NHS
Blood and Transplant

Acronym: REAL

REd cell transfusion in Acute myeloid Leukaemia

Version: 2.0

Date: 09 October 2018

Cross-Referenced in Primary Document: MPD980

Approved by:

Name:	Simon Stanworth	Role:	Chief Investigator
Signature:		Date:	05/10/2018

The protocol has also been approved by Study Statistician, Clinical Operations Manager, Clinical Data Services Manager and Head of Clinical Operations.

General Information

This document was constructed using the National Health Service Blood and Transplant Clinical Trials Unit (NHSBT CTU) Protocol Template FRM4468 Version 1.0, which is based on the MRC CTU Protocol template Version 4.0. It describes the REAL trial, coordinated by the NHSBT CTU and provides information about procedures for entering patients/participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering participants for the first time are advised to contact the Trial Manager to confirm they have the most up to date version.

Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2013, the Principles of Good Clinical Practice (GCP), European Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, the National Health Service Research Governance Framework for Health and Social Care (RGF) and any other applicable national regulations.

Sponsor

The NHSBT is the trial sponsor and has delegated responsibility for the overall management of the REAL trial to the NHSBT CTU. Queries relating to the NHSBT sponsorship of the trial should be addressed to the Research and Development Manager, c/o R&D Office, NHSBT, 500 North Bristol Park, Northway, Filton, Bristol, BS34 7QH, email research.office@nhsbt.nhs.uk or via the trial team.

Funding

This trial is funded by a grant from the NHSBT Trust Fund (TF 63).

Authorisations and Approvals

NHSBT is a non-commercial partner with the NIHR and this clinical trial is therefore eligible for inclusion in the NIHR Clinical Research Network Portfolio.

Trial Registration

This trial will be registered with the ISRCTN Register once it has been adopted onto the NIHR portfolio.

RANDOMISATIONS

To randomise, please visit

www.sealedenvelope.com

choose the REAL trial from the drop down list and log-on as instructed

SAE REPORTING

Within one working day of becoming aware of a reportable SAE, please fax a completed SAE Form to the NHSBT CTU on

01223 588136

Or email information to :(Serious_Adverse_Events@nhsbt.nhs.uk)

Trial Administration

Please direct all enquiries to the Trial Manager in the first instance. Clinical queries will be passed to the Chief Investigator via the Trial Manager.

CTU Details

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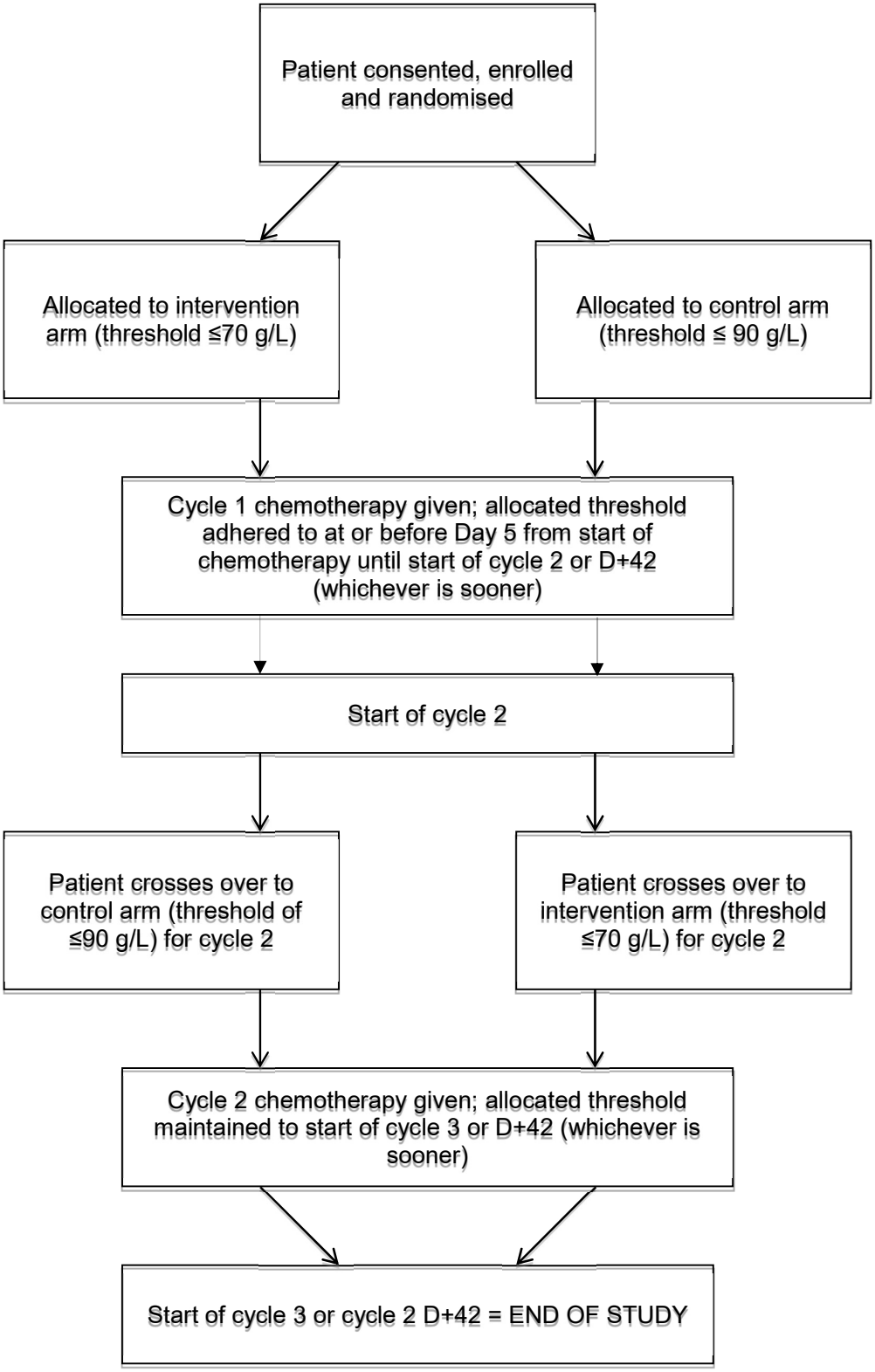
For full details of Trial Committees, please refer to Section 14.

Study Synopsis

Title of clinical study	Red Cell Transfusion in Acute Myeloid Leukaemia
Protocol Short Title/Acronym	REAL
Version	**2.0**
Date	**09 October 2018**
Sponsor name	NHSBT
Funder	NHSBT
Chief Investigator	Dr. Simon Stanworth
REC number	16/WM/0406
IRAS Number	210454
Study design	A feasibility cross-over randomised controlled trial comparing restrictive versus liberal red cell transfusion strategies in adult patients with acute myeloid leukaemia receiving intensive chemotherapy.
Type of participant to be studied	Inclusion Criteria 1. Adults aged ≥ 18 years 2. Diagnosis of *de novo* acute myeloid leukaemia (AML) or relapsed AML 3. Undergoing treatment with intensive chemotherapy with an expectation of receiving a minimum of 2 cycles (excluding stem cell transplant) Exclusion Criteria 1. Patients for whom the attending haematologist feels allocation to either a restrictive or liberal policy of red cell transfusion is not justified (e.g. clinically significant cardiovascular disease) 2. Acute promyelocytic leukaemia (APML) 3. Patients who have been diagnosed with myelodysplasia prior to diagnosis of AML (see main section)
Setting	Haematology patients treated in acute hospitals as inpatient or outpatients
Randomisation	Online randomisation, stratified by centre. Allocation and commencement to restrictive or liberal red cell transfusion threshold must commence at or before Day 5 from start of chemotherapy for cycle 1

Interventions to be compared	Prior to commencement of allocated transfusion policy in cycle 1, patients may receive red cell transfusions according to clinical need Allocation to trial transfusion policy will then apply from at or before Day 5 onwards from start of chemotherapy in cycle 1, to either: 1. ***Restrictive transfusion policy:*** Participants will receive a single unit transfusion if their haemoglobin level is ≤70 g/L. The objective for the attending clinician is then to maintain the haemoglobin level between 71 – 80 g/L with single unit transfusions 2. ***Liberal transfusion policy:*** Participants will receive a single unit transfusion if their haemoglobin level is ≤90 g/L. The objective for the attending clinicians is then to maintain the haemoglobin level between 91- 100 g/L with single unit transfusions For cycle 2 chemotherapy treatment, participants will follow the alternative transfusion policy (i.e. if allocated to restrictive arm for cycle 1, this would be the liberal arm for cycle 2
Study hypothesis	It is feasible to achieve adherence when randomising patients to one of 2 haemoglobin thresholds and maintaining haemoglobin concentrations between either 71-80 g/L or 91-100 g/L
Primary outcome measure(s)	• Percentage of pre-transfusion haemoglobin concentrations being **below the** target range of the assigned red cell transfusion strategy • **Achievement of at least a 15g/L difference between the mean pre-transfusion haemoglobins in the two transfusion groups**
Secondary outcome measure (s)	**Adherence outcomes:** transfusions given per protocol, red cell exposure, adherence to outcome monitoring, recruitment rate, characteristics of recruited participants **Clinical outcomes:** bleeding, thrombosis, culture verified bacterial infections, platelet transfusion, Quality of Life (QoL), transfusion reactions, death **Monitoring outcomes:** compliance with data collection between sites
Duration of Study	• Recruitment for 18 months • Intervention from diagnosis until end of second cycle or cycle 2 Day +42 i.e. the 42nd day after the last dose of chemotherapy (approximately 3 months) • No further follow-up beyond intervention period • Duration of trial – 2 years
Study Schedule	The study schedule can be found in section 6.1 of the protocol.
Sample Size	36 patients (for one complete cycle of chemotherapy) with equal numbers in each arm
Ancillary Studies/substudies	**None**
Trial manager	Heather Smethurst
CTU Project Manager	Ana Mora

Study Schema



Contents

Abbreviations and Glossary

AE	Adverse event
AML	Acute Myeloid Leukaemia
AR	Adverse reaction
ATR	Adverse transfusion reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	NHSBT Clinical Trials Unit
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
HRA	**Health Research Authority**
NCRI	National Cancer Research Institute
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PBM	Patient Blood Management
PI	Principal Investigator
PIS	Patient Information Sheet
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RCT	Randomised controlled trial
RBC	Red blood cell
REC	Research Ethics Committee
R&D	Research and Development
RN	Research nurse
SABRE	Serious Adverse Blood Reactions and Events
SAE	Serious adverse event
SHOT	Serious Hazards of Transfusion
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic acid
WHO	World Health Organisation

1. Background

1.1 Background

Among the patient groups who receive the most transfusions are patients undergoing curative treatment for acute leukaemia. In the UK, Patients with haematological malignancies and disorders are the largest group of red cell transfusion recipients[1].

On a background of growing awareness of non-infectious complications of blood transfusions there is a need for increasing scrutiny of current blood practices in high-use areas such as patients with haematological malignancies. In addition health care costs need to be considered, including the relative differences between restrictive and liberal policies, and the use of more single unit compared to double unit transfusions. Patient blood management (PBM) is an evidence based, international initiative to optimise the care of patients who may need transfusion and an integral part is ensuring that avoidable inappropriate use of blood and blood components is reduced.

In Scandinavia, a recent study of the blood use among AML patients, using the binational, Scandinavian donations and transfusions (SCANDAT) database, found that a patient with acute leukaemia in Sweden and Denmark receives an average of more than 50 transfusions (30 red cell units and 20 platelet units) over the first 6 months of therapy (unpublished observation). Recent AML trials in the UK have also confirmed the high burden and usage of red cell transfusions during intensive chemotherapy for AML with data indicating on average 11-12 units for the first course of intensive induction therapy.

1.2 Current practice for red cell transfusion in AML

There is evidence from multiple sources of considerable variation in practice, reflecting uncertainty in the evidence base defining optimal use of red cells:

- Survey: A survey was distributed to senior clinicians through the National Cancer Research Institute (NCRI) acute leukaemia working group, which included different clinical scenarios. Reported transfusion thresholds for red cell transfusions were varied between clinicians with the most common reported haemoglobin threshold for transfusion being 80g/L;
- Audit data: findings from the National Comparative Audit of red cell use show a median pre transfusion Haemoglobin of 79g/L but again with evidence of variation.
- National guidelines: Recent National Institute for Health and Care Excellence (NICE) guidance (Padhi et al 2015) advocates a haemoglobin threshold of 70 g/L in the majority of patients and individual targets based on symptoms in those with chronic anaemia. No specific recommendation is made for patients on chemotherapy or with acute haematological malignancy.

In addition the continuing practice of multiple unit transfusions was debated at the NCRI group, and assessed by the survey. The survey has shown that some haematologists continue to prescribe 2 unit transfusions of red cells routinely, although recommendations through NHSBT Patient Blood Management (PBM) and NICE guidelines are now promoting single rather than multiple unit transfusions.

In summary, there is uncertainty between individual clinicians in the safety of both lower thresholds (e.g. risk of bleeding, tolerability in a population with acute secondary bone marrow failure) and higher thresholds (e.g. complications of transfusions, costs), indicating a need for research.

1.3 Evidence for safe transfusion thresholds

Cumulative data from randomised controlled trials of red cell transfusions in hospitalised patients with acute illness or planned surgery have underpinned current guidelines. This now indicates that patients with minimal co-morbidity or low illness severity do not benefit from red cell transfusions to maintain haemoglobin concentrations greater than 70g/L. A Cochrane systematic review, identifying 19 such randomised controlled trials involving 6264 patients across a variety of clinical settings, but mainly in surgery, trauma and critical care, concluded that a lower haemoglobin threshold or transfusion trigger was associated with fewer RBC transfusions without adverse associations with mortality, cardiac morbidity, functional recovery or hospital length of stay (Carson et al 2012).

However it is not clear to what extent the findings from these trials in critical illness relate to patients with a predominant failure of marrow production. To date only one small feasibility trial has been published for inpatients with haematological malignancies (Webert et al 2008). This small trial compared haemoglobin thresholds of 80 vs 120g/L and was directed at augmenting rather than restricting red cell use. Proof of principle was demonstrated with separation of haemoglobin between the groups. Outcomes focussed on bleeding risk and donor exposure with no difference found between the two groups (although the study was not powered to detect a significant difference). No measure of quality of life was included. There are several on-going trials, one in patients undergoing haemopoietic stem cell transplant using haemoglobin thresholds of 70 vs 90g/L (Tay J et al, 2011; TRIST trial) a feasibility trial in elderly outpatients with myelodsyplasia (Canada and UK), and one small feasibility trial in AML is on-going in the US, aiming to compare 70 vs 80 g/L (Dezern A et al, ASH, 2015, abstract).

Therefore, current uncertainty in the optimal red cell transfusion strategy exists for patients with haematological malignancies and receiving intensive chemotherapy. These uncertainties are reflected in meetings with haematologists in the UK, and guidelines including recent NICE recommendations which allow for ‘individualised practice’ in patients with haematological malignancies. It is accepted that patients with bone marrow failure will often have transfusion requirements for a much longer period than many critically ill patients. This may extend over months, and functional outcomes and related symptoms are likely to be more important for patients with haematological malignancies. In addition, previously studied groups have tended to be more acutely unwell with clinical outcomes focussing on death and cardiovascular events (Holst et al, 2015). Although AML is a life threatening disease with a high mortality, quality of life and symptomatic anaemia during treatment is a more clinically relevant problem than, for example, in patients admitted to intensive care.

As the population tends to live longer, it is expected that the incidence of haematological malignancies will increase and therefore it is timely to try and address the issue of optimal red cell transfusion thresholds in an acute leukaemia setting. Given the evidence that policies for red cell transfusion in patients with haematological malignancies have become more restrictive, but with evidence of wide variation in practice, this study is designed as a feasibility trial to test adherence to ‘restrictive’ and ‘liberal’ policies of red cell transfusion.

Red cell transfusions are biological agents, and there is awareness of the risks of transfusion-associated immunomodulation, for example in cancer recurrence, or as reported for in hospital infection risk in recent meta-analyses (Rohde et al 2014). In patients with large transfusion burdens allo-immunisation and iron overload can result in additional morbidity. In light of a possible link between blood transfusions and risks of serious infections (Rohde et al 2014) and previous studies showing varying beneficial effects of lowered transfusion thresholds for several other patient groups, we believe that even modest reductions in blood use may have important health effects for this patient group.

1.4 Justification for choice of thresholds and trial design summary

Participants will participate in the study for the first two cycles of chemotherapy. The haemoglobin threshold for the first cycle will be randomised and the participant will cross over to the other threshold for the second cycle. The two primary outcomes of the feasibility trial will be measures of adherence to protocol and achievement of a difference in mean pre-transfusion haemoglobin levels. Participants will be followed from randomisation until the end of the second cycle of intensive chemotherapy.

The thresholds for this feasibility trial were informed by the results of the survey and audits described in section 1.2. The thresholds reflect a common current haemoglobin threshold at (just under) 80g/L, and a need to test two policies around this standard with a likelihood of achieving clinically meaningful separation between the groups.

A cross-over trial design allows each participant to act as their own control, reducing the possibility of any observed difference being due to patient-related confounding factors. It may reduce the amount of variability observed in the outcome measures of interest, and be more statistically 'efficient', and reduces the number of patients required to detect a difference.

1.5 Risks and anticipated benefits

The risks associated with the trial are small. We are not testing a novel treatment nor the efficacy of an existing treatment in a new setting. The proposed transfusion thresholds are within the ranges of current practice and within the ranges described by guidelines. There may be benefits including:

- reduced risk of complications associated with use of liberal red cell transfusion policies;
- the provision of randomised evidence to address this area of clinical uncertainty;
- saving the costs of blood that is not used for transfusion and treatments of complications that are avoided.

Potential harms include the possible risk of receiving an unnecessary red cell transfusion in the liberal arm or the possible adverse effects of not receiving a red cell transfusion when it may have benefits in the restrictive arm. The fact that our thresholds are already part of existing routine care means, it is reasonable to ask participants to accept the possibility of randomisation to either transfusion policy which they may receive in any case outside of the trial setting.

1.6 Patient involvement

A group of inpatients with AML were asked questions about aspects of trial design, willingness to participate and level of interest in the research questions and these patients supported the need for the trial as indicated both in the discussion and anonymous feedback forms.

2. Selection of Sites/Clinicians

The trial sponsor has overall responsibility for site and investigator selection

2.1 Site/Investigator Inclusion Criteria

To participate in the REAL trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been prepared by the REAL Trial Management Group (TMG) and are defined below.

2.1.1 PI Qualifications and Agreements

1. The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up to date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, the HRA, and/or the regulatory authorities.

2. The investigator should be thoroughly familiar with the protocol and other information provided by the Sponsor.

3. The investigator should be aware of, and should comply with, the principles of ICH GCP and the applicable regulatory requirements. A record of GCP training should be accessible for each investigator.

4. The investigator/site should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority (ies).

5. The investigator should maintain a delegation log of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

6. The investigator should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.2 Adequate Resources

1. The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial, to conduct the trial properly and safely.

4. The investigator should ensure that all persons conducting the trial are adequately informed about the protocol and their trial-related duties and functions.

2.2 Site/Investigator Exclusion Criteria

Investigators excluded from, or not on the appropriate professional register cannot be investigators in the trial.

2.3 Approval and Activation

Once the site essential documents have been received a site initiation visit will be scheduled during which the staff will be trained in the protocol and procedures. A training log and a delegation log will be maintained at each site, with copies held by the CTU. Up to date,

signed CVs and GCP certificates of site staff must also be held by the CTU along with a signed declaration from the PI.

If an investigator meeting is held for the purposes of training, it may be possible to activate/initiate a site remotely by providing access to the randomisation website once all the necessary site documentation has been received at the CTU and all necessary approvals are in place.

3. Selection of Participants

There will be no exceptions to eligibility requirements at the time of randomisation. Questions about eligibility should be addressed before attempting to randomise the patient.

The eligibility criteria for this trial have been carefully considered. They are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the study. This is to ensure the safety of the patients, as well as to ensure that the results of the study can be useful for making treatment decisions regarding other patients in similar situations.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria detailed below.

3.1 Participant Inclusion Criteria

1. Adults aged ≥ 18 years
2. Diagnosis of *de novo* acute myeloid leukaemia (AML) or relapsed AML

This includes patients who develop AML following chemo/radiotherapy, provided they have not had a diagnosis of myelodysplasia prior to their AML diagnosis; patients with granulocytic sarcoma requiring intensive chemotherapy; patients with RAEB/RAEBT proceeding to intensive chemotherapy straight after diagnosis (cases to be discussed individually with PI)

3. Undergoing treatment with intensive chemotherapy with an expectation of receiving a minimum of 2 cycles (excluding stem cell transplant)

3.2 Participant Exclusion Criteria

- Patients for whom the attending haematologist feels allocation to either a restrictive or liberal policy of red cell transfusion is not justified (e.g. clinically significant cardiovascular disease)
- Acute promyelocytic leukaemia (APML)
- Patients who have been diagnosed with myelodysplasia prior to diagnosis of AML, whether they have required blood transfusion support or not (but, see above)

3.3 Number of Participants

At least 36 patients, with data collection for one complete cycle of chemotherapy, randomised in a 1:1 ratio

3.4 Co-Enrolment Guidelines

It is anticipated that patients participating in the REAL study will also be enrolled in other AML studies running at the participating sites

3.5 Screening Procedures and Pre-randomisation Investigations

All eligible patients will be approached for consent as soon as possible by the research nurse/PI/delegate to provide information about the study and to seek consent for data collection and follow up; it is recommended that information about this trial be provided at the same time as seeking consent for enrolment into other AML trials. The timeframe within which the patient is approached will be appropriate to his/her clinical condition.

Eligibility will depend upon the disease severity and the need for urgent clinical intervention.

3.5.1 Details of Registration Process

Potential trial patients will be identified on the haematology ward or through the attending haematology team. The Research Nurse (RN) and care teams will screen admission lists daily. All eligible patients will be approached as soon as possible after presentation with AML to obtain informed consent. The local RN/PI/delegate will approach the patient to provide a participant information sheet, answer questions, confirm eligibility and seek their willingness to consent to data collection

Those patients providing consent to participating in the trial, data collection and follow up are enrolled into the trial. The recruited participants will then be given a unique study ID number at randomisation that will be used throughout the study. Patients will be randomised using sealedenvelope.com as described in section 4.

Patients who present out of normal working hours will be identified the next working day.

Patients not eligible to be enrolled in the trial will be entered on the screening log so there is evidence that the patient has been assessed and the reasons for not enrolling are documented.

3.5.2 Informing Trial Participants of Possible Benefits and Known Risks

An information sheet must be provided to the patient at the time of seeking consent, and accompanied by an informed discussion.

3.5.3 Consent

Written informed consent will be obtained from participants before any trial-specific procedures are performed, including taking any blood samples. Participants will be informed that they will be blinded to their allocation and as such will not routinely be informed of their haemoglobin levels during treatment.

The participant is free to refuse to participate in all or any aspect of the trial at any time and for any reason, without incurring penalty or affecting their treatment.

Signed consent forms will be kept by the investigator and the consent discussion will be documented in the medical notes. A copy of the consent form will be provided to the participant, and a copy will be filed in the medical notes of the participant. With consent, a letter will be sent to the participant's general practitioner (GP) informing them of the trial and the participants' involvement in it.

3.5.4 Patients requiring transfusion prior to enrolment

Patients in cycle 1 (without clinically significant bleeding) may be deemed by the clinical team to require transfusion and this be indicated before being approached about the trial to seek consent. These patients may be transfused according to a locally agreed guidelines, which will typically define a threshold of 80 g/L. Once randomisation has occurred (which is anticipated to be on the same working day as consent is obtained) clinicians should adhere to the allocated threshold. All potentially eligible patients must have been randomised before or up to Day 5 from start of chemotherapy.

4. Randomisation

4.1 Randomisation practicalities and blinding

Patients at each site will be randomised using an online randomisation system at sealedenvelope.com. The randomisation number will be recorded on the CRF. Patients will be randomised in a ratio of 1:1 to either the control arm (threshold of ≤90 g/L) or the intervention arm (threshold of ≤70 g/L) for their first cycle of treatment. The patient will cross-over to the other arm for their second cycle of treatment.

The person on the trial team responsible for undertaking the randomisation procedure will not be the same person who gained consent from the patient.

The participant blinding to the trial allocation arm will be tested with a simple directed question asking which treatment arm the participant considers they are allocated to at each study visit.

4.1.1 Randomisation Practicalities

CRFs must be completed at randomisation/enrolment. Patient details, including diagnosis, centre, haemoglobin concentration and details of transfusions already given must be available before attempting to randomise a patient. Written informed consent must have been obtained before the participant may be randomised.

RANDOMISATIONS

To randomise, please visit

www.sealedenvelope.com

choose the REAL trial from the drop down list and log-on as instructed

If difficulties are experienced using the randomisation website, then please contact the Trial Manager, who will be able to randomise the participant on your behalf.

4.2 Randomisation Codes and Unblinding

Randomisation codes and unblinding are considered in Section 5.6

4.3 Co-enrolment Guidelines

It is expected that participants for the REAL trial will also be enrolled in other trials with agreement of the Chief Investigators of the trials if the Principal Investigator does not think it will be detrimental to the patients' wellbeing. Allowing enrolment into REAL at or before day 5 of cycle 1 after start of chemotherapy should help facilitate recruitment into REAL given this is a challenging time for recruiting patients into any study at the time of initial cancer diagnosis.

Patients will not be eligible if already enrolled in a randomised trial for which the primary or secondary outcomes are similar to those in the REAL trial. Patients can be enrolled in observational studies or non-randomised studies.

5. Treatment of Participants

5.1 Introduction

This trial is a cross-over study of a control arm (threshold of ≤90 g/L) vs an intervention arm (threshold of ≤70 g/L) . Participants will be randomised to be in one arm for their first cycle of treatment and the other arm for the second cycle of treatment. The arms are described in the sections below. The trial will compare two different policies for RBC transfusion, “restrictive” and “liberal”. All recruited participants at a participating site should be transfused in accordance with the randomised transfusion policy for that cycle of treatment. Any transfusion required as part of the policy should be commenced within 24 hours of obtaining the haemoglobin result for inpatients and 72 hours for outpatients.

Prior to commencement of allocated transfusion policy in cycle 1, patients may receive red cell transfusions according to clinical need. This recognises the challenge of approaching and consenting patients at the time of new diagnosis and the importance of allowing patients and staff a short period of time to fully consider the trial. During this run-in period, red cell transfusion policies will be consistent with local guidelines, and typically at haemoglobin thresholds of 80g/L.

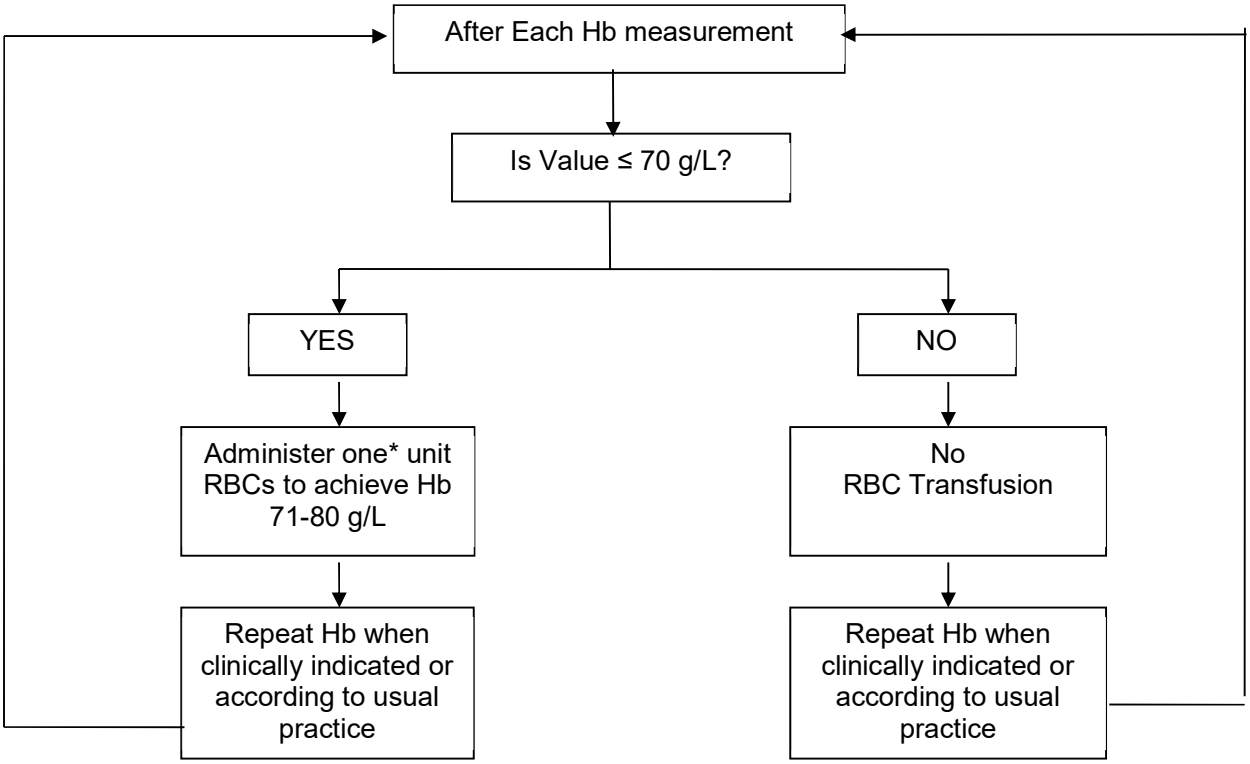
Allocation to either the restrictive or liberal policy will then apply from at or before Day 5 onwards in cycle 1. For cycle 2 chemotherapy treatment, participants will follow the alternative transfusion policy (ie if allocated to ‘restrictive’ arm for cycle 1, this would be the ‘liberal’ arm for cycle 2).

5.2 Intervention Arm: Restrictive Transfusion Policy (RBCs transfused when haemoglobin ≤70g/L)

Following enrolment, the haemoglobin values of participants will be recorded according to routine clinical care. If the haemoglobin value is recorded as ≤70 g/L, red blood cells should be transfused at a dose of 1 unit at a time, with the aim of keeping the haemoglobin range between 71-80 g/L. The timing of repeat haemoglobin measurements should be decided by the attending haematologist. Further red blood cell transfusions should only be administered if the haemoglobin value decreases to a value of 70g/L or less (see figure 1). Any transfusion required as part of the policy should be administered within 24 hours of obtaining the haemoglobin result (up to 72 hours for outpatients). For participants with haemoglobin values significantly lower than the threshold (i.e. where one unit would not be expected to increase the haemoglobin level into the desired range) more than 1 unit at a time may be transfused.

5.2.1 Treatment Algorithm

Figure 1: Intervention Arm: Restrictive transfusion strategy

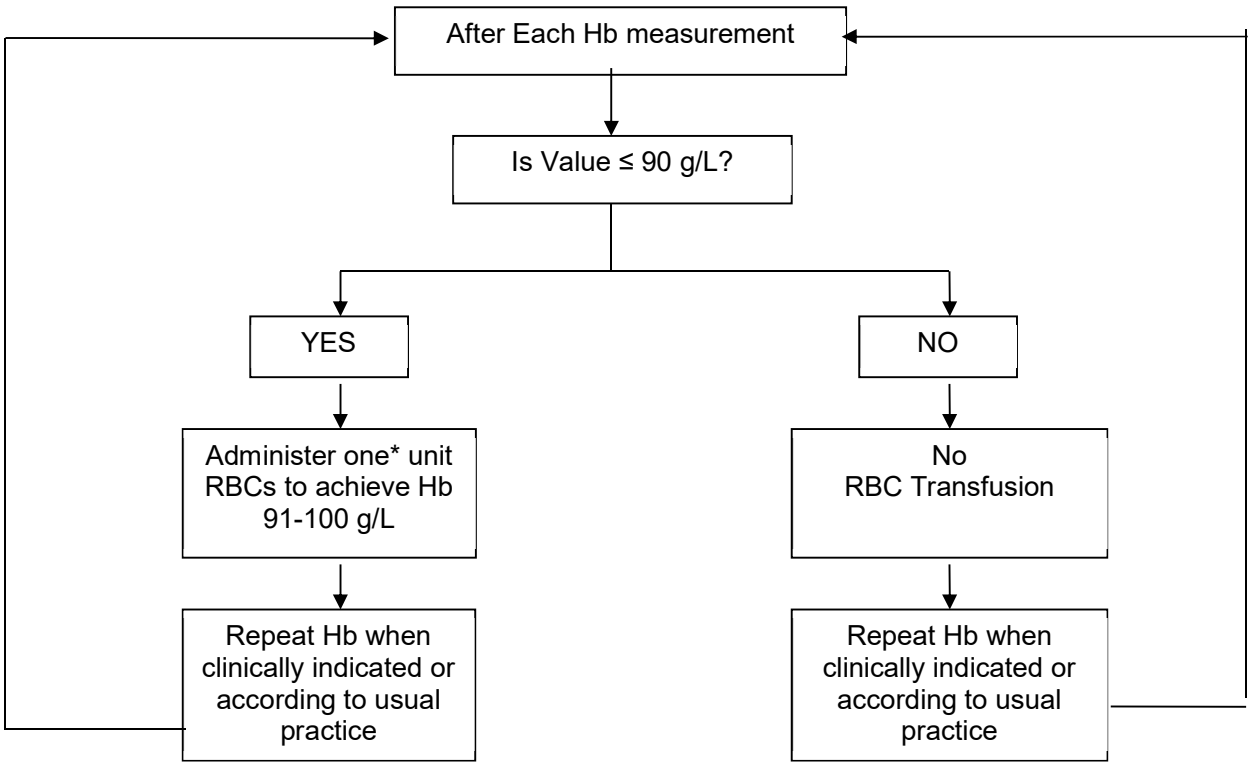


*or 2 units for outpatients at clinician's discretion

5.3 Control Arm: Liberal Transfusion Policy (RBCs transfused when haemoglobin ≤90g/L)

Following enrolment, the haemoglobin values of participants will be recorded according to routine clinical care. If the haemoglobin value is recorded as ≤90 g/L, red blood cells should be transfused at a dose of 1 unit with the aim of keeping the haemoglobin range between 91-100 g/L. The timing of repeat haemoglobin measurements should be decided by the attending haematologist. Further red blood cell transfusions should only be administered if the haemoglobin value decreases to a value of 90g/L or less (see figure 2). Any transfusion required as part of the policy should be administered within 24 hours of obtaining the haemoglobin result (or 72 hours for outpatients). For participants with haemoglobin values significantly lower than the threshold (i.e. where one unit would not be expected to increase the haemoglobin level into the desired range), more than 1 unit at a time may be transfused.

Figure 2: Control Arm: Liberal transfusion strategy



*or 2 units for outpatients at clinician's discretion

5.3.1 Measurement of Haemoglobin Level

The timing and frequency of repeat haemoglobin measurement(s) is at the discretion of the attending clinician(s), guided by the patient's clinical signs and symptoms and the clinician's usual practice. It is anticipated that the haemoglobin concentration will be measured daily for most patients, but this is not mandated as part of applying the transfusion policy.

5.3.2 Obtaining Blood Component

The red cell units will be obtained in the usual way from the hospital transfusion laboratory and the prescription, transfusion record and traceability will be performed as per standard hospital policy.

5.3.3 Accountability

During the trial, the red blood cells issued and transfused will be recorded on the CRF and in the patient's medical record. Any untransfused units will be returned to the transfusion laboratory.

5.4 Duration of randomisation

The first transfusion policy should be followed from at or before day 5 (from start of chemotherapy) of cycle 1 until the end of their first cycle of treatment. The alternate transfusion policy should be followed for the second cycle of treatment. The two cycles should be consecutive courses of intensive chemotherapy. The intention is to undertake the trial over periods of observation for predominantly inpatient stays. It is recognised that some patients may receive intensive therapy as an outpatient but the trial protocol will continue to be applied as far as possible.

5.5 Clinician Discretion to Transfuse in Contravention of the Allocated Policy

Clinicians will have the discretion to transfuse, or not to transfuse, in contravention of the allocated policy but must document their reason(s). This will be done on a CRF with a choice of standardised list of reasons, including

- Acute cardiac ischaemia
- Symptomatic anaemia with significant functional impairment
- Active bleeding with anticipated further drop in haemoglobin
- On-going bleeding not responding to standard haemostatic procedures, thought to be due to low haemocrit
- Participant request/convenience (e.g. bank holiday weekend, patients with antibodies)

Non-compliance does not constitute a participant withdrawal and the patient will continue to be followed up in accordance with the allocated transfusion policies. The numbers and reasons for additional, out-of-protocol transfusions and instances when transfusions were not given when they should have been will be recorded. Possible reasons for additional transfusions outside of the protocol could include periods of bleeding, haemodynamic instability or symptomatic ischaemic heart disease. Possible reasons for not transfusing would be for fluid overload.

Patient safety is of paramount importance, and a few participants may develop significant bleeding. If the attending haematologist feels that immediate red cell transfusion is needed for the patient, regardless of, or before obtaining a further, haemoglobin result (e.g. due to clinical condition or severity of bleeding), then the participant should be managed as per local practice by clinical discretion. Such participants would remain in the trial and remain allocated to their randomised treatment schedule for further transfusion support.
If the participant declines to continue with the assigned threshold for that cycle they should also remain in the trial, unless consent for data collection is declined, see section 3.5.3.

Clinicians and participants will be encouraged to maintain the allocated threshold unless there are significant symptoms and signs considered to be due to anaemia.

5.6 Unblinding

There will be an attempt to blind participants to their treatment allocation. Participants will be asked at the end of each cycle which arm they believe they have been allocated to.

Physicians will not be blinded to the allocation. All attempts should be made to conceal the allocation from the participant and participants will be counselled at enrolment that they will not be informed of their haemoglobin measurement results. Decisions to transfuse should be based on participant symptoms and clinician knowledge of haemoglobin level and treatment allocation. A decision to transfuse outside the protocol does not mandate unblinding of the participant and patients will still not routinely be informed of their haemoglobin level.

5.7 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to the trial treatment, trial follow up and data collection. However, a participant may stop treatment early or be stopped early for any of the following reasons:

- Participant moves to supportive care only prior to the end of the 2nd cycle
- Unacceptable adverse event
- Any change in the participant's condition that justifies the discontinuation of treatment in the opinion of the clinician
- Withdrawal of consent

Participants who undergo one cycle of chemotherapy and proceed straight to allogeneic stem cell transplantation will not be eligible to continue in the study following the first cycle of chemotherapy.

As the patient's participation in the trial is entirely voluntary they may choose to discontinue the trial treatment at any time without penalty or loss of benefits which they are otherwise entitled.. Although the participant is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the participant's rights.

Participants should remain in the trial for the purpose of follow up and data analysis, unless they withdraw their consent from all stages of the trial, in which case, they should be withdrawn. Data collected until the time of withdrawal will be retained and included in the analysis.

5.7.1 Medications not permitted

There are no medications not permitted in this trial. For patients receiving other trial treatments see Section 4.3.

5.7.2 Duration of study/end of study

The randomised transfusion policies will be followed for all eligible participants up to the end of each course of chemotherapy, for two consecutive cycles. For eligible participants, the day of randomisation is defined as (Cycle 1) Day 1 (which must be at or before Day 5 from start of chemotherapy) and the transfusion policies will be followed to the end of the second cycle of intensive chemotherapy (or death). Data collection will occur up to the end of each cycle (day +42 or the start of the next cycle) and follow up QoL assessment will take place at the end of each cycle, i.e. at admission or attendance for commencement of the next cycle of treatment. In the event that no subsequent cycle of treatment is given, participants will be contacted at day +42.

6. Assessments and Follow-up

6.1 Trial Assessment Schedule

Information on all trial-related assessments and follow-ups is summarised in the table below

Table No 1:

Assessment to be performed	(Upto) Day 5 Cycle 1	At Consent	Cycle 1	Mid Cycle 1	Cycle 2	Mid Cycle 2	3 Months
Screen for eligibility	√						
Written consent		√					
Registration and unique ID		√					
Record baseline data		√					
Haemoglobin level(s)			√		√		
Details of RBC transfusion			√		√		
Daily assessment of bleeding			√		√		
Details of other blood components e.g. platelets			√		√		
Details of adjunctive treatments – TXA, epo			√		√		
Serious adverse events			√		√		
Response to chemotherapy			√		√		
Daily functional capacity score, daily visual analogue scale from EQ 5d (see end of document)			√		√		
EQ-5D-5L/ EORTC QLQ C30 forms		√	√ (end)	√	√ (end)	√	
Assessment of success of blinding			√ (end)		√ (end)		
Death							√

6.2 Procedures for Assessing Efficacy

6.2.1 Data Collection

Data collection will be the responsibility of the local research team led by the PI at each site. Overall responsibility for collating data from all centres will reside with the Trial Manager. Data will be recorded on paper Case Report Forms (CRFs). Three patient identifiers (Trial ID number allocated at enrolment, initials, **and age**) will be used on all CRFs. Centres will send copies of completed CRFs to the Trial Data Manager at the CTU, where they will be entered onto the Clinical Trial Database.

Data will be collected by the RN/PI/Designate on the relevant CRFs. All data will be anonymised with participants assigned a unique trial ID number at enrolment. The data will be checked for completeness at the site before being transmitted to the data manager for entry into the trial database. A copy of the consent form and PIS will also be filed in the patient's hospital notes.

6.2.2 Source Documentation

All the source data except for randomisation and questionnaires will be found in the patient medical records at the participating site.

The quality of life questionnaires are their own source data and randomisation number will be provided by sealed envelope.

100% of the consent forms and a sample of CRFs will be checked for consistency against the source documents in the patient's hospital notes at routine monitoring visits by the Trial Manager.

6.2.3 Screening Log

A screening log of all patients admitted with AML will be kept. The total number of admissions, the number of admissions meeting eligibility criteria and the number of eligible patients who provide consent to data collection and follow up will be recorded.

6.2.4 Baseline Clinical Characteristics

Baseline clinical characteristics will be obtained and will include date/time of admission, age, gender, presenting symptoms, routine physiological parameters, etc. This data should be recorded at study enrolment (i.e. when consent has been confirmed).

6.2.5 Laboratory and Transfusion Data

The date and time of all haemoglobin measurements will be recorded as part of standard clinical practice. A record of all haemoglobin results will be requested for each participant. All RBC transfusion episodes will be recorded, including the haemoglobin level prior to transfusion and the total number of RBC units transfused. The number and date of transfusion of other blood components specifically including platelets will be recorded.

A transfusion episode will be defined as single units or multiple units transfused with no check in haemoglobin occurring between units.

We will explore integrated IT approaches to extraction and collection of all routinely available participant data relevant to the trial on IT systems, particularly including key performance indicator data, at recruiting centres.

6.2.6 Outcome Measures

Please see Section 9

6.2.6.1 Monitoring/data collection outcomes

Because the study will take place at several UK sites, each with different methods of recording blood component requests, prescriptions, transfusions and outcomes as well as availability and design of electronic diagnostic decision support, the study will also seek to establish whether these impact on adherence at each centre. The study is not designed to be powered to identify significant differences.

6.3 Procedures for Assessing Safety

Adverse events will be reported as described in Section 7. Bleeding episodes will be prospectively recorded with a daily bleeding score.

6.4 Procedures for Assessing Quality of Life

Quality of life will be assessed using the EQ-5D-5L and EORTC QLQ C30 questionnaires. These will be completed at consent, at mid point of each cycle and again at the end of each cycle (i.e. D+42 or on commencement of the next cycle). The mid point is defined as the time of nadir cytopenia. In DA regimen, this is day 10-12 post chemotherapy; in FLAG-Ida regimen, this is day 10- 16 post chemotherapy. If the participant is unable to complete the questionnaire, it may be completed by a suitable surrogate (carer or research nurse) and reason for this documented.

6.5 Other Assessments

In addition a short daily assessment of quality of life will be completed by the nurse or if at home by carer or participant.

6.6 Early Discontinuation of Treatment Allocation

The participant is free to choose to discontinue the trial treatment allocation at any time but they should always be encouraged, if they are willing, to remain in the trial and allow follow up data to be collected. However, if they do not wish any further data to be collected, this decision must be respected and the participant will be withdrawn from the trial completely. In either case, the appropriate CRF (treatment allocation Discontinuation or Withdrawal) must be completed. See Sections 5.5, 5.6 and 5.8.

Any data and samples already collected will be retained and analysed unless the participant specifically refuses to allow this. Participants should be discouraged from withdrawing consent to the use of data already collected.

Participants who discontinue treatment allocation during cycle 1 will be replaced.

6.7 Loss to Follow-Up

Participants who are unavailable for assessment at the end of cycle 2 will be deemed to be have been lost to follow-up. Such participants will not be replaced unless they are lost to follow-up prior to commencement of cycle 2; this is anticipated to be likely to affect a very small number of participants.

6.8 Trial Closure

The trial will be closed when all participants have been recruited and have completed the trial intervention period.

7. Safety Reporting

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section.

7.1 Definitions of Adverse Events

The definitions to be applied to adverse events recorded in this trial are given in Table 7a below. As this is a trial using red cells, events of interest are those related to red cell transfusion , which are also study outcomes and will be reported separately.

Table 7a: Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a blood component has been administered.
Transfusion Related Adverse Reaction or Event	Any untoward and unintended response to a transfused blood component.
Serious Adverse Event (SAE) or Serious Transfusion related Adverse Reaction	Respectively any adverse event, adverse transfusion reaction or unexpected adverse transfusion reaction that: results in death* is life-threatening** requires hospitalisation or prolongation of existing hospitalisation*** results in persistent or significant disability or incapacity
Unexpected Adverse Transfusion Reaction	An adverse reaction, the nature or severity of which is not consistent with the known reactions to transfusion of a blood component (in the case of this trial, red blood cells). Expected red blood cell transfusion reactions are listed in section 7.3.3.1.

* Death due to the underlying disease or associated conditions will not be reported as an SAE.
**The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

7.2 Adverse Events that do not Require Reporting

Any event that does not meet the definition of serious does not need to be recorded for this trial.

Participants in this study have a bone marrow failure disorder and some may have co-morbidities. Some of these patients will be expected to develop SAEs during the course of the study, many of which will be unrelated to trial interventions. These events are not required to be reported as SAEs, however we will be capturing the listed events below in the CRF. Similarly disease progression, or death as a result of disease progression, are not considered to be SAEs and should be reported on the end of study form.

Expected SAEs:

- Admission to the intensive care unit
- Severe sepsis
- Major organ dysfunction (single or multi-organ)

- Transient ischaemic attack, Thromboembolic and ischaemic events (myocardial infarction, stroke, pulmonary embolus, DVT)
- Acute transfusion reactions to red cell blood components including indicators of transfusion associated circulatory overload (TACO) and transfusion related acute lung injury (TRALI) i.e. Congestive cardiac failure, Pulmonary oedema (definitions as described in SHOT)

If an adverse event meets the definition of an SAE and it is considered unexpected it must be recorded on an SAE form and be faxed / e-mailed to the CTU within 24 hours of the site becoming aware of it.

As this is a trial of a blood component, it is not appropriate to assess causality of any SAE and there is no requirement on the form to do so. However, any red cell transfusion reactions that occur must have their imputability assessed using the definitions in Table 7b below. There are five categories: N/A = Not assessable 0 = Excluded or unlikely, 1 = Possible, 2 = Likely (probable), and 3 = Certain. The severity of any red cell transfusion reaction will also be graded using SHOT criteria as 1 = mild, 2 = moderate or 3 = severe Two clinicians sitting on the TMG will independently review this data at the end of the study.

7.3 Investigator Responsibilities

The Chief Investigator (CI) has overall responsibility for the conduct of the study. As this is a multi-site study, the Principal Investigator (PI) has responsibility for the research at their local site and is responsible for informing the CTU of all reportable serious adverse events that occur at their site following the guidelines below.

7.3.1 Investigator Assessment of AEs

When an AE or AR occurs, the investigator responsible for the care of the patient must first assess whether or not the event is serious using the definitions in Table 7a: definitions. If the event is serious and is on the list of expected events in section 7.1, then the details must be recorded on the AE form. If the event does not fit any of the exempted categories, it must be recorded on an SAE form and faxed to the CTU within 24 hours of becoming aware of it.

7.3.2 Investigator Assessment of Transfusion Reactions

As this is a trial of a blood component, it is not appropriate to assess causality of any SAEs and there is no requirement on the form to do so. However, any transfusion reactions that occur must have their imputability assessed using the definitions in Table 7b. There are 5 categories: unrelated, unlikely, possible, probable and definitely related.

Table 7b: Definitions of Imputability

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial transfusion). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial transfusion). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	The evidence is clearly in favor of attributing the adverse reaction to the blood or blood component.

Definitely	There is conclusive evidence beyond reasonable doubt attributing the adverse reaction to the blood or blood component.

7.3.3 Expectedness of Transfusion Reactions

If the event is a Serious Transfusion-Related Adverse Reaction, the Investigator must assess the expectedness of the event. Please refer to section 7.3.3.1 for a list of expected red cell transfusion reactions. It is highly unlikely that an unexpected Serious Adverse Transfusion Reaction will occur, but the possibility must not be excluded. If a Serious Transfusion Related Adverse Reaction is assessed as being unexpected, the PI must notify the CTU.

7.3.3.1 Expected red blood cell transfusion reactions

Acute transfusion reactions (ATR) are defined (according to SHOT) as those occurring at any time up to 24 hours following a transfusion of blood or components

- Anaphylactic reactions
- Moderate allergic reactions
- Hypotensive reactions
- Mixed febrile/allergic reactions

and may be due to:

- incorrect component being transfused
- haemolytic reactions
- febrile non haemolytic reaction
- transfusion-related acute lung injury (TRALI)
- transfusion-associated circulatory overload (TACO)
- transfusion-associated dyspnoea (TAD)
- bacterial contamination of the component

7.3.4 Investigator Notification

The CTU should be notified within 24 hours of the investigator becoming aware of an event that requires expedited reporting (i.e. any expected or unexpected Serious Transfusion-related Adverse Reaction, major bleeding episodes or SAEs). Investigators should notify the CTU of all such events occurring during the study period.
The SAE/Transfusion reaction or major bleed form must be completed by the Investigator (the consultant named on the delegation of responsibilities log who is responsible for the patient's care). In the absence of the Investigator, the form should be completed and signed by a member of the site trial team and faxed or emailed. The responsible Investigator should subsequently check, annotate and sign the form and re-fax/email to the CTU as soon as possible. The initial report must be followed by detailed written reports as appropriate.

The Investigator must record all expected SAEs that occur during the study period on the SAE listing form, but are not required to immediately notify them to the CTU.

The investigator must follow-up all reported SAEs until resolution or the event is considered stable.

Investigator must supply the CTU, REC and relevant NHS Trust R&D with any supplementary information they request.

7.4 Sponsor's Responsibilities

The CTU (on behalf of the Sponsor) will forward all red cell transfusion reactions and major bleed reports received to the Chief Investigator (or a medically qualified delegate) for review.

The CTU will review all SAE reports and forward to the Data Monitoring Monitoring Committee (DMC) for review, as often as instructed by them, and also provide them as listings for review at DMC meetings. These will be copied to the Chief Investigator for review.

Agree the planned content of both blinded and unblinded DMC reports with DMC members prior to the inclusion of the first trial participant.

The CTU is undertaking the duties of trial sponsor and is responsible for the reporting of any unexpected Serious Transfusion-Related Adverse red cell reactions to the research ethics committee (REC), should any occur, and for preparing annual safety reports to the REC.

7.5 Statutory Reporting

Hospital staff remain responsible for reporting all transfusion-related adverse events to SHOT/SABRE according to standard procedures, as required under the regulations of the EU Blood Directive. Staffs at the institution are also responsible for notifying their local R&D department of SAEs (as per the institutions standard local procedure).

NOTIFICATION OF SAEs/ RED CELL TRANSFUSION REACTIONS

Within five working days of becoming aware of an event , please fax a completed SAE , Major Bleed or Transfusion Reaction form to the NHSBT/ Clinical Trials Unit on:
Fax: 01223 548136

Or email information to
:(Serious_Adverse_Events@nhsbt.nhs.uk)

8. Quality Assurance and Control

8.1 Risk Assessment

A Risk assessment has been conducted which acknowledges the potential risks to the trial. This section provides an overview of the Quality Assurance (QA) and Quality Control (QC) measures that will be put in place to ensure the trial is performed and data generated and recorded in accordance with the principles of ICH GCP.

8.2 Central Monitoring at CTU

The CTU data managers will review all data received for errors and missing data points.

8.3 On-Site Monitoring

The frequency, type and intensity for routine monitoring and the requirements for “for cause” monitoring will be detailed in a separate monitoring plan.

8.3.1 Direct access to patient records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patient consent must be obtained for this.

8.3.2 Confidentiality

The data will be handled in accordance with the principles of the UK Data Protection Act.

9. Statistical Considerations

9.1 Method of Randomisation

The randomisation process will consist of computer generated block randomisation. Patients will be allocated in a ratio of 1:1 and randomisation will be stratified by site.

9.2 Outcome Measures

The occurrence of the primary outcomes and secondary outcomes will be ascertained after analysis from the data sourced from local electronic blood transfusion registers, laboratory value database, and medical records systems. Patient self-reported quality of life will be obtained using the EuroQoL/ EORTC QLQ C30 forms tools at the start of the study and end of cycles.

9.2.1 Primary Outcomes

Adherence: The percentage of pre-transfusion haemoglobin concentrations being **below** the target range of the assigned red cell transfusion strategy will be summarised for each treatment strategy

Haemoglobin difference: Achievement of at least a 15g/L difference between the mean pre-transfusion haemoglobins in the two treatment arms. This comparison will be done for each study day as well as overall.

9.2.2 Secondary Outcomes

Overall haemoglobin difference: mean haemoglobin for the liberal and restrictive strategies using all haemoglobins reported.

Adherence: These will be measured by determining:

- The **proportion of enrolled participants for whom the transfusion policy was successfully followed** until the end of that chemotherapy cycle/death, whichever comes first. The transfusion policy will be defined as having been successfully followed if the participant always received a RBC transfusion within the defined time frame when their haemoglobin dropped below the trigger level, and did not receive any RBC transfusions when their haemoglobin was above the trigger level.
- **The proportion of enrolled participants for whom the transfusion policy was successfully followed but allowing for one 'violation'.**
- The **proportion of transfusions per participant that were correctly given according to their haemoglobin trigger** (i.e. had a haemoglobin value ≤70 g/L in the restrictive transfusion group and a haemoglobin value ≤90 g/L in the liberal transfusion group).
- The **proportion of times a participant received a transfusion contrary to their haemoglobin trigger** (i.e. had a haemoglobin value >70 g/L in the restrictive transfusion group and a haemoglobin value >90 g/L in the liberal transfusion group).
- The overall **proportion of transfusions that were correctly given according to the participant's haemoglobin trigger** (i.e. had a haemoglobin value ≤70 g/L in the restrictive transfusion group and an haemoglobin value less than ≤90 g/L in the liberal transfusion group).
- The overall **proportion of times a transfusion was given contrary to the participant's haemoglobin trigger** (i.e. had a haemoglobin value >70 g/L in the restrictive transfusion group and **an** haemoglobin value >90 g/L in the liberal transfusion group).

- **The overall proportion of transfusions that were given correctly according to the participant's haemoglobin trigger by whether given as inpatient or outpatient**
- **The proportion of inpatient and outpatient transfusions given as single or multiple unit transfusions**
- **Percentages of transfusions performed where the pre-transfusion haemoglobin concentrations fell below, within and above the target haemoglobin range**
- **Percentages of transfusions performed where the post-transfusion haemoglobin concentrations fell below, within and above the target haemoglobin range**
- **Recruitment rate:** the proportion of eligible participants enrolled will be summarised, along with the number of replaced participants and participant tolerability by transfusion strategy **and reasons for withdrawing early from the study.**
- **Red Blood Cell Exposure:** The difference in number of red blood cell units administered will be compared between the intervention groups up to death/end of chemotherapy cycle (whichever comes first).
- **QoL questionnaire compliance:** this will be summarised by treatment strategy and timepoint

Protocol adherence will be measured over time, to determine if adherence rates improve. Adherence rates will also be compared between transfusion arms and between sites. Transfusions will only be viewed as having successfully followed the transfusion policy if they are given within the pre-defined time period of 24 hours after a participant's haemoglobin has dropped below the trigger level. **Key** clinical characteristics of **recruited participants will be compared against** patients recruited to **the** AML 18 and 19 trials (in order to give a measure of patients excluded from this feasibility study which may be attributed to physician discretion).

9.2.3 Clinical Outcomes

- **Death**: All-cause mortality at 3 months post **study completion**

- **Bleeding**: Clinically significant bleeding events are defined as equivalent to WHO Grade 3 or 4. These events will be captured using definitions applied for bleeding assessments conducted using a tool based upon that used in the TOPPS trial and further developed by an international working group – the BEST collaborative.

- **Proportion of participants experiencing thromboembolic and ischaemic events**: Includes myocardial infarction, stroke, pulmonary embolus, clinically overt and line-related thrombotic events. **Line related blockage may have other causes related to the type of line used. (These thromboembolic and ischaemic events may be related to higher haemoglobin concentrations,** although MI may occur more commonly with lower thresholds)

- **Syncopal events**

- **Transfusion reactions**

- **Length of hospital stay**

- **Proportion of participants with at least one blood culture verified bacterial infection**

- **Median EQ-5D-5L Visual Analogue Scale score for symptomatic and non-symptomatic transfusions**

- **Health related quality of life at baseline, middle and end of each cycle using** EQ-5D-5L/ EORTC QLQ C30 forms)

Other Outcomes

- Use of platelet transfusions: The difference in number of platelet units administered will be compared between the intervention groups up to death/end of chemotherapy cycle (whichever comes first).

- **Ability of participants to remain blinded to the transfusion threshold**

9.3 Sample size

This is a feasibility study that will help in planning a larger definitive trial. We propose a sample of 36 patients (who complete a period of observation for one full cycle of chemotherapy) to determine feasibility in the UK. Power calculations based on a two-sided paired t-test indicated that a sample size of 31 patients can achieve 90% power to detect a 15 g/L difference between the two transfusion strategies. We assumed the estimated group standard deviation of 20g/L (informed by the Carson et al 2012 Cochrane systematic review of red cell transfusion thresholds), an intra-class correlation coefficient of 0.25 and a significance level of 0.05. After allowing for a drop-out rate of 10%, and rounding up to an even number to ensure the same number are assigned to each randomisation schedule, the total sample size will be at least 36 patients.

9.4 Analysis Plan (brief)

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

Appropriate statistical methods for the analysis of cross-over trials will be used. These may include mixed-effects models with a random effect for participant, paired methods or another suitable method, with adjustment for any period effect between cycles. The primary analysis will be performed according to intention to treat.

Data from all randomised participants who have received any transfusions will be included in the 'compliance to treatment threshold' analysis. Percentage compliance of pre-transfusion haemoglobin concentrations being **below** the target range of the RBC transfusion threshold assigned will be presented by allocation arm. The percentage of pre-transfusion haemoglobin concentrations falling below, within and above the target range will also be presented by allocation arm. The proportion of transfusions, proportion of participants and proportion of transfusions per participant given correctly, according to the algorithm, will also be calculated for each allocation arm.

The mean pre-transfusion haemoglobin level for each participant (regardless of whether they received a transfusion) will be calculated for each course of chemotherapy, then 2 overall means will be calculated for the restrictive and liberal groups, and the difference determined, looking for at least a 15g/L difference.

We will consider this study feasible and worthy of further development into a larger randomised trial if compliance for adherence is ≥70% in both arms. This will be reported by calculating the percentage of haemoglobin measurements that fall within or above their assigned target range pre- transfusion.

For analysis of other measures of feasibility, all patients who are eligible and ineligible will be documented and the proportion of randomised patients noted. Those who consented to and were enrolled in the trial will be analysed, even if they did not receive any transfusions, to understand reasons for failure to complete the assigned strategy.

Participants who completed QoL questionnaires will be included in the QoL analysis. The minimum required number for this analysis is completed QoL questionnaire at baseline, and after one chemotherapy cycle The percentage compliance with completing the QoL questionnaires will be summarised for each arm and each timepoint.

The mean EQ-5D-5L and EORTC QLQ C30 scores for each arm will be calculated and compared at baseline and after each chemotherapy cycle. Clinically meaningful improvement will be defined as ≥0.08 on the calculated health utility EuroQOL-5D score and ≥10 points on the EORTC QLQ-C30 score **(for all scores apart from fatigue and dyspnoea, for which an improvement is ≤-10).** In addition to aggregate data, the percentages of participants individually achieving a clinically meaningful improvement, at any time point, compared to the baseline score (the first QoL questionnaire at randomisation), in each of the two strategies will be compared.

For other and safety analyses, data from all randomised subjects will be evaluated and descriptive statistics presented. Key clinical characteristics of enrolled participants will be compared against all recruits to AML 18 and 19 trials. The extent of exposure will be summarised (median RBC and platelet units transfused during each chemotherapy course), as well as the clinical course, such as interval between transfusions and transfusion reactions. The incidence of WHO Grade 3 or 4 bleeding and death will be summarised by treatment strategy, and length of hospital stay compared. Comparisons will be made between the two haemoglobin concentration threshold transfusion strategies. Any adverse events potentially related to the transfusion threshold such as cardiac ischaemic events, congestive heart failure, strokes (cerebrovascular accidents, CVA), thromboembolic or syncopal events, will be summarised and compared between the two arms.

10. Ancillary studies

None

11. Ethical and Regulatory Issues

11.1 Compliance

This trial complies with the Declaration of Helsinki (insert version used for protocol)
It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

11.1.1 Site Compliance

The site will comply with the above. An agreement will be in place between the site and CTU, setting out respective roles and responsibilities.

The site will inform the CTU as soon as they are aware of a possible serious breach of compliance, so the CTU can report the breach if necessary, within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a serious breach is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or

- The scientific value of the trial.

11.1.2 Data Collection and retention

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 10 years after the end of the trial. During this period, all data should be accessible to the competent authorities and the Sponsor with suitable notice.

11.2 Ethical Conduct of the Study

11.2.1 Ethical Considerations

Before initiation of the trial, the protocol, all informed consent forms and any information to be provided to the prospective participant will be submitted to a Research Ethics Committee for ethical approval. Any subsequent amendments will be submitted and approved by the same Research Ethics Committee.

The rights of the patient to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol at any stage, if he/she feels it is in the best interests of the participant. The reason for doing so should be recorded. The participant will remain within the trial for the purposes of follow up and for data analysis. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow up without giving a reason and without prejudicing his/her further treatment.

11.2.2 Ethical Approvals

11.3 Other approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site. A copy of the local R&D approval and of the Patient Information Sheet and Consent Form on local headed paper should be provided to the CTU before any patient is entered onto the study.

12. Indemnity

12.1 Definitions

The definitions used in the indemnity clause (section 12.2) are as follows:

“Authority means prior to October 1 2005 the National Blood Authority established under Statutory Instrument 1993 No 586 and from October 1 2005 NHS Blood and Transplant (NHSBT) established under SI 2005 No2529.”

“Entity means the NHS Body or Company participating in the clinical trial or project.”

“Clinical trial or project means such trial or project in relation to proposed new blood products, blood components and tissues produced or to be produced; in relation to proposed diagnostic, therapeutic services and proposed donation procedures which have been approved by the appropriate ethical committee(s) and the Clinical Trials Authorisation Scheme where appropriate and which are conducted under the Authorities protocols.”

“Patients mean patients, healthy volunteers and donors.”

12.2 Indemnity Clause

The Authority is a Special Health Authority which is a member of the National Health Service Legislation Authority (NHSLA) risk pooling schemes for clinical negligence and liabilities to third parties. In addition, when the authority undertakes or sponsors Clinical Trials and Research Projects within its functions in England the Authority, through the Department of Health, has under certain circumstances in place indemnity provisions for non-negligent harm to patients participating in these Trials or Projects. The indemnities referred to above do not relieve the participating entities from their duty of care to the patient particularly in the trial or project. For the avoidance of doubt the Authority cannot accept any responsibility or liability for any breach of the entities of duty of care nor any negligent act or omission committed by the entity, its employees, agents or sub-contractors.

13. Finance

Funding will be provided by the Sponsor (NHSBT). This consists of a grant from the NHSBT Trust Fund (TF 63) and clinical trial management support from CTU core resources. Details of payments to sites to cover the research costs will be provided in the site agreement with the Sponsor.

14. Oversight and Trial Committees

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure.

14.1 Trial Management group (TMG)

A Trial Management Group (TMG) comprising the Chief Investigator, other lead investigators and members of the CTU. The TMG will be responsible for the day to day running and management of the trial. It will meet at least four times a year, more often during set up and close down phases of the trial. At least one face to face meeting will be held each year.

14.2 Trial Steering Committee

The Trial Steering Committee (TSC) has membership from the TMG and independent members, including the Chair. These independent members are Steve Knapper, Janet Birchall, Harpret Kaur. The role of the TSC is to provide overall supervision for the trial and provide advice through its' independent chair. The ultimate decision on continuation of the trial lies with the TSC.

14.3 Data Monitoring Committee

The CTU has a core Data Monitoring Committee (DMC) for all of its trials, chaired by Professor Adrian Newland of Queen Mary, University of London. The group will act as DMC to this study, provide advice to the Chair of the TSC and can recommend premature closure of the trial. For the purposes of this study, the core DMC will be joined by an independent member who can provide expert disease specific advice.

15. Publication

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report and the main findings of the trial have been published. The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications.

15.1 Dissemination

The main form of dissemination will be through publications including abstract presentations at meetings/conferences.

15.2 Authorship

Authorship of final papers will consist of persons who have made a significant contribution to design, management or recruitment of the clinical trial. Authorship of the publication and significant contribution shall be considered by the Trial Writing Committee and approved by the TMG or TSC.

15.3 Identification

A trial identifier should be included on all presentations and publications (e.g. the ISCRTN), as should the name of the Sponsor.

15.4 Timing

It must be made clear that no data may be made public before publication and never without agreement from the CI.

15.5 Acknowledgements

The Study Funder (NHSBT, Trust Fund Grant TF 63), Sponsor and the relevant Trial Committees must be acknowledged on all publications as well as the role of the NHSBT Clinical Trials Unit in providing support for and running this study. The willingness and agreement of Canadian collaborators to share study design will be noted. All contributing PIs in UK will be listed.

16. Protocol Amendments

Version	History	Date
1.0	Final version submitted to HRA	23rd August 2016
1.1	Administrative changes requested by HRA.	4th November 2016
2.0	Changes providing clarity to the section 9 (Outcomes), to be in line with what is stated will be analysed in the Statistical Analysis Plan. Small administrative changes as well.	9th October 2018

17. References

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Appendix

Appendix 1. ECOG/WHO/Zubrod score

The Eastern Cooperative Oncology Group (ECOG) score (published by Oken *et al.* in 1982), also called the WHO or Zubrod score (after C. Gordon Zubrod), runs from 0 to 5, with 0 denoting perfect health and 5 death:[2]

0 – Asymptomatic (Fully active, able to carry on all predisease activities without restriction)

- 1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
- 2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
- 3 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
- 4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
- 5 – Death

Adapted for patient to fill in on a daily basis:

0 – Asymptomatic (Fully active, able to carry on all activities without restriction)

1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)

2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)

3 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)

4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

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