Information sheet about bone marrow removal under general anesthesia

Dear donor,

you have been identified as a suitable **bone marrow donor** for a patient. We would like to thank you again for your willingness to donate. In the following text we would like to provide you with information about the planned donation.

Prior to the transfer (transplantation) of your bone marrow stem cells, the patient will undergo very intensive chemotherapy and radiation (called conditioning). This requires not only the destruction of malignant cells but also the destruction of the patient's normal hematopoietic cells to create the conditions for the transfer of your healthy hematopoietic cells. If the transfer of your donated bone marrow cells is not performed in a timely manner, the likelihood of life-threatening infections increases.

Bone marrow transplantation has been successfully performed since the 1970s and is the method of choice for specific congenital diseases and for children. In 1990, the Nobel Prize for Medicine was awarded for this treatment method.

The hematopoietic stem cells are located in the bone marrow cavity of the large tubular bones as well as in the vertebral bodies and the pelvic bone. Especially in the **posterior pelvic bone**, where the pelvic bone can be felt directly under the skin on both sides, there is a low-risk access route with a very low risk of nerve or blood vessel injury. Very rarely, nerve or blood vessel injury and hemorrhage may occur. There, only one (up to a maximum of two) small skin incisions on each side is made to create the conditions for sufficient bone marrow blood mixture to be collected in syringes via **multiple punctures** of the underlying pelvic bone. The "bone marrow blood" that is drawn contains many stem cells, but they only a small fraction of your total bone marrow.
After collection, your body makes up for the loss within a few weeks by producing new cells.

Preliminary examination
In addition to matching tissue compatibility characteristics, your health suitability is an essential prerequisite for bone marrow donation. This is checked by the extensive examination program on the day of the preliminary examination.

During the preliminary examination, blood will be taken from a vein in your body. From this blood, the characteristics (parameters) required to assess your suitability as a donor will be determined. In addition to the values for the so-called blood count, the function of your organs (organ function parameters) and a check of your blood coagulation (coagulation status), above all possible infectious diseases are ruled out (infection markers determined). These include in particular HIV, syphilis and hepatitis (infectious jaundice), but also other viral infectious diseases. For certain infectious diseases there is a legal obligation to report, which the processing laboratories or we must comply with even without your consent.
All findings obtained during the preliminary examination will be summarized in a doctor's letter (medical expert opinion) and communicated to you. If you agree, your family doctor will also receive a copy of the letter. Pathological findings and the resulting action steps (consequences) will be explained.

In the course of the above-mentioned blood collection, samples are also taken in some cases which are intended to be sent to the patient's transplant center (precollection samples).

Bone marrow collection procedure
As a rule, you will be hospitalized at the MediaPark Klinik Cologne one day before the bone marrow collection. If necessary, you will be examined again by a physician and seen by an anesthesiologist. The collection is then performed in the morning of the next day under anesthesia in the operating room and takes about 1 to 2 hours. For the posterior pelvic bone puncture, you will need to be placed in prone position after anesthesia induction in the operating room. Then, approximately 1/2 to about 1 liter of

bone marrow blood is collected from both posterior pelvic bones, with the amount to be collected is based solely on the patient's weight.
For your protection, the maximum permitted collection amount is 20 ml of bone marrow blood per kg of your body weight (e. g. at 75 kg max. 1.5 liters of collection). After donation, you will remain hospitalized overnight for observation. If there are no abnormalities after the bone marrow collection, you will be discharged the following day after another medical examination.

The main risk associated with bone marrow donation is an anesthetic incident. You will be informed about this in a separate consultation by a specialist in anesthesiology. In rare cases, the prone position before collection may cause nerve damage. Reduced visual acuity (worsening of vision) if the head is not positioned carefully has been reported extremely rarely. Minor postoperative bleeding may occur in the area of the puncture sites. These can be easily controlled by local compression and may lead to local bruising (“blue spots”). Theoretically, there is also the possibility of nerve or vascular injury as well as hemorrhage. Furthermore, the occurrence of an infection in the sense of osteomyelitis (bone marrow inflammation) has been observed very rarely. These complications are extremely rare, as there are practically no major vascular or nerve structures in the surgical area. Furthermore, in a few isolated cases, the blunt end of the puncture instrument (puncture cannula) remained in the bone and had to be surgically removed.

Blood loss during collection regenerates in approximately 1-3 months, according to the amount collected. The iron loss associated with bone marrow collection can be compensated by administering an iron preparation. We will decide whether this is necessary in your case during the consultation.

Only in absolutely exceptional cases is the administration of foreign blood necessary. This results in a very low risk of transmission of hepatitis (hepatitis B 1:500,000; hepatitis C 1:13 million) or other infections (HIV 1:11 million).

You will experience minor to moderate soreness in the area of the injection site for a few days, which can be treated well with painkillers. Overall, these side effects are of a lighter nature and disappear after a few days. To minimize the risk of secondary bleeding, avoid major physical exertion during the first five days and extreme exertion for a further five days, as injury to the ISG joint cannot be ruled out despite the application of the utmost care.

The **journey to** and from the donation should be made by public transport (plane, train, bus, taxi). If you travel by your own car, we recommend an accompanying person who can act as a driver.

In the event of incapacity for work, we will issue an appropriate medical certificate. The donor registry will be informed of this and will reimburse the employer for the loss of earnings.
The donor registry will be informed about the progress of the collection.

Follow-up examination

Within one week after the collection, the donor registry will contact you by phone to inquire about your physical and emotional condition.

30 days after donation, your blood results will be rechecked. We ask your family doctor to take the blood sample required for this purpose. After 6 months, 1, 2, 5 and 10 years you will again be asked in writing by the donor registry how you are feeling.

Second donation

In some cases, a second donation of stem cells or lymphocytes (= white blood cells that help to fight viral infections and malignant neoplasms) is necessary for the same patient for medical reasons. Such a second donation would be made from a vein (as a peripheral blood stem cell donation), a second operation would be excluded here. Before a possible second donation, a new, often shortened health examination takes place. In any case, a new declaration of consent is required from you. We would like to inform you already now about what you would have to expect in case of a second donation.

Information on peripheral blood stem cell donation

In healthy donors, stem cells are found exclusively in the bone marrow. The various blood cells develop from them: white blood cells = leukocytes; red blood cells = erythrocytes; platelets = thrombocytes. A certain type of white blood cells, which serve to defend against bacterial and fungal infections, is called granulocytes. Stem cells can be washed out into the peripheral blood under the influence of certain messenger substances, which occur naturally in the body of every human being, but are also available as drugs. One such messenger substance that stimulates the formation of granulocytes (= white blood cells that serve to defend against bacterial and fungal infections) is the so-called granulocyte colony stimulating factor (G-CSF). The administration of this substance as a drug leads to an increase in white blood cells in the blood, as well as after about 4-5 days to a flushing out ("mobilization") of stem cells from the bone marrow into the bloodstream. The drug (preparation) we use has the trade name **Granocyte®** (chemical short name: Lenograstim). It is a genetically engineered drug (preparation: G-CSF) and has been approved for use in the mobilization of allogeneic stem cells in healthy donors since 1998. It has been approved for use in patients since 1993.

G-CSF is administered over 5-6 days by injection into the subcutaneous fatty tissue (subcutaneous injection). We will explain the details of the administration of the drug to you in the subsequent consultation with the physician.

In the short term, i.e. during and 1-2 days after the application of G-CSF in healthy individuals, the following acute side effects have been observed:

- At the injection site: burning during injection, mild stinging or redness (up to 1%).
- headache, bone and/or muscle pain is frequently observed (70-80%), usually improves after taking paracetamol or ibuprofen
- general feeling of weakness, nausea, night sweats, mild fever occur less frequently, are also alleviated by above mentioned drugs
- an increase in the size of the spleen is common, but does not usually lead to symptoms. Worldwide, few cases of splenic rupture have been described so far. G-CSF was administered in a higher dosage than intended, and there was also evidence in the blood of one donor of an active infection with the so-called Ebstein-Barr virus (cause of Pfeiffer's glandular fever). To ensure greater donor safety, the size of the spleen is measured by ultrasound as part of the preliminary examination.
- In addition to the typical acute side effects mentioned here, other symptoms have also been reported in individual donors (< 0.1%) during treatment with the growth factor (e.g. nausea/vomiting, sleep disturbances, extremely rarely a skin rash in the context of an allergic reaction, weight gain due to fluid retention, capillary leak syndrome with increased permeability of the vessels to fluid, autoimmune phenomena, pneumonia).

The headache and pain in the limbs that occur during treatment with G-CSF do not usually make you unable to work. Nevertheless, you may be restricted in your daily life. In rare cases, the intensity of the side effects also exceeds the usual level. If you are unable to work, we will issue an appropriate medical certificate. The bone marrow donor registry will be informed of this and will reimburse the employer for the loss of earnings. The donor registry will be informed about the progress of the collection.

The documented use in more than 60,000 unrelated donors, as well as the results of the follow-up of these donors, have so far shown that stem cell mobilization with G-CSF **does not cause any permanent side effects**. In this large number of donors, the occurrence of various diseases during the course has been reported, including isolated cases of leukemia and lymphoma. The majority of blood diseases concerned family donors (siblings who donated for a sibling suffering from a malignant blood disease). Overall, there is no statistical evidence for an increased incidence of leukemia or other malignant blood diseases in donors (stimulated with G-CSF) compared to the "normal population".

All findings on the mechanism of action of G-CSF as well as the fact that this substance is also produced in the body itself throughout life, also speak against this assumption.

You should ensure **safe contraception** prior to and during stem cell mobilization

The actual extraction of stem cells from the blood is performed by a so-called blood stem cell separation (synonym blood stem cell apheresis). The **cell separators** used for this purpose are tested and approved devices that extract only very specific components from the blood and in parallel ensure the return of the other blood cells.
They essentially consist of pumps that control the blood flow and a centrifuge that separates the blood into its components. **Two venous accesses** (left and right arm) are required to perform the separation. Venipuncture may cause bruising, and in very rare cases, injury to other vessels and nerves.

A **new, sterile disposable tubing set** is used for each donor, which is closed and thus excludes any possible transmission of infection by blood from previous collections. The tubing set is first pre-filled with saline solution and thus at the same time deflated. You are then connected to the tubing system and your blood flows inside the tubing system into the separator. In parallel, your blood is returned to you via the other access. During the procedure, approx. 185 to 280 ml of your blood is outside your body in the disposable tubing system. At the end of the separation, the set is again rinsed with saline solution so that only a very small amount of your blood remains in the tubing system. In total, the process takes about **3 to 5 hours**. During this time, approximately three to four times the volume of your blood passes through the cell separator. For most donors (95%), performing a stem cell collection on the first of the two days designated for this purpose is sufficient to obtain enough cells for a successful transplant.

The blood cell separator is designed in such a way that any risk to the donor is largely excluded. As with any blood collection, dizziness, fainting, vomiting and hyperventilation may occur if the donor is predisposed to them. States of unconsciousness due to blood loss are rare, as there is no significant loss of blood volume (net blood loss).

To prevent your blood from clotting in the sterile tube set, an **anticoagulant** is added. The substance we use is called ACD. It is composed of citric acid and dextrose. Its mode of action is the binding of calcium ions, which are important for blood clotting and are also important for muscle and nerve activity. For this reason, "tingling" sensations and insensations may occur during donation (especially in the fingertips and around the mouth area). These symptoms can be quickly remedied by administering calcium in tablet form or as an infusion.

Heparin is also used as an additional anticoagulant. This drug can lead to a reduction in platelets in very rare cases when used over the long term. In the short term, this drug does not cause any discomfort for the donor.

In many cases, stem cell collection results in a drop in the blood platelet count (thrombocytes). It can be assumed that after stem cell collection the number of platelets in the blood is below normal for about seven days. However, the occurrence of a bleeding tendency is extremely rare, because the measured values are usually only just below the normal range. Complications such as blood loss, hemolysis, embolism, allergic reactions, or excessive fluid loss are not to be expected and can only occur due to errors in treatment or in handling the device.

Explanations on data protection

We hereby would like to fulfill our legal obligation and inform you transparently about our processing procedures of your personal data.

In the course of the preliminary examination and donation, findings and the progress are documented in a file kept by the physician. The results of examinations, including personal data on the course of donation, are recorded on documentation sheets or by EDP. These remain in the donation center. The collected medical data are passed on to the donor registry and in pseudonymized form to the transplant center. Documentation sheets and donor files are archived for at least 30 years.

The file serves as the basis for the collection of scientific data. Publications based on the data of this investigation will not contain information that allows identification of an individual donor.
With your consent according to Art. 6 para. 1 lit. a) and Art. 9 para. 2 lit. a) DSGV, you authorize us to systematically document and scientifically evaluate the findings collected from you. All information and examination results received from you will be treated as strictly confidential. In particular, side effects and adverse events will be documented without naming names and, if necessary, made known to the scientific-medical community through publication, provided they are of general interest and could be of significance for other donors.

Donor insurance

All actions directly related to the stem cell donation, including the necessary preparatory treatments, are covered by statutory accident insurance (SGB VII § 2 para. 1 No. 13 b).
Commuting accidents on the direct way to and from the donation center are also included in the insurance coverage and are also covered by the statutory accident insurance (Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege / BGW, Bezirksverwaltung Köln, Bonner Straße 337, 50968 Cologne, Phone: +49 221 37720).

You have now read the information sheet. In a few minutes, you will have the opportunity to clarify any unanswered questions in a consultation with a physician. We would like to ask you to confirm that you have read and understood this information sheet by signing it. Please confirm your consent to bone marrow donation in writing on the separate declaration of consent.

Thank you very much!