free to withdraw at any time without giving a reason.

What is in this Participant Information Leaflet (PIL)?

This PIL is divided into two parts. Part 1 should give you enough information to decide whether you might be interested in taking part in the study. Part 2 then gives you more detailed information which should be able to help you make up your mind either way. If you have any questions, there are contact details at the end of the PIL.

Contents

Part 1

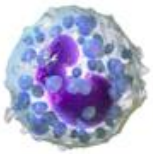
1. Important things you need to know about Myelodysplastic Syndromes (MDS)

- MDS stands for Myelodysplastic Syndromes.
- Blood cells are normally produced by special cells in the bone marrow, called stem cells.
- MDS causes changes in these stem cells making them 'abnormal' or 'dysplastic'.
- These abnormal or dysplastic stem cells can then no longer do their job properly which means that normal blood cells are no longer produced, or too few of them are made.
- MDS can go on to become leukaemia (Acute Myeloid Leukaemia) but this doesn't always happen.
- This study is for patients with a type of MDS which has a **lower risk** of progressing to leukaemia according to the IPSS-R (the International Prognostic Scoring System used to measure the 'grade' p of MDS)

2. How does MDS affect blood cells?

Blood is made up of three main cell types. MDS can decrease or even stop the production of all or some of these types of blood cells:

Red blood cells - carry oxygen and make you feel stronger or more energetic. It is very common for people with MDS to have a low red blood cell count. This can make them very tired and means that they get benefit from blood transfusions or other treatments.



White blood cells (including neutrophils) - help to fight infection. When white blood cells are not produced, a patient is at risk of getting infections. Injections of a drug called GCSF are sometimes helpful to boost the number of white cells in the body.

Platelets - help to clot the blood. When platelets are not produced, a patient is at risk of bleeding. Platelet transfusions are sometimes needed to stop this happening.

MDS is treated in several ways to try to reduce the risk of infections or bleeding and to reduce the need for blood and platelet transfusions.

3. What is this study about?

Some patients with MDS can be treated with a drug called Erythropoietin (EPO). This can work very well for some patients and can reduce the need for blood transfusions. However, EPO doesn't work for all patients or it might work for a while and then stop working. Also, at the moment, there are very few treatments for patients with low white cell counts and low platelets. So, we are looking for new ways to treat these issues in MDS, especially in this group of patients for whom EPO doesn't seem to work.

The Repair-MDS study is a Phase 2 type of clinical trial. Phase 2 trials are conducted to see how a disease responds to a new treatment, comparing dosages, assessing side effects and looking at outcomes. The data gathered will then be the basis for larger scale trials.

More information on types of clinical trials can be obtained from the support group MDS UK – just ask your clinical team.

Repair-MDS is looking at two study treatment groups, both using drugs which are already widely used for other illnesses or purposes and been shown to be safe for those patients. The Repair-MDS will assess whether these drugs can also be used to safely treat patients with MDS. Many drugs used to treat cancer were originally used to treat other illnesses. The term used for this is **Repurposed drugs.**

4. What are the two study treatment groups?

Treatment Group 1: Sodium Valproate (V), Bezafibrate (Ba), Medroxyprogesterone (P). This treatment is called 'VBaP'. Bezafibrate and Medroxyprogesterone were used in an earlier trial (BaP) in acute myeloid leukaemia patients. Several people responded with improved blood cell production. The research team's laboratory has shown that the addition of valproate at low doses could make BaP work better.

Treatment Group 2: Danazol. This drug has been used for many years in patients with low blood counts, but newer studies suggest it may work particularly well in MDS.

There is more information about each of these drugs in Part 2 of this PIL, including how they are administered, for how long, and the common side effects.

5. Why have I been invited to take part?

You have been invited to take part in this study as you have been diagnosed with lower risk MDS. You have either not been suitable for EPO, not responded or stopped responding to EPO, or you have low neutrophil and/or platelet cell count.

6. Do I have to take part?

No. Participation in this study is completely voluntary and choosing not to take part will not affect you or your medical care in any way. You can also choose to withdraw your participation at any time, without giving a reason by contacting one of the members of the research team. Further details about withdrawing from the study are provided later on in this document.

7. What will I have to do if I decide to take part?

If you decide to take part in the study, you will be asked to sign a consent form. You will then go through a period of assessment to make sure the study is fully suitable for you. We'll then collect some important baseline information about your type of MDS and how it affects your blood. After that, if you are suitable for the study, you will be randomised (this is a computer process allocating you at random) to one of the study treatments. Each of the study treatments will be given for 12 months.

There is more information about each of these stages in Part 2 of this PIL.

If you decide to take part in the study and are currently on statin medication to prevent cardiovascular disease, you may still be registered into the study but we will ask you to stop taking statins for the duration of the study treatment. We believe that the benefits of entering the study could be higher than those resulting from the statin medication.

8. What are the potential benefits of taking part in the study?

We do not currently know if the study will help you personally but there is a chance that taking part in this study may improve your blood counts, reduce your need for transfusions and therefore reduce the frequency of your hospital visits. It may also improve your quality of life – for example, you may feel less tired. Furthermore, the information we will get from this study may help to improve the treatment of people with MDS in the future.

9. What are the possible risks/disadvantages of taking part in this study?

- Drug side effects: The study drugs may have some side effects and you may experience some of them. There are more details about these in Part 2 of this PIL.

- Additional bone marrow samples: At 6 months and at the end of study.

- Additional blood samples: There will be twice monthly, and then monthly blood tests, but the samples can be taken at the same time as your regular blood tests, whenever the schedule matches.

- Additional documents: You will be asked to complete Quality of Life questionnaires which may add time to your usual hospital visits, but you can choose to take these home and post them back to the Trials Unit. You will also be asked to complete a diary about your trial medication.

- If you decide to take part in the study, there is no guarantee that the treatment will help you. You will not be eligible for other available MDS treatments during the time you spend on the study, but transfusions will carry on if you need them. If new treatments become available, you can come off this study if you wish to receive them. Your clinical team will be on hand to answer any questions and ensure you get the best care.

10. What are the alternatives for treatment?

If you decide not to participate in this study, other treatment options may be available to you. Your doctor will discuss these with you.

This completes Part 1 of the PIL. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making your decision.

Part 2

1. The study treatments - more details

Treatment Group 1: VBaP

This treatment is made up of three drugs: Sodium Valproate (V), Bezafibrate (Ba), Medroxyprogesterone (P): 'VBaP'.

The research team have already shown that Bezafibrate and Medroxyprogesterone can work and is tolerable in an earlier clinical trial (BaP) that tested the drugs in acute myeloid leukaemia patients. Several people responded with improved blood counts. The research team's laboratory studies have shown that addition of valproate at low doses, used safely to treat many thousands of patients worldwide, will increase the efficacy BaP still more.

Sodium Valproate (V): This is a drug normally used to treat people with epilepsy but has also been studied in other blood cancers. In this study, it will be used to improve the effectiveness of one of the other drugs – Bezafibrate.

Bezafibrate (Ba): This is a drug normally used to treat patients with very high cholesterol levels. In this study, it will be used to improve the function of your bone marrow and help it to make more blood cells. Bezafibrate works much better if it is given along with Medroxyprogesterone (P), the third drug in this group.

Medoxyprogesterone (P): This is a drug which is an ingredient of the oral contraceptive pill but is also been used for men and women in other cancers. In this study, it will be used to improve the function of your bone marrow and help it to make more blood cells. Medroxyprogesterone (P) works much better if it is given along with Bezafibrate, the second drug in this group.

All three drugs in treatment group 1 are taken as tablets (by mouth) at home.

All of them have possible side effects which are listed in the table below. Also, with this combination of drugs, some of the more common side effects could affect the liver, kidneys and muscles.

	Sodium Valproate (V)	Bezafibrate (Ba)	Medroxyprogesterone (P)
Common side-effects	• stomach pain • feeling or being sick (nausea or vomiting) • diarrhoea • dry or sore mouth • swollen gums • shakes (tremors) • unusual eye movements • feeling tired or sleepy • headache • weight gain • thinning hair • changes to the colour or texture of your hair	• stomach pain, • feeling or being sick (nausea or vomiting) • diarrhoea • loss of appetite • muscle aches • skin rashes	• headache • abdominal pain • anxiety • breast pain or tenderness (possibly including men) • changes in skin colour • decrease in amount of urine • difficulty swallowing • dizziness or light-headedness. • excess sweating • increased blood sugars • Fluid Retention (Oedema)

We will pay particular attention to fatigue, dizziness and light headedness. We want to work out when they are the effects of anaemia and when they are side-effects of the medication.

Treatment Group 2: Danazol

This is a drug used to treat people with endometriosis – a disease of the womb or uterus - and hereditary angioedema, a disease which causes swelling of various parts of the body. In this study, it will be used to improve the function of your bone marrow. Danazol works in a different way to the drugs in group 1 – it works by stopping the cells in the bone marrow from ageing, allowing them to make more blood cells for longer.

Danazol is taken as a tablet/capsule (by mouth) at home. Possible side-effects are listed in the table below:

Danazol	
Common side-effects	• Problems with liver function • muscle ache • high blood pressure • skin changes • nausea • blurred vision • low mood • insulin resistance • flushing • rarely risk of blood clots (thrombosis)

You should let your doctor or nurse know about any side effects as soon as possible, using the contact details provided at the end of this information sheet.

During the study, you should take the medication as directed. You will get them from your hospital pharmacy.

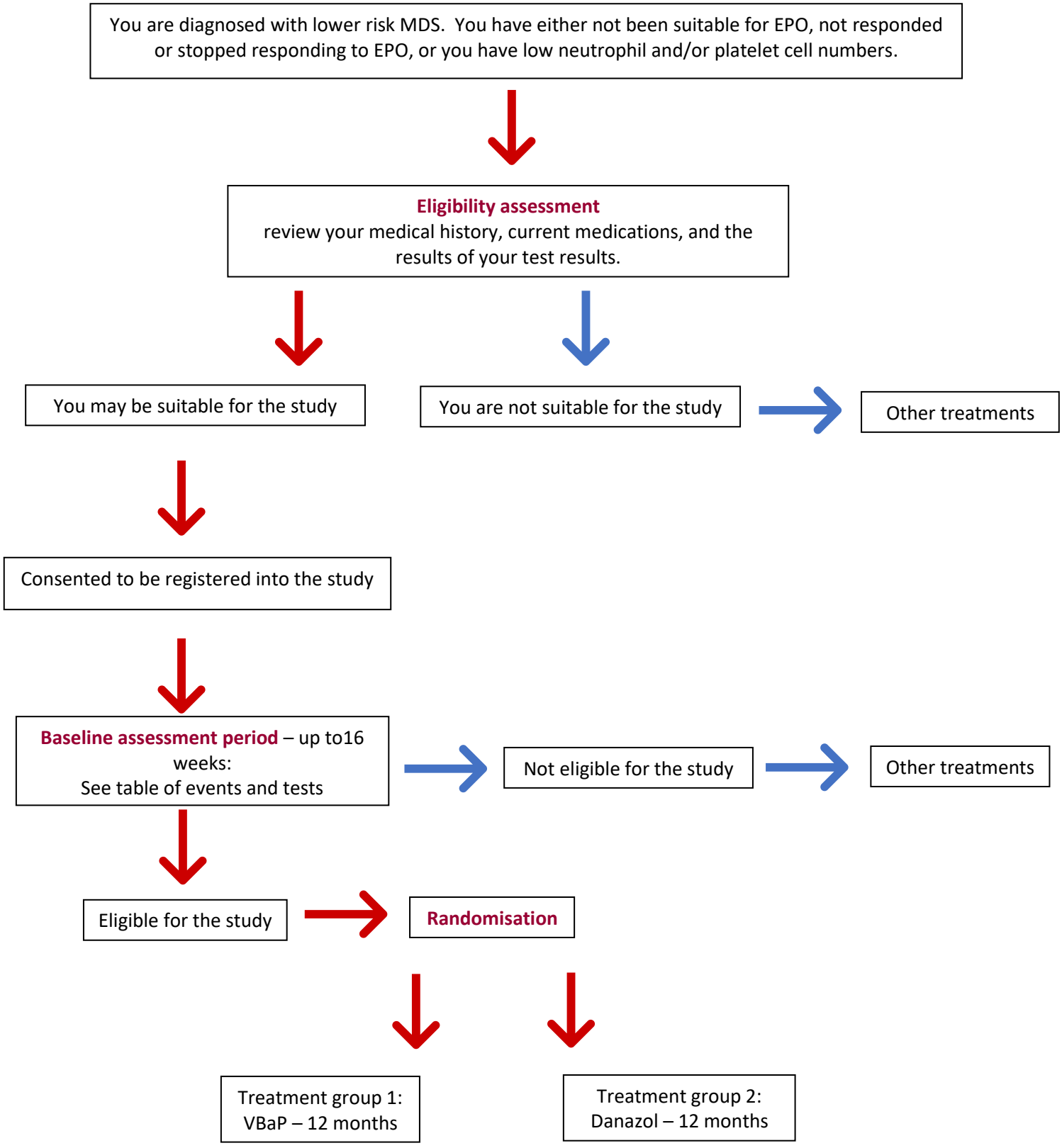
Women of childbearing potential are ineligible to participate in the trial. However, in the very unlikely event of a female becoming pregnant during or within 6 months of stopping trial medication, the outcome of the pregnancy will be reported as part of the trial follow-up even if you have discontinued the trial medication. Although there is no current evidence that any of the trial medication are harmful to sperm, if you are a male participant, you are still required (if your partner is a woman of childbearing potential) to utilize reliable contraceptive methods during the trial and for 3 months after stopping trial medication. In the very unlikely event of a female partner of a male participant becoming pregnant during or within 3 months of stopping trial medication, the outcome of the pregnancy will be reported as part of the trial follow-up even if you have discontinued the trial medication.

Statin medication and this study

If you decide to take part in the study and are taking a statin to prevent (but not treat) cardiovascular disease, you may still be registered into the study but we will ask you to stop taking the statin while on the study treatment. Your cholesterol will still be monitored during the trial and your GP will be aware you are on the study, and that you have stopped taking your statin. If you are concerned about temporarily stopping your statin, please speak to the clinical team.

2. What would taking part involve?

This flow chart explains the pathway if you decide to take part in the study:



Eligibility Assessment:

The first thing that will happen is that your doctor will review your medical history, current medications and the results of your test results. If your doctor thinks you may be suitable for the study, then you will be consented and 'registered' into the study during one of your clinic visits. Your written consent allows the study team to formally assess your suitability for the study.

Baseline Assessment Period:

If you are suitable for the study, then the next stage is called the 'Baseline Assessment Period'. This is a very important part of the study and will take between 4 and 16 weeks to complete. Once you are receiving study treatment the research team can look back at this information and compare how you are doing with how you were doing in the baseline assessment period, to assess whether the study treatment is working for you.

The Baseline Assessment Period can take up to 16 weeks and allows the research team to understand how your type of MDS is affecting your blood cells. They will monitor you carefully to see if you need blood transfusions or if you have any infections or problems with bleeding. You will need to go through the assessments detailed in the table below (Section 3 Tests and appointments during treatment).

What we find out in the Baseline Assessment Period will tell us whether you are definitely eligible to take part in the study. If you are eligible you can then go ahead to the next part of the study – randomisation.

Randomisation:

Randomisation is a process which decides which of the two study groups you go into – Group 1 or Group 2. Neither you nor your doctor will be able to choose which group you go into. Your allocation to treatment will be decided randomly by a computer; this may sound strange, but this is done so we can make a fair comparison between the two treatment options. Using a computer allows us to ensure that equal numbers of participants of different ages and MDS types are in each treatment group. It means that, at the end of the study, any differences we find are due to the two different study treatments, rather than anything else.

Treatment:

Once the computer allocates which of the treatments you are to receive, the pharmacy at your hospital will get your medicines ready. It is important that you take the allocated treatment and that you tell your doctor and the local team if you experience any problems or anything unusual at any point. The treatment will be for 12 months and the study will stop providing the drugs after that period. Your trial medication will stop and you will revert back to your usual clinical care which will be directed by your treating physician.

3. Tests and appointments during treatment

Once you start the study treatment you will be reviewed carefully by your haematology team and the study team to see how well the treatment is working for you and whether you have any side effects from the treatment. These reviews and tests will be done as follows:

			Fortnightly visits for first 4 months									Monthly visits until end of study									
	Registration	**Baseline Assessment**	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	4-6 weeks after finishing study medications
Height		✓																			
Weight		✓			✓		✓		✓		✓		✓							✓	
Physical Examination	✓	✓																			
Bone marrow sample		✓											✓							✓	
Liver and spleen ultrasound		✓																		✓*	
Medical and drug history	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Blood samples		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Blood pressure, pulse, temperature, O_2 saturation		✓	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ECG		✓					✓				✓										
Quality of life questionnaires			✓						✓				✓							✓	
Patient medication diaries				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Optional bone marrow samples		✓											✓							✓	
Optional blood samples					✓		✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Safety follow-up assessment telephone call																					✓

**This ultrasound will happen only if your treatment is Danazol.*

The procedures highlighted in orange in the table are likely to be in addition to your usual care, that is, they would not be done if you were not in the study. There is variation between what different doctors do, and what the needs of individual patients are. So, for some patients, these procedures, including blood samples,

will involve additional visits but for others this may be similar to normal care. The duration of the visits should be similar to your usual visits, but you may need extra 20 minutes to complete the Quality-of-Life questionnaires (but you are welcome to take the questionnaire home and post it back to the Research Team or Trials Unit).

One of the Research Nurses will call you to check if you are able to take the study medication correctly and to ask if there are any problems at all. The research team will also ask you to complete a diary before each visit to ensure your medication is being taken in the correct way and to check for any side effects.

At each appointment you will be asked to bring all of your trial medication, including empty boxes, bottles and foil trays, so that the Research Nurse can check your stock levels and ensure the correct amount of medication is prescribed to cover until your next appointment. You may not get a prescription at every appointment and a prescription may cover several visits depending on your dose.

These tests and reviews are very important and will give the study team a detailed assessment of how the study treatment is working for you. Some of the reviews may be done by phone. Your doctor will discuss this with you.

4. Blood and tissue samples

In addition to finding out whether the treatment works, we want the REPAIR-MDS study to help us understand exactly how these drugs effect your blood and bone marrow. This will allow us to better understand the disease itself. Therefore, we would like your permission to use some of the tissue samples (blood and bone marrow) taken from you in this study for ethically approved research in MDS. The samples will be taken during your standard tests. These will be one bone marrow sample (4ml which is less than one teaspoon) and two blood samples: one will be 10ml (approximately 2 teaspoons) - and the other will be 5ml (approximately 1 teaspoon). More information about this procedure is available from your local team. Samples will be stored for 10 years after the end of the trial, after which they will be discarded, unless further research is requested and approved.

There is no obligation for you to do this. You can still take part in the study even if you do not want us to use your tissue samples for research purposes.

If you do consent for your blood and tissue samples to be used for research, they will be stored and used for current and future ethically approved research on MDS which may take place within or outside the UK. The information attached to these samples will never include your name or address or any information that can identify you personally.

If you give consent for your blood and tissue samples to be used for other research projects, they may include genetic tests. These studies will be approved by an ethics committee now or in the future before any blood or tissue is used for other research projects.

The genetic tests will not predict your personal risk of inheritance and they will have no effect on your insurance or other financial affairs.

The tests are usually those that help us understand how MDS develops and how we can diagnose and treat MDS better.

5. Quality of Life (QoL)

An important part of the study is looking at whether any of the study treatments have an effect on your quality of life or your general well-being. So that we can do this thoroughly, we will ask you to fill in Quality of Life questionnaires in paper format during some of your reviews. This should take around 20 minutes to do or you may take the questionnaire home and post them back to us.

6. Expenses and payments

We are unable to pay you for taking part in the research. You may incur some minor expenses if you take part, such as the cost of car parking for more frequent hospital visits. We will try and keep these to an absolute minimum.

7. What if there is a problem?

Any complaint you have will be addressed. If you are dissatisfied with the treatment that you receive by any member of staff (doctor, nurse etc.) you have the same rights as any NHS patient to voice and register your complaints through the hospital complaints procedure. [Insert local PALS/Complaints Manager contact details].

If you have a complaint in relation to the study, you can contact the University of Warwick, Head of Research Governance via:

Head of Research Governance
Research & Impact Services
University House
University of Warwick
Coventry
CV4 8UW
Email: researchgovernance@warwick.ac.uk
Tel: 024 765 75733

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter: infocompliance@warwick.ac.uk. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

In the event that something does go wrong, and you are harmed during the research due to negligence, then you may have grounds for a legal action for compensation but you may have to pay your own legal costs.

8. What happens if I don't want to carry on with the study?

You are free to withdraw from this study at any time. If you withdraw or are unable to continue the study for any reason, we will only use the information that you have already given us to that point.

9. What happens if the research study stops?

In the unlikely event of the study stopping before the end of your treatment, you will be treated according to the usual procedures at your hospital and in consultation with your doctor. Your progress will be continued to be followed.

10. What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your doctor will discuss this with you and decide whether or not you should continue in the study. If you decide not to continue, your doctor will make arrangements for your future care. If you do continue in the study, you may be asked to read a new Information leaflet and sign a new consent form.

11. What will happen to the results of the research study?

The results of the research will be published in scientific journals over the next few years. You will not be identified in person in any report or publication arising out of this study. If you wish, you can request a summary of the main results of the study when available by emailing repairMDS@warwick.ac.uk.

We will keep your doctor informed of the study progress and they will be pleased to let you or your family know about the study outcome if you wish.

12. Who is organising and funding the research?

The research is being coordinated by the Warwick Clinical Trials Unit, based at the University of Warwick.
The University of Warwick and The Dudley Group NHS Foundation Trust are the Sponsors for this study.
The study is funded by Blood Cancer UK.

13. Who has reviewed the research study?

All research in the NHS is reviewed by an independent group of people, called a UK National Research Ethics Committee, which is there to protect your safety, rights, wellbeing and dignity. The study has been reviewed and given a favourable opinion by an Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA). The study has also been reviewed by the University of Warwick's Sponsorship and Oversight Committee, part of the University's Research & Impact Services and by the Cancer Trials Pharmacy Advisory Service (CPAS) from the National Institute for Health Research (NIHR).

We have worked with patient representatives who have regularly reviewed the study protocol and other documents such as this participant information sheet and will continue to work with us throughout the study. In addition, the study has been reviewed by the Funder: Blood Cancer UK.

14. How will we use information about you?

The University of Warwick will need to use information from you and your medical records in order to undertake this study and we will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly.

This information will include your

- Initials
- NHS number
- And ethnicity

As this will be collected alongside data concerning your health, this is considered to be special category data under the General Data Protection Regulation (GDPR). 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. We will keep all information about you safe and secure.

The University of Warwick and the hospitals taking part in the trial will keep information about you for the duration of your trial and for 10 years after the trial has finished so that we (the trial team at Warwick Clinical Trials Unit) can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

You can also find out more about how we use your information here:
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/ (Copy of this document is available from the research team).

15. What are my choices about how my 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. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

16. Where can you find out more about how your information is used?

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

- at www.hra.nhs.uk/information-about-patients/
- University of Warwick Research Privacy Notice: https://warwick.ac.uk/services/sim/privacynotices/research
- by asking one of the research team members
- by sending an email to infocompliance@warwick.ac.uk

17. Who should I contact if I want further information?

If you would like to talk more about the study or have any questions, get in touch with your doctor or your research nurse. Your local contact for the study is:
[INSERT NAME]
[INSERT CONTACT DETAILS]
Local Researcher: [Insert name and contact details of local investigator]

There is also information about cancer, MDS and research online. Some useful websites are below:

- CancerHelp - an information service about cancer and cancer research studies by Cancer Research UK. Freephone: **0808 800 4040, website** http://www.cancerhelp.org.uk/
- MDS UK Patient Support Group: **Helpline 020 7733 7558** or https://mdspatientsupport.org.uk/
- **Macmillan Cancer Support**: Freephone 0808 800 0000, www.macmillan.org.uk

18. What should I do next?

If you wish to take part in this study tell your doctor or your research nurse. They will then ask you to sign a consent form and register you for the assessment period. You will be given a copy of this information leaflet and a signed copy of the consent form to keep.

If you decide that you do not want to take part just let your doctor know. This will have no effect on any treatment or care that you will receive.

Thank you for taking the time to read this Participant Information Sheet