Adult and Pediatric Donor Advocacy

Terry J. Fry, MD
Head, Blood and Marrow Transplant Section
Pediatric Oncology Branch, NCI, NIH

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Nirali Shah, POB, NCI, NIH
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Objectives

• To compare risks of hematopoietic stem cell donation procedures.
• To review existing guidelines relevant to adult and pediatric hematopoietic stem cell donors.
• To provide a systematic approach for the evaluation of minor hematopoietic cell donors on research protocols.

Not so easy......

History of HSCT donation

• Initially all related donors and all bone marrow
• 1987- first National Marrow Donor Program (NMDP) bone marrow products
• 1997- first NMDP Peripheral Blood Stem Cell (PBSC) collection protocol
• By 2003 PBSC>BM

Where are we now with the Be The Match Registry: 1987→2013?

• Over 10 million donors registered in the BTM Registry file, with access to another 10 million donors worldwide
• More than 1/2 million donors added per yr (39% minority)
  – Compensates for those who hit age 61 plus
  – Continues to add to the pool of donors, with emphasis on enriching the BTM Registry for minority donors
PBSC vs Bone Marrow

- Many retrospective studies on recipient outcomes comparing PBSC to BM
  - First large, multicenter prospective trial
    - BMT CTN, Anasetti et al, NEJM 2012
    - No difference in OS (BM - graft failure, PBSC - cGVHD)

Hematopoietic Cell Sources

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What about the Donor?

BM vs PBSC: Donor Adverse Events

- Serious events similar: BM slightly more (~1.5% vs 0.8%)
- Mild events frequent (70-80%) but generally transient with full recovery in 1 month in most (80% BM vs 90% PBSC)
- Pain, fatigue, anemia
- Very small percentage experience long-term complications (pain in BM, GCSF?)

Ref:
- Faivre et al, BMT 2003 (retrospective, related)
- Miller et al, BMT 2008 (retrospective, related)
- Halan et al, Biomark I 2009 (severe events)
- Pulsipher et al, Blood, 2009 (prospective, unrelated, PBSC only)
- Pamplona et al, BBMT 2009 (Review and general donor advice)
- Pulsipher et al, Blood 2013 (prospective, unrelated, BM vs PBSC)
- DSM trial ongoing (CIBMTR D505-02, Pulsipher PI) (prospective, multicenter, related)

Psychosocial Aspects of HSCT Donation

- Risk?
  - Psychological Trauma (Donor guilt)
  - From donation vs having ill relative?
- Benefit?
  - More obvious with related donors, particularly when “strong emotional connection” to recipient
  - Is there true, direct psychosocial benefit to unrelated donation?

Potte J, J Psychosoc Oncol, 1997
Wilkins and Woodgate, Cancer Nurs, 2007
Wiener et al, J Psychosoc Oncol, 2007
Pachman et al, BMT, 2010
Ethics of HSC Donation

**Adult Donor, Standard Indication Standard collection**

**Adult Donor, Research (no additional donor risk)**

**Pediatric Donor, Standard Indication, Standard collection**

**Related Adult Donor, Research (potential additional donor risk)**

**Unrelated Adult Donor, Research (potential, additional donor risk)**

**Pediatric Donor, Research (potential, additional donor risk)**

**Increasing Ethical Dilemma**

Not Approvable?

Goals and Guidelines

- **Goals of donor evaluation**
  - Protect recipient from transmissible disease
  - Maximize donor safety

- **Guidelines**
  - FACT/JACIE
  - NMDP
  - Sacchi et al, BMT 2008 (WMDA)

**NMDP**

- **8.1600 - Informed consent**
  - General explanation of the indications for and results of HSCT
  - General description donation processes and the risks including alternative methods
  - Ample opportunity to ask questions
  - Right to decline or withdraw at any time without prejudice

- **9.3311 - Examining physician responsible for protecting the safety of the donor**

- **9.4100 - Report to the donor any clinically significant abnormal findings discovered during evaluation**


**FACT/JACIE**

(repeated in BM and Apheresis Center Standards)

B6.2 - Informed Consent: explained in terms the donor can understand, and include at a minimum:

- The risks and benefits of the procedure
- Tests and procedures performed
- The rights of the donor and parent of the donor who is a minor to review the results of such tests.
- Alternative collection methods.
- Protection of medical information and confidentiality
- Right to refuse to donate, informed of the potential consequences to recipient
- Informed consent and authorization in advance to release the donor’s health information to the transplant physician and/or the recipient

From: FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, Fifth Edition

**FACT/JACIE**

B6.3 Donor Evaluation: Criteria and evaluation procedures in place to protect the safety of donors

- Any abnormal finding reported to the prospective donor with recommendations made for follow-up care
- Allogeneic donor suitability should be evaluated by a licensed health care professional who is not the primary transplant physician or health care professional overseeing care of the recipient (Also recommended by ASBMT).

- Additional Reference (van Walraven et al, BMT, 2010)

From: FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, Fifth Edition

**Ethics of HSC Donation**

Adult Donor, Standard

Adult Donor, Research (no additional donor risk)

Related Adult Donor, Research (potential additional donor risk)

Unrelated Adult Donor, Research (potential, additional donor risk)

Pediatric Donor, Standard Indication, Standard collection

Pediatric Donor, Research (no additional donor risk)

Unrelated Adult Donor, Research (potential, additional donor risk)

Pediatric Donor, Research (potential, additional donor risk)
Is the Donor a Research Subject?

- FDA: Donor would be a research subject if they are recipient of test article or control (21 CFR §503(g))
- DHHS: Donor would be a research subject if investigators use their data or private information for research (45CFR §46.102)
- Alternative View: Donors could also be considered as research subjects when the research introduces risks they would not face otherwise

Guidelines for Research Using Allogeneic HSCT Donors

- Related donors generally dealt with by local IRB according to federal standards (Office of Human Research Protections, Food and Drug Administration)
- Approvability considered in context of risk vs benefit analysis
  - to donor (donation risks) or to recipient (transplant procedure risks)?
  - Considered independently?

Research Using Unrelated Donors: NMDP

- Is the Donor a research Subject?
  - Obtaining NMDP donor data specifically for research purposes?
  - Obtaining NMDP donor material (e.g., cells) specifically for research purposes?
  - Using an investigational device on an NMDP donor’s specimen (marrow, peripheral blood stem cells or other tissue)?
  - Giving an NMDP donor an investigational drug or device?

Examples NMDP Research

- Product experimentally manipulated.
- Individually identifiable donor data collected explicitly for research, does not include standard data provided to all transplant centers
- Donor blood or tissue samples for laboratory research studies
- Donor asked to provide blood or marrow to develop (non-standard?) cellular therapies for the recipient
- Collection is altered by the research protocol (e.g., additional stem cell products are requested, altered method of collection)
- Research question focuses on transplant efficacy for those diseases where efficacy has not been established in peer reviewed literature.

Ethics of HSC Donation

- Adult Donor, Standard Indication
- Adult Donor, Research (no additional donor risk)
- Pediatric Donor, Standard Indication (no additional donor risk)
- Pediatric Donor, Research (potential, additional donor risk)
- Related Adult Donor, Research (potential, additional donor risk)
- Unrelated Adult Donor, Research (potential, additional donor risk)

Indications for Hematopoietic Stem Cell Transplants for Age < 20yr in the United States, 2009

- In the pediatric population, allogeneic transplants are performed more often than autologous transplant, almost half for non-malignant diseases
- BM used more commonly than PBSC
Risk of complications during HSC collection to pediatric sibling donors

- Prospective study through the European Group for Blood and Marrow Transplantation
- 453 Pediatric donors
  - 313 Bone Marrow donors
  - 140 Peripheral blood HSC donors
- Large variability between centers
- Serious adverse events were rare
  - 1 patient with a pneumothorax after central line placement
- Difficult to make direct comparison between collection methods
  - Risk of allogeneic blood transfusion to donor highest in:
    - Patients < 4 years of age
    - Volume > 20 cc/kg was collected

Additional Guidelines for Pediatric Donors

- FACT/JACIE
  - B6.2.5 - Informed consent obtained from the donor’s parent or legal guardian
  - B6.3.6 - A donor advocate should be available to represent allogeneic donors who are minors or who are mentally incapacitated
- Assent (as appropriate)
  - Not recognized by federal regulations for research settings but generally accepted to be standard

Children as Hematopoietic Stem Cell Donors

Conditions under which a minor can serve as a hematopoietic stem cell donor:
1. There is no medically equivalent histocompatible adult relative
2. A strong and positive relationship (or anticipated relationship) between recipient and donor
3. Some likelihood that the recipient will benefit from the transplant
4. Clinical, emotional and psychosocial risks to donor be minimized and reasonable in relation to benefit to the donor and recipient
5. Parental permission and donor assent be obtained

Ethics of HSC Donation

- Adult Donor, Standard Indication
- Adult Donor, Research (no additional donor risk)
- Pediatric Donor, Standard Indication (no additional donor risk)
- Related Adult Donor, Research (potential additional donor risk)
- Unrelated Adult Donor, Research (potential, additional donor risk)
- Pediatric Donor, Research (potential, additional donor risk)
Primary Objective:
• Determine if the larger cell dose provided by G-CSF mobilized bone marrow will improve event free survival (EFS) in patients with hematologic malignancies.

Secondary Objectives:
• Evaluate the incidence and time to engraftment.
• Evaluate rates of acute and chronic graft-versus-host disease (GVHD).
• Evaluate short- and long-term toxicities of G-CSF mobilized bone marrow vs. standard bone marrow donation. (donor)
  – Experimental arm: G-CSF 5 mcg/kg/day x 5 days prior to harvest

Federal Risk-Benefit Regulations Governing Pediatric Research
Subpart D
Prospect of Direct Benefit
Yes Prospect of Direct Benefit
No Prospect of Direct Benefit

Prospect of Direct Benefit
• Arising from receipt of the probability and intervention being great in the research.
• Those that accrue directly to the subject or as result of participation in the research.

Minimal Risk:
• When the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (in federal guidelines)

Federal Guidelines: Summary
• Research intervention that does not offer the prospect of direct benefit must expose a child to either:
  – No greater than minimal risk, or
  – To only a minor increase over minimal risk, if the child has the disorder or condition that is the object of study.

Federal Regulations: Pediatric HSC Donors
• Prospect of direct benefit debatable.
  – No medical benefit, ? Psychological benefit.
  – American Academy of Pediatrics: No direct benefit.

• Condition clause.
  – Generally not applicable to a “healthy” donor.

• Risk associated with hematopoietic cell collection.
  – Generally considered greater than minimal risk.

How to allow for the use of pediatric donors on research protocols?

Establish a systematic approach for the evaluation of pediatric hematopoietic cell donors on research protocols.
Step Assessment of Risk to Minor Donors

Research Risk (Summary)

- FDA/DHHS and National Marrow Donor Program (NMDP) all provide guidelines to help define when research risks may be present.
- Donors face research risks when:
  - Research includes additional procedures or interventions
  - Research replaces one or more standard procedures
  - The donor would not serve as a donor except for the research (e.g., novel indication for transplant)
  - The research increases the risks for the recipient (thereby increasing donor research risk such as higher donor guilt)

Research Risks: Minimal Risk

- Federal guidelines:
  - When the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- Institute of Medicine (IOM):
  - Should be based on the risks average, healthy, normal children encounter in their daily lives.

Research Risks: Minimal Risk

Dilemma

- Risk is standardly assessed in comparison to an average healthy child.
  - Risks of the collection procedure may be greater than the risks faced by average, healthy, normal children.
  - Hence IOM approach would suggest that hematopoietic stem cell procurement procedures are more than minimal risk.

Are there Research Risks?

- Research risks:
  - Only those risks that result from the research, as distinguished from risks of therapies subjects would receive even if not participating in the research. (FDA/DHHS)
  - This suggests that risks donors would face if not participating in research do not qualify as research risks.

When a donor would have donated in the clinical setting, standard collection procedures do not pose research risks.

Research Risk (Summary)

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Research Risks: Minimal Risk

Can be approved for all minors

- Federal guidelines:
  - When the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
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Research Risks: Minimal Risk

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Research Risks: Minimal Risk
Subjective Standard
- Assess risk in comparison to what the minor donor would experience outside of the research.
  - Does the “research” introduce risk that is above and beyond what the donor would experience in a clinical setting using standard cell procurement procedures?
  - Additional blood draws would be minimal risk research
  - What about changes to donation that change nature of risk but not increase risk?

Peerzada and Wendler, Transplantation, 2006

Non-Standard Indications for Allogeneic Donor Cells
- Evidence demonstrating benefit or harm of transplant versus standard therapies or disease natural history was insufficient for most pediatric indications. (Ratko TA, et al. CER AHRQ 2012)
- Our view:
  - As long as the “potential of direct benefit” exists for the recipient, the disease-specific indication is irrelevant and thereby acceptable to use the “subjective” standard.
  - Counterintuitive to disallow donating cells for a potentially curative transplant because it cannot be done outside of research.
    - Donor is research subject.
    - Consider as minimal risk those risks that are no greater than what a donor would face in the clinical setting. (vs no risk)

Research Risks: Increase over Minimal Risk
- If no direct benefit:
  - Can be approved by an IRB only if a “minor” increase over minimal risk—AND—
    - Yield generalizable knowledge about the subject’s disorder or condition. (CFR §46.406/50.53)

Minor donors generally cannot be considered as having a “condition” and minor donor participation cannot be approved under this section

Research Risks: Increase over Minimal Risk
- If no direct benefit and cannot satisfy subject’s condition:
  - Can be evaluated for possible approval in category 46.407/50.54
  - Required review and recommendation by a panel of experts, an opportunity for public comment, and final approval by the Commissioner of the FDA or the Secretary of DHHS

An expert 407 panel must be convened for greater than minimal risk research when there is no prospect of direct benefit to the donor and research does not satisfy the subject’s condition clause.

Donor
CHILDREN’S ONCOLOGY GROUP
COG ASCT0631D
A Comparison of Acute and Long-term Toxicities in Bone Marrow Donors with and without G-CSF Treatment Prior to Harvest: A Comparison Study to ASC10628

G-CSF administration felt to be greater than minimal risk.
Donors do not qualify as having a “condition.”

December 2008, 407 Expert Panel:
- Approved
- Mandate of independent donor advocate
- Changes to consent to clarify G-CSF related risks
- December 2009: Made into two separate protocols
- Approval needed from OHRP, CTEP, Commissioner of the FDA and the Assistant Secretary of Health for HHS

ASCT0631 Timeline

Step Assessment of Risk to Minor Donors

| Is the minor donor a research subject? | No |
| Research regulations do not apply. |
| Are there research risks? | No |
| Approvable. |
| Is the risk level greater than minimal risk? | No |
| Approvable. |

Is the minor donor a research subject?

Yes

Are there research risks?

No

Research regulations do not apply.

Is the risk level greater than minimal risk?

No

Approvable.

Research Regulations do not apply.
“We strongly believe that this study has the potential to change the standard of care for sibling donor bone marrow transplants”

• “Because of the long period of closure... and because of the new processes that the centers have to implement to comply with this study, ramp-up has been slow to date.”

• “Getting the 0631/0631D pair through IRBs has been made more complicated by the unfamiliarity of the IRBs...with approval under 407 and what this means.”

• “Even after getting the studies through IRBs, the activation energy has been high because of the need to set up the donor advocate processes.”

Conclusions: Minor donors on research protocols

• Donation of hematopoietic stem cells is not without risk.
• Use of minors on research protocols requires a careful evaluation by the federal risk-benefit guidelines.
  – We endorse use of the “subjective standard” when evaluating risks to donors on research protocols, but this may be controversial.
• Need a systematic approach for the evaluation of pediatric donors who are being asked to donate hematopoietic stem cells to ensure that use is compliant with the federal risk-benefit guidelines and ethically sound.
• Need for consensus
  – Possible meeting