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# Recovery and Safety Profiles of Marrow and PBSC Donors: Experience of the National Marrow Donor Program

*John P. Miller,[1] Elizabeth H. Perry,[2] Thomas H. Price,[3] Charles D. Bolan Jr,[4] Chatchada Karanes,[5] Theresa M. Boyd,[6] Pintip Chitphakdithai,[1] Roberta J. King[1]*

[1] National Marrow Donor Program, Minneapolis, Minnesota; [2] Memorial Blood Centers, St. Paul, Minnesota; [3] Puget Sound Blood Center, Seattle, Washington; [4] Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland; [5] City of Hope National Medical Center, Duarte, California; and [6] American Red Cross, Washington, DC

Correspondence and reprint requests: Roberta J. King, MPH, National Marrow Donor Program, 3001 Broadway Street NE, Suite 100, Minneapolis, MN 55413 (e-mail: rking@nmdp.org).

*STATEMENT OF CONFLICT OF INTEREST: See Acknowledgements on page 36.*

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## ABSTRACT

**The National Marrow Donor Program (NMDP) has been facilitating hematopoietic cell transplants since 1987. Volunteer donors listed on the NMDP Registry may be asked to donate either bone marrow (BM) or peripheral blood stem cells (PBSC); however, since 2003, the majority of donors (72% in 2007) have been asked to donate PBSC. From the donor's perspective these stem cell sources carry different recovery and safety profiles. The majority of BM and PBSC donors experienced symptoms during the course of their donation experience. Pain is the number 1 symptom for both groups of donors. BM donors most often reported pain at the collection site (82% back or hip pain) and anesthesia-related pain sites (33% throat pain; 17% post-anesthesia headache), whereas PBSC donors most often reported bone pain (97%) at various sites during filgrastim administration. Fatigue was the second most reported symptom by both BM and PBSC donors (59% and 70%, respectively). PBSC donors reported a median time to recovery of 1 week compared to a median time to recovery of 3 weeks for BM donors. Both BM and PBSC donors experienced transient changes in their WBC, platelet, and hemoglobin counts during the donation process, with most counts returning to baseline values by 1 month post-donation and beyond. Serious adverse events are uncommon, but these events occurred more often in BM donors than PBSC donors (1.34% in BM donors, 0.6% in PBSC donors) and a few BM donors may have long-term complications. NMDP donors are currently participating in a randomized clinical trial that will formally compare the clinical and quality-of-life outcomes of BM and PBSC donors and their graft recipients.**


## KEY WORDS

National Marrow Donor Program • NMDP • Unrelated donor • Bone marrow donor • Stem cell donor • PBSC

## INTRODUCTION

In 1987, when the National Marrow Donor Program® (NMDP) first began matching volunteer donors with patients in need of a hematopoietic cell transplant (HCT), the only stem cell source available through the NMDP was bone marrow (BM). This changed in 1997 when the NMDP opened a protocol for the mobilization and collection of peripheral blood stem cells (PBSC) that was supported by an Investigational New Drug (IND) application with the Food and Drug Administration (FDA). This first protocol was open only to donors who had previously donated BM, but in 1999, a companion protocol was opened for first-time donors. By 2003, the number of PBSC donations exceeded the number of BM donations. Today, PBSC donations comprise over 70% of all adult donor donations. From the donor's perspective these two stem cell sources carry different

recovery and safety profiles. In 2004, the NMDP began enrolling donors in the PBSC versus Marrow Randomized Trial (0201) sponsored by the NMDP, and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). This trial will formally compare the clinical and quality-of-life outcomes of BM and PBSC donors.

We review the course of donor recovery from BM and PBSC donations and the serious adverse events and long-term complications associated with these two types of donation.

## METHODS

### Study Population

This report summarizes the donation and recovery experiences of first-time BM and PBSC donors whose donations were from November 2001 through March 2006. Also summarized are the acute and long-term complications of a cohort of BM donors whose collections were performed from December 1987 through December 1999 and the entire cohort of PBSC donors whose collections were performed from February 1997 through December 31, 2007.

### Overview of BM and PBSC Donation

All HCT donors donating BM or PBSC receive a medical history and physical examination prior to their donation to exclude the presence of physical conditions that might increase their risk of donation or the risk to the recipient.

### BM Donors

Depending on the volume of marrow they will donate, donors have 1 to 3 autologous units of blood collected prior to their marrow collection to minimize the likelihood of needing allogeneic transfusion. The donor's marrow is collected from the posterior iliac crests under either general or regional anesthesia. NMDP standards allow for a maximum of 20 mL marrow/kg donor weight to be collected. In the early years of the program, virtually all BM donors were hospitalized for 1 or 2 nights, but today, most donors are admitted to a same-day surgical unit on the morning of their donation and are discharged by late afternoon.

### PBSC Donors

PBSC donors receive filgrastim at a targeted dose of 10–12 μg/kg of body weight subcutaneously for 5 consecutive days. On day 5 alone, or on days 5 and 6, the donor's PBSC are collected by leukapheresis. The volume of whole blood processed ranges from 12 to 24 liters per collection, depending on recipient weight and/or degree of CD34 mobilization in the donor. Although the use of central venous catheters is discouraged, central venous catheters were inserted in about 1 in 5 women and 1 in 20 men. Issues surrounding central venous catheters are discussed in this issue of the Journal.

### Data Collection—Pre- and Post-donation Assessment for Marrow and PBSC Donors

A baseline symptom assessment is completed on BM and PBSC donors at the time of their physical examination and on the day of donation. Symptom assessments are also completed on PBSC donors on each day of filgrastim, just prior to the injection. Both BM and PBSC donors are contacted by the donor center post-donation at 2 days, 1 week, 1 month, 6 months, and annually to assess the presense of any new or residual symptoms. Donor symptoms are assessed using selected components of the NCI Common Terminology Criteria for Adverse Events (CTCAE 3.0). In addition, the annual follow-up includes a complete blood count (CBC) and white cell differential. Donors participating in BMT CTN 0201, the PBSC versus Marrow Randomized Trial, are also required to have CBC and differential performed at 1 month and 6 months post-donation.

## RESULTS

### Donor Symptoms Experienced During BM or PBSC Donation

Most BM donors and PBSC donors experienced symptoms during the course of their donation. Symptoms experienced by BM donors are almost always related to the collection of the marrow, whereas symptoms experienced by PBSC donors are most often associated with the administration of filgrastim.

### Symptoms Experienced by BM Donors

Pain was the most common symptom experienced by first-time stem cell donors. Figure 1A illustrates the most common pain sites and percentage of BM donors experiencing pain at various sites over time.

Pain directly related to the collection was most often reported by donors. At day 2 post-donation, 82% of donors reported either back pain or hip pain or both. Pain sites related to the anesthesia were also common, with 33% of donors experiencing throat pain and 17% experiencing headache on day 2 post-donation. Of those donors who experienced pain, the majority reported mild (grade 1) pain regardless of the pain site. By 1 month post-donation the pain had resolved for over 80% of donors. By 1 year the proportion of donors who reported any pain went down to <10%, which was similar to the baseline percentage.

Figure 1B illustrates the 6 most frequently reported symptoms other than pain over time. The most frequently reported symptom was fatigue, with 59% of donors reporting fatigue on day 2 post-collection; (46% mild [grade 1], 12% moderate [grade 2], 1% severe [grade 3] and <1% disabling [grade 4]). By 1

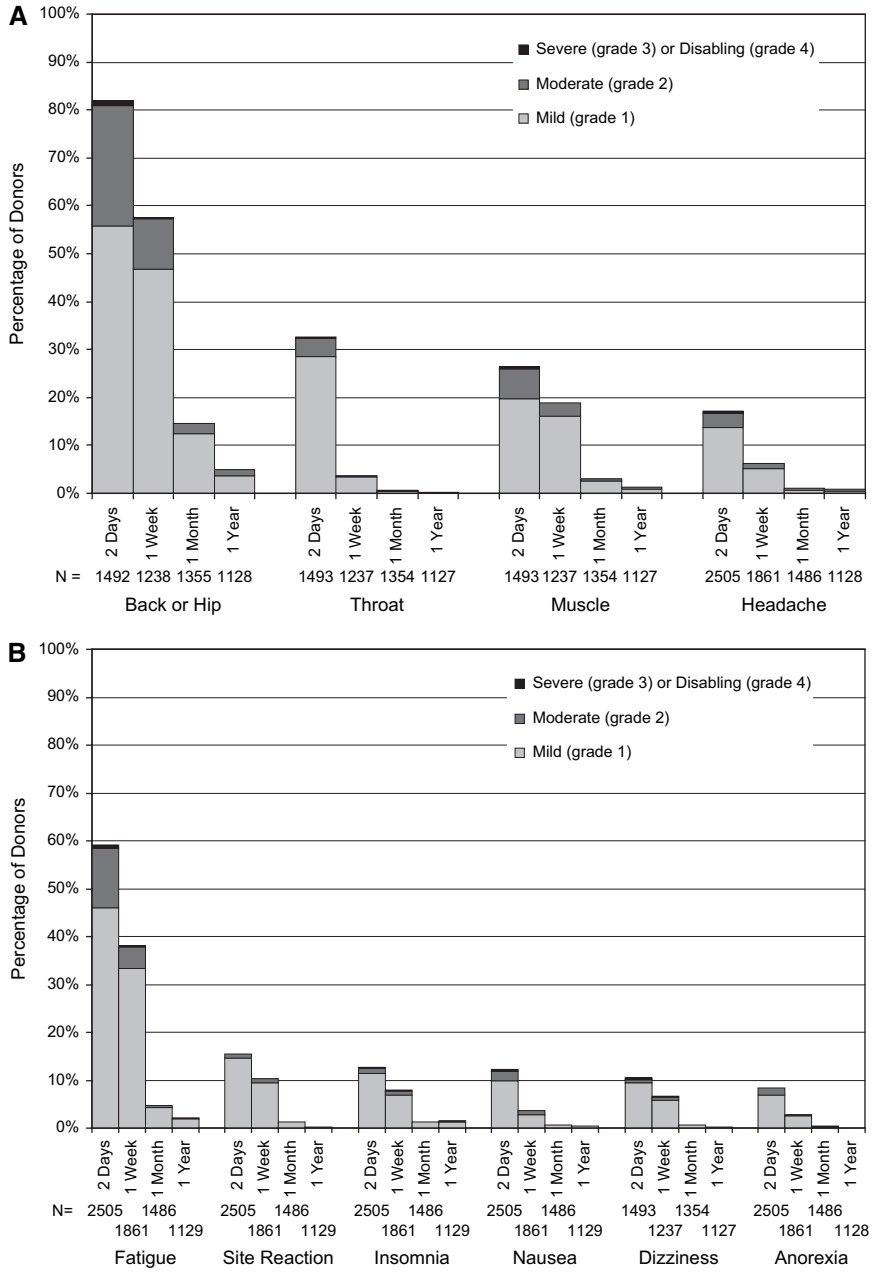


**Figure 1.** (A) Percentage of BM donors reporting pain at selected sites over time. Reports of pain and pain severity were collected at the indicated time points post-donation. Throat pain is largely restricted to donors receiving general anesthesia, whereas headache is more common in donors receiving regional anesthesia, for example, epidural. (B) Six most frequently reported body symptoms experienced by BM donors at the indicated time points post-donation.

month post-donation only 5% of donors were still experiencing some fatigue.

### Symptoms Experienced by PBSC Donors

Among the first-time stem cell donors going through mobilization and PBSC collection between November 2001 and March 2006, the most common symptom experienced was bone pain at various sites with 89% of donors reporting bone pain on day 5, the first day of collection (51% had mild pain, 35% had moderate pain, 3% had severe pain, and <1% reported disabling pain). By 1 week post-donation 90% of donors reported that the bone pain had resolved (Figure 2A).

At some point over the course of mobilization and collection (day 1 to day 5 or 6), 97% of donors experienced some degree of bone pain. The maximum severity of bone pain reported during this time was mild in 41%, moderate in 50%, severe in 6%, and disabling in <1% of donors.

Figure 2B illustrates the 6 most frequently reported symptoms other than bone pain by PBSC

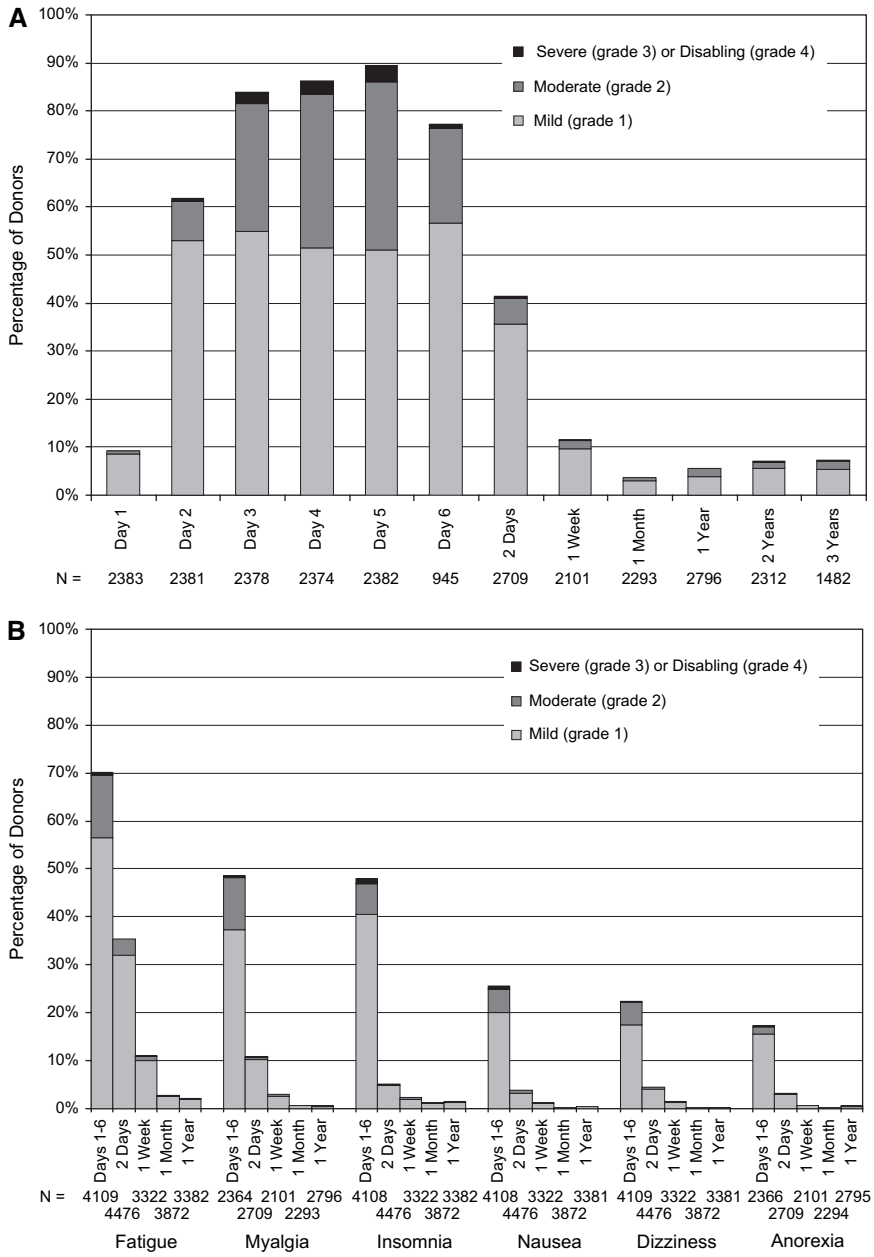


**Figure 2.** (A) Percentage of PBSC donors reporting bone pain over time. Reports of bone pain and severity of pain were collected at the indicated time points during mobilization, collection, and post-donation. Day 1 is the first day of filgrastim administration; day 5 is the first day of apheresis. Bone pain represents pain in at least one of the following sites: general bone pain, back, head, limb, joint, hip, and neck. The severity of bone pain is defined as the maximum grade among these pain sites. (B) Six most frequently reported body symptoms experienced by PBSC donors during mobilization and collection, and at the indicated time points post-donation. The percentages for day 1 to day 6 represent the frequencies of the highest grade of symptoms during mobilization and collection.

donors. Fatigue was the most commonly reported symptom, with 70% of donors experiencing fatigue at some point during mobilization and collection, followed by myalgia (49%), insomnia (48%), nausea (26%), and anorexia (22%). Most symptoms were mild (grade 1).

## Hematology

Donors undergoing either BM or PBSC donation experienced changes in their WBC, platelet, and hemoglobin values during the donation process. BM donors experienced changes in blood cell counts immediately following the donation mostly from loss of marrow and blood, whereas PBSC donors experienced changes in these values during both filgrastim administration and immediately following donation.

## BM Donors

Almost all donors donated autologous units prior to the marrow collection, and the majority (76%)

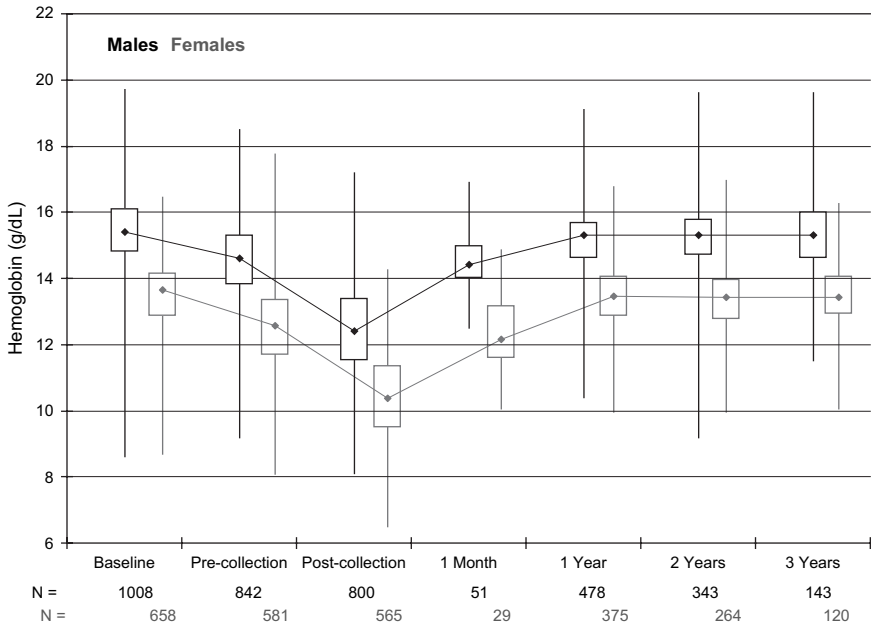


**Figure 3.** Box and whiskers plot of BM donor hemoglobin levels showing the maximum, upper quartile, median, lower quartile, and minimum values at baseline, the day of collection, and the indicated time points post-donation.

received at least 1 autologous unit after the marrow donation.

Immediately post-donation the median WBC of evaluated donors was 9.7 $\times$ $10^9$/L (interquartile range 7.6 to 12.7), compared to a baseline median value of 6.3 $\times$ $10^9$/L (interquartile range 5.3 to 7.4). This post-donation increase in WBC values is most likely because of the stress of the donation and anesthesia. By 1 month post-donation the median WBC of evaluated donors had returned to baseline values and at 3 years post-donation the median WBC was unchanged from baseline.

A slight decrease in median platelet counts was observed from baseline (251 $\times$ $10^9$/L, interquartile range 217 to 292) to immediately post-donation (214 $\times$ $10^9$/L, interquartile range 179 to 252). By 1 month post-donation median platelet counts had returned to baseline levels and remained at baseline levels at 3 years post-donation.

When compared with baseline hemoglobin values (males: median 15.4 g/dL, interquartile range 14.8 to 16.1; females: median 13.6 g/dL, interquartile range 12.8 to 14.1), a decrease in hemoglobin values was observed in both female and male donors immediately post-donation (males: median 12.4 g/dL, interquartile range 11.5 to 13.4; females: median 10.3 g/dL, interquartile range 9.4 to 11.3). A mild decrease in hemoglobin values persisted at 1 month post-donation for both male (median 14.4 g/dL, interquartile range 14.0 to 15.0) and female (median 12.1 g/dL, interquartile range 11.5 to 13.1) donors but returned to baseline levels by 1 year post-donation and remained at baseline levels at 3 years post-donation (Figure 3).

## PBSC Donors

Not surprisingly, by day 5 of filgrastim injections, PBSC donors experienced steep increases in their WBC values to a median of 38.5 $\times$ $10^9$/L (interquartile range 30.7 to 47.1). At 1 month post-donation, WBC values were slightly decreased from baseline (baseline: median 6.3 $\times$ $10^9$/L, interquartile range 5.3 to 7.6; 1 month: median 5.5 $\times$ $10^9$/L, interquartile range 4.6 to 6.6) but by 1 year post-donation, WBC values were indistinguishable from baseline levels and remained there at 3 years post-donation (Figure 4A).

Platelets declined slightly from baseline values over the 5 day course of filgrastim but declined dramatically immediately post-apheresis (baseline: median 253 $\times$ $10^9$/L; interquartile range 219 to 291; day 5 post-apheresis: median 136 $\times$ $10^9$/L; interquartile range 107 to 168). By 1 month post-donation, the majority of donors had platelet values within the normal range (median 242 $\times$ $10^9$/L; interquartile range 209 to 282). At 1 year post-donation, platelet counts returned to baseline levels and remained there at 3 years post-donation (Figure 4B). Significant thrombocytopenia is rare post-donation; donors with this finding are discussed in more detail below.

For both male and female donors, hemoglobin levels remained at baseline levels throughout the 5 day mobilization period but decreased immediately post-apheresis to a median of 13.8 $\times$ $10^9$/L (interquartile range 13.2 to 14.4) for males and 11.7 $\times$ $10^9$/L (interquartile range 11.2 to 12.4) for females on the first day of donation. For both male and female donors, hemoglobin values had returned to baseline levels by

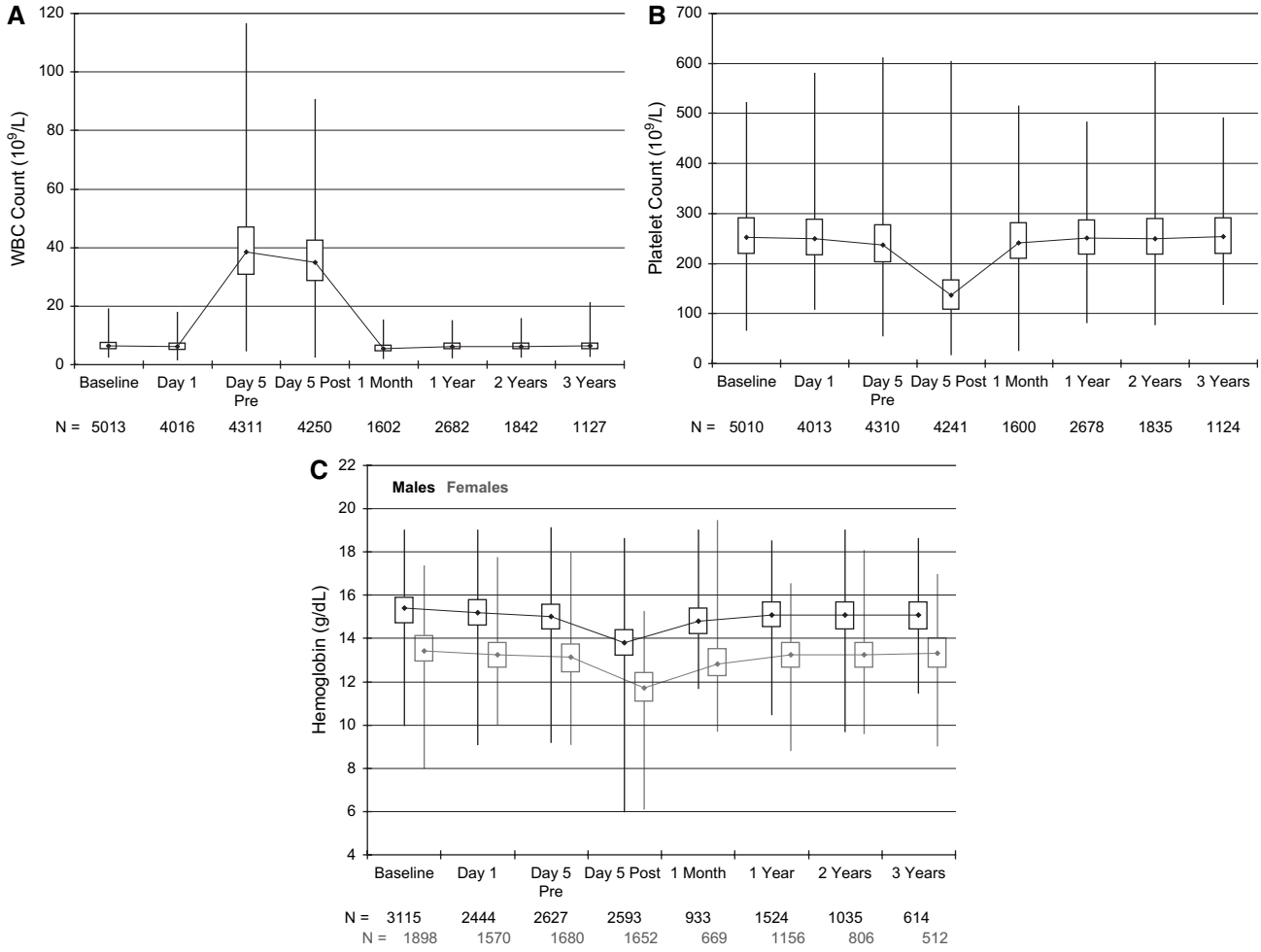


**Figure 4.** (A) Box and whiskers plot of PBSC donor WBC counts showing the maximum, upper quartile, median, lower quartile, and minimum values at the indicated time points during mobilization, collection, and post-donation. (B) Box and whiskers plot of PBSC donor platelet counts showing the maximum, upper quartile, median, lower quartile, and minimum values at the indicated time points during mobilization, collection, and post-donation. (C) Box and whiskers plot of PBSC donor hemoglobin levels showing the maximum, upper quartile, median, lower quartile, and minimum values at the indicated time points during mobilization, collection, and post-donation. (Day 1 is the first day of filgrastim administration; day 5 is the first day of apheresis; pre and post refer to the apheresis procedure.)

1 year post-donation and remained there at 3 years post-donation (Figure 4C).

### Time to Recovery from BM and PBSC Donations

Time to recovery is a donor-reported measure; each marrow and PBSC donor is contacted weekly post-donation until the donor confirms complete recovery from their procedure (Figure 5).

PBSC donors recovered from their donation in less time than BM donors, with a median time to recovery of 1 week for PBSC donors compared to 3 weeks for BM donors. By 4 weeks post-donation, 92% of PBSC donors reported full recovery compared to 69% of BM donors. About 5% of donors follow their initial donation with a second donation of marrow or PBSC weeks to months later. Median time to recovery from these second donations did not differ from median time to recovery from a first donation, with median recovery times of 1 week for PBSC and 3 weeks for BM donors. By 4 weeks post-donation, 94% of PBSC donors and 68% of BM donors reported full recovery.

### Acute and Long-Term Complications from BM and PBSC Donations

As detailed above, almost all BM and PBSC donors experienced mild to moderate symptoms during the course of their donation, but a few experienced serious acute and long-term complications. In the case of NMDP BM and PBSC donors, hospitalization is the most common reason for an adverse event to be rated as serious.

### BM Donors

In a retrospective review of data reported on standardized follow-up forms from 9245 NMDP marrow collections performed between December 1987 and

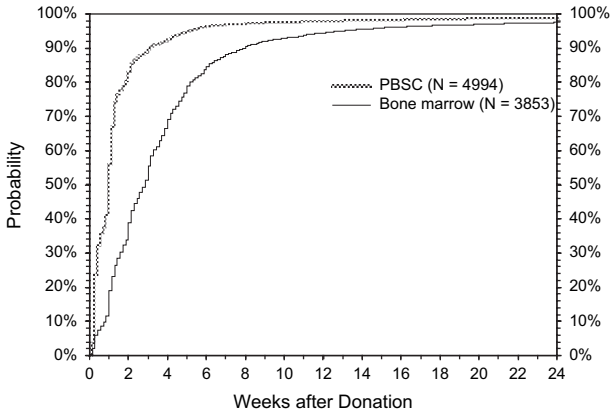


**Figure 5.** Kaplan-Meier plots of time to recovery from stem cell donation (first donations performed from November 2001 through March 2006).

December 1999, 345 (3.7%) donors with a potentially serious medical complication were identified. These complications included excessive pain, adverse acute anesthesia reaction, delayed return to normal activities, and need for additional medical intervention. A panel of 5 physicians reviewed all 345 cases; 125 (1.35% of the 9245 total) were determined to be serious post-donation complications. Of these 125 serious cases, 116 were classified as directly related to the collection with the proximal cause relative to the collection being: (1) mechanical injury to tissue, bone or nerve (n = 69, 55%; 0.7 of the 9245 total); (2) anesthesia (n = 45, 36%; 0.5% of the total); (3) infection (n = 1, 1%; 0.01% of the total); and (4) grand mal seizure (n = 1, 1%; 0.01% of the total).

Of the 116 donors with serious complications, 67 (0.7% of the 9245 total) experienced prolonged recovery times (median 10 months, range 1 to 96 months) related to mechanical injury to tissue from needle aspirations, and required interventions ranging from limited physician involvement and/or physical therapy to surgical intervention and ongoing disability (1 to >10 years). Of the remaining 49 donors (0.5% of the 9245 total) with severe reactions, most were because of severe acute reactions related to the anesthesia. These anesthesia-related acute reactions included complicated post-spinal headaches, cardiac arrhythmias, and pulmonary edema. Acute reactions were short-lived, and all resolved within hours to days after the collection.

Multivariate analyses indicated that regional anesthesia, longer duration of collection, female sex, and older donor age were significant risks for serious complications.

Overall, the incidence of serious complications from marrow donation is low (1.35%), with mechanical injury the most frequent cause of prolonged post-donation recovery and anesthesia-related events the most frequent cause of severe acute reactions.

### PBSC Donors

Serious adverse events in PBSC donors occurred at about half the rate (0.6%) of BM donors and the majority are acute, short-lived events.

On data collected from 7850 PBSC donors from February 1, 1997 to December 31, 2007, a total of 44 (0.6%) serious adverse events were reported to the FDA. After medical monitor review, 39 of the 44 serious adverse events were determined to be related, or at least possibly related, to either filgrastim administration or PBSC donation.

Of the 39 events related to filgrastim and PBSC donation, the majority (37 [95%]) were rated as serious by virtue of the donor being hospitalized. Twenty-five donors were hospitalized with severe symptoms such as headache, nausea and vomiting, chest pain, and tetany because of low calcium; 4 donors with central line complications; 4 with low platelet counts; 2 with pneumonia, 1 with asthma, and 1 with a deep vein thrombosis.

Two donors experienced serious events but were not hospitalized. One had a history of benign microscopic hematuria that progressed to gross hematuria by day 3 of filgrastim administration. By 6 weeks post-donation the gross hematuria had resolved and returned to the baseline level of benign microscopic hematuria.

Another donor, a 40-year-old Caucasian female, developed typical immune thrombocytopenic purpura about 4 weeks post-donation. She was managed with corticosteroid therapy and eventually achieved a lasting complete remission. Three other donors had severe thrombocytopenia following apheresis. In each of these cases, the donors evidenced low or low-normal baseline platelet counts, which fell precipitously during administration of filgrastim. In each case the platelet levels returned to baseline values after PBSC donation. These cases may represent individuals with shortened platelet survival at baseline whose condition is aggravated by the PBSC donation process.

Five of the 39 serious adverse events were complications from central line placement. These events included 2 cases of excessive bleeding controlled with pressure, 1 case of a hematoma after the central line was removed, 1 severe vasovagal reaction, and 1 case of severe hypotension that occurred during apheresis and was apparently cardiac in origin.

## SUMMARY

The recovery and safety profiles for BM and PBSC donors have both similarities and differences. BM donors most often experienced pain after the collection at the collection site or sites related to the anesthesia, whereas PBSC donors most often experienced bone pain during filgrastim administration. Both BM and PBSC donors experienced transient changes in their WBC, platelet, and hemoglobin counts during

the donation process. PBSC donors reported faster recovery from their donation than BM donors, with PBSC donors reporting a median time to recovery of 1 week compared to 3 weeks for BM donors. Although both BM and PBSC donors experienced serious adverse events, these occurred more frequently in BM donors (1.34% versus 0.6% for PBSC donors) and a few led to long-term complications not reported by PBSC donors.

The ongoing BMT CTN randomized trial will formally compare the clinical and quality-of-life outcomes of BM and PBSC donors and their recipients. This trial will help to further demonstrate any differences in the recovery and safety profiles of these 2 types of donations and may help bring further clarity on how best to balance recipient and donor considerations when selecting the stem cell source for transplantation.

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