

Donor

Handbook



Japan Marrow Donor Program



Public Interest Incorporated Foundation Japan Marrow Donor Program

Introduction

This time, you have been chosen
as potential marrow or apheresis donor for a patient.

However, potential marrow or
apheresis donor do not have to donate
bone marrow or peripheral blood stem cells
against their wishes.

This handbook will provide you with
all the necessary information about donation.

Above all, your health and safety is
the topmost priority of the
Japan Marrow Donor Program.

Handling of Personal Information

The Japan Marrow Donor Program (a public interest incorporated foundation; the “JMDP”) recognizes the protection of information on individuals (“personal information”) as an important responsibility. We have established a privacy policy, thoroughly notified all staff and stakeholders of this, and will strive to protect your personal information.

Any personal information (name, address, past medical history etc.) provided by the donor to the JMDP, as well as results of the tests carried out during the coordination process, will be strictly managed in compliance with the “Act on the Protection of Personal Information”.

The potential marrow or apheresis donor’s personal information is used between the JMDP and personnel deemed necessary by the JMDP in coordinating the process between the patient and the donor, namely, the coordinator, physician for confirmatory typing (CT), Collection Center (CC) / Apheresis Center (AC), and Transplant Center (TC).

In addition, this information (without your personal information such as name and address etc.) will be used by institutions, or designated data management institutions and authorized personnel approved by the JMDP, as well as approved researchers, to create statistical data and for research purposes.

Please visit the following website for more details on our privacy policy.

- You “do not agree” to your data being used beyond the coordination process for research to improve the transplant performance or the safety of donors (while your data will be automatically included in the epidemiology study, it will not be used for research if you indicate otherwise).
- You informed us, or have any questions about the correction or changes in your personal information during the coordination process (we will provide the updated information to the Japanese Red Cross Society if you inform us of any changes to the registered information such as name and address).

Please visit the following website for more details on our privacy policy.
<http://www.jmdp.or.jp/policy.html>

About this Handbook

In this handbook,
the person donating bone marrow or
peripheral blood stem cells is the “potential donor”,
and the person undergoing transplantation is the “patient”.

Also, once you become a potential donor,
the entire process of provision of bone marrow or
peripheral blood stem cells,
right up to the coordination of the completion
of the follow-up is the “coordination process”.

This handbook describes the flow of the coordination
process and information that you would need to
understand in becoming a potential donor.

The flow of the coordination process is
summarized on pages 6 to 9.
We would like you to have a rough understanding
of the information here,
carefully read the detailed explanation
under the table of contents,
and consider whether you would like to request
for coordination help.

* Please bring this handbook with you during confirmatory typing (CT)
and for the Donor Information Session for your final consent.

Flow from becoming a potential donor to donating bone marrow or peripheral blood stem cells

1 Notification as a potential donor.

Chapter 1. I. What is the JMDP? (page 12)

We will notify you when your HLA (a type of white blood cell) matches with that of the patient.

Please answer the questionnaire about whether you are interested to donate and your family's wishes, schedule, and health condition.

At the JMDP, donors are not allowed to choose patients or set terms to be fair to everyone.



2 Confirmatory typing (CT)

Chapter 2. I. Confirmatory typing (CT) Stage (page 20)

On the day of confirmatory typing (CT), please present a document confirming your intention to donate.

The coordinator would explain to you in detail during the meeting about the confirmatory typing (CT) stage, and the physician will provide the medical explanation and interview you.

If you still wish to donate, we will collect blood from you to verify your health condition etc.



3 Final consent

Chapter 2. II Final consent (page 24)

Once you are selected as a donor, the coordinator and coordinating physician will confirm with you and your family's final intention to donate in the presence of a witness.

You will not be able to withdraw your offer to donate after you have given your final consent.

If the donor withdraws his/her offer to donate due to strong opposition from the family, the patient may not be able to receive the appropriate treatment. Your family's consent is therefore necessary so that such situations will not happen.



4 Medical examination

Chapter 2. III Once harvest is decided (page 26)

About one month before you donate bone marrow or peripheral blood stem cells, you will undergo a detailed medical examination conducted by a physician at the CC/AC (a JMDP-accredited hospital) to prepare for a safe harvest.



If you are donating bone marrow

Chapter 3. A. Bone marrow harvest (page 31)

5 Collecting blood for autologous blood transfusion

To reduce the possibility of anemia after the harvest, we will collect your blood in advance (1 to 3 weeks before day of harvest) when necessary.



6 Bone marrow harvest

You will be usually hospitalized for about 4 days 3 nights.

You will be hospitalized 1 to 2 days before the day of harvest, undergo health checks, and physicians will explain the process to you.



If you are donating peripheral blood stem cells

Chapter 3. B. Peripheral blood stem cells harvest (page 36)

5 Injecting a drug (G-CSF) to increase your white blood cell count

When you are injected with G-CSF over a period of 3 to 4 days (hospital visit or hospitalization), hematopoietic stem cells will be stimulated into the peripheral blood.



6 Peripheral blood stem cells harvest

The peripheral blood stem cells will be harvested on either day 4 or day 5 after G-CSF injection.

If not enough cells are harvested, we will repeat the procedure again on the following day.

If you receive the injection during your hospitalization, you will be hospitalized for about 5 days 4 nights to 7 days 6 nights. If you receive the injection during your hospital visits over a period of 2 to 4 days, you will be hospitalized for about 2 days 1 night to 4 days 3 nights.



7 Bone marrow/peripheral blood stem cells to patients

Chapter 1. II What is hematopoietic stem cell transplantation? (page 14)

The harvested bone marrow/peripheral blood stem cells are transported to the patient's hospital for transplantation.

The harvested bone marrow/peripheral blood stem cells are transported to the patient's hospital, transplant center (TC).



8 Hospital discharge within a few days after harvest

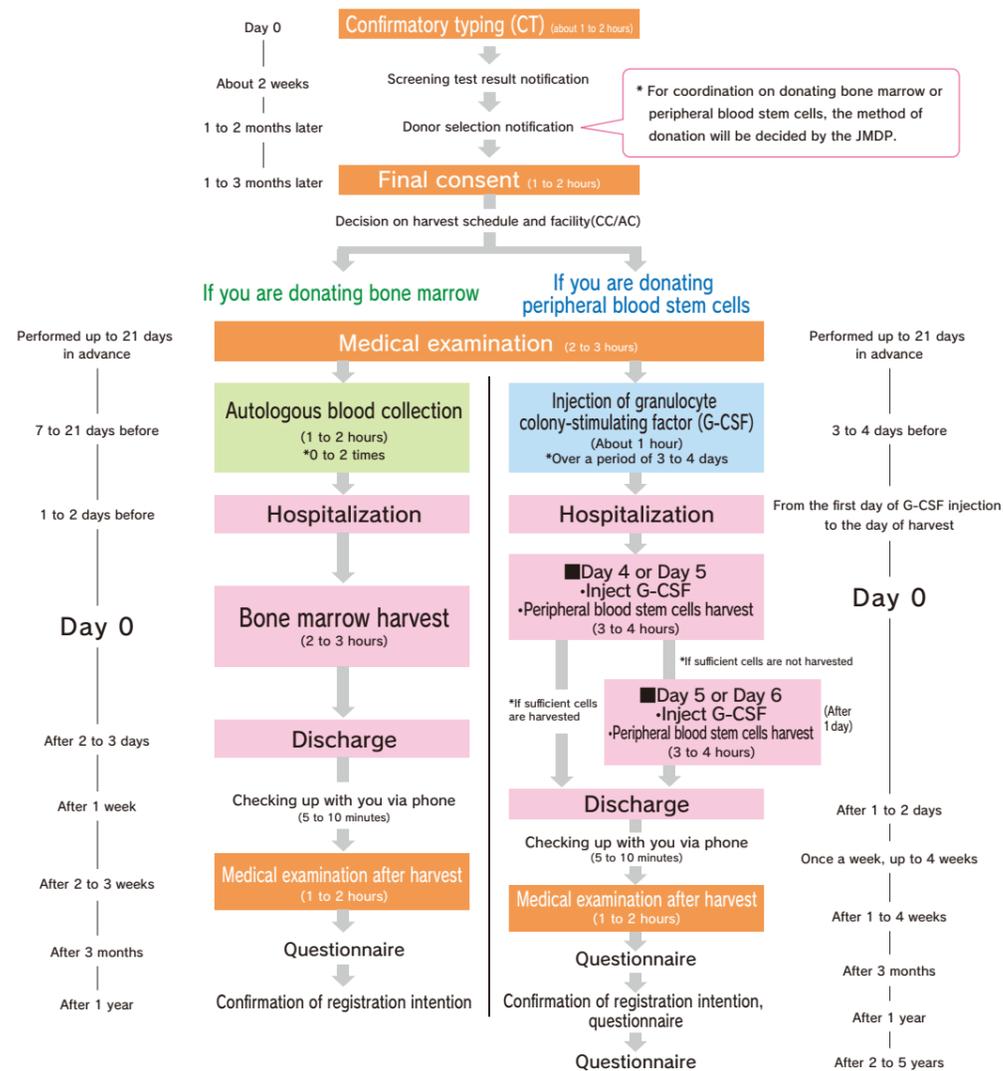
*Depends on method of harvest.

You will be discharged from the hospital a few days after the harvest. The coordinator will regularly check with you on your health condition via phone, and you will be asked to go for a medical examination 1 to 4 weeks after the harvest. The coordinator will follow-up with you until you make a full recovery.



- Medical expenses for the harvest of bone marrow/peripheral blood stem cells will be fully paid by the patient's health insurance. (See Chapter 5, I. Cost Burden of Donors on page 51)
- While we have prioritized the safety of donors, there have been unfortunate instances where some donors have suffered health injuries. In such cases, we will make insurance payout from an accident insurance which the JMDP has enrolled donors in. (See Chapter 5, II. JMDP Group Accident Insurance for Donor Compensation on page 52)
- We may not make the insurance payout depending on circumstances such as the donor's health condition or the patient's situation. (See Chapter 2, IV. Termination and Temporary Suspension of Coordination Process on page 29)

Schedule after confirmatory typing (CT) Stage



Please see the schedule and required time as a rough guideline as it will differ for different people.

Q How often and when do I have to go to the medical institution ?

A About 8 times. Please visit a medical institution during the day on weekdays.

Q Can I visit go at a specific date/time or at my own convenience?

A We will take into account the donor's convenience and adjust the schedule, but there are times when we are unable to do so. If you are not able to visit the medical institution during a certain period, please fill out the reply form and inform to the coordinator/JMDP Donor Center.

Q About when do I have to be hospitalized (harvest)?

A It will take about 2 to 4 months, from the confirmatory typing (CT) to the harvest procedure. We will inform you of the patient's desired transplant timing if it is known at the beginning of the coordination process, but we may inform you again when you are selected as the final donor as the transplant date may change due to the patient's treatment progress etc.

Please let us know as soon as possible if you have any health issues or if the schedule is inconvenient for you.

JMDP's Coordination Process

The JMDP coordinates bone marrow transplantation and peripheral blood stem cells transplantation.

The transplantation method to the patients is the same, but the method of donation is different.

We will guide you on the process depending on the needs of the patient or the situation of the potential donor. Please refer to the "Notice of Coordination Process (Compatibility notice)" that we are sending with this booklet.

① Information on coordination process for bone marrow donation

② Information on coordination process for peripheral blood stem cells donation

③ Information on coordination process for bone marrow or peripheral blood stem cells donation

(We will check with the intentions of the potential donor and the patient, and decide on one donation method when the final a potential donor is selected)

Since the medical treatment on donors is different for ① and ②, please read the respective sections in Chapter 3 and Chapter 6.

As the potential donor may be asked to donate either bone marrow or peripheral blood stem cells for ③, please kindly read both chapters.



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I. What is the JMDP?

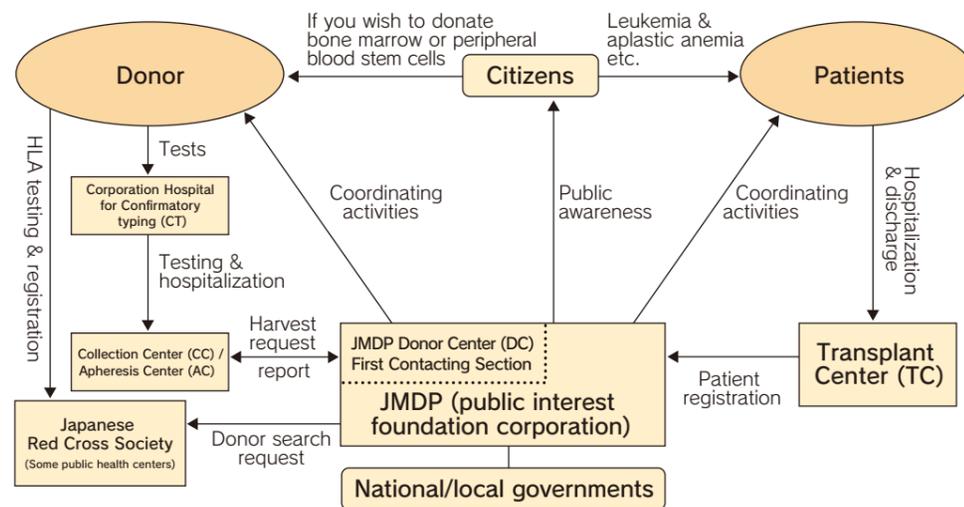


- ◎ The JMDP is a public enterprise that acts as an intermediary between bone marrow transplantation and peripheral blood stem cells transplantation between unrelated individuals.
- ◎ Once the coordination process begins, JMDP Donor Center(DC) of the residential area of the donor will take charge, and the coordinator and physician for confirmatory typing (CT) will be decided for each donor.

1 How the coordination process works

Once you are selected as a donor candidate (“donor”), the initial coordinator in-charge will send you a “Notice of Coordination Process (Compatibility notice)” and a reply form. Once we receive your reply form, the coordination process conducted by DC (7 districts nationwide) will begin. The coordinators and coordinating physicians belong to DC, and the coordinator and physician for CT responsible for the donor is then decided.

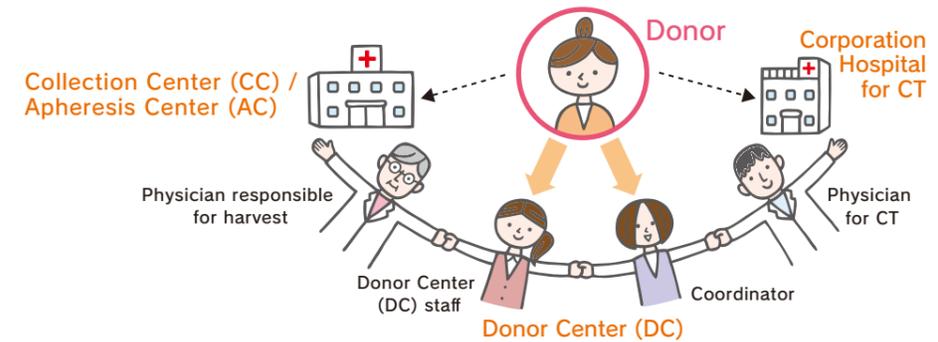
System diagram of the coordination process



2 Roles of coordinator and the physician for CT

The coordinator coordinates with the donors, physicians for CT, CC/AC, and the DC. They will also accompany you for the preparation and explanation of the confirmatory typing (CT) and final consent interview, medical examination at CC/AC, and during your hospitalization and discharge.

The physician for CT is responsible for medical explanation and answering the donor's questions, determining the eligibility of donors and blood collection.



3 Contact method

Please contact DC by phone (weekdays daytime) or fax. The coordinator will contact the donor via a dedicated line for coordination purposes.

Please contact the DC or the coordinator if you have any questions or requests.
Please let us know as soon as possible if you have any health issues or if the schedule is inconvenient for you. Please also let us know if you become a lay judge candidate.

II. What is hematopoietic stem cell transplantation?



© **Hematopoietic stem cell transplantation is a treatment that replaces diseased hematopoietic stem cells (cells that give rise to all blood cells) with healthy ones.**

1 What are hematopoietic stem cells?

Hematopoietic stem cells are cells that give rise to white blood cells, red blood cells, and platelets, and exist in the spongy hematopoietic tissue in the center of the bone called bone marrow. The bone marrow is filled with bone marrow fluid, where red blood cells, white blood cells, and platelets are constantly generated. On the other hand, hematopoietic stem cells are usually absent in the peripheral blood (blood flowing throughout the body), but when you inject a drug called G-CSF (granulocyte colony-stimulating factor) that increases white blood cells, hematopoietic stem cells will also increase in the peripheral blood; we call this peripheral blood stem cells.

Hematopoietic stem cells are also found in the blood of the umbilical cord and placenta.

Blood cells	Roles	When there is a shortage or abnormality
Red blood cells	Carry oxygen throughout the body	Anemia happens
White blood cells	Protect the body from pathogens	More susceptible to infectious diseases
Platelet	Stop bleeding	More susceptible to hemorrhage

(Blood cell function)

2 What is hematopoietic stem cell transplantation?

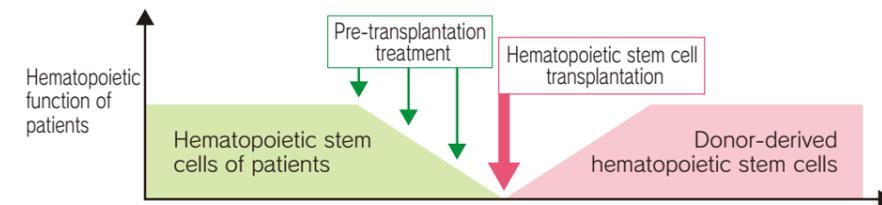
When you are afflicted with blood diseases, your body cannot produce/make blood cells normally, leading to illnesses such as anemia and a comprised immune system. Hematopoietic stem cell transplantation is a treatment method that replaces diseased hematopoietic stem cells with those of healthy people (donors).

Transplantation of cells harvested from the bone marrow is called bone marrow transplantation, while the transplantation of cells harvested from peripheral blood is called peripheral blood stem cell transplantation, and those using cord blood are called cord blood transplantation. At the JMHP, we coordinate bone marrow transplantation and peripheral blood stem cell transplantation between unrelated individuals.

Over 300,000 cases of bone marrow transplantation and peripheral blood stem cell transplantation have already been performed worldwide.

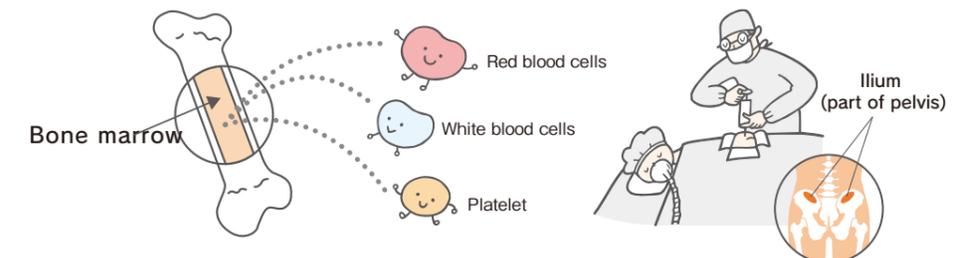
3 Hematopoietic stem cell transplantation method

For patients, it takes 1 to 2 weeks before the transplant procedure to administer large amounts of cancer drugs or radiation to the whole body. This is called **pre-transplantation treatment**, and will destroy normal hematopoietic stem cells as well as diseased cells. As the white blood cell count will also decrease significantly, the immune system in patients is lowered and they become susceptible to infections. For this reason, the patient stays in a dust- and bacteria-free **aseptic room** with clean air exchange during the pre-transplantation treatment process and after transplantation until the patient's body start to produce a stable supply of normal blood cells. On the day of transplantation, hematopoietic stem cells provided by donors that are harvested by bone marrow harvest or peripheral blood stem cell harvest, will be injected into the patient's vein.



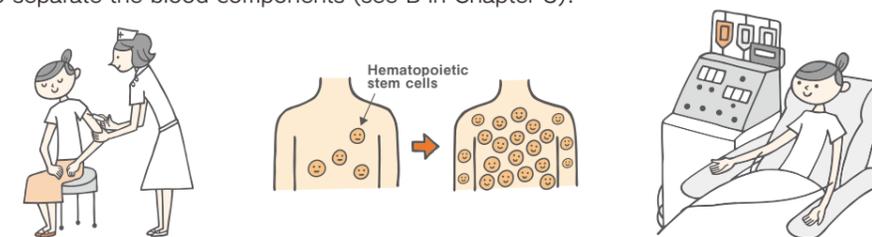
■ Bone marrow harvest method

The donor will undergo general anesthesia. A needle will be inserted into the ilium (part of pelvis), and the bone marrow fluid is aspirated with a syringe (see A in Chapter 3). Also, The bone marrow is the different from the spinal cord of nerve tissue.



■ Peripheral blood stem cells harvest method

The donor is injected with G-CSF for 3 to 4 days before harvest. When the number of hematopoietic stem cells in the peripheral blood has increased, a device will be used to separate the blood components (see B in Chapter 3).



4 When to transplant and the patient's course after transplantation

The timing of the transplantation to a patient is important and can be decided by observing the course of the disease condition. Also, it is necessary to book the limited aseptic rooms and adjust the schedule of the staff at the transplant center (TC).

Even after the patient undergoes transplantation, he/she may still pass away early due to rejection, GVHD (graft versus host disease), and severe infections etc. Even after the donor's hematopoietic stem cells have engrafted and the patient recovered from the transplantation, the original disease that the patient is afflicted with (such as leukemia) may also recur. The disease of all patients is not cured by hematopoietic stem cells transplant.

The coordination process may be terminated or temporarily suspended due to the patient's condition such as a change in the disease condition.
(See Chapter 2, IV. Termination and Temporary Suspension of Coordination Process)

Glossary

Engraftment : When the transplanted hematopoietic stem cells of the donor starts to make blood cells in the patient's bone marrow.

Rejection : When the patient's body eliminates the transplanted hematopoietic stem cells of the donor and left with only the patient's white blood cells.

GVHD (graft versus host disease) : A reaction when the white blood cells in the transplanted hematopoietic stem cells of the donor regard the tissues of the patient's body as "stranger = foreign bodies" and attack the patient's cells.



Q What are the diseases that require hematopoietic stem cell transplantation?

A The main diseases include leukemia, myelodysplastic syndrome, malignant lymphoma, severe aplastic anemia, immunodeficiency, and some congenital metabolic disorders.
Depending on the disease, patients may be cured with chemotherapy and immunosuppressant drugs. But there are many patients who can only be cured with hematopoietic stem cell transplantation.

Bone Marrow Transplantation is also known as "BMT".

Peripheral Blood Stem Cell Transplantation is also known as "PBSCT".

While this is extremely rare, it is possible to transplant the hematopoietic stem cells donated by the donor to two siblings afflicted with the same disease when physicians deem that it is necessary to transplant at the same time, and certain conditions are met.

III. Conditions to become a donor



- ◎ To improve the safety of donors and patients, we have set several conditions for donors.
- ◎ Donors will need to be healthy, indicate their intention to donate, and obtain the consent of their family members.
- ◎ A donor candidate is selected when his/her "HLA" matches with that of the patient.

1 Conditions to become a donor ①

1) You must be of age 18 to 54 when you register with us (Donor shall be between the age of 20 and 54)

Even when you receive a notification from the Japanese Red Cross Society informing you that your registration has been terminated when you reach the age of 55, your registration with us will still continue if you are in the midst of the coordination process until the harvest procedure is completed.

2) Be in good health

- Those who are not taking medication or undergoing treatment for illness.
- Those who do not have medical history such as malignant tumors (cancer), collagen diseases (such as rheumatoid arthritis), myocardial infarction, angina pectoris, stroke, asthma (within 1 year of onset or medication), convulsive disorders (such as epilepsy).
- Those whose maximum blood pressure (systolic pressure) is between 90 mmHg and 150 mmHg, and minimum blood pressure (diastolic pressure) is 100 mmHg and less.
- Those who have not received blood transfusion in the past.
- Those who will not transfer viral hepatitis, syphilis and other diseases to the patients.
- Those who do not have blood diseases and anemia (those who have already covered using hematopoietic drugs are allowed. Those who are currently on hematopoietic drugs are not allowed).
- * Please do not donate blood until the coordination process is over.
- Those who are not excessively obese; 45 kg and above for males, and 40 kg and above for females (people with BMI under 30 = weight (kg) ÷ (height (m) × height (m))

* Other medical history and health condition are respectively determined through interviews or medical examinations. Some conditions will differ between bone marrow donors and peripheral blood stem cells donors.

If the donor's health condition needs to be checked, you may be asked to undergo medical examinations and tests.
Please know that the donor will have to bear all costs.

3) Those who have a sufficient understanding of what is involved in the donation of bone marrow and peripheral blood stem cells.

4) Those who have obtained the consent of their family members (spouse, parents etc.) about donating bone marrow and peripheral blood stem cells.

5) Those who are not pregnant.

We will terminate the coordination process if we find that the donor does not meet the conditions or if the donor requests to withdraw. (See Chapter 2, IV. Termination and Temporary Suspension of Coordination Process)

2 Conditions to become a donor ② (HLA compatibility)

The donor candidate is selected when his or her "HLA" matches with that of the patient. Just like different types of red blood cells, A, B, AB, O type, there are also different types of white blood cells.

This type is called **HLA** (human leukocyte antigen) or histocompatibility antigen.

The HLA has A, B, C and DR locus, each with dozens of varieties and there are tens of thousands of combinations.

Different types of HLA

A locus	B locus	C locus	DR locus	DQ locus	DP locus
A1	B5	B49(21)	Cw1	DR1	DPw1
A2	B7	B50(21)	Cw2	DR103	DPw2
A203	B702	B51(5)	Cw3	DR2	DPw3
A3	B8	B52(5)	Cw4	DR3	DPw4
·	·	·	·	·	DPw5
·	·	·	·	·	DPw6
·	·	·	·	·	
A69(28)	B47	Bw4	Cw9(3)	DR52	DQ8(3)
A74(19)	B48	Bw6	Cw10(3)	DR53	DQ9(3)

Reference: Japanese Society for Histocompatibility and Immunogenetics.

A method called DNA typing delves further into the HLA types. For example, detailed investigation into the A2 confirmatory typing(CT) revealed further subdivision of "02:01", "02:06", "02:07", and "02:10".

3 How we search for donors

After you have registered, **the Japanese Red Cross Society** will conduct a search across all four locus (2 antigens per locus, 8 antigens in total) of HLA A, B, C, and DR locus using the DNA typing method. The results are then registered in the computer system of the Japanese Red Cross Society, and we then search for donors whose HLA are highly compatible with that of the patient.

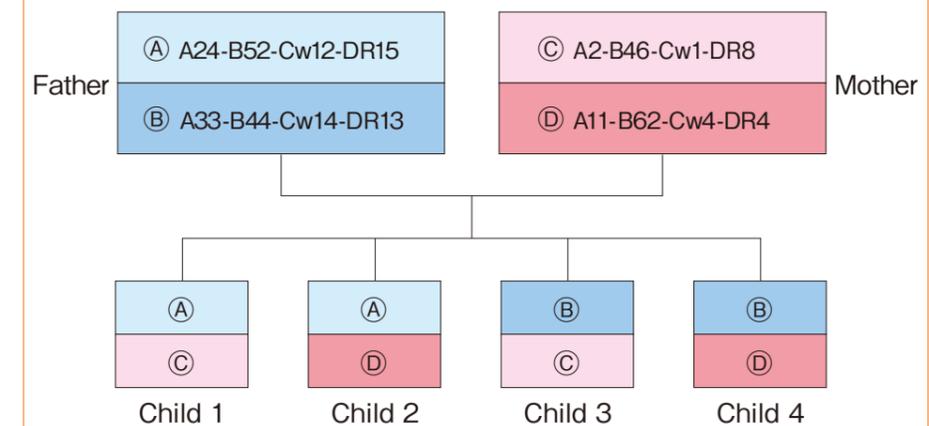
If you registered before August 2009, DNA typing may not have been performed on all donors.

4 Probability of compatible HLA

The HLA type is inherited from parents (one antigen from one parent). This leads to a combination of 4 HA types among siblings, and one therefore has a 1 in 4 chance of being an identical match with his/her siblings.

In Japan, about 30% of related individuals are able to find a person with identical, matching HLA.

There are 4 possible HLA types for children.



Even in transplantation between related individuals, GVHD and rejection are likely to occur when the HLA is not an exact match. Even with transplantation from unrelated individuals, if the HLA is an identical match, we can expect a success rate close to transplantation from related individuals.

As there are many Japanese people with similar HLA, and more than 450,000 donor registrants have registered with us, the JMDP is able to find people with compatible HLA types for about 95% of Japanese patients registered with us.

Q Are there overseas patients?

A There have been cases when the HLA of Japanese donors are identical with that of patients registered with overseas bone marrow banks. The coordination process is basically the same regardless of domestic or overseas. Since the date and place of evaluation and harvest may be restricted, we will inform you at the beginning of the coordination process.

I. Confirmatory typing (CT) Stage



- ◎ **The coordinator and physician for CT will explain to you the process in detail and check with each other that there are no problems before proceeding on with the coordination.**
- ◎ **You will undergo a medical interview and medical examination by the physician for CT after the interview. If there are no problems blood will be collected from you**

1 About the confirmatory typing (CT) stage

1) Schedule adjustment

The coordinator will check with you about your intention to donate and your convenience and adjust the schedule after consultation. If the timing proposed by the coordinator is not convenient for you, please fill out the reply form and inform the coordinator / Donor Center (DC).

2) Interview for confirmatory typing (CT) stage

On the day when you will be undergoing confirmatory typing (CT) stage, the coordinator will be the primary person to explain to you about the method of donation with the "Notice of Coordination Process (Compatibility notice)" that we sent you.

The coordinator will also check with your intention to donate and convenience, if **your family has understood everything and for their consent** (your family may sit in during the interview).

During the interview for the confirmatory typing (CT) stage, please kindly bring along and show us your identity verification documents such as driver's license and health insurance card.

"Coordination process for donating bone marrow or peripheral blood stem cells" for donors

◆ **We will check with you on your intention to donate regarding the method of harvest during the interview for confirmatory typing (CT) stage.**

After the coordinator has explained to you on the different harvest methods of bone marrow or peripheral blood stem cells, **the coordinator will ask if there is any method that you cannot accept** (if you are unable to decide at this juncture, the coordinator will check with you again via phone within a week's time).

We will not request you to donate bone marrow or peripheral blood stem cells using the method that you did not accept.

In the event that you are unable to donate according to the method you have accepted to due to results of the confirmatory typing (CT)s or health reasons, the coordination process will end here.

◆ **Either harvest method will work for the patients but there may be cases where a method is prioritized over the other (such as bone marrow transplantation or peripheral blood stem cells transplantation).**

We will inform you of the patient's preference (priority) if you wish to know, but please kindly understand that the harvest method is subject to change due to the patient's condition or your intention (if there is any donation method that you do not accept) etc.

3) Medical interview, medical examination, blood collection

After the explanation, **if you agree to the following ① to ④, please sign on the "Consent form for confirmatory typing (CT)".** After this, the physician for CT will perform simply medical examinations such as medical interview and blood pressure tests, and draw about 30 ml of blood if there are no problems (the volume of blood collected may differ if the patient is located overseas).

① We perform a screening test for the healthy check of the donor.

Donor screening test

- (i) Blood type: ABO type and Rh type tests
- (ii) Blood count: hemoglobin, red blood cells, hematocrit, white blood cells, platelets
- (iii) Functional tests of liver, kidney etc.: total serum protein, blood glucose, blood urea nitrogen, creatinine, total bilirubin, GOT, GPT, γ -GTP, cholesterol
- (iv) Infectious disease test (tests for pathogen that may infect patients via blood transfusion or hematopoietic stem cell transplantation): syphilis serum test, hepatitis B, hepatitis C, adult T-cell leukemia virus, AIDS (HIV) virus, cytomegalovirus

② For donors who did not undergo DNA typing of all 8 antigens of HLA -A, B, C, and DR locus when the donor registers with us or in past coordination process, we will conduct a detailed DNA typing in this round of confirmatory typing (CT) to determine your HLA type to see if it is compatible with the patient.

③ There may be times when we will store a portion of the blood collected from you during the confirmatory typing (CT) to reconfirm the results of the tests. We will discard the blood collected for the confirmatory typing (CT)s (blood, DNA samples) when the necessary testing is completed. However, we may use some of your DNA samples (after making individual identification impossible) to maintain the quality of HLA testing, or to evaluate reagents used in HLA tests.

④ The results of the HLA-DNA typing may also be used for new searches after the coordination process has ended.

If you are donating peripheral blood stem cells, one of the condition is to locate the blood vessel which can collect blood in your arms. We will check for that during the medical interview for the confirmatory typing (CT) stage.

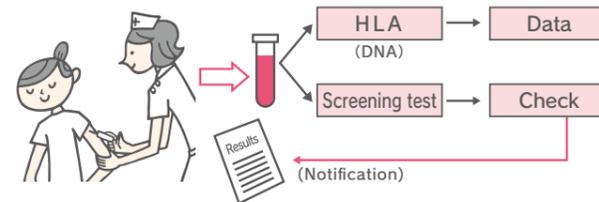
Q How much time does the confirmatory typing (CT) take?

A The time required is about 1 to 2 hours, and will differ depending on the facility. In general, the tests will be conducted from 9 a.m. to 3 p.m. from Mondays to Fridays.

2 Results of general blood test

We will inform you of the results about 2 weeks after your blood is collected. Please note that the blood test includes hepatitis, syphilis, AIDS, and other tests.

If the results of your blood test do not meet the criteria of the JMDP, we may talk to you again for another retest.



3 Potential Donor selection notification

The coordination process for the patient may involve up to 5 donors.

The patient's physician will review all the information (including results of confirmatory typing (CT)s) of all potential donors, and select the potential donor most suitable for transplantation.

This is called **donor selection**.

It will take about 2 weeks to 2 months before you will be notified if you have been selected as the donor.

Please inquire with the district secretary or the coordinator if you wish to know the progress of the selection process.

Q Can I know how many a potential donors are being reviewed?

A There are cases where multiple a potential donors have been matched for the patient, and also cases where not even 1 donor has been found. The number of a potential donors being reviewed or considered is not revealed to DC staffs, physicians for CT, coordinators, and donors themselves. This is to preserve the discretion of the donors.

"Coordination process for donating bone marrow or peripheral blood stem cells" for donors

The harvest method will be decided by the patient side after considering the confirmed intention and the health status of the potential donor during the confirmatory typing (CT) stage. We will inform you of the harvest method once you are selected as the potential donor. After that, we will proceed with the coordination process for you to donate according to that harvest method. As the patient side also starts to prepare for transplantation according to the policy decided in advance, the harvest method generally will not be changed after the potential donor is selected. In the unlikely event that you or your family wishes to change the harvest method, the coordination process may be terminated.

4 Pending selection

If the results of the confirmatory typing (CT)s indicate that the patient can undergo the same extent of transplantation as the selected potential donor, we may ask you to wait for a while as **your selection remains in a pending status**. During this period while you are pending selection, the progress of the coordination process may change and stretch over a long period of time. If there are changes such as health status, environment, or your schedule/convenience etc. during this waiting period, please notify your coordinator or DC. (See Chapter 2, IV. Termination and Temporary Suspension of Coordination Process)

II . Final consent



- ◎ **The interview for the final consent will be conducted with you (the donor), your family, and in the presence of third parties.**
- ◎ **We will check and ask again for your final decision/intention as well as your family's consent in the interview for the final consent.**
- ◎ **You will not be able to withdraw consent after you have signed and stamped your seal on the letter of final consent.**

1 Meaning of final consent

We will arrange to hold the interview for the final consent on a date, time, and place once you are selected as the donor.

After the potential donor and the family representative(s) have fully understood the explanations provided by the coordinator and the physicians for CT, and personally **signed** and **stamped** their seals on the "letter of consent to donate bone marrow" or "letter of consent to donate peripheral blood stem cells" ("letter of final consent"), the donor and family representative are indicating their final intention to donate. **Not only the consent of the potential donor, but the understanding and consent of the family members are also necessary.**

The decision to donate bone marrow or peripheral blood stem cells is entirely of the free will of the potential donor. The potential donor is only allowed to withdraw from the donation process before he/she signs and seals on the letter of final consent; **once the donor signs and seals on the letter of final consent, withdrawal is not allowed.**

Once we have confirmed your final consent, the patient side (patient, patient's physician, transplant center (TC)) will begin Pre-transplantation treatment on the patient about 2 weeks before the transplant procedure on the premise that "the patient will definitely be undergoing transplantation". If the donor decides to withdraw from the donation after we have confirmed the donor's final consent, the patient may not be able to receive appropriate medical treatment.

Please kindly understand that this final consent is very important on many levels.

Q What is a family representative?

A It will be the closest person (parents for singles, spouses for married people) to the donor. Depending on circumstances, siblings and guardians may serve as family representatives too.

Q What is the role of having a third-party present in the interview?

A The third-party witness is present at the interview to make sure that the donor and the family representative understand the thorough explanation provided by the coordinator and the physicians for CT, and that the donor wants to donate out of his/her free will. In principle, the third-party witness is usually arranged by DC, but the donor may request for a related person or relative to serve as the third-party witness instead.

2 Validity of the letter of the final consent

The letter of the final consent is valid for 6 months. If for any reason the donor is only able to donate bone marrow or peripheral blood stem cells 6 months after he/she has signed and sealed the letter of the final consent, the district secretary and the coordinator will

3 Blood collection for testing to verify engraftment

On the day of harvest, 20 ml of blood (not part of the bone marrow or peripheral blood stem cells harvest) will be collected from you for testing. This is for the transplant center (TC) to confirm whether the donor cells have successfully grafted onto the patient after transplantation (including genetic analysis) etc. The donor's consent for this blood collection will be verified at the letter of the final consent.

4 If health problems arise in the donor after the final consent

The JMDP's top priority is the health and safety of our donors. Even if you have given your final consent, we will either postpone or terminate the harvest procedure if we discover health problems in you.

If the patient indicates a date/period that he/she wishes to undergo the transplantation while we are arranging for a date to conduct the interview of the final consent with the donor, we may make an informal decision on the harvest schedule and the CC/AC after consulting with the donor. In this case, after we have verified the donor's final consent, we will proceed with the arrangements concerning the decision.

III. Once harvest is decided



- ◎ A detailed schedule towards the harvest procedure would be decided once we have verified your final consent.
- ◎ Please prepare your physical condition as the harvest approaches. You must notify us if you do not feel well.

1 Deciding the harvest facility (CC/AC)

After we have confirmed your final consent, Donor Center (DC) will notify the patient's physician, and CC/AC accredited by the JMDP will be chosen (we will proceed with the arrangements of the facility if it has been decided in advance). While we will consider the donor's preferences, you may not get to choose to donate in the CC/AC of your choice due for various reasons. CC/AC is not the same hospital as the transplant center (TC)

2 Harvest schedule

DC and the coordinator will arrange the schedules for the harvest and transplant between the donor, the patient side, and the CC/AC, as well as schedule the dates for health examinations, autologous blood collection (if you are donating bone marrow) or G-CSF injection (if you are donating peripheral blood stem cells) etc.

We will respect the donor's schedule as much as possible but please kindly note that the date of harvest is limited due to the patient's medical treatment.

3 Changes to the harvest schedule

Depending on the condition and changes in disease in the patient, the harvest and transplant procedures may not be able to take place on the decided dates. We will readjust the schedule so that the transplant procedure can be performed on a day when the patient has gotten better. There have also been cases when the transplant procedure was terminated because the patient's condition turned for the worse or deteriorated. However, even if the patient does not undergo transplantation, the donor's intention to donate is a pillar of support for the patient in his/her fight against the disease (see Chapter 2, IV. Termination and Temporary Suspension of Coordination Process)

4 Managing the physical condition of donors

Please prepare your physical condition as the harvest approaches. For more details, please read the "Donor Handbook" (pages 13 to 15) that you have been given when the harvest was decided.

Please notify us as soon as possible if you need to observe any abnormalities in your body or need to take medication from illnesses or accidents etc.

<p>Sports etc.</p>	Please do not do stretching exercises (such as training and exercising your muscles) about 2 weeks before you are hospitalized (please do not exercise about a week before you go for your health examination before the harvest procedure). Exercise may cause abnormal values in your blood test results; it is difficult to judge whether it is an abnormal value or pathological due to exercise, and this will lead to an emergency since the patient is preparing for transplantation. If you cannot avoid exercising, please consult your physician before you go for the health examination.
<p>Blood donation</p>	Blood donation may affect your blood test values. Please refrain from donating blood once the coordination process begins, until 6 months after the harvest procedure.
<p>Smoking</p>	Please refrain from smoking as phlegm etc. tends to flow out during anesthesia and obstruct your breathing, and affect the blood test values. Depending on CC/AC, you are also not allowed to smoke within the hospital and its premises.
<p>Alcohol</p>	Please refrain from drinking as it may affect your liver functions.
<p>Pregnancy</p>	The harvest procedure cannot be performed if the donors becomes pregnant out of concern of the health and safety of the mother and the fetus. Please avoid getting pregnant until the harvest is completed (as you will be asked to go on the pill for about 4 weeks before the harvest, please consult with your physician concerning the medication).
<p>Overseas travel</p>	Please inform the coordinator or DC of the period and place if you have already made arrangements for overseas travel. Also, please refrain from traveling overseas about 1 month before the harvest to prevent getting infections.
<p>Vaccinations</p>	Please inform the coordinator, DC, or the physician responsible for harvest of the type and timing if you have already made arrangements for vaccinations. <Vaccination for influenza> If the donor contracts influenza, the harvest procedure will be postponed or terminated, and this will affect the patient. If the donor whose harvest date has been decided (or tentatively decided) somewhere between December to March decides to undergo influenza vaccination on a voluntary basis, we will subsidize half the cost, we will subsidize half the cost so please inform DC or the coordinator.
<p>Nail art</p>	We may observe the color of your nails in order to check your health status. Please refrain from nail art (manicure, fake nails etc.) when you are undergoing the harvest procedure.
<p>Eyelash extensions</p>	During the bone marrow harvest procedure, you will be put under general anesthesia and your eyelids will be taped shut. If you have eyelash extensions, we may ask you to remove them before the harvest procedure so please consult with your physician when you go for health examination before the harvest.

5 Medical examination

The physician responsible for harvest and anesthetist (only for bone marrow harvest) will perform a **medical examination** on you at the CC/AC.

In this health examination, we will make inquiries and perform examination, screening test, urinalysis, chest X-ray examination, electrocardiogram, pulmonary function test (only for bone marrow harvest only) etc. We will also perform a pregnancy test for female donors after consultation.

We may consult with you again for retest or detailed examination if your test results do not meet our criteria.

Depending on the results, the harvest procedure may be terminated even if you have given your final consent.

➔ If you are donating bone marrow, see Chapter 3. A

➔ If you are donating peripheral blood stem cells, see Chapter 3. B

You will be given a “Donor Handbook” once the harvest procedure is decided. Please fill in the necessary columns and bring the handbook with you during medical examinations and on the day of the harvest itself.

- ◆ The Donor Handbook details the precautions need to be taken before and after the harvest procedure, and symptoms that are likely to occur etc. Also, in the unlikely event that we need to perform emergency measures for some reason before or after the harvest procedure, please fill in your contact information.
- ◆ Please keep the Donor Handbook as a record of being a bone marrow or peripheral blood stem cells donor, even after the coordination process has ended. Please show this handbook to the medical institutions when you visit the hospitals which is not CC/AC, or go for medical examinations after the harvest procedure is completed. Please contact the JMDP Donor Center(DC) if you have any health problems of which the causal relationship to the harvest procedure cannot be denied.

IV. Termination and Temporary Suspension of Coordination Process



- ⦿ If you do not meet the requirements to become a donor, or withdraw from your application to become a donor, the coordination process will be terminated. We will not reveal the details/reasons to the patients.
- ⦿ If the coordination process ends due to the circumstances of the patient such as a change in the disease condition, the coordination process might be temporary suspended. We will not inform the donor of the details.

1 Termination of the coordination process

1) Termination of the coordination process due to the donor's circumstances

If you do not meet the requirements (see Chapter 1, III) to become a donor, or withdraw from your application to become a donor, **the coordination process will be terminated**. The patient will not be informed of the termination reasons at all.

Reasons for termination due to donor's circumstances (example)

- When the potential donor is not available
- When the consent of the family members cannot be obtained
- When the physician discovers health problems with the donor

2) Termination of the coordination process due to the patient's circumstances

There have been cases where the coordination process was terminated due to the patient's circumstances. The donor will not be informed of the termination reasons at all.

Reasons for termination due to patient's circumstances (example)

- When the HLA (DNA) typing does not match
- When another a potential donor is selected/decided
- When the medical treatment of the patient changes due to changes in the disease state etc.

Chapter 3. Harvest

A. Bone marrow harvest

3) Donor registration after the coordination process ends

After the coordination process ends, the status of the donor registration is either changed to "Continuous", "Suspended", "or "Canceled". When your status is "Continuous", a new coordination process may start immediately. To avoid this, your status will be changed to "Suspended" or "Canceled" for a certain period of time after the coordination process ends based on your circumstances.

If the coordination process is terminated due to circumstances on the patient side, your status in general will remain as "Continuous".

- ◆ In the event that a new coordination process is started after the earlier coordination process has ended, you will have to undergo another round of confirmatory typing (CT)s (or just the screening test) even if the same tests were performed in the previous round. However, if a new coordination process starts within a year from your last round of confirmatory typing (CT)s or medical examinations, then you may not need to undergo another round of confirmatory typing (CT)s.
- ◆ In the event that the coordination process has ended from the patient side after confirming the your final consent, and you are selected again soon afterwards to be a donor for another patient with the new coordination process already started, we may not interview you again for your final consent.

2 Suspension of coordination process

Depending on the circumstances of the patient side, **the coordination process might be suspended**. As you may be asked to wait for a certain period of time (maximum of 3 months), please let us know if it is inconvenient for you. We will contact you as soon as the patient is ready to resume the coordination process. If it looks unlikely that the coordination can be resumed, the coordination process will be terminated.

We will not inform you of the reasons why the process is suspended.

Reasons for suspension due to patient's circumstances (example)

- When it is necessary to consider whether to perform the transplant procedure due to changes in the patient's condition
- When the patient needs to receive another form of medical treatment before transplantation because the patient's condition is unstable

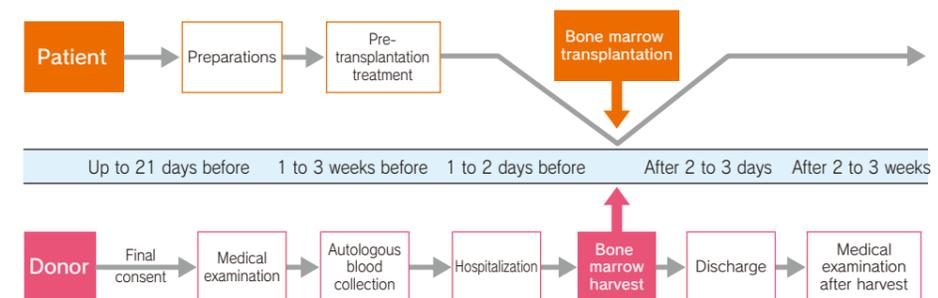
When the coordination process is "suspended" and the results of the confirmatory typing (CT)s indicate that the patient can undergo the same extent of transplantation as the selected donor, we may ask you to wait for a while as your selection remains in a pending status. (See Chapter 2, I. Confirmatory typing (CT))

I. Schedule of bone marrow harvest

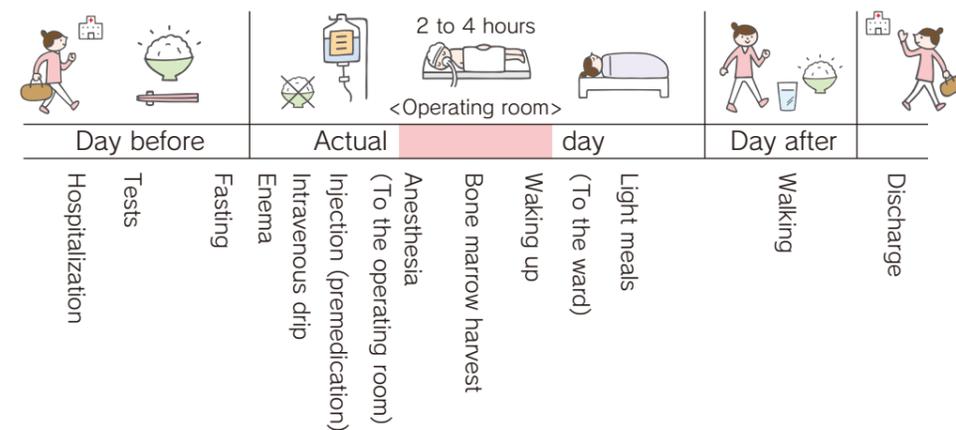


- ◎ Usually, you will be hospitalized for 4 days 3 nights for the harvest procedure.
- ◎ Before you are hospitalized, you will need to undergo a health examination (up to 21 days before the harvest procedure), and get your autologous blood collected (1 to 3 weeks before the harvest procedure) if necessary.

For bone marrow harvest, you will be hospitalized 1 to 2 days before the day of harvest, and generally is discharged 2 to 3 days after the procedure. For specific matters concerning the hospitalization, please check with the coordinator or the physician responsible for the harvest in the CC/AC in advance.



Hospitalization schedule



II. Follow-up from preparation for bone marrow harvest to after the procedure is over



- ⦿ The JMDP will perform the harvest procedure according to strict safety standards.
- ⦿ We will collect your autologous blood according to the volume of bone marrow to be harvested in advance.
- ⦿ You will undergo general anesthesia for the harvest procedure. We will inject a needle right into your iliac (pelvic bone) and aspirate the bone marrow fluid.
- ⦿ You will be discharged 2 to 3 days after the harvest procedure, and the follow-up will begin from there.

1 Autologous blood collection

In order for the donor to get anemic from the bone marrow harvest procedure, we will collect autologous blood from the potential donor about 1 to 3 weeks before the day of harvest.

Depending on the planned volume of bone marrow to be harvested, we may need to collect the necessary volume of autologous blood in 1 to 2 rounds (200 to 400 ml each round).

We may prescribe you with a hematopoietic agent (iron preparation) during that time.

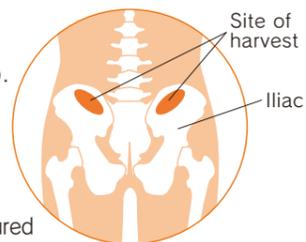
Your autologous blood is refrigerated, stored, and transfused back to you on the day of harvest.

We may not collect your autologous blood depending on the planned volume of bone marrow to be harvested.

2 Harvest

1) Site of harvest

The bone marrow fluid is easily harvested from the iliac (pelvic bone). It is in an area slightly below the back of your waist in the pelvis.



2) Harvest method

You will be asked to lie facing down in the operating room, and punctured with a bone marrow aspiration needle (the size of the bore is about that of a ballpoint pen) from the surface of the skin. A few ml of bone marrow fluid is aspirated with a syringe at a time. We may make a small incision on your skin so that it is easier to puncture the skin with the aspiration needle. There will be a total of about 2 to 6 punctures on the back of your pelvis; 1 to 3 puncture on each side. While we will puncture your pelvis in dozens to hundreds of places to aspirate the bone marrow fluid, the punctures in your bone will naturally and automatically heal.

3) Volume of bone marrow fluid during harvest

The target harvest volume is 15 ml per kg of potential donor's body weight; a volume that is set such that it will not impose a burden on the donor's body. Your body's ability to generate blood will not drop because you donated bone marrow. The number of hematopoietic stem cells in your bone marrow will regenerate blood promptly.

3 Anesthesia

Since your iliac will be punctured with a thick needle many times in order to aspirate the bone marrow fluid with a syringe, most donors undergo general anesthesia. The whole procedure from being transported into to being transported out of the operating room lasts about 2 to 4 hours, to which you will be anesthetized for about 1 to 3 hours.

If we need to perform emergency measures on the donor during anesthesia, we will terminate the harvest procedure immediately and perform the necessary medical treatment.

1) Treatment before anesthesia

We will administer you with a preanesthetic agent before putting you under general anesthesia. We will also secure an intravenous drip route in you to administer various drugs and for transfusion. Depending on the facility, we may perform enema and hair removal (hair shaving etc.) too.

2) Management during anesthesia

Once you start to lose your consciousness after being injected with the anesthesia-inducing drug, we will insert a soft plastic tube into your trachea through your mouth to deliver anesthetic gas and oxygen, and control your breathing with an artificial respirator. In many cases, we may also insert a thin tube (balloon catheter) into your urethra to conduct the urine out of your bladder (urethral catheterization). We will check the volume of urine passed out during anesthesia to help us get an accurate picture of the state of blood circulation and renal function in your body. Also, to prevent the contents of the stomach from flowing back into the lungs during anesthesia (accidental swallowing), we may insert a thin tube (stomach tube) from your nose into the stomach.

During anesthesia, we will regularly measure your blood pressure, which will be continuously and rigorously observed by the anesthesiologists with the electrocardiogram monitor etc. attached to your body.

Once we have confirmed that you are healthy from the health examination conducted before the harvest procedure, we may ask for you and your family members to sign on the letter of consent etc. prepared by the CC/AC.

* Examples of letter of consent prepared by the CC/AC (will differ depending on the facility)

- "Consent Form for Surgery"
- "Consent Form for Anesthesia"
- "Consent Form for Blood Transfusion": consent regarding autologous blood transfusion (including the possibility of transfusing allogeneic blood (blood from other people) if unforeseen circumstances happen during the bone marrow harvest procedure)

4 Symptoms after harvest

* More details in "Chapter 6. References".

1) Symptoms after waking up from anesthesia

You may experience urinary pain after removing the urinary catheter, headaches, sore throat, nausea, and run a fever of 37 to 38 degrees after withdrawing the tracheal tube. These symptoms will usually go away within 1 to 2 days.

2) Pain in the harvest site (waist)

There are individual variation and each donor experiences a different degree of pain. Most donors have continued to experience some pain up to a week after the harvest procedure is over, and there have been some donors who felt the pain for a month and above. In rare cases, the skin where the bone marrow aspiration is performed may form pus or bleed but this will be handled appropriately by the attending physician. There may be marks of the aspiration needle on your skin, but they will gradually fade away.

5 Discharge (return to daily life)

Usually, you will be discharged from the hospital in about 2 to 3 days after the bone marrow harvest procedure is over, and can resume work or school.

However, please keep the wound clean for about a week after the harvest procedure, and avoid excessive exercises and extreme sports.

6 Follow-up after harvest

The coordinator will check with your physical condition via phone after you are discharged. You will undergo a medical examination at the CC/AC 2 to 3 weeks after the harvest procedure.

We will also send you a questionnaire about 3 months after you have donated bone marrow; please kindly fill up that questionnaire.

In the unlikely event that an abnormality appears in your health condition, the physician in charge of the CC/AC will take responsibility and attend to you to administer medical treatment. Please consult early and receive treatment. In that case, we may consult with you about the use of your own health insurance card.

III. Safety and complications of bone marrow harvest (anesthesia)



Ⓢ Complications etc. may occur during the harvest procedure but we will perform the appropriate medical treatment.

1 Complications associated with bone marrow harvest and anesthesia

* More details in "Chapter 6. References".

The following complications have been reported in the past.

Transient : lowered blood pressure, arrhythmia

Others : Suspected complications include anterior teeth trauma, breakage of the bone marrow aspiration needle, laryngeal granuloma, urethral injury, thrombosis and pulmonary fat embolism; 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 in the donor after the harvest procedure; pain and numbness in the harvest site or the gluteal region (buttocks) lasted for a prolonged period of time.

While this is not a case of bone marrow donation via the JMDP, one case of "malignant hyperthermia" has been reported as a complication in a bone marrow donor who underwent general anesthesia between relatives. However, the donor was discharged from the hospital after 3 weeks without no aftereffects (1996).

2 Serious accidents caused by bone marrow harvest and anesthesia

There have been 5 cases of deaths reported in bone marrow donors worldwide. We at the JMDP have helped to coordinate 1,300 cases of bone marrow harvests between unrelated individuals in Japan and no deaths in donors have yet to occur.

■ Bone marrow donor death cases (partial modification including errors in the sources)

Case	Country of origin	Blood relative/ Unrelated individual	Age/Sex	Time of incidence	Cause of death	Source
1	Overseas	Blood relative	57 years old, female	During the procedure	Ventricular fibrillation during the harvest procedure (heart failure) (there had been abnormal ECG readings.)	1)
2	Overseas	Blood relative	Unknown, male	During the procedure	Difficulty in breathing due to the sensitivity reaction toward anesthesia (anaphylactic shock)	1)
3	Japan	Blood relative	35 years old, male	During the procedure	Respiratory arrest while under anesthesia (the respiratory arrest caused cranial neuropathy.)	1)
4	Overseas	Unrelated individual	35 years old, male	After the procedure	Pulmonary embolism (lower extremity thrombosis occurred, causing pulmonary embolism.)	1)
5	Overseas	Blood relative	38 years old, male	After the procedure	Severe pulmonary embolism (donor was diagnosed with antithrombin III deficiency in the past, and this was revealed by the donor's family after death)	2)

Source

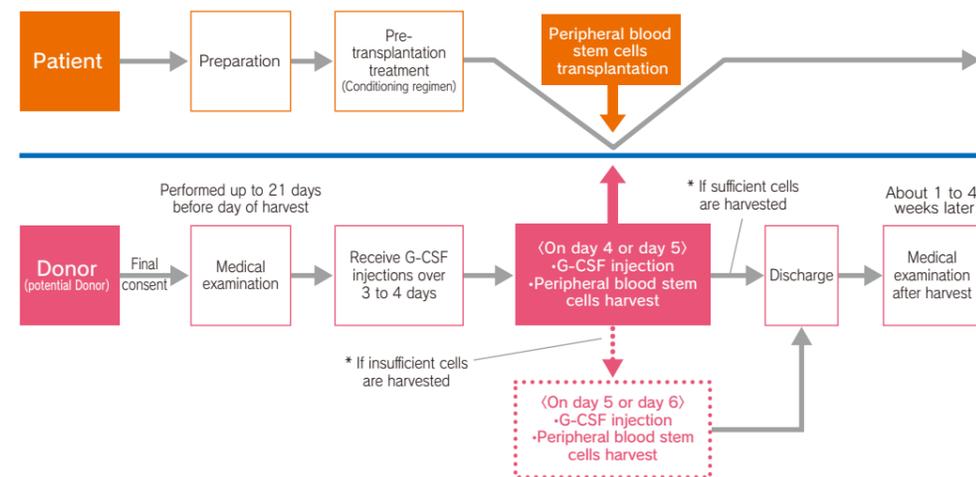
1) Hematopoietic Cell Transplantation, 1999, 2nd Edition, Chapter 40. Bone Marrow and Peripheral Blood Stem Cell Donors)
2) Haematologica | 2009; 94(1), Severe events in donors after allogeneic hematopoietic stem cell donation)

B. Peripheral blood stem cells harvest

I. Peripheral blood stem cells harvest schedule

- ☉ You will be hospitalized for about 5 days 4 nights to 7 days 6 nights if you receive the G-CSF injections.
- ☉ You will need to visit the hospital for about 2 to 4 days if you receive the G-CSF injections, and will be hospitalized for about 2 days 1 nights to 4 days 3 nights after the injections.
- ☉ You will undergo a health examination up to 21 days before the day of harvest.

The days you will be hospitalized will depend on the facility(CC/AC). You will be hospitalized for about 5 days 4 nights to 7 days 6 nights if you receive the G-CSF injections, and for about 2 days 1 nights to 4 days 3 nights if you visit the hospital to receive the injections instead. For more specific details regarding the hospitalization, please check with the coordinator or the physician in the CC/AC in advance.



Hospitalization schedule

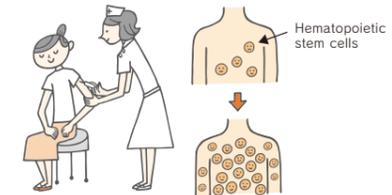
1 to 4 days prior	Day of harvest	Following day	2 days later
G-CSF injections (3 to 4 days)	(G-CSF injections) Venipuncture Harvest (3 to 4 hours) Determining cell count	Discharge or second round of harvest * Depending on the cell count harvested on the previous day	Discharge * If a second round of harvest is performed
Hospitalization * From day 1 of injection to the day of harvest			

II. Follow-up from preparation for peripheral blood stem cells harvest to after the procedure is over

- ☉ The JMDP will perform the harvest procedure according to strict safety standards.
- ☉ We will inject you with G-CSF every day for a period of 3 to 4 days before the day of harvest to increase the number of hematopoietic stem cells in your peripheral blood.
- ☉ We will harvest by using a blood component separation device. Depending on the number of peripheral blood stem cells harvested, we will decide if it is necessary to perform a second round of harvest the next day.
- ☉ You will be discharged at most 2 days after the harvest procedure, and the follow-up will begin from there.

1 G-CSF injections

The G-CSF is a drug that increases the number of your white blood cells. The number of hematopoietic stem cells will increase in your peripheral blood (blood flowing throughout the body) when you are injected with G-CSF 1 to 2 times a day for a period of 3 to 4 days before the harvest. If you intend to visit the hospital to receive the G-CSF injections instead, the coordinator will check with your physical condition via phone after you return home. Also, please bring along your Donor Handbook (see page 28), and contact the listed contact information if you observe any abnormalities in your health



2 Harvest

1) Day of harvest

We will harvest your peripheral blood stem cells on day 4 or 5 after we you have received G-CSF injections (the schedule will differ depending on the facility).

2) Harvest method

The harvest procedure will usually be performed 3 to 4 hours after the G-CSF injections. There are also facilities who will not administer any G-CSF injection on the actual day of harvest itself. Before harvesting, we will try our best to locate a thick vein in both arms (or one arm) and puncture you with a needle to collect and transfuse blood.

We will collect the hematopoietic stem cells in your blood using a blood component separation device and transfuse the rest of the blood into another vein. During the harvest procedure, you will not be able to move the arm with the needle. The time required is about 3 to 4 hours. However, the procedure may take more time depending on the situation.

The safety of our donors is our top priority during the harvest procedure. Medical staff such as physicians, nurses, and clinical engineering technologists will constantly be on standby, and they will perform regular checks on your physical condition including blood pressure measurement.

3) Femoral vein access

One of the condition to becoming a peripheral blood stem cell donor is the presence of a relatively thick blood vessel on the arm. In rare cases, even if we have located and confirmed the presence of a thick vein in the arm during the confirmatory typing (CT) stage or the Medical examination, but am unable to secure this blood vessel on the day of harvest, we may insert a catheter (soft tube) into the blood vessel in your groin (the area which connects to your leg). This is called femoral vein access (see page 39).

We will ask for consent in the letter of final consent regarding femoral vein access. If the donor does not agree to this, the donor will be unable to donate peripheral blood stem cells.

4) Amount of blood circulated in the blood component separation device (volume of processed blood)

The volume of processed blood is set in a range that will not impose burden on the donor's body.

The target volume to be circulated in the blood component separation device is 200 ml of blood for every kg of the donor's body weight, with the upper limit of 250 ml/kg.

If the donor has a body weight of 50 kg, about 10 to 12.5 L of blood will be circulated in the blood component separation device.

5) Number of rounds of harvest

We will determine the peripheral blood stem cell count harvested after the apheresis procedures is over. We will terminate the procedure if we have harvested sufficient amount for the patient's transplantation. If an insufficient amount is harvested, you will undergo a second round of apheresis procedures on the next day.



Femoral vein access

< Specific treatment >

- ⦿ Disinfect the skin around the site where the catheter is inserted.
- ⦿ Apply local anesthesia to the site of puncture and insert the catheter into the vein.

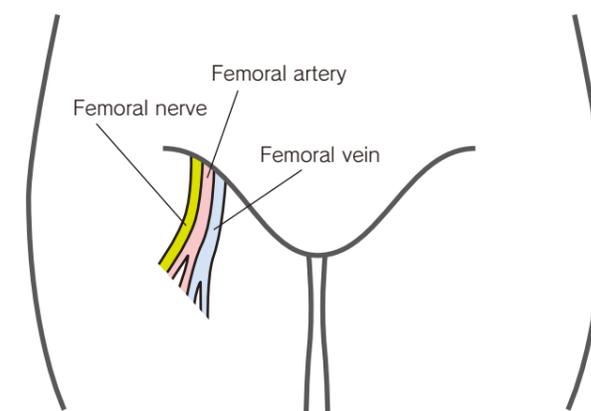
* Depending on the facility, we may remove the hair or make a small incision on the skin to allow easier insertion of the catheter before the treatment. Also, we may affix the catheter to the skin with a string to prevent it from moving around.

< Complications during catheter insertion >

- ⦿ Arterial puncture: To pierce the needle into an artery located alongside a vein. When this happens, the nurse or phlebotomist will apply pressure on the artery to stop the bleeding. Treatment is rarely necessary, but bleeding may result in blood clots (hematoma) flowing back into the abdomen, which will require treatment.
- ⦿ Others: There have been cases of air embolism (accidentally introducing air into the blood vessel during the insertion of catheter) and nerve damage near the veins etc.

< Complications during catheter placement >

- ⦿ Bacterial infections etc. may occur. When infections happen, we will remove the catheter and proceed with treatment such as administering antibiotics.
- ⦿ A thrombus (blood clot) may form in the area surrounding the catheter.



3 Symptoms after harvest

1) Reduction of platelets

Platelets are also collected during the harvest of peripheral blood stem cells. If the platelet count decreases below the reference range, we may separate the blood platelet components from the harvested peripheral blood stem cells and transfuse the blood back into you via intravenous infusion. Since platelets play a role in blood coagulation, you may find yourself more prone to bleeding for several days after the harvest. However, the coagulation process will usually return to normal in a few weeks.

2) Site of harvest (arm)

The puncture site, and the area around it, may swell up or bruise but this will usually subside in 1 to 3 weeks.

4 Discharge (return to daily life)

After we have checked your health condition and discharge you from the hospital (at most the day after the harvest procedure is over), you may be able to resume work or school. However, please refrain from excessive exercises and extreme sports for about a week after the harvest.

5 Follow-up after the harvest

The coordination will check with your physical condition via phone once a week for up to 4 weeks after the harvest is over.

You will undergo a medical examination at a CC/AC 1 to 4 weeks after the harvest.

Also, we will send you a questionnaire 3 months after the harvest procedure, and once a year for 5 years to help us ascertain the long-term safety of G-CSF. Please kindly help us fill up the questionnaires.

The coordination will check with your physical condition via phone once a week for up to 4 weeks after the harvest is over.
You will undergo a medical examination at a CC/AC 1 to 4 weeks after the harvest.
Also, we will send you a questionnaire 3 months after the harvest procedure, and once a year for 5 years to help us ascertain the long-term safety of G-CSF. Please kindly help us fill up the questionnaires.

III. Risks and discomforts of the apheresis procedure



Ⓢ **Complications and side effects may occur with peripheral blood stem cell harvest but appropriate measures will be taken.**

1 Side effects of G-CSF

* More details in "Chapter 6. References".

The following side effects may occur with G-CSF injections.

Depending on the increase of white blood cell count or decrease of platelet count beyond the reference range, and the extent of side effects, we may reduce the dosage or discontinue the administration of G-CSF.

① Possible mild side effects

Bone pain (back pain, chest pain, back pain, joint pain, muscle pain, etc.), headache, lowered blood pressure, rashes, erythema (red spots), nausea, vomiting, fever, malaise, loss of appetite, palpitations, abnormal liver functions, increased uric acid level, renal dysfunction (increased serum creatinine level), and temporary enlargement of spleen.

* Pain will usually subside with pain killers etc.
In most cases, these symptoms will go away within a few days after the G-CSF injections.

② Significant side effects considered to be related to G-CSF injections

Shock thought to be caused from allergy to G-CSF, interstitial pneumonia, angina pectoris, cerebrovascular disorder, splenic rupture, acute iritis, gouty inflammation such as gouty arthritis.

2 Long-term safety of G-CSF

G-CSF was approved in 1991 and is an extremely safe preparation that is widely used as an effective drug for the lowered white blood cell count after treatment with anticancer drugs in cancer patients. We have been collecting scientific data because the long-term safety (over several decades) of its usage has not been confirmed in healthy people. In a study conducted by the Japan Society for Hematopoietic Cell Transplantation, there have been reports of donors who experienced health problems several months to several years after they underwent the harvest procedures, but its causal relationship to peripheral blood stem cells harvest has yet to be established. More details in "Chapter 6. References".

There was a case reported when a Japanese donor passed away one year after donating peripheral blood stem cells to a blood relative in 2003 from the development of acute myelogenous leukemia. The Japan Society for Hematopoietic Cell Transplantation investigated the causal relationship between the death and G-CSF, and determined that the incidence of blood tumors such as leukemia is not different to that of in bone marrow donors. Even in overseas studies, the incidences of reports of blood tumors such as leukemia in the general population, and in bone marrow donors and peripheral blood stem cells donor were the same. The studies therefore deny the increased risk of developing leukemia from G-CSF injections.

3 Complications associated with peripheral blood stem cell harvest

* More details in "Chapter 6. References".

The following symptoms may occur during the peripheral blood stem cell harvest procedure.

General malaise, numbness around limbs, mouth, dizziness associated with vasovagal reflex (VVR), nausea, vomiting, lowered blood pressure

* The numbness around the mouth and in limbs are due to the effects of anticoagulants (hypocalcemia) that are used to prevent the blood circulating in the blood component separation device from coagulating. In many cases, the symptoms will improve with the administration of a calcium preparation.

There has been a case where the harvest procedure was terminated midway in peripheral blood stem cell donor for relatives, but the donor has since recovered with no aftereffects. This was a case where an elderly donor was taking medication due to illness, and the procedure was probably terminated due to severe vasovagal reflex (VVR).

4 Serious accidents caused by peripheral blood stem cells harvest

There have been 12 cases of deaths reported in peripheral blood stem cells donors worldwide. As many of these were due to some risk factors such as high age of donors, and the original presence of had illnesses, the causal relationship with peripheral blood stem cell harvest is not clear. In Japan, peripheral blood stem cell transplantation between blood relatives began in 2000, and about 500 cases are performed annually. The JMDP started to coordinate peripheral blood stem cell transplantation between unrelated individuals from 2010 onwards, and no deaths in related or unrelated donors have yet to occur.

Peripheral blood stem cell donor death cases

Case	Country of origin	Blood relative/ Unrelated individual	Age/Sex	Time of incidence	Cause of death	Source
1	Overseas 1997 and earlier	Related	61 years old, female	4 days after harvest	Cardiac insufficiency (donor had bronchial asthma, high blood pressure and coronary artery disease)	2) 3)
2	Overseas 1997 and earlier	Related	57 years old, female	Within 24 hours after returning home	Apoplexy(past history unknown)	2)
3	Overseas 1996	Related	64 years old, male	After G-CSF administration has ended	Myocardial infarction (donor had coronary artery disease)	1)
4	Overseas 1998	Related	73 years old, male	Several days after harvest	Cerebrovascular disorder (donor had a history of high blood pressure and angina pectoris)	3)
5	Overseas 2000 and earlier	Related	67 years old, male	Approximately day 6 after G-CSF administration (harvested on day 4 and day 5)	Subdural hematoma (donor had a history of abdominal aortic aneurysm surgery and myocardial infarction)	3)
6	Overseas 1999	Related	47 years old, male	Day 4 after G-CSF administration	Sickle-cell anemia crisis (donor had a history of sickle cell anemia)	3)
7	Overseas 2000 and earlier	Related	Unreported, male	Unreported	Cerebrovascular disorder (past history unknown)	3)
8	Overseas unknown	Related	43 years old, male	Passed away in 15 days (date of death unknown)	Cardiac arrest (correlation between the harvest and high blood pressure and/or smoking unknown)	4)
9	Overseas unknown	Related	52 years old, male	Passed away in 17 days (date of death unknown)	Cardiac arrest (correlation between the harvest and smoking unknown)	4)
10	Overseas 2001 and earlier	Related	50 years old, female	After catheter was removed	Air embolism (surgical error occurred during the harvest procedure in which the catheter was inserted into the internal jugular vein instead)	3)
11	Overseas unknown	Related	27 years old, male	During harvest	Cardiac arrest (surgical error occurred during the harvest procedure)	4)
12	Overseas 2011	Unrelated	21 years old, female	During harvest	Bled to death (surgical error in which the catheter was inserted into the internal jugular vein instead, resulting in internal bleeding from the blood vessel into the lungs)	5)

Sources:

- 1) Anderlini P et al.: Allogeneic blood cell transfusion: Considerations for donors. Blood 90: 903-908, 1997.
- 2) Confer DL & Stroneck DF: Bone marrow and peripheral blood stem cell donors. In Hematopoietic Cell Transplantation. Edited by Thomas ED, Blume KG, Forman SJ. Blackwell Science, Inc. Massachusetts, USA, pp 421-430, 1999.
- 3) Corporate information
- 4) Halter, Koderu, Ispizua: Severe events in donors after allogeneic hematopoietic stem cell donation.
- 5) World Marrow Donor Association (WMDA) information

I. Difference between bone marrow transplantation and peripheral blood stem cells transplantation



- ◎ The harvest method from donors will differ significantly between bone marrow transplantation and peripheral blood stem cells transplantation.
- ◎ The transplantation method will be selected after considering the respective characteristics of the patient.

1 From the donor's standpoint

Subjective symptoms such as pain will start to occur in bone marrow donors after the harvest procedure, and in peripheral blood stem cells donor after they received G-CSF injections.

In an overseas questionnaire study of donors who participated in a comparative study of bone marrow harvest and peripheral blood stem cells harvest, the intensity and duration of pain were almost equal.

Also, it has been shown that there is no difference in the incidence of serious complications between bone marrow harvest and peripheral blood stem cells harvest (from a joint survey conducted by the Japan Society for Hematopoietic Cell Transplantation and the European Society for Blood and Marrow Transplantation).

After understanding the differences between these two harvest methods, please consider which harvest method that you cannot agree to.

■ Difference in peripheral blood stem cells harvest

	Bone marrow harvest	Peripheral blood stem cells harvest
G-CSF injection	No	Yes
Apheresis	No	Yes
Autologous blood collection	Yes (no in some cases)	No
General anesthesia	Yes	No
Hospitalization (may differ depending on facility)	Usually 4 days 3 nights	◎ Hospitalized for about 5 days 4 nights to 7 days 6 nights from the day you receive G-CSF injections ◎ Hospitalized for about 2 days 1 night to 4 days 3 nights if you visit the hospital for G-CSF injections
Number of harvest facilities (CC/AC)	About 170 facilities	About 90 facilities (about 100 facilities planned in future)
Number of hospital visits for interviews, tests and harvest procedure	About 7 times	◎ If you are only hospitalized for the harvest procedure, about 8 times ◎ If you are hospitalized right from the day you receive G-CSF injections, about 5 times

Reference material: "Illustrated series on hematopoietic stem cell transplantation for informed consent" authored by Yoshinobu Kanda (1st edition issued on Oct 30, 2009)



Glossary

Apheresis: A procedure that draws blood from a blood vessel in the arm, collects only the necessary cells with a blood component separation device, and transfuses the remaining blood back into the donor.

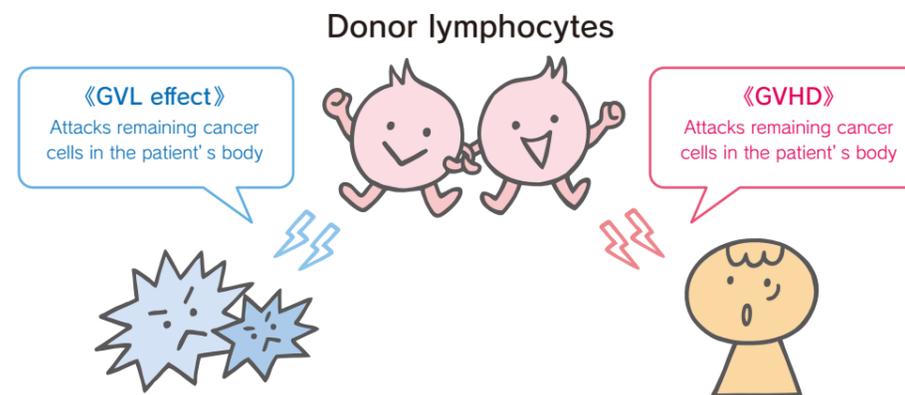
2 From the patient's standpoint

1) Characteristics of transplantation method

It is the same transplantation method via intravenous drip but they each have their own characteristics.

For example, it is known that peripheral blood stem cell transplantation increases GVHD more than bone marrow transplantation because a higher amount of donor lymphocytes is transplanted.

However, on the other hand, when a strong GVHD occurs, it has also been said that the GVL effect (graft versus leukemia effect) where donor lymphocytes attack and kill the remaining cancer cells in the patient's body is also high, and a reduced recurrence rate can be expected.



2) Trend of choice in medical field

For patients with aplastic anemia and pediatric patients who do not require much GVL effect, bone marrow transplantation is the easier choice. Conversely, in patients with advanced leukemia and infections, as well as elderly patients where the GVL effect is expected to occur, mini transplantation procedure using peripheral blood stem cells tends to be chosen instead.



Glossary

Lymphocyte: A type of white blood cell that is responsible for immune function.

Mini transplantation: A non-destructive bone marrow transplantation procedure with lesser Pre-transplantation treatment (Conditioning regimen).

II. Freezing of bone marrow and peripheral blood stem cells



◎The JMDP in principle does not approve of freezing and storing bone marrow or peripheral blood stem cells for transplantation.

The bone marrow and peripheral blood stem cells harvested from donors may be frozen and stored in the following cases.

1) When there is a sudden change in the patient's condition immediately before transplantation etc.

While extremely rare, the bone marrow or peripheral blood stem cells may not be used for transplantation even if they have been frozen and stored. The cells are to be discarded in such cases.

2) When a large number of peripheral blood stem cells is harvested

In peripheral blood stem cell harvest, the surplus cells may be frozen and stored if the patient's physician decides that the number of harvested cells exceeds the single treatment amount for the patient and that further treatment is required. Even in such cases, the cells are to be discarded promptly as soon as the physician determines that the cells will not be used, and are not to be used for purposes other than treatment.

III. Donor registration after bone marrow and peripheral blood stem cells harvest



◎ Donor registrations will be suspended for one year after the harvest, and will not be used in compatibility searches with patients. After one year, as long as there is no specific request by the donor, the donor registration will continue and compatibility search will resume.

1 Donor registration one year after harvest

One year after the harvest, subsequent donor registration will be suspended or canceled, and a letter will be sent to inform you of the continuation of the registration. If you wish to check your registration status, or if you do not wish to continue the registration, please contact the Japanese Red Cross Society Block Blood Center as soon as possible. Also, we will not send letters to donors who are 55 years old and have received notification from the Japanese Red Cross Society that their donor registration (overage) has been canceled.

2 Number of donations

骨At the JMDP, you may donate bone marrow and peripheral blood stem cells up to two times in total, irrespective to blood relatives or unrelated individuals. If you have donated twice, your donor registration will be suspended until the policy of number of times of donation in future is decided.

At present, in order to collect scientific data to ascertain the long-term safety of G-CSF, donors can only donate bone marrow twice, and peripheral blood stem cells once (if you have already started on G-CSF injections even if the harvest procedure is terminated, it will be counted as one time of peripheral blood stem cells donation).

IV. Protecting the privacy of donor and patient



◎ In order to preserve the privacy of donors and patients and the impartiality of the JMDP operations, we will not inform you of information that will identify the patient or the donor, or the post-transplantation process. decided for each donor.

1 Information of donor and patient

Donors and patients will not be informed of each other's personal information such as addresses and names, and the donor will also not be informed of the post-transplantation process of the patient in principle. However, the coordinator may inform the donor of the patient's sex, age, and region of residence if the donor wishes to after giving the final consent. Similarly, the patient's physician will also not inform the patient of such information.

2 Information disclosure

If you are giving an interview on medium that may be accessed by an unspecified number of people such as the Internet (including blogs and social network services), bulletin magazines, newspapers, please do not disclose information such as date and time and venue that may make it possible to identify yourself or the patient. Please contact the JMDP Donor Center (DC) in advance when you receive interviews from the press media etc. You can talk about this to the people around you (family and colleagues).

3 Exchanging letters with the patient

After the harvest procedure, you can exchange letters with the patient via DC or the coordinator. You can exchange up to 2 letters within a year after the harvest procedure is over. Please refrain from writing information that will identify yourself or the other such as names, addresses, and dates of birth.

We cannot help with the exchange of money or goods. We will deliver the letter after confirming the contents of your letter, but please kindly understand that the patient may not always reply to you (this is the same for coordination with overseas patients).

V. DLI (Donor Lymphocyte Infusion)

DLI (Donor Lymphocyte Infusion) is a treatment method in which the lymphocytes (white blood cells) of the donor's bone marrow or peripheral blood stem cells are harvested in the same way as whole blood donations or blood components donations, and the donor lymphocytes are then transfused into the patient.

Among the complications that occur in patients after transplantation, DLI has been clearly shown to be effective for EB virus and B-cell lymphoproliferative disorders as well as the recurrence of leukemia.

When the patient requires DLI after transplantation, we may ask the donor to provide lymphocytes after reviewing the symptoms. During that time, we will confirm the donor's desire again separately from the consent on donating bone marrow or peripheral blood stem cells.

Please let us know if you do not wish to donate donor lymphocytes.

* This is the same for coordination with overseas patients.

VI. Storing your samples

Various studies are being conducted to improve the performance of hematopoietic stem cell transplantation. The Japanese Red Cross Society is currently implementing a project to store a portion of the blood donated by the donors and patients who have agreed to participate in this project, and to give it to researchers who aim to develop medical treatment for transplantation. The JMDP is also taking part in this project. You can check with the person in charge of the CC/AC for more details.

VII. Disclosure of information when genetic information etc. of donor is obtained from the donation of bone marrow or peripheral blood stem cells

A blueprint that creates the body is called a gene, and the genes gathered in each cell is called a chromosome. Changes in the chromosomes (genes) cause various diseases. In rare cases, even a healthy person may be born with altered chromosomes. For example, even if the person does not exhibit any symptoms now, there may be changes in his/her chromosomes that may cause various symptoms (such as infertility) in the future, or even if there are no symptoms in the person himself/herself, their children may inherit it and develop symptoms (such as chromosomal disease) when changes in their chromosomes occur. The frequency of these chromosomal changes is extremely rare (under 1%); there are many people who spend their entire lives not knowing these chromosomal abnormalities if they do not undergo medical testing or examinations.

On the other hand, there have been rare cases where the donor's chromosomal changes were accidentally discovered through medical examination of the patient who underwent transplantation using the donor's bone marrow or peripheral blood stem cells. Such results allow donors to manage their health and think about how they can convey this information to their own children. As this is information that one would not know without undergoing medical examinations, there are also some donors who do not wish to know such information. Therefore, if information pertaining to chromosomal abnormalities is discovered, we will check with you through written final consent in the interview whether you would like us to disclose such information (you may answer this at a later date). If you would like to know more about this, please ask your coordinating physician.

I. Cost burden of donors



- ◎ Medical expenses for harvesting the bone marrow or peripheral blood stem cells will be paid for by the patient's health insurance so the donor does not need to bear any cost.
- ◎ We will pay the actual transportation fees.

1 Transportation fees

We will pay the actual transportation fees in each interview. Also, we will pay the actual transportation fees according to the method you have specified if you have to visit the hospital, or get hospitalized for medical examinations, autologous blood collection, and G-CSF injections etc.

In principle, please kindly make use of public transport such as trains and buses. If you have to take a taxi, please keep the receipt as we will ask for it.

2 Upfront payment

We will pay 5,000 yen of upfront payment when you are hospitalized in the CC/AC. Please understand that this is used to cover the cost of renting hospital gowns, and purchasing towels, toothbrush, and prepaid TV cards.

«Examples of things where the cost will be not borne by the JMDP»

Please understand in advance that the following costs cannot be borne by the JMDP.

- ◎ Consultation fees of necessary medical examinations to confirm your health before donation;
- ◎ Issuing fees for certificates such as identity verification, and the transportation expenses required for these;
- ◎ Temporary absence from work compensation benefit for medical examinations and hospitalization;
- ◎ Childcare expenses for your child during medical examinations and hospitalization, hotel fees for the family members, car rental fees, pet hotel fees etc.;
- ◎ Expenses for the medical certificate necessary for donor's own paperwork;
- ◎ Medical examinations and treatment fees etc. when the chronic illness (such as lower back pain, hernia) deteriorates after donation, or when a symptom that is not caused by the harvest procedure occurs after donation;
- ◎ Expenses such as private therapy that the donor opted for the symptoms that occurred after donation;
- ◎ Cost of living when work becomes difficult due to symptoms after donation;
- ◎ Treatment expenses etc. after being covered by disability insurance under the JMDP group accident insurance;
- ◎ Other expenses that the JMDP has determined that it cannot take responsibility for.

II. The JMDP Group Accident Insurance for Donor Compensation



- ◎ Should an accident happen to you from the donation of bone marrow or peripheral blood stem cells, we will make insurance payout of up to 100 million yen from the accident insurance to which the bone marrow bank has subscribed to.
- ◎ You will be eligible for insurance from the time you sign on the consent form for confirmatory typing (CT)s.
- ◎ You will not need to pay any insurance premium.



1 Outline of the JMDP Group Accident Insurance for Donor Compensation

1) It is an insurance which comprehensively compensates you from the time you leave your home to returning home for the purpose of donating bone marrow or peripheral blood stem cells.

The insurance also covers injuries and accidents that occur on your trips to and from the hospital. This is limited to 7 days since you left home for bone marrow donation, and limited to 8 days since you left home for peripheral blood stem cells donation.

2) We will make insurance payout for accidents caused by bone marrow and/or peripheral blood stem cells harvest, and related medical treatment.

Medical treatment related to the harvest procedure includes the following items.

- ◎ After you have signed the "Consent form for confirmatory typing (CT)s", medical treatments such as confirmatory typing (CT) to determine your eligibility as a donor, health examinations before the harvest, autologous blood collection, and G-CSF injections.
- ◎ Medical treatment such as physical examination after the harvest. However, this is limited to those who visit a hospital within 3 months from the day after the day of bone marrow and/or peripheral blood stem cells harvest.
- ◎ Medical treatment (DLI) such as collecting blood for patients who did not completely recover after transplantation. However, this is limited to procedures that were performed within two years from the day after the day of bone marrow and/or peripheral blood stem cells harvest.

3) The compensation contents are as follows.

Death benefit	100 million yen	In the event that the donor passes away due to injuries within 180 days from the day of the accident, we will make the full payment of death benefit and permanent disability benefit.
Permanent disability benefit	3% - 100% of the aforementioned	In the event that the donor is physically disabled within 180 days from the day of the accident, we will make 3% to 100% of the amount of the death benefit and permanent disability benefit depending on the extent of injury.
Hospitalization benefit (up to 180 days)	10,000 yen per day	When the donor is unable to return to his/her normal work and/or maintain his/her normal lifestyle, and when the donor is hospitalized, we will make the payment for hospitalization benefit for the number of days that donor is hospitalized (up to 180 days from the day of the accident). * We will only make the payment for hospitalization benefit for injuries due to peripheral blood stem cells harvest if you are hospitalized for 4 days and more.
Hospital-visit benefit (90-day limit up to 180th day)	5,000 yen per day	When the donor has difficulty fulfilling his/her normal work duties and/or maintaining his/her normal lifestyle, and when the donor has to visit the hospital (including house visits) within 180 days including the day from the day of accident (*), we will make the payment for the hospital-visit benefit for the number of actual days (up to 90 days) the donor visited the hospital.

* As most of the symptoms (such as headache, nausea, fever) from peripheral blood stem cells harvest are transient, the donor will only receive payment if he/she visits the hospital and is hospitalized for 4 days or more since the start of receiving medical treatment.

4) When making insurance payout

If the donor has an accidental injury during the period described in point 5), we will make the insurance payout (including injuries caused by bone marrow or peripheral blood stem cells harvest, and from related medical treatment).

5) Period of making insurance payout

The period is the earlier of any of the following points listed where the donor leaves his/her home to undergo bone marrow or peripheral blood stem cells harvest surgical procedure and related medical treatment.

- ① When donor arrives back home
- ② At 12 p.m. on the 7th day counting from the day following the day the donor left home (for bone marrow donation).
At 12 p.m. on the 8th day counting from the day following the day the donor left home (for peripheral blood stem cells donation).

6) When insurance payout cannot be made

Insurance payout cannot be made for injuries caused by the following causes.

- 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
- Cerebral disorders, diseases, or loss of sanity not attributable to bone marrow or peripheral blood stem cells harvest surgical procedure and related medical treatment
- Surgical operation not attributable to bone marrow or peripheral blood stem cells harvest surgical procedure and related medical treatment
- Other medical measures

Insurance payout cannot be made for the following injuries.

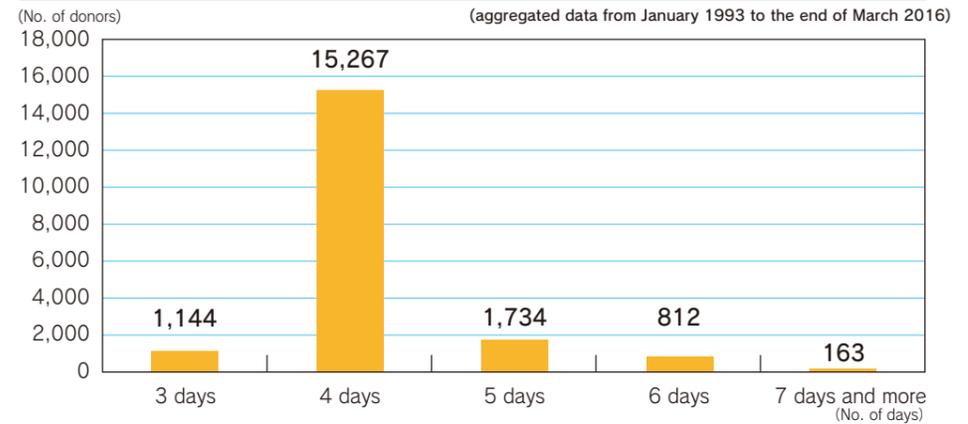
- Cervical compression syndrome with only subjective symptoms (also known as "whiplash injury")
- Lumbago with only subjective symptoms

(Partially quoted from the special clause)
 The Group Accident Insurance for bone marrow donors was revised in November 1999 and implemented in December 1999.
 The Group Accident Insurance for peripheral blood stem cells donors was implemented in October 2010.

I. Bone marrow donation

The JMDP has established a "donor safety committee" to analyze data on bone marrow harvest, and are reviewing ways to further improve the safety of donors.

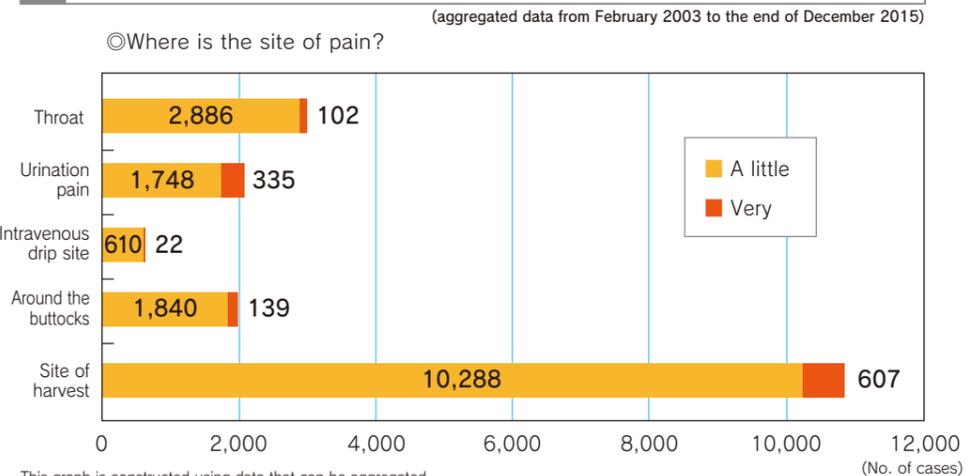
1 Number of days of hospitalization of bone marrow donors



Approximately 30% of the 163 donors who were hospitalized for 7 days and more were out of the circumstances of the convenience of the hospital that performed the harvests. Of the remaining 70%, 40% of them were hospitalized longer than scheduled due to health reasons. In addition, 30% had to be hospitalized longer as the harvest procedures were postponed.

There are 184 "total cases of transplants from overseas donors to Japanese patients" that are not included in the graph.

2 [Number of responses: 13,084] from the questionnaire at the time of hospital discharge

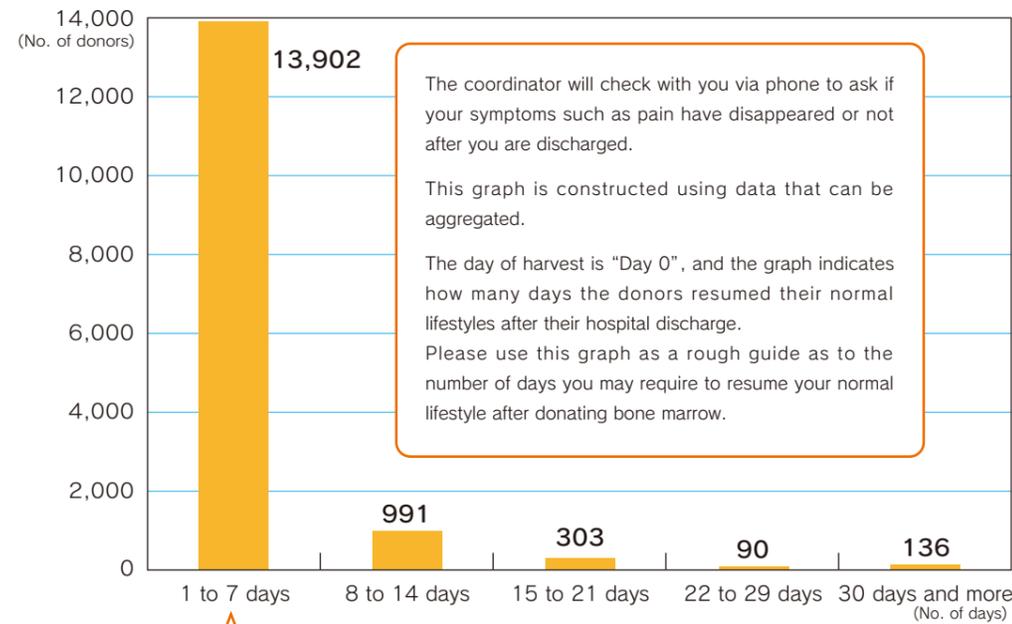


This graph is constructed using data that can be aggregated.

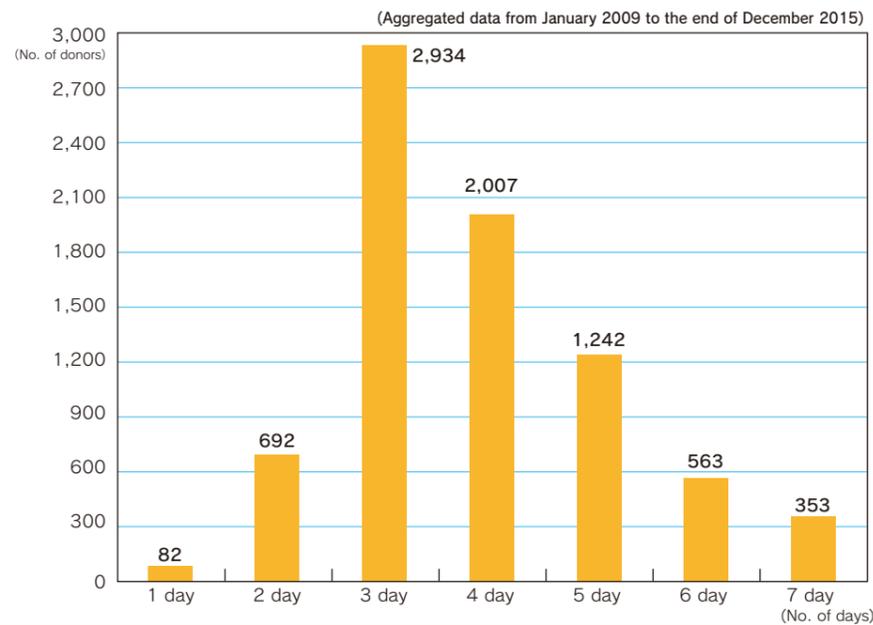
* Due to multiple responses per donor, the number of responses and the total number do not match.

3 Number of days required to return to normal lifestyle

(aggregated data from January 1993 to the end of December 2015)

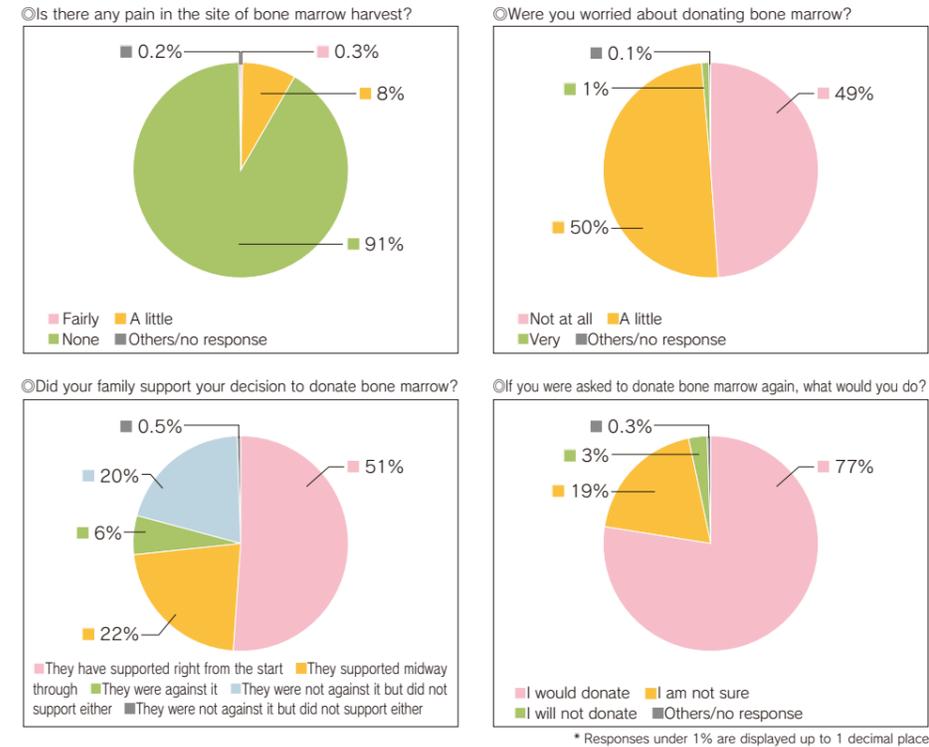


This graph is constructed using data that can be aggregated, and further classified into one-day units of "1 day to 7 days". *Due to different aggregation periods, the total number of donors do not match that of the above graph.



4 [Number of responses: 13,419] from the questionnaire sent 3 months after hospital discharge

(aggregated data from February 2003 to the end of December 2015)



5 Drugs used during hospitalization

(aggregated data from January 1993 to the end of March 2016)

Antibiotics (to control inflammations etc.)	12,690 / 18,603 (68.2%)	(Used for a very short period)
Pain killers (to relieve pain)	6,847 / 18,542 (36.9%)	
Iron preparations (to prevent anemia)	5,448 / 18,524 (29.4%)	
Fever medication (to bring down fever)	1,823 / 17,908 (10.2%)	

* This is a summary of the report of when the donors were discharged from CC/AC. Please understand that there may be variations in the aggregated data.

6 Symptoms and test results of day after the harvest

(aggregated data from January 1993 to the end of March 2016)

- **Fever of 38°C and above** 1,478 / 17,715 (8.3%)
Subsided within a day in most donors
- **Urination pain** 2,068 / 14,801 (14.0%)
Pain and discomfort after catheter is removed from the urethra.
- **Abnormalities in site of harvest** 214 / 18,763 (1.1%)
including swelling, bleeding, and hematomas at site of needle puncture.
- **Infectious diseases** 158 / 18,767 (0.8%)
Infections not at the site of needle puncture, but upper respiratory tract infections (cold) and urinary tract infections/
- **Liver dysfunction** 409 / 18,700 (2.2%)
Temporary
- **Walking on the day after harvest**
 - Unable to walk 103 / 18,471 (0.6%)
 - Able to walk a little 4,184 / 18,471 (22.7%)
 - No problems with walking 14,182 / 18,471 (76.8%)

7 1. Complications associated with bone marrow harvest and anesthesia

(aggregated data from January 1993 to the end of March 2016)

Amongst the complications associated with bone marrow harvest and anesthesia that were reported, 159 cases (as of end March 2016) were covered under the hospital-visit benefit, and 38 cases were covered by the permanent disability benefit of the JMDP group accident insurance.

- **Lowered blood pressure** 4,507 / 18,770 (24.0%)
Systolic pressure lowered to 80 mmHg or less during anesthesia. Temporary.
- **Blood in urine** 169 / 14,669 (1.2%)
Most of it is caused by irritation to the insertion of the urinary catheter. Most of such cases cannot be seen with the naked eye, and are temporary.
- **Arrhythmia (irregular pulse)** 85 / 18,779 (0.5%)
Temporary; symptom will improve.
- **Denture damage, loose teeth** 45 / 18,795 (0.2%)
This happens when the tracheal tube is inserted or withdrawn from you during general anesthesia.
Please inform us in advance if you have dental implants.
- **Breakage of harvest needle** 32 / 18,785 (0.2%)
There have been cases when the harvest needle broke during the harvest procedure. There have also been cases where an incision on the skin has to be made to retrieve the broken needle.
- **Laryngeal granuloma (1 case)**
This happens when a benign tumor forms in the larynx due to irritation from the insertion of the tracheal tube, and was removed via surgery.
(There have been rare cases of a temporary change in voice due to the irritation from the tracheal tube.)

■ Deep vein thrombosis in lower right leg (1 case)

A blood clot was found in the deep vein of the lower right leg of the donor after the bone marrow harvest procedure was over. The blood clot disappeared after the donor received medical treatment.

■ Pain in lower left limb (1 case)

After the bone marrow harvest, donor began to experience numbness appeared from the left femoral region to the knee, and pain in the harvest site for a long period. The donor resumed a normal lifestyle but the pain continued. The donor exhibited gradual improvements and the follow-up process ended there.

■ Urinary tract injury (2 cases)

After the bone marrow harvest procedure was over, blood was observed in the site where the urinary catheter was removed. In addition to applying pressure to stop the bleeding, donors were prescribed with complete bed rest, given painkillers, and their hospital discharge were postponed. Coordinators follow-up with the donors until the symptoms improved.

■ Other complications

6 cases each: corneal erosion, lower back pain, femoral lateral cutaneous nerve palsy (left/right); **5 cases each:** severe backpain in bone marrow puncture site, drug rash, pain and numbness in femoral region; **4 cases each:** subcutaneous hematoma, pain at the harvest site (tenderness, pain), jaw arthritis (left/right), numbness in fingers of right hand; **3 cases each:** re-hospitalization from worsening backpain, ulnar nerve palsy and desensitization (left/right), lower limb neuropathy and peripheral neuropathy, severe pain in puncture site, numbness and pain in hands (left/right/both hands); **2 cases each:** dura mater damage due to epidural anesthesia, pyelonephritis, laryngeal granuloma (without surgery), slipped disk (lumbar), iliac puncture pain (left/right), pneumonia (postoperative, accidental swallowing), lip erosion (upper lip/lower lip), sacroiliitis, difficulty walking due to lower backpain from the buttocks, brachial plexus paralysis (left/right), feeling of numbness in left hip, teeth damage, eyelid swelling in both eyes, mouth sores, subconjunctival hemorrhage, lower backpain, pain from harvest site/hip to thighs; **1 case each:** residual bone fragments, temporary deterioration of hearing difficulty, dermatitis at bone marrow harvest site, bacteremia and septic sacroiliitis, prolonged phlebitis at intravenous injection site, periostitis, thoracolumbar fascia pain, acute tonsillitis, bilateral iliopsoas hemorrhage, bronchopneumonia, lower backpain and numbness in lower right limb, traumatic sciatic nerve injury, meralgia paraesthetica in lower right limb, spondylosis, antibiotics anaphylaxis, meralgia paraesthetica in left femoral region, pain in left femoral region and lower back, pelvic pain, lumbar fasciitis, upper gastrointestinal bleeding, external laryngeal ulcers, poor swallowing, linear fractures in the left iliac spine, folliculitis (mandibular), swelling at harvest site and fever, hematoma and iliac inflammation after bone marrow harvest, viral esophagitis, penile erosion, nodules at the intravenous injection site, numbness in right forearm radial side, myofascial pain, dental crown damage, peri-arthritis of shoulder, cubital tunnel syndrome, detached and/or fractured left iliac, lumbar (intervertebral) disk disorder, superficial punctate keratitis, corneal epithelial defect in right eye, contact dermatitis from face to neck, discomfort in the left lateral knee, skin erosion at intravenous injection site, urethral obstruction, persistent fever, subcutaneous hematoma due to leakage from blood vessel during autologous blood collection, swelling of upper right lip, numbness in upper left lip and upper lips, transient cheilitis after surgery, discomfort and pain in lower left limb, right sciatic nerve pain, neuropathic pain at harvest site, superior cluneal nerve injury in left hip, paresthesia of front of right thigh, pain persistence and augmentation at puncture site, numbness in entire lower right limb and left hip pain during walking, discomfort and persistent pain in left shoulder, internal derangement of both knee joints, numbness and discomfort in knee, deep vein thrombosis, neck pain, pain and numbness at harvest site, left clavicular fracture (due to fall), pain from harvest site to thighs, hyperventilation attacks, pain in the median part of the right elbow, numbness in the left lower limb, urethral injury, dull pain at puncture site, sensory mononeuropathy, complex regional pain syndrome, pain in the posterior superior iliac spine, peripheral neuropathy in third toe, epidermolysis bullosa in both cheeks from compression, transient skin rash (due to anesthesia), facial edema, right superior cluneal nerve injury, pain from right neck to shoulder, hip pain, hematoma and internal bleeding after arterial puncture (DLI)

* All these symptoms are either cured or disappeared.

* There has only been 1 case of rheumatoid arthritis reported in the past; only a part of it was covered by the insurance because it was deemed that the donor was predisposed to rheumatoid arthritis and that rheumatism could not have developed just from the bone marrow harvest procedure.

* 6 and 7 is summarized from the reports at the time of discharge from the CC/AC. Please understand that there may be variations in the aggregated data.

7 2. Complications associated with bone marrow harvest and anesthesia

In the cases in 7-1, we have extracted a selection of complications that happened within a 5-year-period between April 2011 to March 2016.

4 cases:

Pain and numbness in thigh, pain at harvest site (tenderness, pain)

3 cases each:

Femoral lateral cutaneous nerve palsy (left/right), numbness and pain in hands (left/right)

2 cases each:

dental crown damage, drug rash, feeling of numbness in fingers of right hand, pain from harvest site/hip to thighs, lower backpain, lumbar pain, severe pain in bone marrow puncture site

1 case each:

Corneal erosion, swelling of upper right lip, eyelid swelling in both eyes, mouth sores, lip erosion (upper lip/lower lip), numbness in upper left lip and upper lips, transient cheilitis after surgery, jaw arthritis (left/right), pain from right neck to shoulder, persistent fever, hyperventilation attacks, transient skin rash (due to anesthesia), subcutaneous hematoma due to leakage from blood vessel during autologous blood collection, pain in the median part of the right elbow, discomfort and pain in left shoulder, left clavicular fracture (due to fall), sacroiliitis, severe puncture pain (left/right), swelling at harvest site and fever, pain and numbness at harvest site, dull pain at puncture site, hip pain, hematoma between left gluteal muscles, right superior cluneal nerve injury, neuropathic pain at harvest site, right sciatic nerve pain, superior cluneal nerve injury in left hip, feeling of numbness in left hip, urethral obstruction, urethral injury, feeling of numbness from left hip to foot, numbness in entire lower right limb and left hip pain during walking, paresthesia of front of right thigh, discomfort and pain in lower left limb, numbness in lower left limb, internal derangement of both knee joints, numbness and discomfort in knees, lower limb neuropathy and peripheral neuropathy, deep vein thrombosis in lower limbs, walking difficulty, sensory mononeuropathy, complex regional pain syndrome, pain in the posterior superior iliac spine, peripheral neuropathy in third toe, hematoma and internal bleeding after arterial puncture (DLI).

* All these symptoms are either cured or disappeared.

* There has only been 1 case of rheumatoid arthritis reported in the past; only a part of it was covered by the insurance because it was deemed that the donor was predisposed to rheumatoid arthritis and that rheumatism could not have developed just from the bone marrow harvest procedure.

8 Health injuries in donors who donated to unrelated individuals (in order of occurrence)

A case where donor developed acute hepatitis C

In March 1998, a donor who donated bone marrow to an unrelated individual developed acute hepatitis C after the bone marrow harvest procedure.

Course

About 2 weeks after donating bone marrow, the donor developed acute hepatitis C and was re-hospitalized for treatment, to which the donor recovered. The donor returned to work and resumed a normal lifestyle. Investigation on the cause of this onset indicated that the donor may have been infected during the bone marrow harvest procedure. However, it was not possible to identify the medical procedure that left to the infection.

Countermeasure

The JMDP has notified harvest facilities across Japan the preventive measures for similar cases as follows.

- ① Recommends the use of disposable bone marrow harvest needles
- ② To comply with the "autologous blood management manual" that describes the collection, storage, and transfusion procedures of blood for autologous blood transfusion, and has notes on how to handle contaminated blood

A case where a retroperitoneal hematoma was observed in the donor after the bone marrow harvest procedure

In September 2000, a considerable large hematoma was found in a donor who donated bone marrow to an unrelated individual.

Course

After the bone marrow harvest procedure, the donor complained of lower abdominal pain and underwent medical examinations such as CT scan that confirmed the presence of a hematoma at the retroperitoneum (there was a bleeding blood clot situated between the peritoneum and the abdominal wall). The donor's hemoglobin levels decreased to 6.7 g/dL (12.3 g/dL before donating bone marrow) for a short while. The donor soon recovered from anemia without transfusion and returned to society.

Countermeasure

The JMDP has issued an "emergency safety information" on warnings on the site and depth of bone marrow puncture to all harvest facilities across Japan. The accident investigation committee conducted an investigation and reviewed measures to prevent similar reoccurrences. They came to the conclusion that while there was a high possibility that the harvest needle had damaged the blood vessels inside the ilium, it was not possible to identify the actual site where bleeding occurred and the cause of bleeding.

A case where the donor had persistent lower backpain over a long period of time after the bone marrow harvest procedure

In March 2003, a donor complained of prolonged pain in the lower back for a long period of time after the donor donated bone marrow to an unrelated individual.

Course

After the donor was discharged from the hospital when the bone marrow harvest procedure was over, he underwent MRI examinations for persistent pain. Results showed that there were incomplete fractures in the bilateral iliac bones and bone marrow edema. The donor was thus re-hospitalized again for another week and the pain subsided 8 months later.

Countermeasure

The JMDP conducted an investigation to determine the cause and to prevent such reoccurrences. Results of the investigation indicated that the following 2 points might have been the reasons as to why the donor's pain at the harvest site had persisted for a long period of time.

- ① Presence of incomplete fractures which is thought to be evidenced by the image of the irregular cortical bone and image of discontinuity of the cortex observed through the CT scans
 - ② Possibility of hematoma due to hemostasis after harvest
- The JMDP has issued a "safety information" where donors can promptly report to the authorities when pain persists for more than a month, or when they have taken painkillers continuously for a week or more.

A case where donor was suspected of pulmonary fat embolism after the bone marrow harvest procedure

In August 2003, the donor was found to have decreased oxygen saturation levels after the donor donated bone marrow to an unrelated individual.

Course

After the oxygen saturation levels in the arterial blood was observed, the donor underwent lung CT scans to which pulmonary fat embolism was suspected.

The donor was immediately put on oxygen inhalation and given treatment with steroid hormones, to which the donor's respiratory condition improved the following day. The donor soon returned to society.

Countermeasure

The JMDP issued an "emergency safety information" to all harvest facilities across Japan. While the JMDP also conducted an investigation to determine the cause and to prevent such reoccurrences, no specific cause could be found.

As a countermeasure, the JMDP issued a "safety information" where in the event that oxygen saturation levels are found to be persistently decreased after the bone marrow harvest procedure, the donor in question is to undergo medical examinations including chest X-P examinations, lung CT scans, MRI, lung scintillation imaging, and vascular ultrasound.

In addition, the JMDP notified the harvest facilities to look into the bronchoalveolar lavage in order to ensure safety.

A case where a hematoma was found in the left ilio-lumbar region after the bone marrow harvest procedure

In August 2003, a hematoma was found in the left ilio-lumbar region of the donor after donating bone marrow to an unrelated individual.

Course

On the following day after the bone marrow harvest procedure, the donor complained of tenderness in the left lower abdomen, and was thus subjected to medical examinations such as CT scan to which a hematoma and gas were found in the left iliopsoas.

Donor was put on hemostatic agents and antibiotics and the donor's hemoglobin level was reduced to 12.8 g/dL at one time (16.1 g/dL before donating bone marrow).

While the donor had tenderness in the left lower abdomen, the donor could walk and overall physical condition such as appetite was good.

The donor soon recovered and returned to society.

Countermeasure

The JMDP has issued an "emergency safety information" on warnings on the site and depth of bone marrow puncture to all harvest facilities across Japan.

While the JMDP also conducted an investigation to determine the cause and to prevent such reoccurrences. Results of the investigation indicated that the cause of the hematoma was likely to be due to the penetration of the harvest needle. The JMDP issued a "safety information" to harvest facilities to adjust the depth of the puncture.

A case where a hematoma was found in the left iliopsoas region after the bone marrow harvest procedure

In October 2009, a hematoma was found in the left iliopsoas region of the donor after donating bone marrow to an unrelated individual.

Course

Two hours after the bone marrow harvest procedure, the donor complained of abdominal pain in the left inguinal region and was prescribed with painkillers. However, the pain did not subside and a CT scan was performed on the donor. Results of the CT scan confirmed pelvic hemorrhage and angiography was performed on the donor. Embolization was immediately performed on the artery that was thought to be the blood vessel responsible for bleeding using Spongel, and the donor was put under observation and prescribed with painkillers and complete bed rest. The donor's hemoglobin level was reduced to 9.4 g/dL at one time (13.2 g/dL before donating bone marrow).

Countermeasure

The JMDP has issued an "emergency safety information" on warnings on the length of the puncture needle and the thickness of the ilium, and depth of bone marrow puncture to all harvest facilities across Japan.

The JMDP also conducted an investigation to determine the cause and to prevent such reoccurrences. Results of the investigation indicated that the cause of the hematoma was likely to be due to the penetration of the harvest needle, and recognized that there are individual differences in the shape of the pelvis. The JMDP also issued a "safety information" to harvest facilities to take into account the donor's BMI etc., and to choose the shortest possible bone marrow harvest needle.

A case where a hematoma was found in the left gluteus medius after the bone marrow harvest procedure

In March 2015, a hematoma was found in the left gluteus medius of the donor after donating bone marrow to an unrelated individual.

Course

The donor was discharged 2 days after the bone marrow harvest procedure but was admitted into the A&E when the pain at the harvest site became more severe on day 4 after harvest, and when swelling in the left buttock, pain deterioration, and numbness of thighs appeared on day 5.

CT scans revealed pseudoaneurysm in the superior gluteal artery and bleeding in the gluteus medius. Due to the progression of anemic symptoms, arterial embolization was subsequently performed on the third day of hospitalization, to which the symptoms of anemia improved and the donor's general condition stabilized. The donor soon recovered and returned to society without any pain and the numbness.

Countermeasure

The JMDP has issued an "emergency safety information" to all accredited harvest facilities for bone marrow harvest between unrelated individuals and called their attention to this case. The JMDP also conducted an investigation to determine the cause and to prevent such reoccurrences.

Results of the investigation indicated that harvest facilities are to pay attention to the puncture site and puncture depth, to feel the site after puncturing, and to always puncture the needle perpendicular to the surface of the bone in bone marrow harvest procedures, and that the bone marrow harvest needle should be 3 inches and shorter in principle (2 inches and shorter is preferable). The JMDP also issued a "safety information" that prohibits the use of the bone marrow harvest needles longer than 3 inches.

9 Cases covered by the permanent disability benefit

As of end March 2016, the permanent disability benefit covered the following 38 cases.

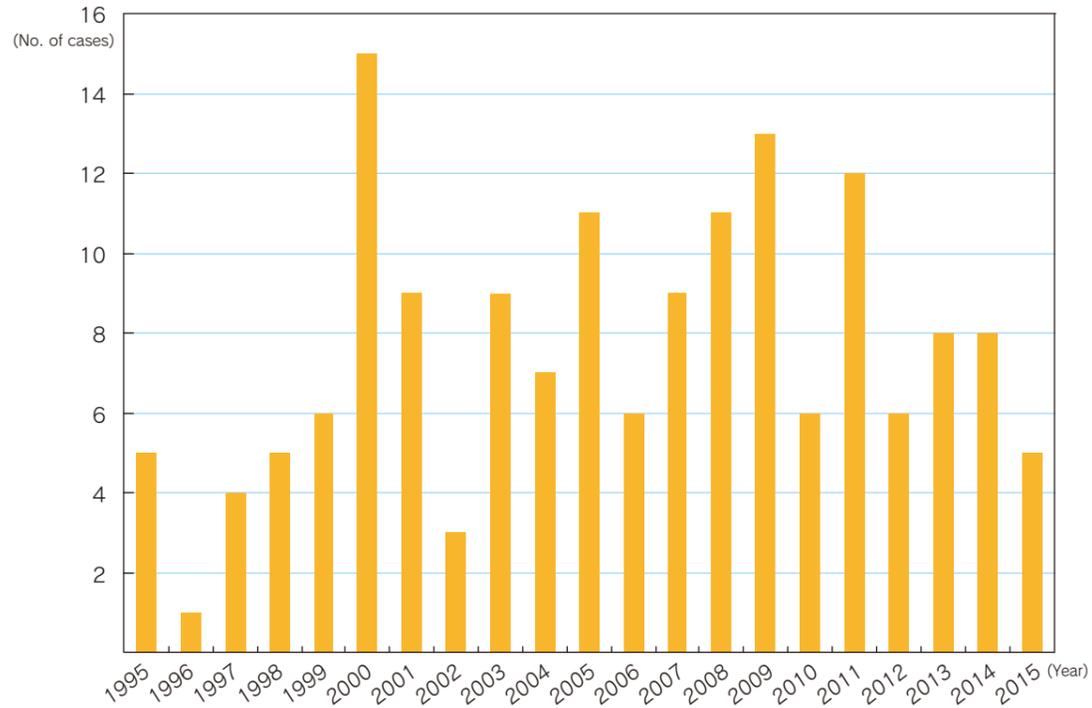
- ① **Ulnar neuropathy in left hand**
The ulnar neuropathy was assumed to be caused by ulnar nerve compression during the bone marrow harvest procedure, to which paresthesia remained in the ulnar in the left hand (4th and 5th fingers).
- ② **Transient hemiplegia and residual, mild decrease in sensation**
The donor suffered from transient hemiplegia on the left side after waking up from general anesthesia. The donor recovered quickly without medication, was discharged and resumed a normal lifestyle. However, the donor had residual, mild hypoesthesia and numbness in the ulnar in the left hand (part where the little finger joins the palm).
- ③ **Mononeuropathy of the lateral femoral cutaneous nerve**
Mononeuropathy of the lateral femoral cutaneous nerve occurred in the donor after the harvest procedure was over. While the donor had no difficulties in his/her everyday life, there was residual numbness in the right inguinal region.
- ④ **Decreased sensation in right buttock region**
Decreased sensation in right buttock region occurred in the donor after the harvest procedure was over. While the donor had no difficulties in his/her everyday life, the decreased sensation did not disappear.
- ⑤ **Postoperative causalgia in hips**
Donor had persistent lower backpain for a long period of time after the harvest procedure was over. Residual pain in the site of bone marrow harvest (hips).
- ⑥ **Reflective sympathetic dystrophy**
Donor experienced residual pain and numbness from around the left hip to the left femoral region after the harvest procedure was over.
- ⑦ **Traumatic sciatic neuropathy**
Donor experienced residual pain in lower left limb and numbness after the harvest procedure was over.
- ⑧ **Sacroiliitis**
Donor experienced sacroiliitis and residual pain after the harvest procedure was over.
- ⑨ **Left lateral femoral cutaneous nerve disorder**
Donor experienced numbness and sensory disorders such as tactile sensation in the left thigh and deficit of thermal sensation after the harvest procedure was over. While the numbness disappeared afterwards, paresthesia remained.
- ⑩ **Postoperative causalgia in hips**
Donor had persistent pain from left hip region to buttock for a long period of time after the harvest procedure was over. Residual pain in the left hip region.
- ⑪ **Right lateral femoral cutaneous nerve disorder**
Donor experienced numbness and sensory disorders such as tactile sensation in the right thigh and deficit of thermal sensation after the harvest procedure was over. While the numbness disappeared afterwards, paresthesia remained.
- ⑫ **Slipped disk, cervical spinal canal stenosis**
Slipped disk and cervical spinal canal stenosis became more apparent in the donor after the harvest procedure was over. Residual symptoms such as numbness in the left femoral region, inability to raise both arms vertically, and Gower's sign.
- ⑬ **Lower backpain in bone marrow puncture site in right iliac**
Donor experienced pain in the bone marrow puncture site and persistent decreased in sensation in the lower right limb.
- ⑭ **Left sacroiliac joint refractory pain**
Donor experienced numbness from left hip to buttock and persistent dull pain after the harvest procedure was over.
- ⑮ **Bone pain after bone marrow harvest procedure**
Donor experienced persistent pain in the bone marrow harvest site due to increased bone formation after the harvest procedure was over.
- ⑯ **Lumbar radiculopathy**
Donor developed lumbar radiculopathy after the harvest procedure was over, and had persistent lower backpain and paresthesia.
- ⑰ **Lumbar radiculopathy and left ulnar neuropathy**
Donor developed lumbar radiculopathy after the harvest procedure was over, and had persistent lower backpain and paresthesia. Donor also suffered an injury on the left ulnar nerve that led to paresthesia in the ulnar in the left hand (5th finger)
- ⑱ **Lumbar (intervertebral) disk disorder**
Donor was diagnosed with lumbar (intervertebral) disk disorder after the harvest procedure was over, and experienced discomfort in hip region and persistent numbness in toes.

- ⑲ **Peripheral neuropathy in left hip**
Donor experienced persistent numbness from left hip region to toes after the harvest procedure was over.
- ⑳ **Peripheral neuropathy in right femoral region**
Donor experienced paresthesia in anterior and lateral right femoral region after the harvest procedure was over.
- ㉑ **Peripheral neuropathy with neuropathic pain**
Donor experienced persistent pain in right hip region and numbness in lower right limb after the harvest procedure was over.
- ㉒ **Lower backpain and lower backpain with internal derangement of both knee joints**
Donor experienced persistent lower backpain after the harvest procedure was over and was diagnosed with lumbago. As donor tried to walk with lower backpain, donor experienced pain in both knees and was subsequently diagnosed with internal derangement of both knee joints with persistent pain.
- ㉓ **Numbness in the left lateral femoral cutaneous nerve region**
Donor experienced persistent numbness in the left lateral femoral cutaneous nerve region after the harvest procedure was over.
- ㉔ **Persistent discomfort and pain in left shoulder**
Donor experienced persistent discomfort and pain in left shoulder after the harvest procedure was over.
- ㉕ **Numbness and discomfort from left hip joint to left femoral region and knee**
Donor experienced persistent numbness from left hip joint to left femoral region and knee after the harvest procedure was over, and was diagnosed with left meralgia paresthetica.
- ㉖ **Numbness in left hip region**
Donor experienced persistent numbness from left inguinal region to left hip region after the harvest procedure was over.
- ㉗ **Pain in puncture site and lower backpain**
Donor experienced persistent pain in puncture site and lower backpain after the harvest procedure was over.
- ㉘ **Rheumatoid arthritis**
Donor experienced neuropathic symptoms (joint, swelling, as well as decreased grip strengths in both hands) with rheumatoid arthritis after the harvest procedure was over.
- ㉙ **Sacroiliitis**
Donor experienced persistent pain in lower left limb and lower backpain after the harvest procedure was over.
- ㉚ **Numbness and pain in both hands**
Donor experienced persistent pain and numbness in both hands (4th and 5th fingers in both left and right hand respectively) after the harvest procedure was over.
- ㉛ **Persistent pain from harvest site to femoral region**
Donor experienced persistent pain from harvest site to femoral region after the harvest procedure was over.
- ㉜ **Cutaneous gluteal neuropathy**
Donor experienced persistent numbness and pain in the superior cluneal nerve injury in left hip after the harvest procedure was over.
- ㉝ **Pain in femoral region and numbness in lower limbs**
Donor experienced persistent pain in femoral region and numbness in lower limbs after the harvest procedure was over.
- ㉞ **Pain in right posterior superior iliac spine as well as pain and numbness in right lateral femoral region**
Donor experienced persistent pain in right posterior superior iliac spine as well as pain and numbness in right lateral femoral region after the harvest procedure was over.
- ㉟ **Prolonged pain in bilateral pelvic puncture site**
Donor experienced persistent pain in bilateral pelvic puncture site after the harvest procedure was over.
- ㊱ **Tenderness at harvest site and pain during movement**
Donor experienced persistent tenderness in bilateral posterior iliac crest (harvest site) as well as pain during movement after the harvest procedure was over.
- ㊲ **Lumbago**
The lumbar disc disorder may have become more apparent and donor experienced persistent dull pain in lower back after the harvest procedure was over.
- ㊳ **Right superior cluneal nerve injury**
Donor experienced persistent pain in right gluteal region after the harvest procedure was over.

* For more details on the cases covered by the permanent disability benefit, please visit the JMDP homepage.

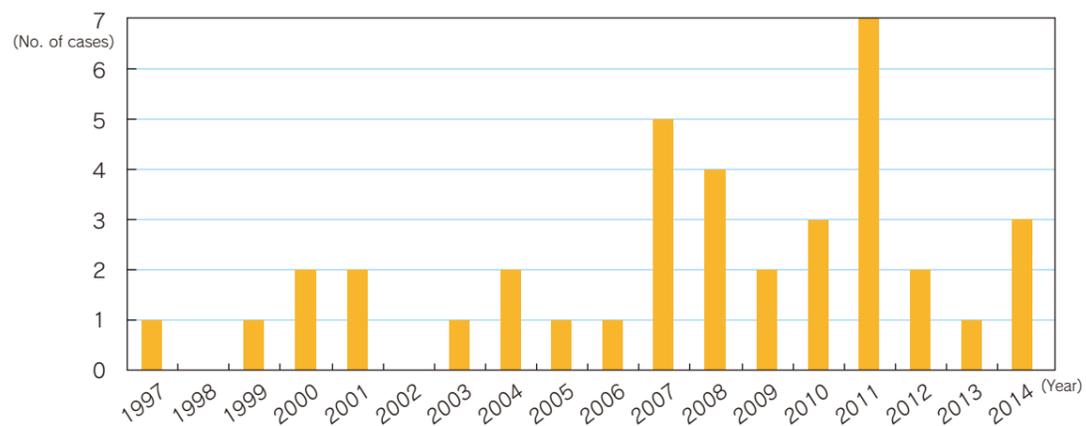
10 Number of yearly bone marrow harvest cases covered by the JMDP Group Accident Insurance
(covered between 1995 to the end of March 2016)

1 : Hospital-visit benefit



* Please visit the JMDP homepage for the list of cases covered by the "JMDP Group Accident Insurance".

2 : Permanent disability benefit



* There were no applications by bone marrow donors for the permanent disability benefit between 1995 to 1996.

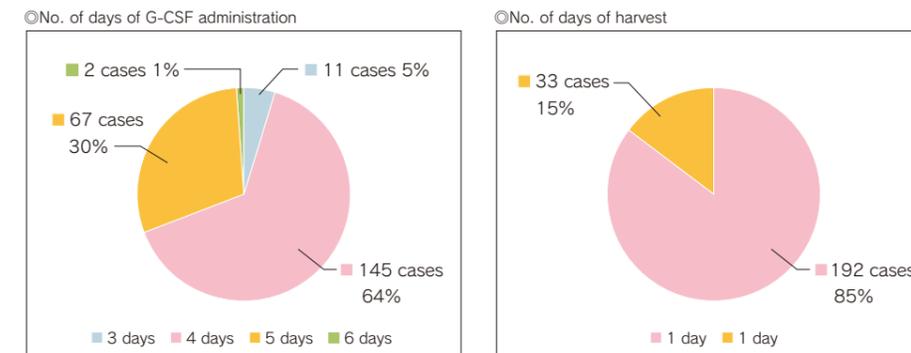
II. Peripheral blood stem cells donation

A. Peripheral blood stem cells harvest between unrelated individuals

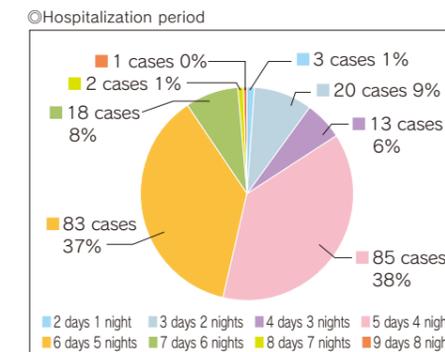
(aggregated data from March 2011 to the end of September 2016)

Between March 2011 to the end of September 2016, the JMDP has helped in coordinating 225 cases of peripheral blood stem cells harvest procedures implemented between unrelated individuals. We analyzed the data and are currently looking into ways to further improve the safety of donors.

1 No. of days of G-CSF administration, and harvest [No. of responses: 225]
(aggregated data from March 2011 to the end of September 2016)



2 Hospitalization period of peripheral blood stem cells donors [No. of responses: 225]
(aggregated data from March 2011 to the end of September 2016)



3 Status of adverse effects, and development of complications [No. of responses: 225]
(aggregated data from March 2011 to the end of September 2016)

Subjective, physical findings

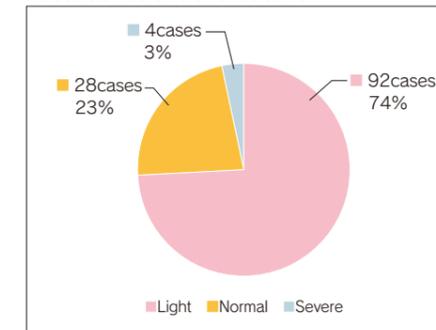
	Day 3 after G-CSF injection				Day of harvest				During hospital discharge				After hospital discharge			
	Mild	Moderate	Serious	Severe	Mild	Moderate	Serious	Severe	Mild	Moderate	Serious	Severe	Mild	Moderate	Serious	Severe
Fever	19				10		1		10							
Fatigue	39	2			33	2			37	2			20	3		
Insomnia	16	4	1		23	5			8	4			5			
Dizziness	1				2				2				4	1		
Loss of appetite	4				3	1			4				3			
Nausea	2					1			3	1			2			
Vomiting									1				1			
Skin rash	3				3				5	3			3	1		
Reactions on injection site					2				1	1			3			
Splenomegaly	6				5				3							

Pain

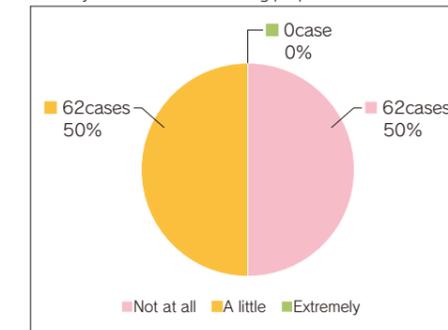
	Day 3 after G-CSF injection				Day of harvest				During hospital discharge				After hospital discharge			
	Mild	Moderate	Serious	Severe	Mild	Moderate	Serious	Severe	Mild	Moderate	Serious	Severe	Mild	Moderate	Serious	Severe
Back	38	4			27	3			13				4			
Bone pain	40	5			44	5	1		16	2						
Headache	30	1			22	4			14	1			3	2		
Lower backpain	123	10	1		102	14	1		59	5			5	1		
Puncture site	2				6				8	2			5	1		
Joints	17	1			21	2			6	2			2	1		
Arms	4				1	1			6	2			1	1		
Limbs	4	1			4	1			2					1		
Muscles	12	1			11	3			8	1			2			
Neck	11				7	1			4				1	2		
Throat	4				1				3							

4 Based on questionnaire sent 3 months after hospital discharge [No. of responses: 124]
(aggregated data from March 2011 to the end of September 2016)

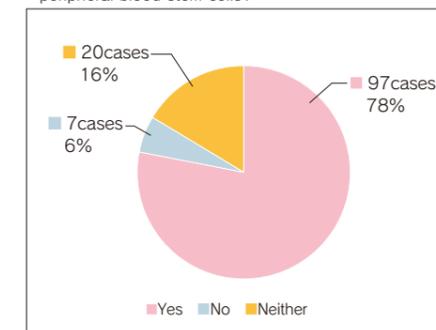
Do you experience any pain in the site where peripheral blood stem cells were harvested from?



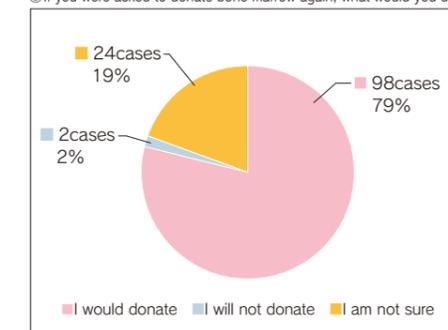
Were you worried about donating peripheral blood stem cells?



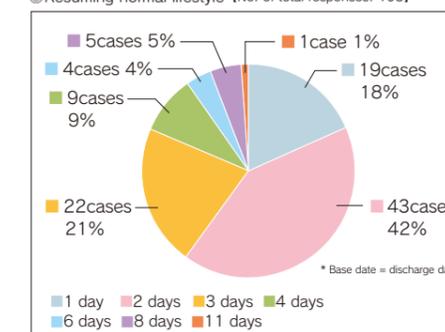
Did your family approve of your decision to donate peripheral blood stem cells?



If you were asked to donate bone marrow again, what would you do?



Resuming normal lifestyle [No. of total responses: 103]



B. Peripheral blood stem cells harvest between related individuals

(aggregated data from 2000 to 2005)

The JMDP has coordinated a total of 225 cases of peripheral blood stem cells donations between unrelated individuals from March 2011 to the end of September 2016. We have also published data on donations between blood relatives * for your reference.

* The Japan Society for Hematopoietic Stem Cell Transplantation has conducted medical examinations and questionnaires once a year for 5 years as a "Follow-up project on allogeneic peripheral blood stem cells donors" on donors who provided peripheral blood stem cells for blood relatives during 2000-2005 (ended in 2010). The following 1 to 4 are analyzed data based on cases obtained through this project.

Other than the aforementioned "Follow-up project on allogeneic peripheral blood stem cells donors", the Japan Society for Hematopoietic Stem Cell Transplantation is also following up on donors who donated bone marrow as well as peripheral blood stem cells for blood relatives since 2005 ("Follow-up project on blood hematopoietic stem cells donors"). The cases in this project will not be reported as they are still currently under study, but you can refer to the website of the Japan Society for Hematopoietic Stem Cell Transplantation for more details.

<http://www.jshct.com/index.shtml>

1 Relatively short-term severe health abnormalities

① Probably temporary due to G-CSF injection 9/3264 donors = 0.28%

Symptoms	No. of donors	Calculated from the day of first injection of G-CSF	
		Day of onset	Day of disappearance
Abnormalities in liver function	8	Days 3 to 10	Days 11 to 36
Loss of appetite, nausea, vomiting	1	Day 4	Day 19

② Probably temporary due to harvest procedure 19/3264 donors = 0.58%

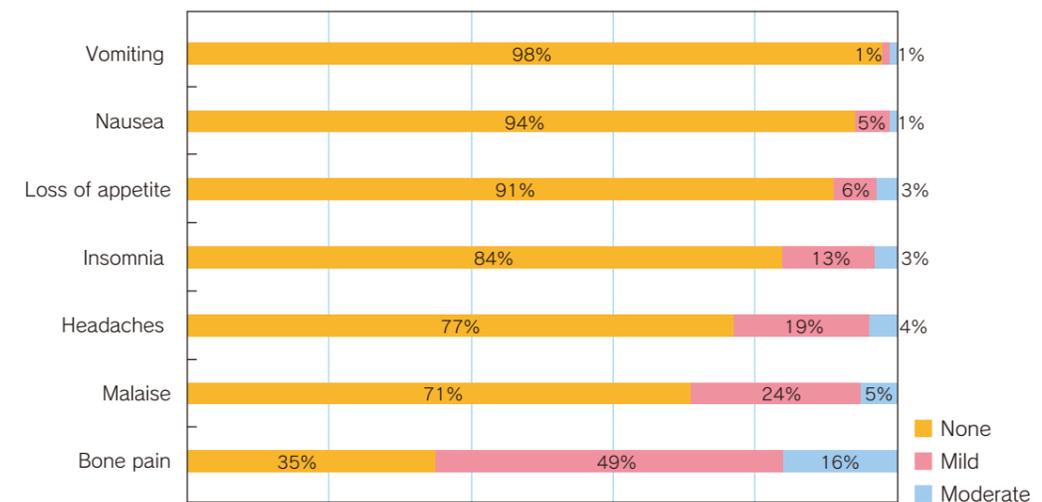
Symptoms	No. of donors	Calculated from the day of first injection of G-CSF	
		Day of onset	Day of disappearance
Thrombocytopenia	13	Days 2 to 6	Days 8 to 111
Vasovagal reflex	2	Day 4	Days 4 to 5
Tetany	1	Day 4	Day 6
Paresthesia in limbs	1	Day 4	Day 6
Hematoma in puncture site	1	Day 7	Day 13
Migraines	1	Day 9	Day 10

③ Clearly severe 19/3264 donors = 0.58% * Causal relationship with G-CSF not yet established.

Symptoms	No. of donors	Calculated from the day of first injection of G-CSF	
		Day of onset	Day of disappearance
Heart attack	4	Days 2 to 4	Days 4 to 6
Deep vein thrombosis	1	Day 14	—
Peritoneal fluid, pericardial effusion, systemic edema	1	Day 7	Day 9
Blood in phlegm	1	Day 3	Day 5
Subarachnoid hematoma (operation)	1	Day 23	Day 48
Retroperitoneal hematoma/anemia (operation)	1	Day 4	Day 25
Hemorrhagic stomach ulcer	1	Day 8	Day 16
Interstitial pneumonia	2	Days 3 to 25	Days 6 to 70
Gout attack/ acute cholecystitis (operation)	1	Day 2	Day 19
Fever or infection	5	Days 2 to 7	Days 12 to 32
Slipped disk	1	Day 7	Day 62

* There have been 25/5921 cases of short-term "clearly severe health abnormalities" reported in bone marrow donors, and this statistic is not significantly different from that of in peripheral blood stem cells donors (based on a joint survey conducted by the Japan Society for Hematopoietic Stem Cell Transplantation and Ministry of Health, Labour and Welfare Scientific Research Unit)

2 Other non-severe health abnormalities where the causal relationship with G-CSF injection and harvest procedure cannot be denied that appeared within 30 days





3 Health conditions of donors from annual medical examinations

(6233 reports obtained from 1708 donors in a maximum period of 5 years)

No health abnormalities	Health abnormalities present * Only the main abnormality is stated when there are multiple abnormalities in any one donor
1223/1708 (71.6%)	485/1708donors (28.4%) A.Abnormalities present even before donation: 109 (6.4%) B.Abnormalities that appeared after donation, and thought to be temporary or due to lifestyle (colds, traffic accidents, pregnancies, high blood pressure, diabetes, surgeries etc.): 133 (7.8%) C.Abnormalities that appeared after donation but not listed in B:C-1)Non-neoplastic, non-severe:204(11.9%) C-2)Non-neoplastic, severe:26 (1.5%) C-3)Tumors other than blood: 12 (0.7%) C-4) Hematological tumor: 1 (0.06%)

* The (%) is a ratio of the total number of 1708 donors

4 Relatively long-term, severe health abnormalities where the causal relationship with the peripheral blood stem cells harvest procedure is unclear and cannot be denied

	Symptoms	No. of donors	Month of onset after donation
C-2) Non-neoplastic, severe: 26 donors	Abnormal thyroid function	7	10 to 34 months later
	Uterine fibroid	3	14 to 36 months later
	Chronic rheumatoid arthritis	2	20 to 23 months later
	Cerebral infarction	2	7 to 33 months later
	Subarachnoid hematoma	1	9 months later
	Cataracts	1	7 months later
	Fundus hemorrhage	1	33 months later
	Atopic dermatitis	1	12 months later
	Uveitis	1	20 months later
	Bronchial asthma	1	20 months later
	Endometriosis	1	20 months later
	Idiopathic thrombocytopenic purpura	1	27 months later
	Molar pregnancy	1	9 months later
	Cerebral aneurysm	1	24 months later
	Pancreatic cystic tumor	1	49 months later
IgA nephropathy	1	44 months later	
C-3) Non-hematological tumors: 12 donors	Breast cancer	6	4 to 43 months later
	Stomach cancer	1	23 months later
	Uterine cancer	1	10 months later
	Brain tumor	1	6 months later
	Pharyngeal cancer	1	13 months later
	Lung cancer	1	54 months later
C-4) Hematological tumors: 1 donor	Prostate cancer	1	55 months later
	Acute myelogenous leukemia	1	14 months later

* There is another case where a donor with pre-existing myeloproliferative disorder developed leukemia 48 months later.

Reference Information

©There are insurance products that will may insurance payouts for hospitalization for bone marrow donations. Please contact the insurance company you would like to buy the product from for more details.

©There are local governments that have introduced a subsidy system for donors.

Please refer to the JMDP website for more information on the local governments.
http://www.jmdp.or.jp/donation/about/post_202.html

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