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

Submission date 19/07/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 05/08/2021	**Overall study status** Completed	
Last Edited 06/06/2025	**Condition category** Cancer	

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

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04997811

Clinical Trials Information System (CTIS)
2020-005446-42

Integrated Research Application System (IRAS)
1003603

Central Portfolio Management System (CPMS)
48916

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

Primary study design
Interventional

Study design
Multi-centre open-label randomized Phase II trial

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 20 0mg 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 ≥ 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 109/L over 16 weeks + evidence of bleeding (assessed using the ISTH Bleeding Assessment Tool) OR
4.3. Mean neutrophils < 1.0 x 109/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 10e9/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 10e9/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
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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. 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?
HRA research summary			26/07/2023	No	No

Participant information sheet	version 2.0	22/04/2021	04/08/2021	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes