

Title:

SECTION 12.0

**PROTOCOL FOR THE COLLECTION OF
G-CSF MOBILISED PERIPHERAL BLOOD
STEM CELLS AND FOLLOW UP OF
UNRELATED DONORS**

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Work Instructions / Forms

Prescription for Human Stem Cell Collection:	Form HPC
Information for Donors: PBSC (Peripheral Blood Stem Cell) Mobilisation and Collection after using G-CSF:	Form G Info
Consent Form Granulocyte Colony Stimulation Factor (G-CSF) Treatment and Peripheral Blood Stem Cell (PBSC) Donation:	Form G Consent

New Zealand Bone Marrow Donor Registry

Verification of HPC Collection:	Form GC002
Medical Assessment at Work Up of Unrelated PBSC or Bone Marrow Donors	Form GMA
Interpretation of Third Party Physical Exam at Workup	Form G43
Donor Infectious Disease Markers at Workup	Form 50
Draft letter to Medical or Nursing Staff to administer G-CSF	Form GDL Admin
G-CSF Administration:	Form G Admin
Reactions to G-CSF and their Management:	Form G React
Symptom Monitoring Protocol of PBSC Donor During Administration of G-CSF:	Form GSM
Apheresis Procedure:	Work Instruction GA
Peripheral Blood Stem Cell (PBSC) Collection Details:	Form G Collection Report
Donor Assessment Post Donation at 72 Hours:	Form 70
Donor Long Term Follow up:	Form 77
Donor Follow up Blood Tests	Form 78

SECTION 12.0

PROTOCOL FOR THE COLLECTION OF G-CSF MOBILISED PERIPHERAL BLOOD STEM CELLS AND FOLLOW UP OF UNRELATED DONORS

Collection of stem cells from an NZBMDR donor will be approved under criteria listed in the publication “ Indications for Haematopoietic Stem Cell Transplantation” compiled by the Bone Marrow Transplant Study Group of the Haematology Society of Australia and New Zealand.

If a Transplant is considered Non-standard, High Risk or Experimental under these criteria the Scientific Advisory Committee will make a decision as to whether the collection will be approved. If the collection is approved the donor must be informed of the committees reasoning before deciding whether to proceed with donating stem cells.

NZBMDR will release donors to Transplant Centres participating on BMDW and/or WMDA. Other Transplant Centres are required to forward credentials before a donor will be released.

NZBMDR allows a one antigen mismatch at HLA-A, B, DRB1* between patient and donor.

12.1 INTRODUCTION

This protocol describes the procedures to be followed for the use of G-CSF mobilised peripheral blood stem cell HPC (A) collections from unrelated donors. The protocol has been adapted from the Anthony Nolan Trust (ANT)/British Bone Marrow Registry (BBMR) Study and Australian Bone Marrow Donor Registry (ABMDR).

The aim of the protocol is to

- (i) Provide information regarding the collection procedure for HPC (A)
- (ii) To monitor success and safety of G-CSF/HPC(A) collections under the defined conditions;

12.1 FORMS REQUIRED TO REQUEST A DONOR WORKUP

To request 'Work Up' on a donor for collection of HPC (A), Final Compatibility Test Results and Form HPC or its equivalent are required

**Refer: Form HPC: Request for Human Stem Cell Collection
Final Compatibility Test Results**

12.2 DONOR MANAGEMENT

PRE-DONATION EVALUATION OF BONE MARROW DONORS

Before any testing is commenced the identification of the Donor must be confirmed by a legal document such as a passport, birth certificate or Drivers license

12.2.1 Donor Information and Counseling

A third party donor information session and medical assessment must be conducted by a haematologist who is not part of the team treating the patient

The purpose of this session is for the Haematologist to provide a full range of information regarding the Marrow/PBSC collection procedure. A medical examination will also be performed with a range of tests to ensure the safety of the donor and patient.

The donor must be given the opportunity to have an advocate or third party (e.g. family member or friend) present at the pre donation evaluation session.

Particular care must be taken over the peripheral venous [access](#) assessment.

Topics to be covered by the Donor Centre Coordinator or authorised representative and the third party haematologist include

- Tissue Typing - **Brief description showing why this donor has been chosen**
- Patient Details - **Age group, Sex, Continent, Racial Background (if appropriate)**
- **Transplant from the Patient point of view**
 - Reason for Transplant
 - Conditioning and work-up for patient (up to 14 days)
 - Point of no return
 - Post transplant complications including GVHD with the possibility of death
 - Success rate of unrelated transplantations
 - If the Transplant is an experimental procedure, or clinical trial (if known) the donor should be made aware of this situation
 - First signs of Engraftment (21 days)
- **Procedure for Donor**
 - Blood samples for Infectious Disease markers and other blood tests
 - Pregnancy test
 - Collection process
 - Address where collection will take place
 - Risk of donation by Apheresis and Marrow collection
 - Time off work and other activities such as sport
 - Patient progress reports if wanted (at 2 months, 6 months, and 1 year, then yearly)
 - Possibility of a second collection
 - Possibility of the transplant not being successful
 - Samples for research – if requested and approved by scientific committee
 - Cover for expenses and lost wages
 - Insurance
 - Patient/Donor Confidentiality
 - Agreement for Letter to Donor's GP with medical results and notice of HPC collection

Donors must be informed and counselled with specific reference to G-CSF/PBSC treatment for apheresis collection. The written 'Form G INFO', should be provided. Because of the unavoidable and technically detailed nature of this information it must be accompanied by careful explanation. Potential donors with learning difficulties who may have difficulty understanding the donor information sheets should be excluded from the protocol.

12.2.2 Medical Clearance

(i) A full medical history will be taken and the donor will require a range of tests to be performed to ensure that he/she is a satisfactory candidate for bone marrow/PBSC donation and the loss of up to 1500 mls of marrow/blood if a marrow collection is performed. Blood tests include a full blood count, blood grouping, urea, electrolytes, liver function tests, chest X-ray, ECG and antibody testing for CMV, HIV, HbsAg, STS, HCV, and HTLV1, EBV and Toxoplasmosis.

Recent published literature has suggested that **administration of G-CSF may precipitate life-threatening or fatal sickle cell crisis in persons with sickle cell disease.**^{1 2 3 4} If the donor's ancestors came from Countries which have a prevalence of Sickle Cell Disease they should have laboratory screening performed. This may be performed by haemoglobin solubility testing or haemoglobin electrophoresis.

(ii) **NZBS Blood Donor Session Record Form** or its equivalent must be completed to the satisfaction of the Donor Centre.

(iii) The Verification of Prescription for Mobilised Stem Cell Collection, Form GC002, must also be completed at the time of donor work up to ensure the plans for HPC (A) collection are considered acceptable and verified by all parties involved.

(iv) Bone marrow (HPC (M) donation, collection and known side effects must be explained including the risks related to general anaesthesia. It should be explained to HPC (A) donors that failure to obtain an adequate collection will necessitate consideration of conventional bone marrow donation.

When signing Form G Consent, the donor is asked whether they would be happy to consent to donate Bone Marrow in the event of unsuccessful mobilisation of peripheral blood stem cells using G-CSF. If they do not consent or the third party haematologist considers the donor an anaesthetic risk this must be reported to the Transplant Centre.

(iv) For HPC (A) donations the apheresis procedure must be explained as well as the administration of G-CSF, its known side effects and the uncertainty over long term adverse effects. If possible, arrangements should be made to visit an apheresis unit or to view a video on apheresis.

(v) If the donor is female a pregnancy test must be performed and she must be advised not to become pregnant or attempt to become pregnant until at least one month after the stem cell collection. Adequate contraception may need to be discussed.

If the donor does not consent to a pregnancy test after discussions with the Haematologist, then we will not proceed with the collection

If the donor is breast-feeding, HPC (A) collection is not advisable.

(vi) The policy regarding anonymity between donor and patient must be discussed in detail.

(vii) The donor should be prepared for the eventuality that for a variety of reasons the graft may not be successful.

(viii) The donor has the right to withdraw but must be made aware of the consequences for the patient if the donor withdraws once patient conditioning has commenced.

After full information has been provided the donor will be asked if they agree to G-CSF mobilised HPC (A) collection. If the donor is in doubt about the procedure, they must be informed that a conventional bone marrow donation is possible.

Both Form G Consent to donate PBSC and Form GB Consent to donate marrow if the donor does not mobilise should be signed at this time. If the donor elects not to receive G-CSF but will donate bone marrow, Form B, Intent to Donate Bone Marrow, (Refer: NZBMDR Form B) should be signed.

(ix) Venous assessment and use of CVC

The use of a Central Venous Catheter is not an option except in exceptional circumstances

Particular care is taken over the peripheral venous assessment as central venous access is not routinely permitted. Venous assessment should be performed at the verification typing stage by the venepuncturist and again at the donor's physical assessment or workup, prior to donation. At the time of workup the person who undertakes the collection procedure ideally performs this assessment. Failure to obtain good venous access may result in a need to abort the procedure and consideration of conventional HPC(M) donation subject to donor counselling, medical and anaesthetic assessment and agreement by all parties.

It is only permitted to perform a central venous line insertion in the unusual circumstance that the HPC(A) collection was not possible on the day because of an unexpected or exceptional reason and the donor had previously been passed as physically suitable with suitable venous access for HPC(A) collection at the workup. venous line insertion must only occur after discussion with, and approval by, the chair of the Scientific Expert Advisory Committee (SEAC) or his/her nominee. This discussion can be facilitated by the Executive Officer or his/her nominee.

The donor will be admitted to the FACT accredited Hospital associated with the NZBS collection centre

Consent and counselling will be given by the Radiology department

A central line will be inserted under radiology guidance and collection of HPC (A) will proceed at the hospital on the same day as per FACT Standard 6.3.2.2

Patient care, donor follow up and reporting of adverse events is the responsibility of the hospital

At workup the Apheresis nurses who will carry out the apheresis procedure will assess the peripheral venous access.

If they are satisfied that the peripheral access is suitable for a 2 day collection the donor will be passed as suitable for an apheresis collection.

If the peripheral access may only be suitable for a 1 day collection the donor must be counselled that if insufficient cells are collected on the first day their venous access will be reassessed and if unsuitable for another apheresis collection a marrow collection may be required

12.2.3 Forms to be completed after Donor Assessment for Peripheral Blood Stem Cell Collection

Refer: NZBMDR Form G Consent:

Consent Form for Granulocyte Colony Stimulating Factor (G-CSF) Treatment and Peripheral Blood Stem Cell Collection

Refer: NZBMDR Form GC002:

Verification of Prescription for Mobilised Stem Cell Collection

Refer: NZBMDR Form GMA:

Medical Assessment at Workup of Unrelated PBSC or Bone Marrow Donors

Refer: NZBMDR Form G43:

Interpretation of Third Party Physical Exam at Workup HPC, Apheresis

Refer: NZBMDR Form 50:

Donor Infectious Disease Markers at Workup (within 30 days of transplant)

Where a donor is considered suitable, and consent has been obtained after full disclosure of risk, the Transplant Centre can be notified and plans for G-CSF administration and stem cell collection will be finalised.

If the donor is not available for a bone marrow collection should insufficient HPC, Apheresis cells be collected the Transplant Centre must be notified immediately and advised that they can request freezing the HPC product prior to patient conditioning.

12.2.4

Counseling Donors Identified with Abnormal Test Results

All donors identified as having abnormal test results must be contacted by the professional body identified in SOP 806.

Follow up tests or treatment should be arranged by this body in consultation with the donor.

NZBMDR Medical Officer is to be informed with appropriate details and information about temporary or permanent unavailability of the donor. This information is to be recorded in the donors file.

The Transplant Centre must be informed in writing if issues of donor health pertain to the safety of the patient, a delay in completing donor clearance or the removal of the donor from the Registry

12.3 G-CSF Administration

- i) The donor must be counselled by the Collection Centre and must be given written Information on G-CSF. NZBMDR is responsible for ensuring that this takes place.
- ii) **The prescription, transport and coordination of the administration of G-CSF will be by NZBMDR.**
- iii) G-CSF will be administered at a dose of 10 µg/kg/day subcutaneously.
- iv) NZBMDR must ensure that the donor is clear about the G-CSF commencement date. This should be communicated in writing as well as re-iterated verbally.
- vi) G-CSF is given as a subcutaneous injection, usually in the abdominal region, once or twice a day for a period of four days including the morning of the apheresis on day five. If insufficient cells are collected, a second apheresis may be required the next day, after an additional injection on the evening of Day Five.
- v) If there are any side effects following the administration of the first dose of G-CSF the donor will contact NZBMDR. Otherwise NZBMDR will be in close contact during the period of the GCSF injections.

- vii) A report on any donor symptoms experienced should be recorded in the donors file. A contact name and telephone number must be given to the donor to respond to any enquiries concerning unexpected donor reactions.

Refer: NZBMDR Form GDL Admin:

Draft letter to Medical or Nursing Staff who may be asked to Administer G-CSF

Refer: NZBMDR Form G Admin-012: G-CSF Administration

Refer: NZBMDR Form G React: Reactions to G-CSF and their Management

Donors will be advised to avoid any strenuous physical activity during the 4 day period of G-CSF treatment.

- viii) Self-administration may be appropriate at the discretion of the Collection Centre. If self-administration is undertaken, the Collection Centre or NZBMDR representative must train the donor in self-injection.
- ix) On day 5, after the 4-day G-CSF treatment period, the donor will attend the Apheresis Centre.

12.4 Peripheral Blood Stem Cell (HPC (A) Collection by Apheresis

- (i) This must take place in an NZBMDR accredited Centre which regularly undertakes donor or patient apheresis procedures of three to four (3-4) hours duration, involving dual venous access. Arrangements must be made to ensure that a resuscitation team is available.
- (ii) Care must be taken to ensure that the donors or recipients name and details are not given to the other party by any staff members or written on documents which the other may see.
- (iii) CD34+ counts must be readily obtained from Cell Markers in order to determine whether another apheresis procedure is required the following day. The Laboratory should participate in the Australasian CD34+ Quality Assurance Program (CD34+QAP) under the umbrella of the Royal College of Pathologists of Australia (RCPA), or NEQAS CD34 external QA scheme
- (i) T-cell depletion, CD34+ selection or other technique is not recommended as a routine. Red cell depletion should not be required, although plasma depletion may be performed, depending on the donor and recipient ABO blood groups. It is recognised that there are some specific clinical situations where T-cell depletion or CD34+ selection is indicated by protocol and this must be clearly described on the prescription for stem cells.
- (ii) If after two (2) apheresis procedures the cell count is $<2 \times 10^6$ CD34+ / kg 'ideal' recipient body weight, it may be necessary to proceed to a bone marrow collection. After agreement between the Collection Centre and Donor Centre, this option can be offered to the Transplant Centre at a time to be arranged and after a review of the donor's fitness to donate post HPC (A) collection. (It may be determined that a bone marrow collection is unnecessary after CD34 analysis of the HPC (A)

collections at the Transplant Centre).

If a bone marrow collection is required, a yield of 2×10^8 MNCs / kg 'ideal' recipient body weight count should be the target.

- (iii) Due to a donor medical condition, donor preference or donor body mass it may have been decided prior to collection that the donor will not be available for a marrow collection in the circumstance that an insufficient CD34+ collect is obtained. This information MUST be given to the TC prior to or at the time of donor clearance
- (iv) The risk of failure to obtain sufficient cells from mobilised allogeneic blood for transplantation is estimated to be low (0.08% German experience 2011). Consequently taking a back up autologous blood unit is not recommended.

12.5 Collection reporting

Refer: NZBMDR Form G Collection Report: Peripheral Blood Stem Cell HPC(A) Collection Details

This form should be completed following a stem cell collection by a senior member of the Collection team. Page 1 should accompany the stem cells to the Transplant Centre. The entire form should be forwarded to NZBMDR.

If any data is not available to accompany the stem cells the data must be forwarded to the collection centre the following day

12.6 Processing and Storage after HPC (A) Collection

- i) **Sterility**

The sterility of the peripheral blood stem cells should be ascertained using liquid and/or semi-solid culture medium for full bacteriological and fungal cultures. All tubing, containers and other equipment and fluids that come into contact with the donations during processing or storage must be sterile.
- ii) **Labelling**

Containers must be clearly and unambiguously identified using labels that remain intact under the storage conditions used.

The unit containing stem cells must be labelled with the name of the product (e.g. allogeneic HPC (A), the donor national identification, patient's name and ID, date of collection, the presence and type of anticoagulant and additive media if any, ABO and Rh (D) group and the volume of the product.
- iii) **Addition of Anticoagulants**

ACD-A will have been added to the HPC (A) product during collection on the cell separator in concentrations (1:12 to 1:15) as programmed by the apheresis machine.
- iv) **Cell Concentration for Transportation of HPC, Apheresis**

For long distance transportation and storage of HPC, Apheresis the final concentration of nucleated cells in the collection is important for viability. The concentration of nucleated cells should be reduced by the addition of autologous plasma in the processing laboratory to less than 250 to $300 \times 10^9/L$ (<2.5 - $3.0 \times 10^8/ml$).

It is not mandatory to reduce cell concentration for short distance transportation such as between collection and transplant centres in Australia and New Zealand.

Note: If the TC requests plasma, a request for 150-200 mls of plasma should be indicated on the Notification form to the Collection Centre

v) **Storage at the Collection Centre**

Standard Operating Procedures to include the designated storage area, procedures for quarantine of HPC (A) and procedures for validating the conditions of storage achieved in any given area must be available.

This should include 24-hour temperature control and prevention of microbiological contamination.

Unmanipulated HPC (A) may be stored unfrozen for up to 72 hrs at $+4 \pm 2^{\circ}\text{C}$.

12.7 TRANSPORT OF HPC (A)

12.7.1 Transport of HPC (A) to Australian & New Zealand Transplant Centres. ^{5 6 7}

If two collections are required, the first collection can be stored at 4°C overnight and transported fresh with the second the next day. Products should be hand carried as per Section 14.0 Guidelines for Couriers

In exceptional cases HPC (A) can be cryopreserved and shipped in a dry shipper. Consent for Cryopreservation must be obtained from the donor prior to collection

refer: Fresh HPC (A) collections, but not HPC (M), show temperature-related loss of CD34+ viability during storage and transport

V ANTONENAS1 ET AL , CYTOTHERAPY (2006) VOL 8, NO 2, 158-165

12.8 RECORD KEEPING

A file must be kept by NZBMDR on each donor for 30 years. This file must contain Records of the apheresis collection, medical assessments, and post donation follow-up reports

12.9 POST DONATION FOLLOW-UP.

This should comprise:

- (i) Follow-up telephone calls by NZBMDR Coordinator within 72 hours to complete Form 70. Form 70 to be continued weekly until donors health is stable

Refer: NZBMDR Form 70: Donor Assessment by Telephone at 72 hours.

- ii) A medical assessment with blood tests should be undertaken at 6 months.
- iii) If the donor's blood count has not returned to pre collection status at 6 months the NZBMDR Medical Director will ensure that appropriate advice/action is given
If any abnormal results may have an adverse effect on the patient the Transplant Centre must be contacted in writing.

**Refer: NZBMDR Form 77 Long Term Donor Follow up:
Long-Term follow-up Protocol Following Administration of GCSF and
Apheresis.
NZBMDR Form 78 Blood Tests at Donor Follow up**

12.10 SERIOUS ADVERSE EVENTS

All serious adverse effects must be reported within 24 hours to the National Management Board of the NZBMDR. A report will be sent to the World Marrow Donor Association (WMDA) Serious Adverse Events subcommittee.

13.0 REQUESTS FOR SUBSEQUENT GCSF STIMULATED COLLECTIONS OF PBSC

A second donation of GCSF stimulated PBSCs for the same patient will be considered by the medical review team.

A second donation of GCSF stimulated PBSCs for a different patient will not be considered unless the donor is the only potential donor in the world for that patient

References

1 Wei and Grigg, BLOOD 97: 3998-9 2001

2 Adler et al. BLOOD 97: 3313-4, 2001

3 Abboud, Laver and Blau, LANCET 351: 959, 1998

1 Wei and Grigg. BLOOD 97:3998-9, 2001.

2 Adler et al. BLOOD 97:3313-4, 2001.

3 Abboud, Laver and Blau. LANCET 351:959, 1998.

5 Guidelines for the collection, processing and storage of human bone marrow and Peripheral stem cells for transplantation. Transfusion Med, 1994; 4:165-172.

6 Guidance notes on the processing, storage and issue of bone marrow and blood stem cells. NHS Executive HSG (97), 19, 24 March 1997.

7 Donor work-up and transport of bone marrow - recommendations and requirements for a standardised practice throughout the world from the Donor Registries and Quality Assurance Working Groups of the World Marrow Donor Association (WMDA). Bone Marrow Transplant 1997; 20: 621 - 629