

# Repurposed drugs to improve blood counts and reduce transfusions in myelodysplastic syndromes

<b>Submission date</b> 19/07/2021	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 05/08/2021	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 06/06/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Over 7,000 people in the UK are living with myelodysplastic syndromes (MDS). About 1,600 of these individuals (23%) die each year from their disease. MDS affects the production of blood cells by the bone marrow, causing chronic fatigue, bleeding, and recurrent infections. Many patients die because their disease transforms into the even more aggressive blood cancer: acute myeloid leukaemia (AML). The general outlook for AML is poor, but when AML arises from MDS it's even worse. At diagnosis, MDS patients are categorised according to the likelihood of developing AML or dying very early for other reasons. This determines their treatment plan. Groups are termed low risk, intermediate risk or high risk. High-risk patients are often eligible for AML trials. However, very few trials are available for low-risk patients. Low-risk patients have a 20-35% risk of developing AML within 5 years of diagnosis. Meanwhile their quality of life is poor due to low blood counts. Most die prematurely from infections or complications related to MDS irrespective of whether they progress to AML. This study will be in low risk and some intermediate risk patients and will test the ability of already existing drugs to improve blood cell production in these patients. Currently, drugs that boost blood cell production in MDS patients are very limited and patients become resistant to such treatments or fail to respond to them at all. Consequently, the current backbone of care for low-risk MDS patients is transfusions. Donor red blood cells and platelets are used to restore the deficit in blood cells being produced by the patient's bone marrow. These transfusions place a heavy burden on patients with frequent hospital visits and impact on their quality of life. This study aims to improve this situation. Studies performed on patient's blood samples will also investigate key questions about how the drugs work if they are successful. The results of these important experiments will inform a better understanding of MDS and help design future trials.

### Who can participate?

Patients aged 18 years and over diagnosed with lower-risk MDS, who have either not been suitable for erythropoietin injections (EPO), have not responded or stopped responding to EPO, or they have a low neutrophil and/or platelet cell count.

### What does the study involve?

The study will test two new experimental treatment options, taking already existing drugs currently used for other purposes or conditions, and now using them to treat MDS. Treatment Group 1 receive sodium valproate (V), bezafibrate (Ba), and medroxyprogesterone (P). This treatment is called 'VBaP'. Bezafibrate and medroxyprogesterone were used in an earlier trial 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 receive 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. The study is trying to find out if these 'repurposed' drugs can be used to treat MDS patients and to improve their blood counts, reduce their need for transfusions, improve their quality of life, and prolong their survival.

### What are the possible benefits and risks of participating?

Taking part in this study may improve patient's blood counts, reduce their need for transfusions and therefore reduce the frequency of their hospital visits. It may also improve their quality of life – for example, participants may feel less tired. Furthermore, the information from this study may help to improve the treatment of people with MDS in the future. The study drugs may have some side effects. Additional bone marrow samples are required at 6 months and at the end of study. Additional blood samples are twice monthly and then monthly, but the samples can be taken at the same time as regular blood tests whenever the schedule matches. Participants will be asked to complete quality of life questionnaires which may add time to their usual hospital visits, but they can choose to take these home and post them back to the Trials Unit. Participants will also be asked to complete a diary about their trial medication.

### Where is the study run from?

University of Warwick Clinical Trials Unit (UK)

### When is the study starting and how long is it expected to run for?

September 2020 to June 2025

### Who is funding the study?

Blood Cancer UK

### Who is the main contact?

Bethany Foster (trial manager)

Dr Steve Jenkins and Dr Manoj Raghavan (Clinical CIs)

repairMDS@warwick.ac.uk

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-treatment-for-low-risk-myelodysplastic-syndromes-repair-mds>

## Contact information

### Type(s)

Scientific

### Contact name

Miss Bethany Foster

### Contact details

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**Type(s)**

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**Additional identifiers****Clinical Trials Information System (CTIS)**

2020-005446-42

**Integrated Research Application System (IRAS)**

1003603

**ClinicalTrials.gov (NCT)**

NCT04997811

**Protocol serial number**

CPMS 48916, IRAS 1003603

**Study information****Scientific Title**

Repurposed drugs to improve haematological responses in myelodysplastic syndromes

**Acronym**

REPAIR-MDS

**Study objectives**

The repurposed drugs combinations in this trial (VBAP or danazol) can be used to treat myelodysplastic syndrome (MDS) patients in order to: (i) improve their blood counts (ii) reduce their need for transfusions (iii) improve their quality of life.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

Approved 20/05/2021, East of Scotland Research Ethics Service (EoSRES, Tayside Medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK; +44 (0)1382 383848; tay.eosres@nhs.scot), REC ref: 21/ES/0037

## **Study design**

Multi-centre open-label randomized Phase II trial

## **Primary study design**

Interventional

## **Study type(s)**

Treatment

## **Health condition(s) or problem(s) studied**

Myelodysplastic syndromes

## **Interventions**

Randomisation:

Randomisation will use a minimisation algorithm adjusting for age (70 years and older or <70 years of age), Revised International Prognostic Scoring System for MDS (IPSS-R; very low, low or intermediate) and transfusion requirements (NTD, LTB, HTB).

Interventions:

The REPAIR-MDS Trial has two interventions/treatment groups:

VBaP arm

Sodium valproate tablet 500 mg BD, (starting 200 mg BD), bezafibrate standard release tablet 400 mg tds, (starting 200 mg tds) and medroxyprogesterone acetate tablet 400 mg BD

VBap starting doses:

Sodium valproate 200 mg bd, increasing to 500 mg bd after 2 weeks

Bezafibrate 200 mg tds, then from Week 4 increasing fortnightly in 200 mg increments to 400 mg tds

Medroxyprogesterone 400 mg bd

Danazol arm

Danazol 1 x 200 mg capsules tds (starting 1 x 200 mg od)

Danazol 200 mg od, increasing fortnightly by 200 mg increments to 200 mg tds

Dose for both arms will follow a set titration according to clinical outputs/absence of adverse effects.

For both arms, the minimum duration of therapy for patients to be included in the final analysis will be 12 weeks. A full treatment period will be considered 12 months of study therapy. At this point, the trial medication will stop and the patient will revert back to their usual clinical care.

In both arms, the Investigational Medicinal Product (IMP) will be dispensed at each clinic visit (fortnightly during the first 3 months and then monthly). IMPs will be self-administered by the participant at home with clear instructions provided by the research team during each clinic visit. IMPs will need to be taken orally, must not be crushed and the IMPs are not available as a liquid.

## **Intervention Type**

Drug

## Phase

Phase II

## Drug/device/biological/vaccine name(s)

Sodium valproate, bezafibrate, medroxyprogesterone acetate, danazol

## Primary outcome(s)

Haematological improvement (HI) in each arm and in the trial overall, with 25% or more of the participants having HI in each arm and overall. HI will be assessed in each participant by comparing post-randomisation FBC parameters (haemoglobin, platelet and neutrophil counts) and transfusion requirements, with their individual baseline as determined by the International Working Group (IWG) 2018 haematology response criteria in patients with MDS. Baseline assessment will be determined by the mean FBC parameters (haemoglobin, platelet and neutrophil counts) and transfusion burden (non-transfused [NTD], low transfusion burden [LTB], high transfusion burden [HTB]) during a 16-week lead-in to randomisation to either VBaP or danazol treatment; Timepoint(s): 12 months

## Key secondary outcome(s)

1. Burden of red cell and/or platelet transfusions measured by comparing mean haemoglobin, platelet and neutrophil counts in addition to transfusion requirements collected during the 16-week evaluation lead-in period to data collected 8 weeks from the start of trial treatment
2. Duration of haematological improvement (i.e. clinically meaningful response as per the IWG 2018 criteria) will be assessed in each participant by comparing post-randomisation full blood counts parameters (haemoglobin, platelet and neutrophil counts) and transfusion requirements, with their individual baseline as determined by the IWG 2018 haematology response criteria in patients with MDS. Baseline assessment will be determined by the mean full blood counts parameters (haemoglobin, platelet and neutrophil counts) and transfusion burden (NTD, LTB, HTB) during a 16-week lead-in to randomisation to either treatment arm.
3. Quality of life measured using patient-reported health-related quality of life (QoL) scores (EQ5D-5L, EORTC-QLQ-C30, HM-PRO and QOL-E) at time of randomisation (baseline), 12 weeks post-randomisation, 24 weeks post-randomisation & 12 months post-randomisation
4. Overall survival assessed using Kaplan Meier curves at 12 months post-randomisation
5. Health resource use measured utilising data collected via the Clinical Report Forms in respect to clinic attendances, admissions, blood transfusion episodes and trial drug and through the use of patient diaries collected at randomisation, 12 weeks, 24 weeks and 12 months post-randomisation

## Completion date

30/06/2025

## Eligibility

### Key inclusion criteria

Current participant inclusion criteria as of 14/06/2023:

1. Provision of written informed consent
2. Age  $\geq$  18 years and able to give informed consent
3. Diagnosis of myelodysplastic syndrome with an IPSS-R score of less than or equal to 3.5
4. Haematological parameters:
  - 4.1. Mean haemoglobin  $<$  100 g/l over 16 weeks (pre-transfusion) OR

- 4.2. Mean platelets < 100 x 10<sup>9</sup>/L over 16 weeks + evidence of bleeding (assessed using the ISTH Bleeding Assessment Tool) OR
- 4.3. Mean neutrophils < 1.0 x 10<sup>9</sup>/L over 16 weeks + history of infection (the requirement for antimicrobial therapy and hospital admissions associated with infection)
5. No response to erythroid stimulating agents (ESAs) OR have ceased to respond to ESAs OR are Predicated not to Respond to ESAs by current UK guidelines (NB Patients with thrombocytopenia and/or neutropenia, without anaemia, are eligible as they are predicated not to respond).
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-3
7. Expected survival > 12 months

Previous participant inclusion criteria:

1. Provision of written informed consent
2. Age ≥18 years and able to give informed consent
3. Diagnosis of myelodysplastic syndrome with an IPSS-R score of less than or equal to 3.51
4. Haematological parameters:
  - 4.1. Mean haemoglobin <100 g/l over 16 weeks (pre-transfusion) OR
  - 4.2. Mean platelets <100 x 10<sup>9</sup>/l over 16 weeks + evidence of bleeding (assessed using the International Society on Thrombosis and Haemostasis (ISTH) Bleeding Assessment Tool) OR
  - 4.3. Mean neutrophils <1.0 x 10<sup>9</sup>/l over 16 weeks + history of infection (the requirement for antimicrobial therapy and hospital admissions associated with infection)
5. No response to erythroid stimulating agents (ESAs) OR have ceased to respond to ESAs OR are predicated not to respond to ESAs by current UK guidelines
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-3
7. Expected survival >12 months

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

### **Sex**

All

### **Total final enrolment**

32

### **Key exclusion criteria**

Current participant exclusion criteria as of 14/06/2023:

1. Abnormal liver function (if the patient has Gilbert's syndrome, then abnormal direct bilirubin is an exclusion)
2. Cockcroft Gault CrCl < 20 ml/min
3. Current systemic treatment for low-risk MDS
4. History of allogeneic bone marrow transplant

5. History of having received ESAs and/or G-CSF in the past 16 weeks
6. Currently receiving statin medication for secondary prophylaxis of cardiovascular disease, cerebrovascular, or peripheral vascular disease (Please note patients receiving statin medication for primary prophylaxis of cardiovascular disease – i.e. the patient has no prior history of ischaemic heart disease or cerebrovascular disease - can still be entered)
7. Currently receiving fibrate medications
8. Currently receiving sodium valproate, carbamazepine or phenytoin for the treatment of epilepsy
9. Prior cytotoxic chemotherapy or hypomethylating agents for AML/MDS (e.g. azacitidine)
10. Concurrent active malignancy requiring treatment
11. History of any androgen-dependent tumour (patients with prostate cancer are excluded when a biopsy-proven diagnosis of prostate cancer has been made OR their PSA is known to be elevated OR they are on active treatment for prostate cancer, including hormonal therapy).
12. Currently receiving vitamin K antagonist anticoagulation (though patients receiving direct oral anticoagulants (DOACs) can be included)
13. History of venous thromboembolism (VTE)
14. Cardiac failure NYHA Class III or IV
15. Women of childbearing potential, pregnant or lactating
16. The physician or patient considers VBaP or danazol to be inappropriate for the patient
17. Known HIV
18. Abnormally high CK level
19. Presence of isolated del 5q
20. Acute porphyria
21. Contraindications to any of the trial medications or known hypersensitivity to any of the investigational products
22. Previous randomisation in the REPAIR-MDS trial
23. Participation in a clinical trial of an investigational medicinal product in the last 16 weeks

Previous participant exclusion criteria:

1. Abnormal liver function (if the patient has Gilbert's syndrome, then abnormal direct bilirubin is an exclusion)
2. Cockcroft Gault CrCl < 20 ml/min
3. Current systemic treatment for low-risk MDS
4. History of allogeneic bone marrow transplant
5. History of having received ESAs and/or G-CSF in the past 16 weeks
6. Currently receiving statin medication for secondary prophylaxis of cardiovascular disease or cerebrovascular disease (Please note patients receiving statin medication for primary prophylaxis of cardiovascular disease – i.e. the patient has no prior history of ischaemic heart disease nor cerebrovascular disease - can still be entered)
7. Currently receiving fibrate medications
8. Currently receiving sodium valproate, carbamazepine or phenytoin for treatment of epilepsy
9. Prior cytotoxic chemotherapy for AML/MDS
10. Concurrent active malignancy requiring treatment
11. History of any androgen-dependent tumour (patients with prostate cancer are excluded when a biopsy-proven diagnosis of prostate cancer has been made OR their PSA is known to be elevated OR they are on active treatment for prostate cancer, including hormonal therapy).
12. Currently receiving vitamin K antagonist anticoagulation (though patients receiving direct oral anticoagulants (DOACs) can be included)
13. History of venous thromboembolism (VTE)
14. Cardiac failure NYHA Class III or IV
15. Women of childbearing potential, pregnant or lactating
16. The physician or patient consider VBaP or danazol to be inappropriate for the patient



17. Known HIV
18. Abnormal CK level
19. Presence of isolated del 5q
20. Acute porphyria
21. Contraindications to any of the trial medications or known hypersensitivity to any of the investigational products
22. Previous randomisation in the REPAIR-MDS trial
23. Participation in a clinical trial of an investigational medicinal product in the last 90 days

**Date of first enrolment**

21/12/2021

**Date of final enrolment**

30/06/2024

## **Locations**

**Countries of recruitment**

United Kingdom

England

Scotland

Wales

**Study participating centre**

**Russells Hall Hospital**

The Dudley Group NHS Foundation Trust  
Pensnett Road  
Dudley  
United Kingdom  
DY1 2HQ

**Study participating centre**

**Aberdeen Royal Infirmary**

Foresterhill  
Aberdeen  
United Kingdom  
AB25 2ZN

**Study participating centre**

**University Hospitals Birmingham NHS Foundation Trust**

Mindelsohn Way  
Edgbaston

Birmingham  
United Kingdom  
B15 2GW

**Study participating centre**  
**Colchester General Hospital**  
Turner Road  
Colchester  
United Kingdom  
CO4 5JL

**Study participating centre**  
**University Hospital of Wales**  
Aneurin Bevan Health Board  
Heath Park Way  
Cardiff  
United Kingdom  
CF14 4XW

**Study participating centre**  
**The Royal Bournemouth Hospital**  
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Bournemouth  
United Kingdom  
BH7 7DW

**Study participating centre**  
**Royal Hallamshire Hospital**  
Glossop Road  
Broomhall  
Sheffield  
United Kingdom  
S10 2JF

**Study participating centre**  
**St James University Hospital**  
Beckett St  
Harehills  
Leeds  
United Kingdom  
LS9 7TF

**Study participating centre**

**Royal Cornwall Hospital**

Treliske

Truro

United Kingdom

TR1 3LJ

**Study participating centre**

**Guy's and St Thomas' Hospital**

20 St Thomas St,

London

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SE1 9RS

**Study participating centre**

**Kings College Hospital**

Denmark Hill

London

United Kingdom

SE5 9RS

**Study participating centre**

**Northampton General Hospital**

Cliftonville

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**Study participating centre**

**University College London Hospital**

Euston Road

London

United Kingdom

WC1H 8NJ

**Study participating centre**

**The James Cook University Hospital**

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United Kingdom  
TS4 3BW

**Study participating centre**  
**Kent and Canterbury Hospital**  
Ethelbert Road  
Canterbury  
United Kingdom  
CT1 3NG

**Study participating centre**  
**Wythenshawe Hospital**  
Southmoor Rd  
Wythenshawe  
Manchester  
United Kingdom  
M23 9LT

**Study participating centre**  
**Basingstoke and North Hampshire Hospital**  
Aldermaston Rd  
Basingstoke  
United Kingdom  
RG24 9NA

**Study participating centre**  
**Nottingham University Hospital**  
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NG5 1PB

**Study participating centre**  
**New Cross Hospital**  
Wolverhampton Rd  
Heath Town  
Wolverhampton  
United Kingdom  
WV10 0QP

**Study participating centre**

**Dorset County Hospital**

Williams Avenue  
Dorchester  
United Kingdom  
DT1 2JY

**Study participating centre**

**University Hospitals of North Midlands**

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Stoke-on-Trent  
United Kingdom  
ST4 6QG

**Study participating centre**

**Castle Hill Hospital**

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Cottingham  
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HU16 5JQ

**Study participating centre**

**Blackpool Victoria Hospital**

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United Kingdom  
FY3 8NR

**Study participating centre**

**Royal Berkshire Hospital,**

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RG1 5AN

**Study participating centre**

**Worcestershire Acute Hospital**

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United Kingdom  
WR5 1DD

**Study participating centre**  
**Worcestershire Royal Hospital**  
Charles Hastings Way  
Worcester  
United Kingdom  
WR5 1DD

**Study participating centre**  
**Broomfield Hospital**  
Court Road  
Broomfield  
Chelmsford  
United Kingdom  
CM1 7ET

**Study participating centre**  
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Leicester  
United Kingdom  
LE1 5WW

**Study participating centre**  
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United Kingdom  
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## **Sponsor information**

**Organisation**  
University of Warwick

**ROR**

<https://ror.org/01a77tt86>

## Organisation

Dudley Group NHS Foundation Trust

## Funder(s)

### Funder type

Charity

### Funder Name

Bloodwise (Blood Cancer UK); Grant Codes: 20010

### Alternative Name(s)

### Funding Body Type

Private sector organisation

### Funding Body Subtype

Other non-profit organizations

### Location

United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study are/will be available upon request from the Repair MDS Trial Management Group (TMG) via [repairmds@warwick.ac.uk](mailto:repairmds@warwick.ac.uk). Summary data including baseline characteristics and outcome data will become available after the primary publication and the data will be available for up to 5 years from the end of the study. The data will be shared with any researchers for whom the scope and purpose of the data sharing are agreed upon by the TMG. All participants have agreed to use of data for research, no identifiable data will be released, and patients will have a unique trial number assigned. There are no ethical or legal restrictions. The researchers encourage data sharing, and all reasonable requests will be reviewed favourably.

### IPD sharing plan summary

Available on request

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			26/07/2023	No	No

<a href="#">Participant information sheet</a>	version 2.0	22/04/2021	04/08/2021	No	Yes
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes