Published in final edited form as:

ISBT Sci Ser. 2015 April 1; 10(Suppl 1): 108–114. doi:10.1111/voxs.12150.

Protecting the Health and Safety of Cell and Tissue Donors

David F. Stroncek and Lee England

Cell Processing Section, Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, Maryland USA

Abstract

Centers involved with collecting the starting material for cell and tissue therapies are obligated to protect the recipient's and donor's health and safety. All donors face risks during and after the collection which can be minimized by prescreening donors and excluding those that the collection would place at increased risk of physical harm. Another important part of protecting donors is the use of appropriate collection facilities. Donor risk can also be reduced by using specially designed collection devices and ancillary equipment, using only trained collection staff and limiting the volume or quantity of biologic material collected. Donors should be monitored during and after the collection for adverse events, and should adverse events occur, they should be promptly and appropriately treated. Protecting the safety of cell, gene and tissue donors is particularly difficult because of the wide variety in the types of donors and material collected. Biological material used to manufacture cell and tissue therapies is collected from healthy volunteers, matched-related, matched-unrelated and autologous donors. Precautions should be taken to ensure that the team of medical professionals evaluating related donors is not the same as the team caring for the transplant recipient in order to be sure that the donor evaluation is not biased and the donor is not coerced into donating. In conclusion, protecting cell and tissue donors requires the use of the practices developed to protect blood donors and the implementation of many other measures.

Keywords

Cellular therapies; donors; donations; apheresis; marrow donation; marrow aspiration

Introduction

Facilities collecting blood for transfusion, and cells and tissue for therapeutic purposes, must establish policies and practices to both ensure the product's safety and the donor's suitability. Product safety measures protect the recipient from exposure to transfusion transmitted viral infections (TTVs) and is accomplished by asking donors screening questions that look for risk factors that expose them to transmissible infections as well as screening blood work to check for active infections. These screening tests must be done within a specified time frame of blood and cell collection. Protecting the health and safety of donors is equally as important. Most people feel an ethical obligation to protect both

recipients and donors when collecting biological material, but there are also federal guidelines as well as standards from accrediting organizations and IRBs that should be followed.

There are many practical reasons to protect donor health and safety. Maximizing donor safety maintains the confidence and trust of donors and increases the likelihood that a person will become a repeat donor. Donors face a number of risks including potential physical and psychological harm, the loss of employment and insurability and the loss of privacy. This chapter will focus on, perhaps, the greatest risk to donors; that of physical harm.

Blood collection centers have developed numerous practices and processes to protect the health and safety of donors. The general principals used by blood collection centers also apply to people donating biological material for cell, gene and tissue therapies, but protecting the health and safety of these donors is more complicated. The type of donors used for manufacturing cell, gene and tissue therapies is as highly variable as the types of cells and tissues collected.

Risks and Donor Type

Risk to benefit analysis is an important consideration when looking at donor safety. Every reasonable attempt should be made to minimize the risk that all donors encounter, however the level of risk a donor should be permitted to encounter varies among the different types of donors. In addition, the seriousness of the recipient's condition, uniqueness of the product, the potential benefit of the therapy and the relationship between donor and recipient also affects the degree of risk a donor may be willing to assume, and therefore the collection center must place high regard to donor safety to protect them from taking excessive risks.

The starting material for cell and tissue therapies are collected from two types of donors: autologous and allogeneic. Autologous donors provide cells and tissues for self while allogeneic donors provide for others. Allogeneic donations can be further broken into categories: 1) minimally matched product for others, 2) HLA-matched products for a related recipient and 3) HLA-matched products for an unrelated recipient. The issues involved with protecting the health and safety of each of these types of donors varies, and all donors should be required to sign informed consent documents.

Healthy subjects often donate cells and tissue which requires no special matching and which will be used to manufacture therapies for strangers. These donors are much like blood donors in that they derive no direct benefit from their donation so the level of risk they face during the collection should be minimal (Table 1).

The most common type of cell and tissue donor is the autologous donor who donates cells that are used to manufacture therapies for themselves. When a person is donating cells that will be used to treat their own medical condition they derive direct benefit and they can be exposed to more risk than a healthy volunteer (Table 1). If the condition of an autologous donor is serious and the potential benefit of the therapy is significant, they may undergo considerable risk. As a result, the donor eligibility criteria for autologous donors may be extremely different (Table 2).

It is also common for people to donate highly matched cells or tissue to manufacture products for a relative or an unrelated person; for example hematopoietic stem cells for HLA-matched related or unrelated people needing a transplant. Because of the high degree of donor-recipient matching required, these products are very unique and these donors can assume more risk. However, matched related donors should not be exposed to more risk than matched unrelated donors even if related donors are willing to assume more risk. Minimizing the risks to donors of highly matched products for related recipients, however, can be challenging, and, in general, are much more difficult than minimizing the risk of subjects donating matched or unmatched cells or tissues for strangers.

Robust mechanisms are in place to protect the health and safety of healthy subjects donating hematopoietic stem cells (HSCs) for strangers. The World Marrow Donor Association and organizations similar to the US National Marrow Donor Program (NMDP) and have been set up in many countries to help protect the health and safety of unrelated hematopoietic stem cells donors [1]. These organizations actively work to minimize donor risk. They have defined standards and procedures relating to donor eligibility, donor screening and cell collection. They have specific centers focused solely on evaluating the donors and collecting cells. These organizations also actively collect data on the donors' experiences and adverse events and assess trends. By analyzing this data, they can develop new methods to minimize donor risk and, if necessary, they can modify standards and practices to further minimize risk.

Protecting people donating cells or tissue that is highly matched such as hematopoietic stem cells for transplantation for a relative is more problematic. Subjects donating cells or tissue for an HLA-matched sibling should not be subjected to more risk than a subject donating a similar matched product to a stranger. The AABB and FACT have standards to address the safety of these donors, however, health care professionals assessing the eligibility of matched related donors and collecting the HSCs are often the same as those caring for the transplant recipient [2]. As a result, the health care professionals evaluating the donor and collecting the HSCs are not entirely free to act solely in the best interest of the donor. When the team responsible for protecting the health and safety of related donors has such a conflict of interest, the potential donor may be subjected to more risk than donating through a marrow donor program. The matched related donor may have a medical condition that results in a greater than minimal possible risk for donating HSCs and that would normally make them ineligible to donate HSCs for a matched unrelated recipient, yet they may be asked to donate for a sibling.

Care must also be taken to avoid making the matched related donors feel coerced into donating. Related donors may derive considerable indirect benefit from donating for a relative and they may feel that they cannot refuse to donate even if they have a medical condition that would increase the risk of the collection. They may also be aware of risk factors for TTV infections that they do not want their family to know of causing a potential loss of privacy. It is important to create a situation which allows a potential donor to decline to donate. It is likely more difficult to refuse to donate if the team counseling the potential donor is the same as the team caring for the recipient. For these matched related donors,

efforts should be made to ensure that an impartial group is assessing the donor and collecting the cells.

Additional considerations are required for pediatric donors. There should be a strong family relationship between the donor and recipient and a high probability of benefit. For donors less than 18, the parents or guardian would give consent, but the minor, if possible, should assent to the procedure and the screening questions should be tailored to the age of the minor donor.

Commons Risks to Donor Health

The collection itself is generally when the donor faces the greatest risk. Most types of collections are also associated with risks immediately after the collection and some are associated with risks long after the collection. For some types of collections people can donate more than once, and repeat donations can create additional risks. Some donations require the donor to undergo anesthesia and receive drugs or growth factors which could put a fetus at risk. If this is the case, female donors should not be pregnant. Some drugs given to donors may present both immediate and possible long-term risks to the donor.

The nature of the risks that a donor faces is highly dependent on the collection and consequently the methods used to protect donors are variable and are collection dependent. Existing procedures and instruments have been validated for the collection of many types of cells. However, new collection methods must often be developed and validated. While the new methods are generally similar to those in use for other purposes, they are usually not identical. When these new methods are developed, the procedures used must be validated and potential risks to the donors must be anticipated.

Protecting Donors

Many factors are involved with minimizing donor risks. These include prescreening, making the collection as safe as possible, monitoring the donor after the collection, promptly intervening when problems arise and monitoring donor outcomes. The donor should be prescreened for factors that would place them at increased risk of donation. Prescreening might include health history questions, physical exam, blood tests and other medical evaluation. If large volumes of blood are to be collected, the donor's hemoglobin should be measured before the donation and potential donors with low levels should be excluded from donating. If marrow is to be aspirated to manufacture bone marrow stromal cells or a skin biopsy obtained to manufacture induce pluripotent stem cells, the donor's platelet count and coagulation measures should meet pre-defined criteria to be sure that they are not at increased risk from bleeding. Autologous donors are less likely to be excluded from donating. For example, autologous donors with extremely low platelet counts might be given a platelet transfusion prior to the collection procedure. This would not be acceptable for other types of donors.

The collection should occur in a facility suited to the specific needs of the collection and using equipment specifically designed for the collection. The collection staff should be well trained and experienced. Some procedures can be performed in an outpatient setting while

others must be performed in a more acute care setting. The type of facility used will depend on the nature of the procedure, the condition of the donor and the type of adverse events that might occur. For example the collection from healthy subjects of blood, small quantities of marrow, or leukocytes by apheresis can generally be safely performed outside of an acute care medical center. However, the collection of leukocytes by apheresis for autologous donation must usually be performed in an acute care medical center because of the patients underlying medical condition and central venous access catheters are often needed for the collection. Autologous donors may need treatments or testing immediately before or after the collection that are only available in an acute care setting. Autologous donors may also need more intensive nursing care during the collection.

When possible instruments and devices specifically designed and validated to collect specific types of cells should be used. There are many benefits from using such established devices such as blood cell separators to collect PBMCs or PBSCs. The risks associated with the use of these blood cell separators is well known as are the methods that can be used to minimize these risks. Performance limits of these instruments are also well defined. Standard operating procedures, training materials and methods for validation are also available.

The collection staff should be trained specifically for each collection procedure they perform. Their experience should be validated and staff should periodically undergo retraining. Standard operating procedures should be developed and followed. The risks that the collection presents to the donor can be reduced by limiting the volume of material collected, the volume of blood processed and the duration of the procedure.

Donors should be monitored after the collection and they should not be allowed to leave the collection center until they have met established criteria to indicate that it's safe for them to leave. For people donating blood or small quantities of marrow this may only mean that their blood pressure and pulse have returned to baseline, generally 10 to 15 minutes after the collection, but people donating large quantities of marrow may have to remain hospitalized for a day to allow them to recover from general or regional anesthesia and to be sure that their vital signs and hemoglobin level are stable.

Donors should be given instructions concerning appropriate post collection care. For example marrow donors must keep the aspiration site dry for a day or two in order to minimize the risk of infection. If a donor has received a sedative prior to the donation, it may not be appropriate for them to drive an automobile immediately after the collection. Donors should be advised concerning possible post-donation adverse effects such as excessive pain or abnormal drainage from the site and how these potential problems should be treated. It may be prudent to contact the donor a day or two after the collection to be sure they are recovering as expected and that no expected or unexpected adverse events have occurred.

For some types of donation longer term follow-up of the donor may be appropriate [1]. Many centers contact people who have donated marrow one or two weeks post-donation to be sure that their recovery is progressing as expected. When using a relatively new

collection procedure that could have long-term adverse effects related to the collection, periodic evaluation over many months or years may be needed. Post-donation follow up might include laboratory tests.

Both expected and unexpected adverse events related to the collection should be documented. The incidence of adverse events should be monitored and if the events are occurring more frequently than expected, procedures should be reviewed and possibly changed. If appropriate, donor outcomes should be published in medical journals so that other groups performing similar collections may benefit. It may be appropriate for new collection procedures to be performed as part of a research protocol under the supervision of an Institutional Review Board whose goal is to protect the safety of human subjects participating in research.

Specific Types of Donations

Apheresis Collections

Many cell therapies make use of leukocytes collected by apheresis as starting material. Monocytes isolated from peripheral blood mononuclear cell (PBMC) concentrates are used to make dendritic cells, T cells obtained from PBMC concentrates are used for donor lymphocyte infusions and to manufacture genetically engineered T cells such as chimeric antigen receptor (CAR) T cells, and natural killer cells can be isolated for culture and expansion. Peripheral blood stem cells (PBSCs) collected by apheresis are also a source of hematopoietic stem cells for transplantation. Several different blood cell separators have been specially designed to collect peripheral blood leukocytes and they have been validated and approved for this use. As a result the collect of leukocytes by apheresis is relatively safe [3, 4].

One of the potential hazards of apheresis is hypocalcemia due to the citrate anticoagulant used during the collection [5]. Hypocalcemia can be quickly corrected by stopping or slowing the flow of blood through the blood cell separator. However, ending a collection is not a good option when cells are being collected for autologous use or from a specially matched recipient. In addition, if large quantities of leukocytes are needed, the rate of collection can be slowed only to a limited degree. As a result, many centers administer calcium intravenously to the donor during the collection to treat or prevent citrate toxicity, however, care must be taken to avoid giving too much calcium, because calcium is also toxic [5]. Alternatively, heparin can be used in place of or in addition to citrate, but this could result in systemic anticoagulation and place the donor at risk of bleeding.

If a healthy subject donating an apheresis product that does not require specific matching has veins that will not support the large gauge needles needed for an apheresis collection, the donor would be excluded rather than exposing them to the risks associated with the insertion of a central venous catheter. However, because autologous apheresis products cannot be collected from another person, central venous catheters are often placed for the collection by apheresis of autologous cells.

While leukocyte apheresis procedures are designed specifically to collect mononuclear cells, a considerable number of platelets are also collected with PBMC and PBSC products. As a result the donor's platelet count will be lower after the collection. If the donor's platelet count is normal prior to the collection, the fall in platelet count will generally not be enough to place the donor at increased risk of bleeding. Some centers measure donor blood counts before and after the collection to determine if he/she has developed clinically significant thrombocytopenia. Since platelet counts return to normal within a few days, thrombocytopenic healthy subjects should not require platelet transfusions, but they should be counseled to avoid activities that could lead to trauma.

The Collection of Mobilized Peripheral Blood Stem Cells

The risks associated with collecting PBSC concentrates for transplantation are very similar to collecting PBMCs with a few important differences. PBSC collection procedures are generally longer in duration since more cells are needed and consequently more blood is processed. Because of the longer duration of PBSC collection procedures, citrate toxicity is more problematic. In addition, since more cells are collected, more of the donor's platelets are lost and thrombocytopenia is more problematic.

Perhaps that most important difference between PBSC and PBMC concentrate donors is that they are generally given a growth factor to increase the concentration of circulating stem cells or to mobilize stem cells. The most widely used growth factor is granulocyte colony-stimulating factor (G-CSF). For healthy subjects, typically a dose of 5 to 10 micrograms is given subcutaneously daily. The circulating levels of CD34+ cells begin to increase after about 3 days and reach a peak after 4 to 6 days of G-CSF administration [6, 7]. Generally, the PBSC concentrate collections begin after 4 or 5 days of G-CSF [8]. Some centers only collect one allogeneic PBSC concentrate, while others collect two. Many centers reduce donor risk by attempting to limit the donation to a single apheresis procedure since a second collection increases the chance that a central venous catheter will be needed and increases the loss of platelets and requires an additional dose of G-CSF. To avoid a second collection the quantity of CD34+ cells collected by the first procedure can be immediately measured and if adequate quantities of CD34+ cells have been collected, no further G-CSF is given and a second collection is not performed. If more cells are needed, another dose of G-CSF is given and another product is collected the following day.

To ensure that one collection contains sufficient quantities of CD34+ cells, the concentration of CD34+ cells in the donors' blood can be measured immediately prior to the collection and since the quantity of CD34+ cells collected is highly correlated with the concentration of CD34+ cells in the peripheral blood [9], this information can be used to estimate the volume of blood that must be processed by the blood cell separator to collect the targeted dose of CD34+ cells required for the transplant. If the donors' pre-collection CD34+ cell count is low, more blood must be processed, but if the CD34+ cell count is high, less blood must be processed and the procedure can be shortened which reduces donor risk.

The use of G-CSF in healthy subjects has been challenging and in some ways controversial. Challenging because of the high frequency of minor adverse events experienced by healthy subjects given G-CSF and controversial because of potential long-term adverse events [3,

10]. Most healthy subjects experience some adverse events related to G-CSF including headache, bone pain, insomnia or nausea [4, 10, 11]. Fortunately, these symptoms disappear within a few days after the last dose of G-CSF is given. Rare events associated with G-CSF administration include autoimmune reactions and ruptured spleens. Most subjects given G-CSF experience mild enlargement of their spleen [12] and rarely spontaneous splenic rupture. If a healthy subject receiving G-CSF experiences unexplained abdominal pain, a ruptured spleen should be considered.

Health care professionals responsible for administering G-CSF should be aware of these potential adverse events so they can appropriately counsel and evaluate the donor. If a donor is experiencing a severe reaction it must be determined if the donor is experiencing a more severe grade of an expected adverse event, a severe but uncommon G-CSF related event, or a problem unrelated to G-CSF. Then the donor must be treated appropriately.

There has been considerable concern about G-CSF administration being associated with an increased risk of leukemia and hematologic malignancy in healthy subjects [13, 14], but the careful monitoring by the NMDP of healthy unrelated marrow donors given G-CSF has not found any increased risk of cancer or leukemia or any other long term adverse effects due to the administration of G-CSF [15, 16].

Other factors are now available for mobilizing hematopoietic stem cells. Plerixafor mobilizes HSCs by a different mechanism than G-CSF and when used in combination with G-CSF it increases the level of circulating CD34+ cells more than G-CSF alone. Plerixafor has been approved for use with G-CSF to mobilize hematopoietic stem cells (HSCs) and it is being used to mobilized autologous HSCs in patients whose HSCs mobilized poorly in response to G-CSF or following chemotherapy [17, 18]. Plerixafor has also been used as a single agent to mobilize CD34+ cells in healthy subjects [19] and in combination with G-CSF in research studies [18]. This increased level of mobilization could make collections safer since it would allow for shorter collections and avoid second collections in a great proportion of donors.

Biosimilar G-CSF products are also available [20]. Biosimilars are also known as Similar Biotherapeutic Products (SBPs) and are similar in quality, safety and efficacy to a licensed biotherapeutic product [20]. Two licensed forms of recombinant forms of G-CSF have been available for many years: Granocyte (lenograstim, Chugai, Tokyo, Japan) and Neupogen (filgrastim, Amgen, Vienna, Austria). Extensive clinical data shows that Granocyte and Neupogen administration is safe and they are effective for mobilizing CD34+ cells for transplantation. A number of biosimilar forms of G-CSF manufactured by different companies are now available [20].

While it would be advantageous to have these alternative drugs available for HSC mobilization such as plerixafor or biosimilar forms of G-CSF, if a drug is not specifically approved by the FDA, EU or another regulatory agency for use in healthy subjects, it should be used with caution. Initially, a new mobilizing agent should only be used for mobilizing HSCs in healthy subjects in well-designed research studies that have been approved by an IRB. These studies should not only assess the drug's effectiveness, but its safety should be

assessed as well. Donors should be monitored very closely for both immediate and post-donation adverse events. If initial studies find that the drug is effective and safe, then it should be tested in larger multicenter studies before it is used routinely in healthy subjects. Even after a drug is being used routinely in healthy subjects, further monitoring and reporting on both immediate and long-term effects may be necessary to fully understand uncommon adverse effects.

The Collection of Marrow

Marrow is collected by multiple aspirates. Marrow can be collected from several different sites: the sternum, anterior iliac crest and posterior iliac crest. Since collecting marrow from the posterior iliac crest is safest, it is best to only allow collection from this location. When collecting small quantities of marrow for the production of BMSCs, only 15 to 50 ml is required and this volume can be collected by a few aspirates from a single site within a few minutes using local anesthesia [21]. Protecting the donor is relatively easy. When aspirating these small quantities of marrow from healthy subjects it is best to require that the donors' platelet count and coagulation times be normal to avoid excess bleeding, but few other donor safety exclusion criteria are necessary.

Collecting marrow for transplantation is much different. Typically 500 to 1500 ml of marrow is aspirated from multiple sites over an hour or two [22]. The collection of these large quantities of marrow requires that the donor undergo general or regional anesthesia. Consequently, the donor is exposed to the risk of both the collection and anesthesia. Of course, donors of these large volumes of marrow should have normal platelet counts and coagulation tests. General or regional anesthesia also presents a significant risk to the donor. The risks of anesthesia are worse if the donor is in poor health. Consequently, donors with health problems which would increase the risks associated with anesthesia are excluded. Since anesthesia risk and the risk of serious complications is greater in healthy older subjects [4], some marrow donor registries also exclude donors greater than 60 years of age. Conversely, the amount of marrow collected from pediatric donors must be based on their total body weight.

Conclusions

Protecting the health and safety of cell and tissue donors involves many of the same approaches used to protect blood donors such as health history screening, pre-donation testing and physical examination. However, the types and quantities of cells and tissue collected are extremely variable and the methods used to protect donor health and safety are unique for each donation type. In addition to health history screening and physical exam, methods often used include donor age restrictions, limits on the quantities of cells that can be collected, specifying the collection methods, limiting the collection duration and post donation follow up.

Acknowledgements

This work was supported by the Intramural Research Program of the NIH Clinical Center, Bethesda, Maryland, USA.

Reference List

1. Shaw BE, Ball L, Beksac M, Bengtsson M, Confer D, Diler S, Fechter M, Greinix H, Koh M, Lee S, Nicoloso-De-Faveri G, Philippe J, Pollichieni S, Pulsipher M, Schmidt A, Yang E, van Walraven AM. Donor safety: the role of the WMDA in ensuring the safety of volunteer unrelated donors: clinical and ethical considerations. *Bone Marrow Transplant*. 2010; 45(5):832–838. [PubMed: 20173787]
2. O'Donnell PV, Pedersen TL, Confer DL, Rizzo JD, Pulsipher MA, Stroncek D, Leitman S, Anderlini P. Practice patterns for evaluation, consent, and care of related donors and recipients at hematopoietic cell transplantation centers in the United States. *Blood*. 2010; 115(24):5097–5101. [PubMed: 20228276]
3. Pulsipher MA, Chitphakdithai P, Miller JP, Logan BR, King RJ, Rizzo JD, Leitman SF, Anderlini P, Haagenson MD, Kurian S, Klein JP, Horowitz MM, Confer DL. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2009; 113(15):3604–3611. [PubMed: 19190248]
4. Pulsipher MA, Chitphakdithai P, Logan BR, Shaw BE, Wingard JR, Lazarus HM, Waller EK, Seftel M, Stroncek DF, Lopez AM, Maharaj D, Hematti P, O'Donnell PV, Loren AW, Leitman SF, Anderlini P, Goldstein SC, Levine JE, Navarro WH, Miller JP, Confer DL. Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2013; 121(1):197–206. [PubMed: 23109243]
5. Bolan CD, Cecco SA, Wesley RA, Horne M, Yau YY, Remaley AT, Childs RW, Barrett AJ, Rehak NN, Leitman SF. Controlled study of citrate effects and response to i.v. calcium administration during allogeneic peripheral blood progenitor cell donation. *Transfusion*. 2002; 42(7):935–946. [PubMed: 12375668]
6. Stroncek DF, Clay ME, Smith J, Ilstrup S, Oldham F, McCullough J. Changes in blood counts after the administration of granulocyte-colony-stimulating factor and the collection of peripheral blood stem cells from healthy donors. *Transfusion*. 1996; 36(7):596–600. [PubMed: 8701454]
7. Stroncek DF, Clay ME, Herr G, Smith J, Jaszcz WB, Ilstrup S, McCullough J. The kinetics of G-CSF mobilization of CD34+ cells in healthy people. *Transfus Med*. 1997; 7(1):19–24. [PubMed: 9089980]
8. Stroncek DF, Clay ME, Smith J, Herr G, Ilstrup S, Kunkel LA, McCullough J. Composition of peripheral blood progenitor cell components collected from healthy donors. *Transfusion*. 1997; 37(4):411–417. [PubMed: 9111279]
9. Grigg AP, Roberts AW, Raunow H, Houghton S, Layton JE, Boyd AW, McGrath KM, Maher D. Optimizing dose and scheduling of filgrastim (granulocyte colony-stimulating factor) for mobilization and collection of peripheral blood progenitor cells in normal volunteers. *Blood*. 1995; 86(12):4437–4445. [PubMed: 8541532]
10. Stroncek DF, Clay ME, Petzoldt ML, Smith J, Jaszcz W, Oldham FB, McCullough J. Treatment of normal individuals with granulocyte-colony-stimulating factor: donor experiences and the effects on peripheral blood CD34+ cell counts and on the collection of peripheral blood stem cells. *Transfusion*. 1996; 36(7):601–610. [PubMed: 8701455]
11. McCullough J, Kahn J, Adamson J, Anderlini P, Benjamin R, Confer D, Eapen M, Hirsch B, Kuter D, Lazarus E, Pamphilon D, Stroncek D, Sugarman J, Wilson R. Hematopoietic growth factors--use in normal blood and stem cell donors: clinical and ethical issues. *Transfusion*. 2008; 48(9):2008–2025. [PubMed: 18564401]
12. Stroncek DF, Dittmar K, Shawker T, Heatherman A, Leitman SF. Transient spleen enlargement in peripheral blood progenitor cell donors given G-CSF. *J Transl Med*. 2004; 2(1):25. [PubMed: 15268759]
13. Avalos BR, Lazaryan A, Copelan EA. Can G-CSF cause leukemia in hematopoietic stem cell donors? *Biol Blood Marrow Transplant*. 2011; 17(12):1739–1746. [PubMed: 21745453]
14. Martino M, Fedele R, Massara E, Recchia AG, Irrera G, Morabito F. Long-term safety of granulocyte colony-stimulating factor in normal donors: is it all clear? *Expert Opin Biol Ther*. 2012; 12(5):609–621. [PubMed: 22444029]
15. Confer DL, Miller JP. Long-term safety of filgrastim (rhG-CSF) administration. *Br J Haematol*. 2007; 137(1):77–78. [PubMed: 17359373]

16. Navarro WH, Switzer GE, Pulsipher M. National marrow donor program session: donor issues. *Biol Blood Marrow Transplant*. 2013; 19(1 Suppl):S15–S19. [PubMed: 23085601]
17. Sheppard D, Bredeson C, Huebsch L, Allan D, Tay J. A plerixafor-based strategy allows adequate hematopoietic stem cell collection in poor mobilizers: results from the Canadian Special Access Program. *Bone Marrow Transplant*. 2014
18. Fruehauf S. Current Clinical Indications for Plerixafor. *Transfus Med Hemother*. 2013; 40(4):246–250. [PubMed: 24415962]
19. Devine SM, Vij R, Rettig M, Todt L, McGlauchlen K, Fisher N, Devine H, Link DC, Calandra G, Bridger G, Westervelt P, Dipersio JF. Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction. *Blood*. 2008; 112(4):990–998. [PubMed: 18426988]
20. Shaw BE, Confer DL, Hwang WY, Pamphilon DH, Pulsipher MA. Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of the World Marrow Donor Association. *Haematologica*. 2011; 96(7):942–947. [PubMed: 21719883]
21. Sabatino M, Ren J, David-Ocampo V, England L, McGann M, Tran M, Kuznetsov SA, Khuu H, Balakumaran A, Klein HG, Robey PG, Stroncek DF. Establishment of a Bank of Stored Clinical Bone Marrow Stromal Cell Products. *J Transl Med*. 2012
22. Stroncek DF, Holland PV, Bartch G, Bixby T, Simmons RG, Antin JH, Anderson KC, Ash RC, Bolwell BJ, Hansen JA. Experiences of the first 493 unrelated marrow donors in the National Marrow Donor Program. *Blood*. 1993; 81(7):1940–1946. [PubMed: 8461478]

Table 1

Relationship Among Donor Type, Donor-Recipient Matching and the Maximum risk a Donor Should be Exposed.

	Allogeneic Donors			Autologous
	Minimally Matched	Highly Matched for Related Recipient	Highly Matched for an Unrelated Recipient	
Direct Benefit to the Donor	None	None	None	High
Uniqueness of the Product	Low	High	High	High
Permissible Donor Risk	Minimal to Slight	Minimal to Moderate	Minimal to Moderate	High

Table 2

Comparison of Eligibility Criteria for Healthy* and Autologous Subjects† Donating Small Quantities of Marrow for the Production of Bone Marrow Stromal Cells at the NIH Clinical Center

	Healthy Subjects	Autologous Donors
Examination	Afebrile Normal blood pressure Normal heart rate	Afebrile
Medical History	Must not be pregnant	Must not be pregnant
Laboratory Tests		
Hemoglobin	Women; 12.0 gm/dL Men; 12.5	No lower limit
Neutrophil Count	$1 \times 10^3/\mu\text{L}$	No lower limit
Platelet Count	$150 \times 10^3/\mu\text{L}$	No lower limit
Prothrombin Time	15.2 seconds	No upper limit
Partial Thromboplastin Time	37.3 seconds	No upper limit

* Donating marrow to manufacture BMSCs to treat complications following allogeneic hematopoietic stem cell transplantation

† Donating marrow to manufacture BMSCs to treat left ventricular failure due to ischemic vascular disease