Donor's Guide Book

for Bone Marrow/Peripheral Blood Stem Cell Donors

Bone Marrow Donor Registry of Japan

Japan Marrow Donor Program

Guide for Bone Marrow/Peripheral Blood Stem Cell Donors

Table of Contents

* Please be sure to read this guide and the "Supplementary Information" before the confirmation test and the final-consent meeting. Moreover, please be sure to bring this guide to the test and final-consent meeting with you.

Donation Schedule Subsequent to the Confirmation Test

- Bone marrow or peripheral blood stem cells (PBSC) donation requires approximately eight visits to a medical facility. Normally, the donation procedure is undertaken during the day on weekdays. Please be sure to consider those requirements fully.

- It will take approximately two to four months to complete the entire process from the confirmation test to the bone marrow or PBSC harvesting. A precise schedule may be occasionally presented to you. Moreover, you may be asked to postpone the harvest procedure according to the patient's condition. The number of days from the confirmation test to the harvesting varies depending on the conditions of each case, and thus the schedule chart indicated on the next page should be considered only as rough guidelines.

- In case any problem has occurred on your health or schedule, please inform us as soon as possible.

- In this guidebook, a bone marrow or PBSC donor(s) is referred to as "donor(s)." A patient(s) who receives a transplant is referred to as the "patient(s)."

Confirmation Test
Notification of general blood test result
Notification of donor selection result

- The details of the bone marrow/PBSC donation are explained by the coordinator and coordinating physician.
- Confirmation of decision to donate (Please inform us if you have any preference as to the bone marrow or PBSC harvest method.)
- Confirmation on your health condition
- Blood collection (approx. 25 ml) * In certain cases, blood may have to be collected again.

↓

Final Consent
Decision on the harvesting facility

- You will be notified as to whether you have been chosen as a donor. If you have been chosen, the method to be undertaken will also be indicated.

↓

Health Examination Before Harvesting

- Final confirmation will be requested in regard to your willingness to donate either bone marrow or PBSC (your family's consent is also required).
- Drafting the agreement
- Medical interview and examination
  (Blood, urine, chest x-ray, electrocardiogram, pulmonary-function tests and other tests)
  * Blood may have to be collected again in some cases.

↓

Case 1: Bone Marrow Donation
Autologous Blood Collection (0 - 2 times)
↓
Hospitalization Average length of hospital stay: 3 nights 4 days (depending on the facility)
↓
Bone Marrow Harvest
↓
Discharge
↓
Follow-up by telephone
↓
Post-Harvest Health Examination
↓
Questionnaire
↓
Confirmation on the decision to sustain registry membership

Case 2: PBSC Donation
Granulocyte colony-stimulating factor (G-CSF) injection (3 - 4 days)
The number of days required for the donor to be admitted to the medical facility after the day on which he/she received granulocyte colony-stimulating factor (hereinafter referred to as G-CSF) injection, as well as the number of days required for him/her to be discharged from the facility after the procedure, will be determined by the facility, at which the harvesting will be/has taken place, based on the respective situations of the donor and facility.
↓
G-CSF injection (On the fourth or fifth day after the procedure)
↓
* When the sufficient amount of cells has been collected
↓
PBSC harvest

* When the number of cells collected is insufficient
↓
G-CSF injection (On the fifth or sixth day after the procedure)
↓
PBSC harvest

Discharge
↓
Follow-up by telephone
↓
Post-Harvest Health Examination
↓
Questionnaire
↓
Confirmation on the decision to sustain registry membership

Chapter 1
What Is the Bone Marrow Donor Registry?

1. Once you have been chosen as a donor candidate (hereinafter referred to as the “donor”), you will receive the donor coordination notification (acceptance notification) and a reply form from the person in charge of the initial-stage coordination. Once you have returned the documents to us, we will begin coordination at our donor coordination office.

2. The donor coordination office is comprised of coordinators and coordinating physicians. Once donor coordination has been initiated, a coordinator and a coordinating physician will be assigned to each donor. Furthermore, in some cases the coordination work may be conducted by a staff member belonging to the coordination office (hereinafter collectively referred to as the “coordinator”).

P.5

1. The coordinator communicates with, and coordinates between, the donor, coordinating physician, donor coordination office and harvesting facility.
   Furthermore, a coordinator will prepare for the confirmation test and meeting for the final consent and explain the details of the test and meeting to the donor, and he/she will be present at the site each time the donor receives the health examination and becomes admitted to, and discharged from, the facility at which the harvest procedure will be (or has been) undertaken.

2. The coordinating physician is in charge of determination of the donor’s eligibility and blood collection. He/she is also responsible for answering the donor’s medical questions.

3. If you have any questions or particular requests, please contact our office or your coordinator. If you become a candidate for a judge, please inform us as well.

4. When you need to contact your coordinator, please do so by telephone during the day or via fax at any time. The coordinator will get back to you as soon as possible.

5. The coordinator will be present upon your hospitalization, harvesting and discharge from the hospital. Moreover, even after your discharge the coordinator/donor coordination office will follow up by telephone or mail in regard to your health condition. Please understand that this is to ensure the safety of the donor. We appreciate your cooperation.

Handling of Personal Information

In compliance with the Act on the Protection of Personal Information, any personal information (name, residential address, medical history, etc.) of bone marrow or PBSC donors and the results of the tests conducted on such donors during the coordination process will be strictly managed.

Any required portion of the donor's personal information will be mutually used among the Japan Marrow Donor Program (JMDP) and the coordinator, coordinating physician, harvesting facility, transplant facility and parties with whom the JMDP has specifically acknowledged the necessity of sharing the information.

Additionally, all the necessary information, excluding personal information such as the name and residential address, will be used to create the statistical database of the Bone Marrow Donor Registry project.

Please inform the donor coordination office or your coordinator if:

- You *do not agree with* our policy that the data provided during the coordination process will be used for research that will be conducted for the purpose of improving the transplant success ratio and donor safety. (Although we don't ask your consent prior to the research because it is a study of the immune system, if you request that we not use your data, your data will not be used for the research.)
- You want to correct or change your personal information or have questions regarding such corrections and changes during the coordination process. (If any change has been made to the registration data such as name and address, the updated information will be provided to the Bone Data Center.)

Chapter 2
What Are Bone Marrow/PBSC Transplants?

1. The hematopoietic stem cells, which form white blood cells, red blood cells and blood platelets, are normally present in the bone marrow, with only a slight amount of hematopoietic stem cells being present in the peripheral blood (the blood that circulates throughout the body). However, it has been discovered that if G-CSF, the agent that facilitates an increase in the production of white blood cells, is injected, the number of hematopoietic stem cells increases in the peripheral blood as well. Thus there are two PBSC harvest methods: One is to harvest PBSC from the bone marrow and the other is to harvest from the peripheral blood (see page 10). The bone marrow transplant is a therapy in which the hematopoietic stem cells taken from the donor's bone marrow is transplanted into the patient. The peripheral blood stem cell transplantation (also known as PBSCT) is a therapy in which hematopoietic stem cells harvested from the donor's peripheral blood are transplanted into the patient.

Blood cell type	Role	If insufficiency or abnormality occurs
Red blood cell	To circulate oxygen throughout the body	Anemia attack occurs.
White blood cell	To protect the body against pathogens	The body becomes prone to infection.
Blood platelet	To stop bleeding	The body becomes prone to bleeding.

2. Leukemia, aplastic anemia and immunodeficiency disease cause abnormality in the hematopoietic stem cells, thus hindering those cells from creating normal white blood cells and thereby causing anemia and immunodeficiency.

3. Bone marrow/PBSC transplants are therapies that replace diseased hematopoietic stem cells with healthy cells. Although some of those diseases can be cured through chemotherapy or immunosuppressant, there are many patients who can be cured only through a bone marrow or PBSC transplant. The major hematopoietic stem cell diseases include leukemia, myelodysplastic syndrome, malignant lymphoma, severe aplastic anemia, immunodeficiency and some types of congenital metabolic disorders.

4. Of all the hematopoietic stem cell allograft cases around the world, nearly 300,000 bone marrow/PBSC transplants have been conducted thus far between blood relatives and unrelated individuals.

5. Those who donate healthy bone marrow aspirate are bone marrow donors, and those who donate hematopoietic stem cells are PBSC donors. Each harvest method differs greatly (see the next section). The hematopoietic stem cells harvested from the donor are slowly injected into the patient's vein through the intravenous system over a period of several hours.

6. Systemic radiation therapy and a large amount of anticancer drug are given to the patient prior to the transplantation procedure for a period of one to two weeks. This will destroy not only the diseased cells but also normal hematopoietic stem cells. This procedure is called transplantation conditioning (i.e. pretreatment). After the pretreatment the number of white blood cells in the blood decreases significantly, thus causing the patient to lose resistance and become more prone to infection. For this reason, the patient must spend his/her time in a sterilized aseptic room, which maintains a flow of clean air without dust or bacteria.

7. For the patient the timing of the transplantation is an important point. It is carefully determined by observing the condition of the disease. It is also necessary to arrange the aseptic room, of which availability is limited, as well as the scheduling of the facility staff.

8. Even after the transplantation, the patient could die during the early post-operative stage due to the graft rejection, a GVHD (graft-versus-host disease) whereby the transplanted lymphocytes attack the patient's body, or a severe infection. Moreover, there is a chance that the patient's original disease such as leukemia may recur even though the donor's hematopoietic stem cells have been successfully engrafted and thus the patient has recovered. Therefore, it is possible that a patient cannot be cured by a bone marrow or PBSC transplant.

- Bone Marrow/PBSC Transplant

[Bone Marrow Harvest]
Once anesthesia is given to the donor, injection needles with the thickness similar to that of a ball point pen filler are inserted into the donor's ilium (the pelvic bone) to harvest the bone marrow aspirate.

* Bone marrow is a spongy hematogenous tissue that continuously produces red blood cells, white blood cells and blood platelets. The bone marrow is filled with the bone marrow aspirate containing hematopoietic stem cells, which create blood cells. The blood cells produced in the bone marrow aspirate will then enter the blood stream. The bone marrow has no correlation with the spinal cord (the nervous system).

[PBSC Harvest]
G-CSF is injected hypodermically into the donor for a period of four to six consecutive days.
On the fourth or fifth day after the initiation of the G-CSF injection, once the number of hematopoietic stem cells in the peripheral blood begins to increase, the PBSCs required for the transplant are harvested using a blood component separator.

- Differences Between Bone Marrow Harvest and PBSC Harvest

	Bone Marrow Harvest	PBSC Harvest
G-CSF Injection	Not performed	Performed
Autologous Blood Collection	Performed (Not required in some cases)	Not performed
General Anesthesia	Performed	Not performed
Length of Hospital Stay * Depending on the facility	Approx. 3 nights 4 days	- If hospitalized only for harvesting: 1 night and 2 days - 2 nights and 3 days - If hospitalized from the first day of the injection period throughout the procedure: 4 nights 5 days - 6 nights 7 days
Number of Harvesting Facilities	Approx. 170	Approx. 5 - 10 (It will be increased to approximately 100 facilities in the future.)
Number of Visits to the Facility for Interview, Test and Harvesting	About 7 times	- If hospitalized only for harvesting: About 8 times - If hospitalized from the first day of the injection period throughout the procedure: about 5 times

Chapter 3
Comparison between Bone Marrow Transplant and PBSC Transplant

1. From the Patient's Perspective

Although the bone marrow transplant and PBSC transplant use the same transplantation technique, namely infusion, each method has its own advantages and disadvantages. For example, it has been known that while the PBSC transplant shows higher GVHD incidence because more of the donor's lymphocytes are transplanted than in the bone marrow transplant, the strength of GVHD has a correlation with the effect of the donor's lymphocytes that attack leukemia cells as alien matter (the GVL effect). It can therefore be expected that this may reduce the recurrence rate.

In Japan there is no data that compares bone marrow transplants and PBSC transplants conducted between unrelated individuals. In the medical setting, for example, the bone marrow transplant tends to be chosen for aplastic anaemia and child patients, while the PBSC transplant tends to be used for patients with advanced-stage leukemia or infectious diseases as well as for mini-transplant (non-myeloablative transplant, i.e. to conduct transplantation by reducing the intensity of the pretreatment) for patients of advanced age. Thus the characteristics of each method are taken into account when the method of harvesting is selected.

2. From the Donor's Perspective

According to the results of questionnaires conducted in overseas countries on donors who have participated in the comparison test between the bone marrow transplant and PBSC transplant, the bone marrow donors began to feel certain subjective symptoms such as pain after the procedure, and the PBSC donors began to feel such symptoms once the G-CSF injection was initiated. The intensity and duration of the pain were nearly equal between the two methods.

Regarding the long-term effect, joint research conducted by the Japan Society of Hematopoietic Cell Transplantation and the European Blood and Marrow Transplant Group has revealed that there is no difference in the incidence rate of severe complications between the bone marrow harvest and the PBSC harvest.

As shown in the table on the next section, each method has its own advantages and disadvantages. Generally, however, it is said that there is no difference in donor's burden between the two harvest methods.

- Summary of Comparison between Bone Marrow Transplant and PBSC Transplant

		Bone Marrow Transplant	PBSC Transplant
Donor's Perspective	Advantage	- No G-CSF injection or apheresis is required.	- Neither autologous blood collection nor operation under general anesthesia is necessary.
	Disadvantage	- Side effects of general anesthesia (see Chapter 8) - Pain, infections and bleeding in the harvest site - Autologous blood collection is often required to prevent anemia.	- Side effects of G-CSF (pain in the bone, headache, joint pain, etc.) - Complications during the harvest procedure (see Chapter 9) - Decrease in the blood platelets due to the harvesting - The long-term safety of G-CSF administration is unknown.
Patient's Perspective	Advantage	- It tends to be chosen for aplastic anemia and child patients.	- It tends to be chosen for patients with advanced-stage leukemia or infectious diseases as well as for mini-transplant for patients of advanced age. - As compared to the bone marrow transplant: (1) hematopoiesis recovery is faster; (2) the GVL effect may be more enhanced; and (3) immune recovery may be faster in this method.
	Disadvantage	- It requires donor's autologous blood collection, and thus it may prolong the coordination period as compared to the PBSC transplant.	- As compared to the bone marrow transplant: (1) the incidence of acute GVHD can be slightly higher; and (2) the incidence of chronic GVHD is higher in this method.

Reference material: *Illustration Series for Informed Consent: Hematopoietic Stem Cell Transplant*, by Yoshinobu Kanda (First edition published on October 30, 2009)

Chapter 4
Donor Requirements
− HLA: The Key Point of Transplantation −

1. In order to maximize the safety to the patient and the donor, the donor candidate must be:

1) Between 18 and 54 years old (the age of the donor subject to the search for a match ranges from 20 to 54 years old)
Even though the donor has reached the age of 55 and received the notification of the termination of his/her donor registration (due to the age limitation), if the donation coordination is still progressing upon his/her receipt of the notification, the coordination will continue. Once all the procedures are complete, the registration will be terminated.

2) Those who are healthy:
- Those who are not currently under medical treatment or on medication
- Those who don't have histories of malignant tumor, collagen diseases (such as chronic rheumatism), myocardial infarction, angina pectoris, apoplexy, asthma (attack during the past one year) and convulsive disorder (e.g., epilepsy)
- Those whose systolic blood pressure ranges from 90 mmHg to 150 mmHg, and diastolic blood pressure of 100 mmHg or less
- Those who have never received blood transfusion
- Those who have no infectious disease such as viral hepatitis and syphilis that can be transferred to the patient
- Those who have no blood disease or those who are not anemic (The donor is eligible if the donor has been cured by taking a hematic agent. The donor is not eligible if he/she is currently on a hematic agent. Please refrain from donating your blood until the coordination process is complete.)
- Those who weigh at least 45 kg (males) and 40 kg (females) and who are not excessively obese (BMI: weight kg ÷ (height m × height m) = less than 30)
- Other information:
In the event any abnormality is suspected, the donor may be asked to receive medical examination or test(s). This is to confirm the donor's health condition. Please be advised that the donor will bear the cost of such examination and testing.

3) Those who fully understand the details of the bone marrow/PBSC donation process

4) Those who have obtained consent from their family (the closest family members such as spouse and parents)

5) Those who are not pregnant

* Other medical histories and health conditions will be individually assessed upon medical interview and/or examination. Some of the donor requirements differ between the bone marrow transplant and the PBSC transplant.

2. A person whose HLA type matches that of the patient is chosen as a donor candidate.
As with the blood types of red blood cells, which are A, B, AB and O, white blood cells also have blood types. These types are referred to as HLA (human leukocyte antigen) or histocompatibility antigen. HLA types include A-locus, B-locus, C-locus and DR-locus. Each locus has several types or several tens of types, and the number of their combinations can reach several ten thousand.
HLA types will be further investigated. For example, when A2 is more closely examined it can be further classified into 0201, 0206, 0207 and 0210.

3. Once the registration process is complete, four loci of A, B, C and DR (two antigens for each locus, a total of 8 antigens) are tested at the Bone Marrow Data Center.
All A-, B-, C- and DR-loci of the donors, who registered after August 2009, have been tested through the DNA typing method. The test results are registered in the database of the Central Bone Marrow Data Center in order to search for a donor who has high HLA compatibility with the patient.

4. The HLA types are paired. Because one of a pair of HLA is passed on from one of our parents, a pair is divided into four types between the siblings, and thus the probability of an HLA match is one-fourth between them. In Japan, approximately 30% of patients can find their HLA match among their blood relatives.

5. Even if a transplant was conducted between blood relatives, if HLA types do not match between the donor and recipient, this will increase the incidences of GVHD and graft rejection. As well, even if it was performed between the unrelated individuals, if the HLA types matched between them, the success rate similar to that of a blood-relative transplant can be expected.

6. In Japan there are many people who have similar HLA types to each other. Today the number of donor registrants has exceeded 350,000, and thus approximately 95% of the domestic patients who have registered in the Bone Marrow Donor Registry can find an HLA match.

7. A donor occasionally encounters a patient with a matching HLA in the bone marrow donor registry of a foreign country.
Even in such an international case, the basic coordination procedures are the same as those used domestically. When the dates and locations of tests and bone marrow/PBSC harvesting are specified, we will discuss with you before starting the coordination process.

Chapter 5
Confirmation Test

1. Regarding the timing of the transplantation, if the patient's preference is known to us upon the initiation of coordination, we will notify the donor (in some cases, a specific date may not yet be determined). The coordinator will contact the donor to discuss the date of transplant with due consideration to his/her free will and schedule. However, if there is any date we should avoid, please notify us by using the reply form or calling your coordinator/coordination office. Furthermore, the date specified by the patient may change due to the progress of the treatment or other reasons. Thus we will update the information when you are selected as a donor.

2.Upon the confirmation test/consultation meeting, the coordinator mainly explains the details of bone marrow/PBSC donation and confirms that the donor will accept or reject either harvest method. (If you cannot make a decision at the confirmation test/consultation meeting, you will be contacted by telephone for confirmation within a week after the meeting.)

The donor will never be asked to undergo the harvest procedure to which he/she does not agree. In the event it is obvious that the harvesting cannot be carried out through the method that the donor has agreed upon due to a health reason, the coordination process will be terminated. Although at the Bone Marrow Donor Registry we do not voluntarily inform the donor with the patient's preference regarding the transplantation methods (either method is acceptable/bone marrow transplant is preferred/PBSC transplant is preferred) in order to secure the donor's free will, if the donor him/herself wants to know the patient's preference, the information will be given. However, please understand that the patient's request may change according to the status of the disease and/or the donor's will (whether or not the donor has rejected either harvest method).

Once the candidate has been selected as a donor, the patient's physician will determine which harvest procedure should be taken based on the donor's will and health condition.

3. At the confirmation test/consultation meeting we will ask the donor whether he/she has understanding and consent of the family, which is one of the most important requirements for bone marrow/PBSC donation (the donor's family can attend the meeting as well). The meeting takes approximately an hour and-a-half to two hours. The available days for the tests are Monday to Friday, 9:00 a.m. to around 3:00 p.m. (depending on the facility).

4. After the explanation, if the donor agrees to the following items 1) through 4) he/she will be asked to sign the "Confirmation Test Agreement." Next, the coordinating physician will conduct a basic health examination such as a medical interview and blood pressure measurement. Subsequently, approximately 25 ml of the blood will be collected (if the patient is in an overseas country, a different amount of blood may be collected).

    1) General blood testing is conducted for the purpose of the donor's health check.

        General Blood Test (Donor Screening Test)

        (1) Blood type: Testing for ABO/Rh blood types
        (2) Blood count: Hemoglobin, red blood cells, hematocrit, white blood cell and blood platelet counts
        (3) Liver and kidney functional tests: Serum whole protein, blood glucose, urea nitrogen, creatinine, total bilirubin, GOT, GPT, γ-GTP, total cholesterol
        (4) Testing for infectious diseases (testing for pathogens that may infect the patient through transfusion or a hematopoietic stem cell transplant): Serologic test for syphilis, hepatitis B, hepatitis C, adult T-cell leukemia virus, AIDS (HIV) virus, cytomegalovirus

    2) If the donor's HLA types were not tested through DNA typing for all eight antigens of A-, B-, C- and DR-loci upon registration or at any time during the past coordination process, they will be investigated thoroughly during this confirmation test in order to assess the compatibility with the patient.

    3) In some cases, the donor's blood collected during the confirmation test may be partially saved and used in the event the test results must be reconfirmed. Although the sample blood (blood/DNA specimens) will be discarded after the completion of the required testing, DNA specimens will be partially used in order to maintain the HLA test quality, as well as to evaluate the reagent used for HLA testing, once the donor's identity has been made unidentifiable.

    4) The HLA-DNA typing results will be used for a new search for the match even after the entire coordination process has been completed.

5. The donor will be informed of the results of the general blood test approximately two weeks after the date of blood collection. If any abnormality has been detected, the donor may be asked to receive another blood test that requires blood collection. Additionally, please be advised that the blood tests include hepatitis, syphilis and AIDS for the purpose of the health check. The donor will be notified of the results of those tests.

6. If multiple numbers of matching donors have been discovered for a single patient, arrangements with up to five donors can proceed at the same time. However, in some cases only one match may be found. The number of donor arrangements that are progressing at the same time for the same patient won't be informed to the donation coordination office, coordinating physician, coordinator or the donor him/herself, in order to maintain each donor's free will.

7. After the confirmation test will take approximately two weeks at the earliest and a maximum of two months to send the notification to the donor.
   The patient's physician selects the donor who is most suitable for the transplant based on all the test results conducted on the donor, as well as those of other donors, and then determines which harvest procedure should be taken. Upon the selection of the donor, he or she will be informed of the selected harvest procedure.
   As a general rule, the harvest procedure cannot be reversed once the donor has been selected because the patient will undergo pretreatment for the transplant according to the harvesting policy thus determined. If the donor or his/her family should make a request to change the harvest method, the entire coordination process may be terminated in some cases.

   1) If you have been selected as a donor, the date and location of a briefing (which will be conducted to confirm the final decision regarding the donation of the donor and his/her family) will be coordinated. At this point, if the patient's preference regarding the date of transplant is known to us, we may consult with the donor and his/her family to tentatively select the date of the harvest procedure and facility. For most PBSC donor cases, it is a common practice that the date of the harvest procedure is coordinated before the confirmation of the final consent.

   2) Even though you have not been selected as a donor, the donation coordination office or the coordinator will ensure that you will be notified in regard to the decision. If you want to know the result quickly, please inquire with the donation coordination office.

   3) Furthermore, if it has been determined that your eligibility for the transplant is equivalent to that of the selected donor, you may be asked to wait for a certain period of time as a "selection pending" status. The pending period may be extended due to a change in the progress status of the coordination with the selected donor. If there is any problem, please contact your coordinator or the donation coordination office.
   (See Chapter 16 for details on termination and "pending" coordination status.)

Chapter 6
Final Consent Is an Extremely Important Commitment

1. Once you have been selected as a donor, the coordinator and coordinating physician will explain to you about the harvest method suggested by the patient upon selecting the donor in the presence of yourself, your family and a third-party witness, and will then confirm your final decision regarding donation.

2. The third-party witness will receive a thorough explanation regarding the donation process, and will then attend the meeting to confirm whether the donor him/herself and his/her family understand the process and that the bone marrow/PBSC donation is the donor's voluntary will. (Although a witness is selected by the JMDP as a general rule, if the donor has a particular person whom he/she wants to designate as a witness, please inform us.)

3. Once you have fully understood the process and the final consent (i.e. the "Bone Marrow Donation Agreement" or the "PBSC Donation Agreement") has been signed (via signature) and sealed (each party must bring his/her own seal to the meeting) by yourself and a representative of your family, it will be deemed the final confirmation of the decision to donate the bone marrow or PBSC. The family representative can be the donor's closest person. For example, if you are single the representative can be your parent, or if you are married this can be your spouse. Depending on the donor's situation, the family representative may be one of the donor's siblings or the donor's guardian.

4. Donation of the bone marrow/PBSC is totally up to an individual's free will. As long as it is before the final consent is signed and sealed, you may reverse your decision to donate. However, once the final consent has been signed and sealed, you cannot reverse your agreement. Once the donor's final decision to donate the bone marrow/PBSC has been confirmed, the patient side (i.e. the patient, his/her physician and harvesting facility) will begin pretreatment approximately two weeks prior to the transplant, assuming that "the patient can definitely receive the transplant."
   If the donor overturns his/her agreement after his/her final consent has been confirmed, this may cause an unfortunate event such as the patient's death due to the inability to receive the transplant.

5. The harvest method cannot be reversed once the final consent has been given. This is because doing so will cause the harvesting schedule and facility to be rearranged, as bone marrow harvesting and PBSC harvesting require different facility systems (including the specialists, the room and equipment required for harvesting).
   Please understand that extreme importance is attached to the final consent.

6. The health and safety of donors are our number-one priority at the Bone Marrow Donor Registry. Therefore, even after the final consent, if any situation that may harm the donor's health arises, or if a new abnormality has been observed, the harvest procedure may be postponed or even cancelled in order to protect the donor's health.

7. The final consent is valid for six months. If, for any reason, you haven't made any bone marrow/PBSC donation after six months since the signature and sealing of the final consent, we will reconfirm your willingness to donate. Please reconsider your situation and your feeling toward the donation at this point. (In the event the coordination was terminated due to some reason on the part of the patient after the confirmation of your final consent, and subsequently you are selected as a donor for a new coordination process with a new patient, the final consent confirmation meeting can possibly be omitted.)

8. The consent from the donor alone is not sufficient for bone marrow/PBSC donation. It also requires the understanding and consent of the donor's family.

Chapter 7
From Final Consent to Bone Marrow or PBSC Harvesting

1. Once you (as the donor) have signed the final consent, the JMDP will notify the patient's physician and choose a harvesting facility from among the facilities authorized by the JMDP. (If the facility has been unofficially determined, the decision will be finalized.) Although we will do our best to arrange the facility of your preference, your wish may not be granted depending on the situation. The harvesting facility differs from the transplant facility in which the patient will receive the transplantation procedure.

2. The coordinator and donation coordination office will coordinate the schedule for the harvest and transplantation procedures among the three parties of the donor, patient side and harvesting facility. They will also plan the health examination, autologous blood collection (for bone marrow harvesting) and G-CSF injection (for PBSC).
   Your schedule will be taken into account as much as possible. However, please understand that the harvesting schedule may be limited depending on the progress of the patient's treatment.

3. Once the harvesting facility has been chosen and when the date of harvest is approaching, please try to maintain your physical condition for the harvest procedure.
   For more details, please read the "Donor Notebook" (see Chapter 10) provided to donors whose harvesting has been confirmed. If you have noticed any abnormality in your health condition due to a disease (e.g., taking medicine), or if you have been involved in an accident, please inform us as soon as possible.

Sports and Exercise: Please absolutely avoid any muscle training and other similar activities for the period of two weeks before the hospitalization. (This condition will also apply to the period approximately one week before the pre-operative health examination.)
Exercise may affect the blood test, causing abnormal values, and it will be difficult to determine that this abnormality is caused by exercise or the disease. If the patient has already begun pretreatment for the transplant, this will cause a state of emergency, so please take an extra caution. If, for any reason, you cannot avoid exercise or prolonged exertion, please consult the coordinating physician upon your pre-harvest health examination.

Blood Donation : Blood donation may affect the result of the blood test. Please refrain from donating your blood during the period from the start of coordination until six month prior to the harvest procedure.

Smoking : Please refrain from smoking, because it may cause the body to produce phlegm while you are under anesthesia, damage the respiratory function and/or affect the results of the blood test.

Drinking : Please refrain from excessive alcohol consumption, because it may affect the

liver function.

Pregnant : Please avoid becoming pregnant because, if you are pregnant, the harvest procedure cannot be performed in order to protect the health and safety of the donor and child. (We ask the donor to stop taking the birth-control pill four weeks prior to the harvest procedure. Please consult your physician if you are on the pill.)

Traveling Overseas: If you have any plan to travel overseas, please inform your coordinator or the donation coordination office regarding the dates and destination of travel. Furthermore, please refrain from traveling overseas approximately one month prior to the harvest procedure in order to avoid infections.

Vaccination : If you are planning to receive a vaccination, please inform your coordinator or the donation coordination office with the type and date of the vaccination you will have. Furthermore, if the donor has contracted influenza, the harvest procedure may have to be postponed or canceled just before the scheduled harvest procedure. If this is the case, the patient will be greatly affected. Thus the JMDP will bear half of the entire cost of a flu vaccination for the donor whose harvest procedure has been officially (or unofficially) scheduled for sometime during between December and March (*), if the donor voluntarily decides to receive such a vaccine. If you want to have this aid, please make a request to the donation coordination office or your coordinator. (*There is no time restriction for a novel influenza.)

Nail Art : Please refrain from applying nail art (such as nail polish or artificial nails) on the day of the harvest procedure, because your nail color may be examined during the procedure in order to confirm your health status.

4. At the harvesting facility the physician in charge of the harvest procedure and an anesthesia specialist (for bone marrow harvest) conduct donor's health examination. The health examination includes a medical interview, general blood test, urine test, chest x-ray, electrocardiogram and lung function test (for bone marrow harvest). For a female donor, pregnancy test is discussed and conducted with the donor's consent. If any abnormality is detected as a result of these tests, a close examination will be discussed with you.

5. If any abnormality is detected during the pre-harvest health examination, the harvest procedure may be canceled even after the final consent was given. The details of the cancellation will be informed to you in an appropriate communication method.

6. In the event the determination of the date for harvest/transplant would delay due to the situation of the patient's side, your coordinator will periodically update the situation with you. Moreover, even after the date has been chosen, the transplant may not be performed due to the change in the patient's disease condition. In order to perform a transplant at the patient's best condition, the procedure will be rescheduled. Unfortunately, it is not rare for the patient's disease to

advance, in which case the scheduled transplantation procedure will be canceled. However, even though the patient has no choice but to give up receiving a transplant, the donor's good will serves to emotionally support the patient, who must gain strength in order to fight the disease. (See Chapter 16.)

7. On the day of harvest (or before the harvest procedure), less than 20 ml of the blood may be collected separately from the bone marrow or PBSC for the purpose of testing. The blood sample will be used to confirm the engraftment of the bone marrow or PBSC in the patient after performing the transplantation procedure at the transplant facility. (The confirmation procedure includes genetic analysis.) Your consent will be confirmed on this procedure via the final consent.

Chapter 8
Bone Marrow Harvest

1. Once your health (as a donor) has been confirmed through the health examination, you and your family may be asked to sign the "Agreement Regarding Anesthesia and Bone Marrow Harvest." At this point the anesthesia specialist may provide you with an explanation.

2. Approximately one to three weeks prior to the bone marrow harvest, the donor's autologous blood collection will be conducted. The autologous blood with the amount required for the bone marrow harvest will be collected once or twice (200 ml to 400 ml each time). Upon each procedure, you may be prescribed a hematic drug (a ferric preparation).
   If the amount of bone marrow required is small, autologous blood collection will not be necessary.

3. Generally, for the bone marrow harvest you will be hospitalized one to two days before the harvest and discharged from the hospital two to three days after the harvest. For more specific information on the preparation for hospitalization, please inquire with your coordinator or the physician in charge of the harvesting facility.

I. How Is the Bone Marrow Harvest Performed?

1. At the Bone Marrow Donor Registry a bone marrow harvest is performed by strictly following the safety standards. For donor safety, the amount of the bone marrow aspirate harvested is limited within the safe range.

2. The bone marrow aspirate is harvested from the ilium (the pelvic bone), because it is more easily harvested. The bone marrow puncture needles (being similar in thickness to a ballpoint pen filler) are inserted through the skin of the donor in the area slightly below the waistline at the dorsal pelvis, and the bone marrow aspirate is harvested by suction using injectors. Some facilities may incise the donor's skin slightly to facilitate needle insertion.

3. Using the bone marrow puncture needles and injectors, several milliliters of the bone marrow aspirate are harvested at a time by suction. The number of puncture holes ranges one to three on each of the left and right sides of the dorsal pelvis, for a total of two to six. The same puncture holes on the pelvis are used multiple times, and the number of insertions that the pelvis would receive range from several tens to a hundred. However, those puncture holes on the bone will eventually close through the natural healing process.

4. The guideline for the amount of the bone marrow aspirate to be harvested from the donor is 15 ml per one kg of the patient's bodyweight. However, the harvesting amount will be determined

within the permissible range so that it will not cause a burden to the donor.
The harvesting of bone marrow will not cause the donor to lose the ability to produce blood. It is said that the number of bone marrow cells from the harvest site will quickly return to normal after the procedure.
In order to prevent the donor from suffering anemia, the donor's autologous blood is stored in the refrigerator beforehand and re-transfused to the donor on the day of the harvest procedure.

Π. Safety and Complications of Bone Marrow Harvest (Anesthesia)

1. Anesthesia
The bone marrow harvest procedure is performed at one of the facilities authorized by the JMDP, which have abundant experience in the harvesting of bone marrow.
Because the bone marrow aspirate is harvested by suction, inserting thick injection needles into the ilium (the pelvic bone) multiple times, it is necessary to anesthetize the donor prior to the procedure. In most cases the procedure is performed under general anesthesia. However, the specific method of anesthesia is determined by the anesthetist in charge.
If the emergency treatment must be performed on the donor while under anesthesia, the bone marrow harvest procedure will be halted immediately and the appropriate treatment will be undertaken.

2. Pretreatment for Anesthesia
Some facilities may give an enema to the donor or shave the donor's body hair before administering general anesthesia. They may also administer a preanesthetic medication to the donor by injection. Moreover, the intravenous injection route is secured for the administration of various drugs and blood transfusion.

3. Once a drug with which to introduce anesthesia into the body is given to the donor by injection and the donor becomes unconscious, a soft plastic tube is inserted into the trachea of the donor from the mouth to control breathing by sending anesthetic gas and oxygen through the tube using the ventilator into the lungs. Occasionally, a thin tube (balloon catheter) may be inserted into the donor's urethra to expel urine from the body (urethral catheterization). This procedure is performed in order to precisely observe the blood circulation and kidney function of the donor while under anesthesia by measuring the amount of urine. Furthermore, while the donor is under anesthesia, his/her conditions are closely and continuously monitored by the anesthesia specialist through the ECG monitor and the periodic blood pressure measurement.

4. The harvest procedure requires approximately two to four hours from the point the donor enters the operating room until he/she comes out of the room. Of those two to four hours, the donor is under anesthesia for approximately one to three hours.

5. In Japan, each year approximately 1200 bone marrow harvest procedures are performed between unrelated individuals. Regarding serious adverse events caused by bone marrow harvest and anesthesia, a total of four fatal cases have been reported around the world to date. Of the bone marrow harvest procedures (between unrelated individuals) arranged by the Bone Marrow Donor Registry of Japan, no fatal case has occurred.

● Fatal Event Related to Bone Marrow Donation (The original document has been partially revised for the correction of errors.)

	Country of Origin	Blood relative / Unrelated individual	Age / Sex	Time of Incidence	Cause of Death
1	Overseas	Blood relative	57 yrs. Male	During the procedure	Ventricular fibrillation during the harvest procedure (heart failure) (There had been abnormal ECG readings.)
2	Overseas	Blood relatives	Unknown Male	During the procedure	Difficulty in breathing due to the sensitivity reaction toward anesthesia (anaphylactic shock)
3	Japan	Blood relatives	35 yrs. Male	During the procedure	Respiratory arrest while under anesthesia (The respiratory arrest caused cranial neuropathy.)
4	Overseas	Unrelated individuals	35 yrs. Male	After the procedure	Pulmonary embolism (Lower extremity thrombosis occurred, causing pulmonary embolism.)

(Source: *Hematopoietic Cell Transplantation*, 1999, Second Edition, Chapter 40 "Bone Marrow and Peripheral Blood Stem Cell Donors")

A complication of general anesthesia is malignant hyperpyrexia. One incidence of this complication in the unrelated bone marrow donor (which was not arranged by the Bone Marrow Donor Registry) has been reported thus far. Fortunately, the donor was discharged three weeks later without any sequela (1996).

6. Complications Accompanying Bone Marrow Harvest and Anesthesia

Arrhythmia and decreased blood pressure have been reported as transient complications. Other than those, the suspected complications include anterior teeth trauma, breakage of the bone marrow puncture needle, laryngeal granuloma, urethral injury, thrombosis and pulmonary fat embolism.

Moreover, the following cases have been reported: a transient paralysis of the left half of the body after awakening from anesthesia; a hematoma occurred in the retroperitoneum and the left ilio-lumbar region after completing the harvest procedure; onset of hepatitis C to the donor after the harvest procedure. Additionally, there have been cases in which pain and numbness in the harvest site or the gluteal region (buttocks) lasted for a prolonged period of time.

For more detailed information, please refer to the "Supplementary Information" of this guide.

Furthermore, at the JMDP, we have established the Donor Safety Committee to examine measures to further improve donor safety by analyzing data in regard to the harvesting of bone marrow.

III. After Bone Marrow Harvesting

1. After awakening from anesthesia, you may experience micturition pain due to the removal of the urethral catheter; headache; sore throat due to the removal of the tracheal tube; nausea and a fever of 37□ to 38□. However, these symptoms will usually disappear in a day or two. The intensity of pain at the harvest site (pelvic region) varies depending on the individual. Although in most cases it lasts for one to seven days, it can occasionally last more than a month. In rare cases the skin of the regions where the bone marrow puncture needles were inserted may suppurate or bleed, but the physician in charge will treat them appropriately. Although needle marks may remain on the skin after the procedure, they will fade away over time.

2. In most cases the donor can be discharged two to three days after the bone marrow harvest procedure and return to work or school. However, please keep the wounds clean and avoid excessive exercise after the procedure for a period of approximately a week.
   If any abnormality is detected in your health condition, the physician in charge of the harvest procedure, with responsibility as your doctor, will conduct a medical examination. Please do not hesitate to receive a medical consultation and any required treatment.

3. The coordinator will follow up by telephone regarding your health condition even after the bone marrow harvest procedure.
   Two to three weeks after the procedure, the donor will receive the post-harvest health examination at the harvesting hospital. Moreover, after a certain period of time has passed the JMDP will send you a questionnaire, so please complete the form and mail it back to us. Your cooperation is greatly appreciated.

Chapter 9
PBSC Harvest

1. Granulocyte Colony-Stimulating Factor (G-CSF) Injection
   Once the donor's health has been confirmed through the health examination and the pretreatment has begun, G-CSF will be injected once or twice a day for a period of four to six consecutive days in order to harvest a sufficient amount of PBSC from the donor's peripheral blood. Two G-CSF products have been authorized in Japan: Gran and Neutrogin. A daily dose of Gran is 400 micrograms per 1 m^2 of the donor's body surface area, while that of Neutrogin is 10 micrograms per 1 kg of the donor's body weight.
   The question of whether the donor should receive the injection as an outpatient or inpatient (and, if so, the time zone for the injection) will be determined in consideration of the donor's schedule and the situation at the harvesting facility. If the individual is to receive the injection as an outpatient, the coordinator will follow up by phone regarding the donor's health condition after he/she goes home.

2. PBSC Harvest
   The number of days required for the G-CSF injection until the donor's hospitalization, as well as the number of days the donor has to stay in the hospital after the harvest, will be determined based on the donor's schedule and the situation at the harvesting facility.
   The PBSC harvest will be performed on the fourth or fifth day of G-CSF administration (the schedule will vary according to the facility).
   If an adequate amount of PBSC could be harvested at the first harvest (on the fourth or fifth day of G-CSF administration), the second harvest will not be required. If the amount of PBSC was insufficient at the first harvest, the second harvest will be performed on the next day after the re-injection of G-CSF.
   Once the donor's health condition is confirmed, he/she will be discharged.

I. How Is the PBSC Harvest Performed?

1. At the Bone Marrow Donor Registry, the PBSC harvest is performed through strict adherence to safety standards.

2. On the day of harvest, G-CSF is hypodermically injected into the donor. Approximately three to four hours after the injection, the PBSC harvest is performed.

3. The PBSC is harvested by continuously repeating the following procedure: Only the hematopoietic stem cells are extracted from the blood using a blood component separator and the

remaining blood is returned to another vein.
Before harvesting, the injection needle is inserted into the thickest possible vein of each arm (this could be only one arm) of the donor for collection and retransfusion. One of the PBSC donor requirements is that the donor must have somewhat thick blood vessels in the arms. However, in the event no ideal vessel can be found on the day of harvest, a soft tube called a catheter may be inserted into the vessel in the groin (this procedure is called femoral venous access).
The donor's consent for femoral venous access is also confirmed at the meeting for the final consent. If the donor's consent on this procedure is not thus confirmed, PBSC cannot be donated.

Femoral Venous Access

Femoral venous access is the procedure in which a soft tube (a catheter) is inserted into a vessel in the groin of the donor who is under topical anesthesia for the purpose of blood collection/retransfusion.

In some cases the donor's body hair may be shaved or the inserted catheter may be secured to the skin with a thread to prevent it from moving. In some facilities, however, the donor's skin may be incised slightly to facilitate the insertion of the catheter. Then, following the removal of the catheter, the donor will stay in the hospital on the day of the procedure to confirm hemostasis.

Although bleeding or infections are occasionally reported, an appropriate treatment will be swiftly undertaken when it occurs.

Upon the medical interview conducted during the confirmation test, the physician will confirm whether the donor has thick veins in the arms. On the day of harvest, femoral venous access will be performed only if no thick vein can be found in the donor who was deemed to have thick veins.

4. A period of approximately three to four hours is needed to complete the PBSC harvest procedure. The donor cannot move either arm during the procedure.

5. The guideline for the amount of blood circulated in the blood component separator (the amount of blood to be processed) is 200 ml/kg up to a maximum of 250 ml/kg. The amount of blood to be processed will be determined within the range that will not burden the donor.
Once the harvest procedure is complete, a blood test will be performed in order to confirm the blood-platelet count.

Π. Safety and Side Effects of PBSC Harvest

1. In Japan, the PBSC transplant between blood relatives began subsequent to the approval of the application of health insurance to this area in the year 2000. Each year, approximately 450 cases each of bone marrow and PBSC transplants are performed between blood relatives for the purpose of hematopoietic stem cell transplantation.
Please refer to "Supplementary Information" in this guide for more detailed information on the side effects of PBSC harvesting on blood-relative donors.

2. Side Effects of G-CSF

The side effects of G-CSF injection have been reported, as described below. However, most such side effects are temporal. In the event an increase in the white blood cells or decrease in the blood platelets exceeds the standards, or based on the intensity of the side effect(s), the G-CSF dosage may be decreased or its administration may be stopped.

If you are receiving the G-CSF injection as an outpatient, please bring your Donor Notebook each time you visit the hospital. If you experience any intense side effect(s), please inform the contacts listed in the Notebook. You will receive appropriate treatment if necessary (see Chapter 10).

1) Side Effects During or Immediately After the G-CSF Injection Period

○ Minor Side Effects

Lower back pain, chest pain, bone pain, backache, joint pain, muscle pain, pressure decrease, rash, red spots, nausea, vomiting, fever, headache, malaise, palpitation, liver dysfunction, increased uric acid level and renal dysfunction (increased serum creatinine level) have been reported. Moreover, the spleen may become temporarily enlarged. All these symptoms will disappear within a few days, once the G-CSF administration period has ended, but an analgesic drug may be prescribed for pain if necessary.

○ Serious Side Effects Deemed Related to G-CSF Injection

Shock (as attributable to allergic reaction to G-CSF), pneumonitis, angina-like attack and cerebrovascular disease have been reported. Moreover, although such occurrences are extremely rare, it was reported that the spleen swell significantly, whereupon it ruptured, and thus an operation was required. Furthermore, aggravation in inflammation such as acute iritis and gouty arthritis has been observed.

2) Long-Term Effects of G-CSF

G-CSF was approved in 1991. Since then, it has been commonly used as an effective drug to reduce the white blood cell count after anti-cancer treatment. G-CSF can be considered a highly safe drug. However, because the long-term (longer than several decades) safety of G-CSF toward healthy individuals has not yet been confirmed, scientific data is being gathered.

A fatal blood-relative PBSC harvest case was reported in Japan in 2003. In that case, the donor developed acute myeloid leukemia approximately a year after the harvest. The causal relationship of the death and G-CSF was investigated through the Blood-Relative PBSC Donor Follow-Up Project, which was initiated in 2000 by the Japan Society for Hematopoietic Stem Cell Transplantation (hereinafter referred to as the Society). Consequently, it has been determined that there was no difference in the incidence of hematological tumors such as leukemia between the PBSC transplant and bone marrow transplant. Furthermore, according to research comparing the overseas bone marrow/PBSC donors and the general population conducted by the European Blood and Marrow Transplant Group, there was no difference in the incidences between the two procedures. In the research conducted by the National Marrow Donor Program (NMDP), it has been reported that the concern that G-CSF may increase the risk of leukemia can be denied.

Furthermore, a health examination and questionnaire survey have been conducted on cooperative donors once a year for a period of five years under the Society's Blood-Relative PBSC Donor Follow-Up Project.

The research has revealed that some donors developed health issues during that five-year period,

even though they were healthy at the time of the harvest. However, it is unclear whether there is a direct causal relationship with the PBSC harvest.

3. Side Effects that May Occur During the PBSC Harvest Procedure

In some cases the donor may experience general malaise, numbness of the limbs and/or around the mouth, dizziness due to the vasovagal reflex (VVR), nausea, vomiting and pressure decrease. The numbness of the limbs and/or around the mouth is caused by the anticoagulant that prevents the blood circulating in the blood component separator from coagulating (hypocalcemia). In most cases this can be improved by administering a calcium preparation. Furthermore, because blood platelets are also collected during the PBSC harvest, if the number of blood platelets is lower than the standard level after the harvest, the platelet components will be separated from the harvested PBSCs and then retransfused into the donor via the intravenous injection.

In the past years an event of cardiac arrest, which occurred to the blood-relative PBSC donor during the harvest, was reported. It was the case of an advanced-age donor with a disease, who was on medication. It was determined that the incident may have been caused by a serious VVR. Fortunately, the donor recovered without any sequela.

The PBSC harvest is performed by a specialist, and top priority is placed on donor safety. During the process the donor's health is periodically checked through medical interviews and blood pressure measurements.

4. In overseas countries, eleven fatal events in blood-relative PBSC donors have been reported. These events occurred within 30 days after PBSC harvesting, and it has been concluded thus: "Although the correlation between the death and PBSC harvest is unclear, its presence cannot be denied completely."

It was pointed out that, in any case, there were certain risk factors such that the donor was old or he/she had an underlying disease (but no fatal case involving unrelated donors has been reported). In Japan, PBSC harvesting has been performed under the strict observation of the qualification standards and guidelines stipulated by the Japan Society for Hematopoietic Cell Transplantation based on the cases in overseas countries. Therefore, no fatal event or adverse event that left severe prognostic symptoms has ever occurred, either during the harvest procedure or 30 days after the harvest procedure.

● Fatal events occurred within 30 days after the harvest procedure, whereupon it was concluded: "Although the correlation between death and PBSC harvest is unclear, its presence cannot be denied completely."
(All cases occurred in overseas countries and involved blood-relative donors. No fatal event involving blood-relatives has ever been reported in Japan.)

	Country of Origin Year of Incident	Relative Unrelated	Age / Sex	Time of Incidence	Cause of Death
1	Overseas In or before 1997	relative	61 yrs Female	Four days after the procedure	Cardiac insufficiency (The donor had bronchial asthma, high blood pressure and coronary artery disease.)
2	Overseas In or before 1997	relatives	57 yrs Female	Within 24 hours after going back home	Apoplexy (past history unknown)
3	Overseas in 1996	relatives	64 yrs Male	After completion of G-CSF administration	Myocardial infarction (The donor had a coronary artery disease.)
4	Overseas In 1998	relatives	73 yrs Male	A few days after the procedure	Cerebrovascular disorder (The donor had a history of high blood pressure and angina pectoris.)
5	Overseas In or before 2000	relatives	67 yrs Male	Apprx. the sixth day of the G-CSF administration (harvested on the 4th and 5th day)	Subdural hematoma (The donor had a history of abdominal aortic aneurysm surgery and myocardial infarction.)
6	Overseas In 1999	relatives	47 yrs Male	On the fourth day of the G-CSF administration	Sickle-cell anemia crisis (The donor had a history of sickle cell anemia.)
7	Overseas In or before 2000	relatives	Unreported Male	Unreported	Cerebrovascular disorder (Past history unknown)
8	Overseas In or before 2001	relatives	50 yrs Female	Immediately after catheter removal	Air embolism(Technical error occurred during the harvest procedure in which a catheter was inserted into the internal jugular vein)
9	Overseas Unknown	relatives	43 yrs Male	Passed away in 15 days (date of death unknown)	Cardiac arrest (It is not known if there is any correlation between the harvest and high blood pressure and/or smoking.)
10	Overseas	relatives	52	Passed away in 17	Cardiac arrest (It is not known if

	Unknown		yrs Male	days(the date of the death is unknown)	there is any correlation between the harvest and smoking.)
11	Overseas Unknown	relatives	27 yrs Male	During the procedure	Cardiac arrest (Technical error during harvest)

III. After the PBSC Harvest

1. Although the skin color of the areas where the needles were inserted may become bluish, it will usually disappear in one to three weeks.

2. Please refrain from excessive exercise or heavy labor for the period of about a week after the harvest procedure. If any abnormality is detected in your health condition, the physician in charge of the harvest procedure, with responsibility as your doctor, will conduct a medical examination. Please do not hesitate to receive a medical consultation and any required treatment.

3. You will receive a post-harvest health examination one to four weeks after the PBSC harvest. Your coordinator will check your condition over the phone once a week for a period of four weeks after the harvest. Moreover, the JMDP will send you a questionnaire three months after the harvest, and then once a year for a period of five years, in order to confirm the long-term safety of G-CSF. Your cooperation is greatly appreciated.

Chapter 10
Donor Notebook

1. The Donor Notebook, which is jointly issued by the Japan Society for Hematopoietic Stem Cell Transplantation and the Japan Marrow Donor Program, will be handed out to blood-relative and unrelated bone marrow/PBSC donors whose harvests have been decided.
   In your copy of the Notebook, enter all the necessary information and bring it with you to the facility on the days of pre-harvest health examination and the harvest procedure.

2. The Donor Notebook contains precautions to be taken before the harvest and information regarding possible side effects. It also contains contact information in the event an emergency response is required for some reason before and after the harvest.

3. Please keep the Donor Notebook safe as proof that you are a bone marrow/PBSC donor, even after the coordination process is completed.
   Please present your Donor Notebook to the medical institution each time you visit for your medical consultation and health examination. If you encounter any health issue, of which correlation with the harvest cannot be denied, please report it to the Donation Coordination Office.

Chapter 11
Cryopreservation of Bone Marrow/PBSC

Generally, the Japanese bone marrow registry does not authorize the cryopreservation of bone marrow and PBSC for the purpose of transplantation. However, in a special situation, such that the patient's condition has suddenly changed immediately before the transplant, we may temporarily cryopreserve the bone marrow or PBSC harvested from the donor.

Although it is extremely rare, the harvested bone marrow or PBSC may not be used for transplantation due to the reason described above. If this is the case, the harvested bone marrow or PBSC will be discarded.

Furthermore, for the PBSC harvest, when the amount of hematopoietic stem cells harvested from the donor exceeds that required for a single therapeutic dose of the patient, and if the physician in charge of the patient has deemed it necessary to further treat the patient, the excess portion may be cryopreserved. However, in this case as well, it will be discarded as soon as the physician has decided not to use the excess portion, and it won't be used for any purpose other than treatment for the patient concerned.

Chapter 12
Donor Registration After Bone Marrow/PBSC Harvest

1. For both bone marrow/PBSC donations, the registration will go into “pending” status for a period of one year after the harvest. This means that a matching patient will not be searched, and thus you will not be asked to donate your bone marrow or PBSC again for a period of one year from the last harvest.

2. One year after the last harvest, you will receive a letter from us to confirm your donor registration for the future. Upon receipt of the letter, please let us know if you will continue, hold or cancel your donor registration. This letter is not to ask you about your preference between the bone marrow or PBSC harvest procedure.
   However, if you want to continue your registration but are only able to donate through one of the two procedures due to a health-related reason, you may be registered as a “donor who can donate only the bone marrow or PBSCs.”
   Please note that if you have already received notification of the termination of your donor registration (due to the age limitation) from the Data Center, you will not receive the above letter.

3. The registration of a donor who has donated the bone marrow and/or PBSCs between the blood relatives and unrelated individuals more than twice in the past will be placed in pending status until the number of future donations is determined.
   The bone marrow donation can be made a maximum of two times. For PBSC donation, the number of donations from a single donor is limited to one because scientific data pertaining to the long-term effect of G-CSF injection on the donor is insufficient and is still being collected. (Even though the PBSC harvest is canceled in the middle of the donation process, if G-CSF injection has already begun it is determined that the donor has made one PBSC donation.)

Chapter 13
To Protect Donor and Patient Privacy

1. In order to protect donor and patient privacy and maintain the fairness of the Bone Marrow Donor Registry project, we will not give away private information (such as a name and address) either to you (as the donor) or to your matching patient. Moreover, as a general rule, we will not inform you of the patient's progress after the transplant. However, if you make a request after giving the final consent, your coordinator will inform you of the patient's sex, approximate age and the district of his/her residence. The donor's information, such as sex, approximate age and the district of his/her residence will be given to the patient by the patient's physician.

2. A donor cannot set any conditions on the patient to whom he/she is donating.

3. Except when you provide the facts pertaining to your bone marrow or PBSC donation to the people around you (e.g., your family and/or people in your workplace), when you use the Internet or contribute your story about donation experience in the online newsletter of the publication to which you subscribe, please do not disclose any information which may identify yourself or your matching patient such as the date and location of the bone marrow or PBSC donation. If you are going to be interviewed by the press, please consult our Donation Coordination Office in advance.

4. You may exchange letters with your matching patient through the Donation Coordination Office or coordinator after the harvest procedure. The maximum frequency of such exchanges is twice for each individual, and the exchanges must take place within the period of a year, counting from the date of harvest.
   In those letters, please do not include any personal information that may reveal your identity, such as your name, address and date of birth.
   We cannot pass your money and/or gifts to your matching patient. Please be advised that the contents of your letters will be inspected by the JMDP, and thus they may or may not be delivered to the patient, and that you may not always receive a reply from the patient (the same can apply to overseas cases).

Chapter 14
The Donor Has No Burden of Expense

1. Medical expenses for the bone marrow/PBSC harvest are covered by the patient's health insurance. Thus there is no burden of expense on the donor.

2. The travel expense for each meeting will be reimbursed later. Moreover, all the travel expenses for visiting the harvesting facility for health examinations, autologous blood collection, G-CSF injection, as well as hospitalization and hospital discharge, will be reimbursed through the method specified by the donor. In principle, please use public transportation such as trains and buses.

3. Upon hospitalization at the harvest facility, 5,000 yen will be given to the donor as a preparation allowance. Please understand that this allowance is for the rental of a hospital gown and the purchase of a towel, toothbrush, TV card and other items.

4. Even though you (as the donor) must take a break from work in order to visit, or become hospitalized at, the harvest facility, you will not receive any compensation for your absence from work nor an allowance for daycare services for your child(ren) while you are in the hospital.

Chapter 15
The Bone Marrow Donor Registry's Group Accident Insurance for Donor Compensation

If an adverse event befalls the bone marrow/PBSC donor during the donation process, the insurance will be paid to the donor and/or the donor's family up to 100 million yen by the JMDP through the accident insurance plan in which the JMDP participates. The insurance will be applied as soon as the consent has been signed by the donor for the confirmation test. The donor pays no premium.

Outline of the Bone Marrow Donor Registry's Group Accident Insurance for Donor Compensation

1. The insurance is to comprehensively compensate bone marrow/PBSC donor during the entire donation process from the point he/she leaves his/her home to the point the donor returns home.

2. This insurance will also be applied to any adverse event the donor has encountered on the way to/from the hospital.
   (For the bone marrow harvest, the insurance will only cover adverse events that have occurred up to seven days after the date on which the donor left his/her home. For the PBSC harvest, the insurance will only cover adverse events that have occurred up to eight days after the day on which the donor left his/her home.)

3. The insurance will be paid to the donor or the donor's family for any adverse event that occurs due to the bone marrow blood or PBSC harvest, as well as medical treatment related to such procedure(s).

4. Medical treatment related to the harvesting of bone marrow blood/PBSC includes:
   (1) The confirmation test for the evaluation of the donor's eligibility which will be conducted after the donor has given his/her consent to the bone marrow/PBSC donation (i.e. after signing the Confirmation Test Agreement), the pre-harvest health examination conducted in preparation for the bone marrow/PBSC harvest, autologous blood collection and G-CSF injection (in the case of PBSC donation);
   (2) Post-harvest health examinations conducted to monitor the donor's health condition after the bone marrow/PBSC harvest. However, the insurance will only cover adverse events that have occurred during the medical examinations received within three months, counting from the day after the bone marrow/PBSC harvest procedure.

   (3) Medical treatment (DLI: donor lymphocyte infusion) such as blood collection to

treat the bone marrow/PBSC transplant recipient (patients) who has not fully recovered after the transplant. However, the insurance will only cover an adverse event that occurred during the treatment that was performed within two years, counting from the day after the bone marrow/PBSC harvest. (* Additionally, for adverse events that have occurred sometime after those two years, the application procedure will be undertaken for each individual case, subsequent to investigation.)

<Compensations>

Death benefit……...100 million yen
Physical impediment benefit……3% - 100% of the above amount
Hospitalization benefit (up to 180 days)……10,000 yen per day
Hospital-visit benefit (up to 90 days before the 180th day)…….5,000 yen per day

[When Insurance Will Be Paid]

(i) The insurance will be paid when the donor has become injured due to an adverse event during the period described in the following section. (This insurance includes injuries due to the bone marrow/PBSC harvest procedure and medical treatment related to such procedures.)

(ii) The above-described period refers to the point where the donor leaves home until either of the points listed below, whichever comes first:
  (a) When the donor arrives home; or
  (b) At 12 noon on the 7th day reckoning from the next day of the date on which the donor left home (for bone marrow donors); or
  At 12 noon on the 8th day reckoning from the next day of the date on which the donor left home (for PBSC donors).

[Amount of Insurance to Be Paid]

(i) Death Benefit: If the donor passes away due to the injury within 180 days from the incident, the full amount of death/physical impediment insurance will be paid to the donor's family.

(ii) Physical impediment benefit: When physical impediment has occurred to the donor within 180 days from the incident, 3% - 100% of the amount of death/physical impediment insurance will be paid to the donor/donor's family according to the intensity of the physical impediment.

(iii) Hospitalization insurance benefit: When the donor has become unable to return to his/her normal work and/or maintain his/her normal lifestyle, and in addition to this condition he/she has been hospitalized (including near-hospitalization), the daily benefit of the hospitalization insurance will be paid for the number of days of hospitalization (up to 180 days from the incident).

For any injury caused by the PBSC harvest (*1), compensation will be paid only for the case in which the donor has been hospitalized for a period of four or more days.

(iv) Hospital-visit insurance benefit: When the donor has difficulty fulfilling his/her normal work duties and/or maintaining his/her normal lifestyle, and in addition to such conditions, when he/she had to visit the hospital on a regular basis for a while

(including home visits by the doctor), the insurance benefit will be paid to the donor for the number of such visits (i.e. days) (up to 90 days). However, this is limited to the period of 180 days, counting from the date of the incident.

For any injury caused by the PBSC harvest procedure (*2), the compensation will be paid only for the case in which the donor has been hospitalized for a period of four or more days.

Because injuries of (*1) and (*2) are often transient symptoms such as headache, nausea and fever, the insurance will be paid only when hospitalization or hospital visits are required even after four days have passed since the physician initiated the treatment.

[Major Cases When Insurance Cannot Be Paid]
For example, the insurance will not be paid for an injury that occurs due to the following reasons:

○ Self-inflicted
○ Suicide, physical fights, criminal acts
○ Driving without a license, driving under the influence of alcohol
○ Earthquakes, volcanic eruptions, tsunami
○ War and other disturbances, nuclear reaction
○ Brain diseases, diseases and insanity not caused by the bone marrow/PBSC harvest, as well as medical treatment related to such procedures
○ Surgery and other medical treatment not caused by the bone marrow/PBSC harvest, as well as medical treatment related to such procedures

Insurance will be paid for the following injuries:
○ Cervical compression syndrome (i.e. whiplash), only when subjective symptoms are present
○ Lower back pain, only when subjective symptoms are present

(Partially cited from the clause containing special policy conditions)
The group accident insurance for bone marrow donors was revised in November 1999 and implemented in December 1999.
The group accident insurance for PBSC donors was implemented in October 2010.

Chapter 16
Termination and Pending of Coordination

1. The JMDP has set forth several donor requirements (see Chapter 4). If it is then deemed that the donor does not meet the requirements, the coordination will be terminated. Additionally, if the donor requests the termination of the coordination, it will be terminated.
   The reason(s) for such termination will not be indicated to the patient.

Primary Reasons for Termination of Coordination Given by Donors

- **Due to the donor's schedule**
- **When the consent of the donor's family cannot be obtained**
- **When it has been determined that the donor has a health issue(s)**

2. Once the donor chooses to continue the donor registry membership after the coordination has been terminated, a new search for a match will begin.
   Because a match(es) may be found immediately after the renewal of the membership, registration for the donor who cannot undergo the new coordination process may be canceled or the coordination will be placed in the pending status for a certain period of time.

3. In some cases the coordination may be terminated due to the patient's situation. Although there are various reasons for termination, in no individual case can the reason(s) for the termination be revealed to the donor.

Primary Reasons for Termination of Coordination Given by the Patient Side

- **HLA (DNA) mismatch**
- **Another donor has been chosen**
- **Change in the treatment policy due to the change(s) in the patient's disease condition**

4. Occasionally, a new coordination process may begin immediately after the current coordination has been terminated. If this is the case, please be advised that you will need to have another confirmation test (or a general blood test only) even though you had it during the previous coordination process. However, if the new coordination process has begun within a year from the date of the previous confirmation test or that of the pre-harvest health examination, this process may be omitted.

5. The coordination may be halted for a while due to the instruction given by the patient side. This is not a termination of the coordination but is the pending status. If this is the case, the donor will be notified. Because you will have to wait until the coordination resumes, please let us know if you have any situation that doesn't allow you to do so.

6. There are various reasons that the coordination must be placed in the pending status due to the patient's situation, such as when it is necessary to determine whether the transplant

should be continued when the patient's disease condition has changed or the patient's condition is unstable and other treatment must be performed before the transplantation. However, the specific reasons behind the pending status will not be revealed to the donor.

7. As soon as the patient returns to the state in which he/she can resume the coordination process, the donor will be informed. If there is no prospect that the patient's condition will improve to the point where he/she can resume the coordination process, the coordination will be terminated.

DLI (Donor Lymphocyte Infusion)

DLI is a method of treatment in which the bone marrow/PBSC donor's lymphocytes are transfused into the patient body. It is an abbreviation for donor lymphocyte infusion.

It has been discovered that, of the complications occur in patients after the transplant, DLI is particularly effective on recurrent leukemia and the B-lymphocyte proliferative disorders caused by EBV (Epstein-Barr virus).

In the event DLI is required for the patient who has received a bone marrow/PBSC transplant through the Bone Marrow Donor Registry, the JMDP may ask the donor to donate his/her lymphocytes after examining the patient's symptoms. If this is the case, the JMDP will confirm the donor's will separately from the consent pertaining to the bone marrow/PBSC donation. If you (as the donor) have decided not to donate, please inform us of your decision. The lymphocytes will be collected using the same procedure as that used for a whole-blood donation or a component donation.

* The same principle will be applied to overseas cases.

Disclosure of Donor's Genetic Information When It Has Been Discovered Through Bone Marrow/PBSC Donation

When the patient who has received the bone marrow/PBSC transplant undergoes bone marrow testing such as the engraftment confirmation test, an abnormality may be discovered in the genetic information of the transplanted cells by chance. Moreover, when the disease has recurred to the patient immediately after the bone marrow/PBSC transplant, it may reveal that the pathological cells are derived from the donor cells.

Not all genetic information will be investigated in the bone-marrow engraftment confirmation test. Furthermore, although it is extremely rare that such information surfaces, once it happens the donor will be informed of the fact according to his/her will to receive such information, because it may affect the donor's health.

The donor's will to receive such information will be confirmed in writing during the meeting for the final consent. (It is acceptable to reply at a later date.)

* When any necessity to contact the donor regarding the above matter arises after the bone marrow/PBSC donation, the donor's personal information (such as his/her address) may be provided to the JMDP by the Data Center.

Specimen Preservation

Medical research must be conducted in order to improve the transplantation results for patients as well as donor safety. The blood specimen (approximately 15 ml) will be collected from each donor who is willing to cooperate with the specimen preservation project for the purpose of research. If the donor is willing to participate, the specimen preservation project will be explained to the donor separately from that of the bone marrow/PBSC donation. Consequently, his/her consent will be confirmed, whereupon the blood will be collected at the harvesting facility sometime during the period from the pre-harvest health examination to the hospital discharge.

Furthermore, the specimen will be stored in the facility designated by the JMDP after the personal information, such as the name and address, is removed.