Clinical Guidelines for the use of Granulocyte Transfusions

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Purpose:
This document outlines:

1) Information on the granulocyte components available in England
2) The clinical indications for the use of granulocyte transfusions
3) The process for provision of granulocytes in England

These guidelines are not meant to be prescriptive and the decision for each request for granulocyte transfusions should be made following detailed assessment of the clinical details, in conjunction with the referring Consultant (or their designated deputy).

Associated Controlled Documents:
SPN223 – NHSBT Portfolio of Blood Components and Guidance for their Clinical Use
SOP3636 – Request Management – Pooled Granulocytes
SOP363 – Processing of Pooled Granulocytes in Additive/Plasma Mixture
SOP6531 – Selection and Provision of Buffy Coat Units Suitable for Pooled Granulocyte Production
FRM3349 – Consultant Approval for Non-standard Components

Method:
Recommendations are based on review of the literature and accepted current clinical practice in consultation with NHSBT and NHS consultants.

Status:
Submitted for document control July 2004
Revised and resubmitted: December 2006, November 2010, September 2012, March 2016, July 2021, Feb 2026

Definitions:
ANC – Absolute Neutrophil Count
CBT – Cord Blood Transplant
CMV – Cytomegalovirus
G-CSF – Granulocyte Colony Stimulating Factor
GVL – Graft Versus Leukaemia
Hct – Haematocrit
HLA – Human Leucocyte Antigen
HT – High Titre
MDS – Myelodysplastic Syndrome
MRD – Minimal Residual Disease
OBOS – Online Blood Ordering System
ProGrEs - PROspective Granulocyte usage and outcomEs Survey
RBCs – Red Blood Cells
Ta-GvHD – Transfusion associated Graft versus Host Disease
TRALI – Transfusion Related Acute Lung Injury
WBCs – White Blood Cells
WHO – World Health Organization

1. Background

Functioning white blood cells (WBCs) are a vital component in the defence against infections. Neutrophils are a subtype of granulocytes and are the most abundant circulating WBC in healthy adults, playing a critical role in protecting against bacterial and fungal infections. Normal neutrophil counts range from 2.0 to 7.5 × 10^9/L, and in most cases, neutropenia is a consequence of impaired production in the bone marrow with marrow occupying diseases such as leukaemia, and marrow-toxic drugs such as chemotherapy representing typical causes of reversible neutropenia. Severe neutropenia, defined by the WHO as below 0.5 x 10^9/L, is associated with an exponential increase in risk of severe infection(1)(2), but even if the number of neutrophils are normal, patients may suffer from a similar inability to fight infections if there is a congenital or acquired impairment of neutrophil function(3). Despite appropriate antimicrobial therapy, infections in these situations may lead to hospitalisation, organ damage, or death. As with anaemic and thrombocytopenic patients, the effects of neutropenia can potentially be ameliorated using components derived from allogeneic blood donations from volunteers, with the aim of reducing infection severity, duration and complications in these high-risk patients(4).

Although there is evidence that donated granulocytes are functional(5,6) and relatively well tolerated(7,8), published controlled trials in both adults and children have at most shown promising results, but have often been underpowered, inconclusive, or conflicting(9–15). The most recent study (RING) suggests that the efficacy of granulocyte transfusions is dose dependent, with at least 10^{10} granulocytes per transfusion needed to treat or prevent infection, and higher doses (e.g. ≥0.6 x 10^9 granulocytes/kg/dose) offering the greatest chance of benefit. The RING study showed that the primary composite outcome of survival and infection was no different between the granulocyte and control groups (42% vs. 43%, p>0.99), even when analysed by intention-to-treat (49% vs. 41%, p =0.64). However, a post-hoc analysis compared high dose (≥0.6 x 10^9 granulocytes/kg/dose) and low dose (<0.6 x 10^9 granulocytes/kg/dose) groups, and found significantly better outcomes in the high dose group (59% vs. 15%, p <0.01)(16). The authors of the RING study noted several challenges in conducting randomised trials of granulocyte transfusions: difficulty obtaining consent due to strongly held clinical perception around granulocyte transfusions, discrepancies between study protocol and physicians' decisions to transfuse granulocytes, failure to achieve target doses of granulocytes, and fewer patients meeting the inclusion criteria than anticipated. Many of these challenges resonate through the systematic reviews undertaken over past decades, meaning the general quality of available evidence around the benefits of granulocyte transfusions remains low.

An emerging area of interest for granulocyte transfusions is their use alongside cord blood allogeneic stem cell transplantation (CBT) in high-risk myeloid malignancies. It is well established that the graft-versus-leukaemia (GVL) effect—mediated primarily by donor-derived T cells—is central to maintaining remission following allograft(17). Although CD8+ T cells are believed to drive this GVL effect, immune reconstitution after CBT is typically through early CD4+ T cell expansion, with delayed CD8+ T-cell recovery(18). It was noted that in CBT recipients who received granulocyte transfusions for refractory infection, a transient early CD8+ expansion was seen, along with remission induction(19). This prompted the GRANS trial, designed to assess the reproducibility and characteristics of this in vivo T-cell expansion and its effect on disease response. Of the 10 patients enrolled, nine demonstrated the same early, marked T-cell expansion as seen in pre-trial observations, with lymphocyte populations skewed toward CD8+ T cells rather than the usual early CD4+ dominance. Nine patients achieved haematological remission, and eight became MRD-negative(20). Given that relapse is the most common cause of treatment failure in this group, these early findings have prompted further trials incorporating granulocytes into CBT protocols for high-risk paediatric leukaemia independent of concomitant bacterial or fungal infection. Use of granulocytes in this setting remains in the domain of clinical trials.

The use of granulocyte transfusions should, like all blood components, be limited to patients in whom the possible benefits are thought to outweigh the risks. While granulocytes appear to have a role in treating refractory bacterial and fungal infections in severely neutropenic patients, and potentially in remission induction CBT patients, the use of granulocytes is associated with severe challenges. Production is technically complex and donor-/resource-intensive. Granulocytes expire at midnight the day following donation, and therefore, are only available on the days following large scale blood donation. Each of the three manufacturing centres (Manchester, Colindale, Filton) aim to produce three adult doses per day from Tuesday to Saturday, with no production on Sundays and significantly reduced capacity on Mondays (see section 5.3). By the time they reach hospitals, the granulocytes often have <8 hours of their shelf-life remaining, frequently requiring an uncommonly used blood component to be transfused at the end of a shift or out of hours. To allow for production challenges, granulocytes should ideally be requested the day prior to transfusion, to allow diversion of appropriate donations for testing and manufacture. However, given the nature of the clinical circumstances under which granulocytes are usually transfused, cases should be discussed with the NHSBT patient-facing consultant as soon as granulocytes are considered, and efforts will be made to source same-day granulocytes if available when there is clinical need.

Both available granulocyte products (see section 2) are ‘contaminated’ with red cells and platelets. While this can be beneficial for patients who also require red cell or platelet support, it necessitates ABO compatibility. As the only non-leucoreduced blood component within the NHSBT portfolio, granulocytes must also be irradiated to prevent transfusion-associated graft-versus-host disease (TaGvHD)(21). Finally, granulocyte transfusions are associated with a higher risk of adverse events compared to other components, including an increased incidence of TRALI, HLA alloimmunisation, and febrile non-haemolytic reactions(22).

Given the established challenges of conducting randomised trials around granulocyte transfusions, and the need to understand indications, safety and outcomes following granulocyte transfusions, a registry of all cases of granulocytes was established in England in 2017; the PROspective Granulocyte usage and outcomEs Survey (ProGrES). This database provides a resource to enable exploration of evidence of benefit of granulocyte transfusions. All clinicians requesting granulocytes for patients in England will be asked to provide clinical information for the study, and the approving NHSBT consultant will record a minimal (anonymised) dataset about the case to refer on to the Clinical Trials Unit (23).

2. Source of Granulocytes

Pooled Granulocytes – Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated
'Buffy Coats' – Leucocytes, Buffy Coat, Irradiated
Apheresis Granulocytes – Granulocytes, Apheresis, Irradiated – No longer available

	Pooled Granulocytes	'Buffy coats'	Apheresis granulocytes
Recommended adult dose	2-3 pools	10 units	1 donation
Number of donors	20-30 donors (10 per pool)	10 donors (1 per unit)	1 donor (1 per unit)
Volume (ml)	222mls per pool	59mls per unit	299mls
Neutrophils (10^{10})	0.82 per pool	0.105 per unit	6.37 per unit
Haematocrit (%)	23%	45%	9%
Platelets (10^9)	507 per pool	75 per pool	160 per unit
Adapted from: Joint UKBTS Professional Advisory Committee Position Statement: Granulocyte Therapy(24)			

Patient weight	Suggested dose
<25kg	10-20ml/kg*
≥25kg	2-3 pools
~15ml/kg achieves RING doses *max 2 pools	

Pooled granulocytes are the standard granulocyte component produced by NHSBT. An adult dose is 2-3 pools, and each pool contains buffy coats from 10 whole blood donations, processed to remove some of the excess red cells and platelets, suspended in plasma from one of the male donors contributing to the pool. Even with this processing they have a Hct of 23%, meaning RBC transfusion requirements may be diminished while using this component, but that a significant rise in Hct or need for venesection is unlikely. A standard adult dose of pooled granulocytes contains the equivalent of 3-6 adult therapeutic doses of platelets; platelet transfusion requirements will likely be nullified in the absence of platelet refractoriness. Most adults will receive neutrophil doses significantly below that of the high dose arm of the RING study; with patients weighing as little as 40kg needing 3 pools to achieve ≥$0.6x10^9$ neutrophils/kg/dose. Larger adults or those able to tolerate larger fluid volumes should be considered for three pools per day, if production capabilities and regional clinical need allow.

2.2 'Buffy Coats'

Patient weight	Suggested dose
<50kg	10-20ml/kg*
≥50kg	10 units
~35ml/kg achieves RING doses *max 10 units	

When clinical demand exceeds capacity for pooled granulocyte production 'buffy coats' may be offered as an alternative to pooled granulocytes. An adult dose of 'buffy coats' contains approximately half of the neutrophils contained within the adult dose of the standard pooled granulocyte product. It should be noted that both the volume and Hct of this product is higher (590ml and 45%). A standard adult dose of 10 units (10 buffy coats) contains the equivalent of just under 3 adult therapeutic doses of platelets.

2.3 Apheresis Granulocytes – **no longer available**

Apheresis granulocytes offered several advantages as a blood component, including a higher neutrophil count per dose, reduced donor (and consequently HLA) exposure, smaller component volume and lower levels of platelet and red cell contamination compared with the pooled granulocyte and 'buffy coat' products. However, collection of this component requires stimulating health volunteer donors with steroids and/or granulocyte colony-stimulating factor (G-CSF) raising ethical and safety concerns around exposure of healthy unrelated volunteer donors to potential side effects(25–27). In addition, constraints on granulocyte collection (including inability to obtain appropriate sedimenting agents) mean that apheresis granulocytes ceased to be available in England from 2018. While apheresis granulocytes remain the primary source of granulocytes in many countries outside the UK, there is a move towards developing pooled whole blood derived components using manufacturing methods and specifications like those of NHSBT.

3 Clinical Indications for Granulocyte Transfusions

3.1 Overview

The following recommendations are based on the available evidence to date. However, there are additional circumstances under which it may be reasonable to transfuse granulocytes, and discussion with the NHSBT patient-facing consultant on call (through Hospital Services) is encouraged. Granulocytes will only be released following approval by the NHSBT consultant on call. Although the evidence base is inadequate to provide definitive guidance, it is recognised that granulocytes for therapeutic use are usually given to patients where other evidence-based interventions have proven ineffective and where death due to infection is considered otherwise almost certain.

3.2 Therapeutic

3.2.1 *Reversible numerical/functional neutropenia*

- Therapeutic granulocyte transfusions should be considered for patients filling **ALL** the below criteria:

1) Severe neutropenia, defined as ANC <0.5 x 10^9/L, due to congenital or acquired bone marrow failure syndrome, **OR**, severe acquired functional neutropenia, due to conditions such as MDS*.
2) Receiving active treatment attempting to achieve disease remission (including if treatment has been paused due to active infection).
3) Neutrophil recovery (numerical and functional) expected in the near future (weeks).
4) Proven or highly probably fungal or bacterial infection that is unresponsive to appropriate antimicrobial therapy – demonstrated by visible spreading lesions on skin/mucosa/radiological examination, or failure of established infection markers to improve(28).

- *There is little evidence to guide the use of granulocyte transfusions in patients with acquired neutrophil dysfunction e.g. myelodysplasia. There must be compelling clinical evidence of poor function given there is no diagnostic test for this.

3.2.2 *Irreversible functional neutropenia*

- Therapeutic granulocyte transfusions may also be indicated for patients with a known congenital disorder of neutrophil function, regardless of neutrophil count. While recovery of functional neutrophils is not expected, as long as they meet all the other criteria above, granulocyte transfusions should be considered as a potentially appropriate therapy.

3.3 Prophylactic

- Granulocytes have been used as **secondary prophylaxis** for patients with ongoing infection in whom further definitive myelosuppressive treatment is required for disease control, where there is concern over development of life-threatening infection during subsequent predictable severe neutropenia. Such cases will be considered on an individual basis. Granulocytes are **not** indicated for **primary** prophylaxis (see section 3.5).

3.4 Other

- Granulocytes are indicated when used in the setting of an approved clinical trial (e.g. for immunomodulatory purposes in CBT in paediatric high-risk myeloid malignancies).

3.5 Where Granulocytes are not indicated

1. Bone marrow failure where neutrophil recovery is not anticipated
2. Sepsis in the absence of neutropenia or known neutrophil dysfunction
3. Pyrexia of unknown origin – i.e. no evidence of proven or highly probably fungal or bacterial infection
4. Viral infection in the absence of additional proven or highly probably fungal or bacterial infection
5. Primary prophylaxis in patients with expected/current neutropenia but no evidence of infection

3.6 When to stop Granulocytes

- Granulocyte infusions should be given until one of the following events:

1) Evidence of endogenous neutrophil recovery – ANC >1.0 x 10^9/L on 2 consecutive days
    - Neutrophil increments due to granulocyte transfusions are unlikely to exceed 1.0 x 10^9/L (and are anecdotally in the range of 0.1-0.2 x10^9/L).
2) Resolution of infection
    - It is recommended, in the setting of ongoing neutropenia, to continue until inflammatory markers are near-normal, and radiological features are resolved, to avoid relapse on cessation of treatment).
3) Clinical deterioration despite a minimum of three days of transfusions*
4) A severe reaction to granulocytes occurs*

- *Discuss risk benefit balance with NHSBT consultant in these situations.
- As granulocytes are manufactured on a named patient basis, where changes in the medical condition of the patient mean granulocytes are stopped early, this should be relayed to NHSBT to allow resources to be appropriately reallocated, and wastage avoided.

4 Compatibility Requirements, Substitution Strategies

4.1 Pre-Granulocyte Transfusion Testing

- ABO/Rh group and antibody screen
- CMV IgG (baseline, and taken prior to transfusion)(29)
- HLA typing
- Anti-HLA class I and II antibody screen

4.2 ABO

- **Granulocytes are routinely available as either group O or A**, and contain both red cells and plasma, requiring ABO compatibility rules for both to be followed.

Recipient Group	1st choice	2nd choice
O	O	N/A
A	A	O HT neg
B	O HT neg	N/A
AB	A HT neg	O HT neg

- Granulocytes must be ABO compatible with the recipient's plasma and crossmatch compatible by immediate spin (for ABO incompatibility) in those not eligible for electronic issue.
- Where group O granulocytes are used for non-O recipients, or group A granulocytes are used for AB recipients, they must be 'high-titre negative'. Only the donor of the resuspending plasma strictly needs to be high-titre negative for pooled granulocytes (for 'buffy coats' all donors must be high-titre negative).
- For ABO mismatched stem cell transplant recipients, both the patient and stem cell donor blood groups must be considered. Granulocytes will be managed as per red cells, (i.e. group O for the majority of cases), and 'HT negative' where anti-A or anti-B in the plasma of the granulocyte component may react with patient or donor red cells(30).

4.3 RhD

- RhD negative granulocytes should ideally be provided for:
  - RhD negative patients with childbearing potential
  - RhD negative patients <18 years of age
  - Patients with immune anti-D, even if not currently detectable
  - Transfusion-dependent D-negative adults
- Where RhD negative patients of childbearing potential receive RhD positive granulocytes, anti-D prophylaxis should be undertaken as per NHSBT guidelines(31).
  - In the absence of childbearing potential, anti-D prophylaxis is not indicated.
- To calculate the volume of red cells transfused, use the following equation:

RBC = Hct x Vol x N

RBC	= Volume of donor red cells transfused
Hct	= Haematocrit of pack(s)
Vol	= Average volume of the pack(s)
N	= Number of packs transfused

4.4 Other Red Cell Antibodies

- More extensive matching or compatibility testing in the presence of red cell antibodies or to prevent their formation is not required (i.e. IAT crossmatch).
- Attempts to provide granulocytes that are negative for antigens other than ABO and RhD are not required:
  - Acute intravascular haemolysis leading to significant symptoms is unlikely for antibodies other than ABO as a result of the small volumes of antigen positive red cells present in pooled granulocytes.
  - As granulocytes are not transfused for correction of anaemia, more rapid turnover of the red cells present in the granulocyte packs is not an issue.
- A decision regarding risks and benefits needs to be made by the clinician caring for the patient and the NHSBT consultant where the patient has non-ABO alloantibodies and there is a risk of delayed haemolytic transfusion reactions.
- Attempts to provide more extensive matching will lead to delay and potentially to the supply of a lower quality component (e.g. reduced granulocyte content, increased volume, exposure to female plasma if relying on individual buffy coats).

4.5 CMV

- As granulocytes are not leucocyte-reduced, there is a risk of CMV transmission from CMV IgG positive donors. CMV IgG negative granulocytes should ideally be provided for recipients who are at risk of CMV disease(32):
  - Pregnant women
  - Infants <28 days post estimated date of delivery
  - CMV negative patients or where the CMV status is unknown
- Where NHSBT are unable to supply CMV negative granulocytes for patients in the above categories, the risk of failing to give granulocytes and associated morbidity/mortality from bacterial or fungal infection would need to be balanced against a risk of subsequent CMV disease. This requires discussion between an NHSBT consultant and the hospital consultant responsible for treating the patient.

4.6 Volume

- Where the recipient has difficulty tolerating larger volumes, 'buffy coats' should be avoided
- If the recipient will struggle to tolerate a standard dose of pooled granulocytes, then one pool for adults or 10ml/kg for children under 25kg may be used
- It should be noted that the available evidence suggests that if there is benefit to be derived from giving granulocytes, it is likely from higher doses e.g. ≥ 0.6 x 10^9 granulocytes/kg/dose.
    - One pool in a 70kg adult provides 0.12 x 10^9 granulocytes/kg/dose.

4.7 HLA

- HLA compatible granulocytes can only be provided by apheresis and as such are not available in England.

4.8 Irradiation

- As granulocytes contain a large number of white blood cells which can, like a bone marrow donation, establish themselves in the recipient and form an immune system or 'graft'. This unmatched, unintended graft may cause Transfusion Associated Graft Versus Host Disease (TA-GVHD) affecting the host's liver, bone marrow, gut and skin and is almost universally fatal.
- Granulocytes should always be irradiated, and no substitution strategies are available.

4.9 Testing following a reaction

- Investigations following a transfusion reaction should follow those laid out in the BSH guidelines(33).
- In the case of platelet refractoriness, repeat HLA antibody screening should be undertaken.
- In the case of a severe reaction following granulocyte transfusion (i.e. TRALI, hypoxia, and/or hypotension), repeat HLA antibody screen and HNA antibody screen should be undertaken

5. Practicalities

5.1 Storage, release and transportation

- Granulocytes are stored at 22±2°C ideally without agitation.
- If granulocytes are agitated in error this does not preclude their transfusion as there is limited evidence that agitation affects them functionally(34,35).
- All testing for mandatory microbiological markers must be completed before granulocytes are issued; if incomplete this should be discussed with the NHSBT consultant on call prior to release.
- The times of dispatch and infusion should be recorded; traceability and all other regulatory aspects of blood component transfusion apply to granulocytes.

5.2 Administration

- Granulocytes expire at midnight the day following donation and should be infused as soon as possible after collection; their short shelf-life reflects reducing granulocyte activity over time as opposed to concerns about bacterial contamination.
- If there is an inability to complete the transfusion prior to midnight, the clinicians caring for the patient should discuss with the NHSBT consultant on call whether the risks and benefits are in favour of transfusing a short time past expiry, or of discarding the component.
- Granulocytes should be transfused through a standard red cell giving set; other than the screen filter present in a red cell giving set, no further filter should be used.
- The whole dose of granulocytes should be infused over 1-2 hours.

5.3 Availability and manufacturing sites

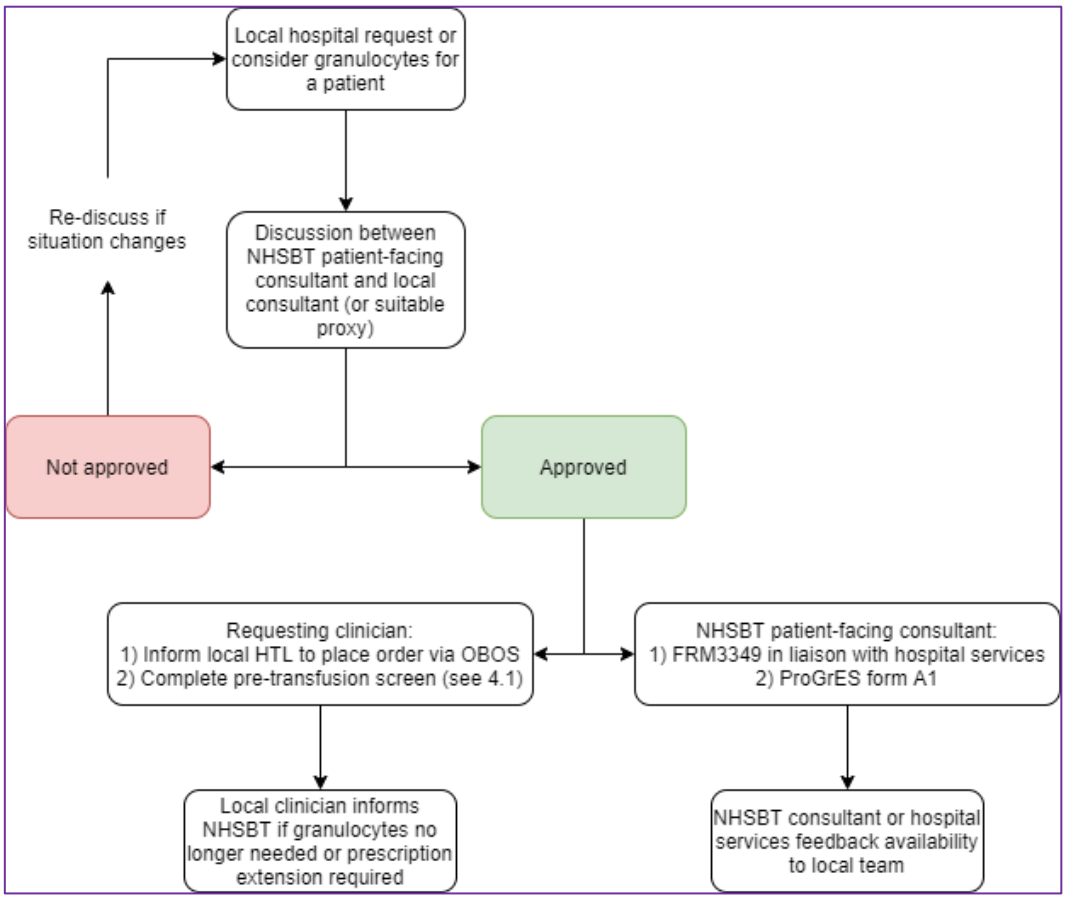
- Granulocytes are manufactured in three sites: Manchester, Filton, and Colindale
- During a normal working week, availability is as follows:
  - Tuesday-Saturday – each site aims to produce 6 pools (2-3 adult doses)
  - Sunday – no production at any sites
  - Monday – Colindale and Manchester only: limited number of O pos, CMV unselected, HT neg pools. Higher specification component (e.g. O neg, CMV neg) **may** be available depending on raw component availability and will be provided, if possible, but will require discussion between the NHSBT consultant and relevant manufacturing centre.
- Bank holidays have a significant impact on production ability (due to the reduced availability of donors) both on the bank holiday and the day after; NHSBT may be able to manufacture pooled granulocyte doses on these days, but production is not guaranteed, and availability will be advised on a case-by-case basis.

5.4 Requesting Pathway

5.4.1 Smart divert numbers for patient-facing on call NHSBT consultant

- North – 01912 615053
- London and the Southeast – 01268 724316
- Midlands and the Southwest – 01179 594666

5.4.2 Process Flow Diagram



5.4.3 *Duty of the requesting clinician:*

- The requesting clinician or a suitable proxy should collect information about the case to discuss with the NHSBT patient-facing consultant including:
  - Patient demographics – Name, NHS number, DOB, Sex
  - Transfusion details – ABO/RhD group, recent antibody screen results
  - Clinical details – Patient weight, baseline CMV IgG status (if known), underlying cause of neutropenia, treatment intent, allo-HSCT status including donor blood group (if known)
  - Indication details – Clinical history describing the indication for granulocytes, positive microbiology and/or imaging results
  - Contact details – For the referring clinician, and the responsible consultant
- If approved the requesting clinician should place an order via their hospital transfusion laboratory on the Online Blood Ordering System (OBOS), including whether CMV negative granulocytes are required.
- Inform team member planning to transfuse granulocytes of planned arrival time, short shelf-life, and administration specifics (see section 5.2).

5.4.4 *Duty of the NHSBT 'patient facing' consultant:*

- Provide agreement on whether granulocyte transfusion is indicated or not
- If indicated:
  - Check appropriate pre-granulocyte transfusion testing has, or is being sent (see section 4.1)
  - Discuss the risks/practicalities of granulocyte transfusion
  - Inform hospital services of approval for granulocyte transfusion and approve FRM3349 (completed and sent by Hospital Services)
  - Make requesting clinician aware of planned provision schedule and review date
  - Submit anonymised details of the request to the ProGrES database by completing form A Part 1 and emailing to progres@nhsbt.nhs.uk, including contact details for the responsible consultant
  - Complete FRM4544 and appropriate handover document based on region
- If not indicated:
  - Provide advice on situations where re-discussion may be appropriate

5.4.5 *Duty of local Hospital Transfusion Laboratory*

- Request via OBOS
- Coordinate delivery with hospital services

5.4.6 *Duty of Hospital Services*

- Complete and send FRM3349 to NHSBT 'patient facing' consultant
- Alert NHSBT 'patient facing' consultant to any difficulties in providing agreed granulocyte requests

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