

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 Mobilised Stem Cell Collection:	Form GC001
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
Verification of Prescription for Mobilised Stem Cell Collection:	Form GC002
Intent to Donate Bone Marrow in the event of Unsuccessful Mobilisation of Peripheral Blood Stem Cells using G-CSF:	Form GB
Medical Assessment at Work Up of Unrelated PBSC or Bone Marrow Donors	Form GMA

New Zealand Bone Marrow Donor Registry

Interpretation of Third Party Physical Exam at Workup	Form G43
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 G70
Weekly Donor Follow-up:	Form 76
Draft letter to Consultant Haematologist or General Practitioners:	Form GDL Follow Up
Long Term Follow-up Protocol Following Administration of G-CSF & Apheresis:	Form G Long Term Fu

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 searched by 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 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 (PBSC) 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 acceptability to donors of the collection procedure in comparison with conventional bone marrow stem cell donation;
- (ii) to monitor success and safety of G-CSF/PBSC collections under the defined conditions;

12.2 DONOR MANAGEMENT

12.2.1 Donor Information and Counselling

A third party donor information session 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. The standard procedure for selection, confirmatory typing and medical examination will be the same for HPC, Apheresis donors as for HPC, marrow donors in addition to a careful assessment of venous access.

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. These tests include a full blood count, blood grouping, urea, electrolytes, liver function tests, chest Xray , ECG and antibody testing for CMV, HIV, HbsAg, STS, HCV, and HTLV1.

To request 'Work Up' on a donor for collection of HPC, Apheresis, Form 117, (Final Compatibility Test Results), Form MC003 (Formal Request for Stem Cell Collection) and

Form GC001, are required.

Refer: Form GC001: Prescription for Mobilised Stem Cell Collection
Form 117: Final Compatibility Test Results
Form MC003: Formal Request for Stem Cell Collection

- (i) Donors must be informed and counselled with specific reference to G-CSF/PBSC treatment and for apheresis collection. The written 'Form G INFO' , and the Amgen Video "Peripheral Blood Stem Cell (PBSC) Donation 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.

Refer: NZBMDR G INFO:
Information for Donors: PBSC (Peripheral Blood Stem Cell) Mobilisation and Collection after using G-CSF

- (ii) Donors must read and understand Form G INFO and sign the Form G Consent. This should be witnessed by the medical officer as well as a third party during the counselling process.

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, Apheresis collection are considered acceptable and verified by all parties involved.

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

- (iii) Bone marrow donation, collection and known side effects of bone marrow donation must be explained including the risks related to general anaesthesia. It should be explained to HPC, Apheresis donors that failure to obtain an adequate collection will necessitate consideration of conventional bone marrow donation. NZBMDR Form GB: Intent to donate Bone Marrow in the event of unsuccessful mobilisation of peripheral blood stem cells using G-CSF should be signed unless the third party haematologist considers the donor an anaesthetic risk

Refer: NZBMDR Form GB:
Intent to donate Bone Marrow in the event of unsuccessful mobilisation of peripheral blood stem cells using G-CSF

- (iv) For HPC, Apheresis 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 and to view a video on apheresis.
- (v) If the donor is female, she must be told that she must not now 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 is breast-feeding, HPC, Apheresis collection is not advisable.

- (vi) The policy regarding anonymity between donor and patient should 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 once conditioning has commenced.

After full information has been provided the donor will be asked if they agree to G-CSF mobilised HPC, Apheresis 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 and Form GB should be signed at this time. If the donor elects not to receive GCSF but will donate bone marrow, Form B, Intent to Donate Bone Marrow, (Refer: NZBMDR Form B) should be signed

12.2.3 Donor Assessment before Peripheral Blood 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)

Particular care should be taken over the peripheral venous assessment. The person who will undertake the apheresis procedure should ideally carry this out. Failure to obtain good venous access may result in a need to abort the procedure and consideration of conventional bone marrow donation (subject to donor counselling and agreement).

Central venous access is not an option.

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.

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 agreed.

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.
If the Transplant Centre has requested PBSC but the donor will only donate bone marrow the Transplant Centre must be notified immediately

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 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 or to 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 Form G INFO to take away. The NZBMDR is responsible for ensuring that this takes place.
- ii) **G-CSF will be prescribed and the coordination of its administration will be by the Collection Centre in liaison with the NZBMDR and Apheresis Centre.** Donors may carry G-CSF with them supplied by the Collection Centre, or the Collection Centre can arrange for G-CSF to be obtained at the local hospital pharmacy or couriered to them.
- iii) G-CSF will be administered at a dose of 10 µg/kg/day subcutaneously.
- iv) The Collection Centre Coordinator must ensure that the donor is clear about the G-CSF commencement date and apheresis date. This should be communicated in writing as well as re-iterated verbally.
- v) A standard letter, Form GDL Admin, should also be sent to the health professional administering the G-CSF locally, which will detail the dosage and the schedule.
- 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 with apheresis usually being possible on the fifth day. If necessary, a second apheresis may be required the next day, after an additional injection on Day Five.
- vi) Following the administration of the first dose of G-CSF the donor should remain under the supervision of the Collection Centre or the local health professional for a period of one hour in case of any adverse reactions. A contact number should be provided to the donor in case they have any concerns
- vii) A report on any donor symptoms experienced should be recorded on the Symptom Monitoring Protocol, Form GSM. A contact name and telephone number should be included to deal with enquiries concerning unexpected donor symptoms.

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
NZBMDR Form GSM: Symptom Monitoring Protocol of PBSC Donor during Administration of G-CSF

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

- viii) Self-administration is not a preferred option but may be appropriate at the discretion of the Collection Centre. If self-administration is undertaken, the Collection Centre must train the donor in self-injection for the first treatment.

The Symptom Monitoring Protocol of PBSC Donor during Administration of G-CSF

(Form-GSM) should still be completed by the donor on these occasions.

- ix) On day 5, after the 4-day G-CSF treatment period, the donor will attend the Apheresis Centre for review prior to the first apheresis to be undertaken that day.

Some education or information on the Protocol should be given to professional colleagues, if required, whose services may be called upon to administer G-CSF to donors.

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

Refer: NZBMDR Work Instruction GA: Apheresis Procedure

- (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 should be taken that the donor does not meet the recipient.
- (iii) CD34+ counts must be readily obtained 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. These circumstances must be previously approved by the Institutional Ethics Committee of the Transplant Centre.
- (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, Apheresis collection. (It may be determined that a bone marrow collection is unnecessary after CD34 analysis of the HPC, Apheresis 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) The risk of failure to obtain sufficient cells from mobilised allogeneic blood for transplantation is estimated to be low (5.6% German experience October 2000). Consequently taking a back up autologous blood unit is not recommended.

**Refer: NZBMDR Form G Collection Report:
Peripheral Blood Stem Cell (HPC, Apheresis) Collection Details**

This form should be completed after the stem cell collection by a senior member of the Collection team. Pages 1 should accompany the stem cells to the Transplant Centre.

The entire form should be faxed to NZBMDR.

12.5 Processing after HPC, Apheresis 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, Apheresis), 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, Apheresis 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 $300 \times 10^9/L$ ($<2.5 - 3.0 \times 10^8/ml$). This is particularly important if HPC, Apheresis have been collected on the Baxter CS3000 (small collection chamber) or using the Auto HPC, Apheresis software on the COBE Spectra.

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: request for 150-200 mls of plasma should be indicated on the Notification form to the Collection Centre

v) **Storage**

Standard Operating Procedures to include the designated storage area, procedures for quarantine of HPC, Apheresis 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, Apheresis may be stored unfrozen for up to 72 hrs at $+4 \pm 2^\circ C$.

12.6 TRANSPORT OF HPC, APHERESIS

12.6.1 Transport of HPC, Apheresis to Australian & New Zealand Transplant Centres.

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If two collections are required, the first collection can be stored at 4°C overnight and transported fresh with the second collection the next day.

Refer: Section 14.0 Guidelines for Couriers

Transport of HPC, Apheresis to International Transplant Centres

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, Apheresis can be cryopreserved and shipped in a dry shipper.

refer: Fresh HPC, Apheresis collections, but not HPC, Marrow, show temperature-related loss of CD34 viability during storage and transport

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

12.7 RECORD KEEPING

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

12.8 POST DONATION FOLLOW-UP.

This should comprise:

- (i) Follow-up telephone calls by NZBMDR Coordinator within 72 hours to complete Form G70, and at one week to complete FormG76. Form G76 to be continued weekly until donor is back to normal.

Refer: NZBMDR Form G70: Donor Assessment by Telephone at 72 hours.

Refer: NZBMDR Form 76: Weekly Donor Follow-up

- ii) A medical assessment should be undertaken at 3 months and annually for five years.
- iii) Any abnormal results should be reported to NZBMDR Medical Director. It is the NZBMDR's responsibility to ensure that appropriate advice/action is given in relation to abnormal results. If any abnormal results may have an adverse effect on the patient the Transplant Centre must be contacted in writing.

**Refer: NZBMDR Form G Long Term FU:
Long-Term follow-up Protocol Following Administration of GCSF and Apheresis.**

12.9 SERIOUS ADVERSE EVENTS

All serious adverse effects must be reported within 24 hours to the National Management Board of the NZBMDR. A monthly report is 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 will be considered by the medical review team for the same patient .

Donation of GCSF stimulated HPC, Apheresis for a different patient will not be considered unless the donor is the only potential donor in the world for a 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