Adult and Pediatric Donor Advocacy

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

Acknowledgements:
Nirali Shah, POB, NCI, NIH
David Wendler, Bioethics, NIH
Willis Navarro, NMDP

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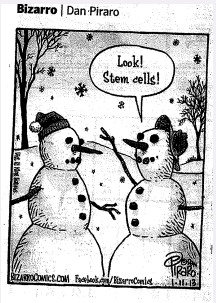
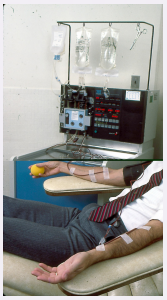
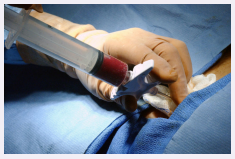
Objectives

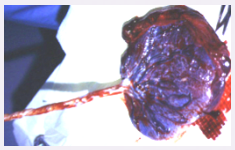
- To compare risks of hematopoietic stem cell donation procedures.
- To review existing guidelines relevant to adult and pediatric hematopoietic stem cell donors.
- To provide a systematic approach for the evaluation of minor hematopoietic cell donors on research protocols.

Not so easy……









History of HSCT donation

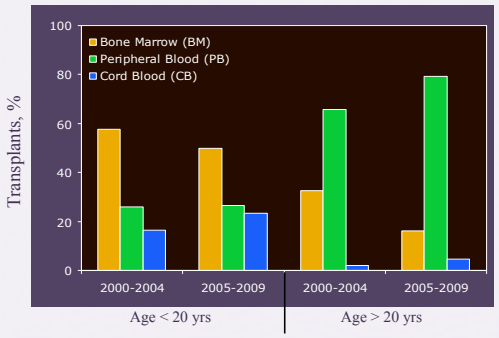
- Initially all related donors and all bone marrow
- 1987- first National Marrow Donor Program (NMDP) bone marrow products
- 1997- first NMDP Peripheral Blood Stem Cell (PBSC) collection protocol
- By 2003 PBSC>BM

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

NATIONAL MARROW DONOR PROGRAM BE THE MATCH

Allogeneic Stem Cell Sources by Recipient Age
2000-2009



CIBMTR Summary Slides, 2011

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

	Bone Marrow	Peripheral Blood
Cell manipulation	• Unmobilized	• G-CSF mobilized
Procurement Methods	• Needle aspiration	• Apheresis
Cells collected	• Stem cells	• Stem cells • Donor lymphocyte infusion
Risks to recipient	• Non-engraftment	• cGVHD
Benefits to recipient	• Less cGVHD	• Higher cell dose (stem cells & T cells) • Faster engraftment • Lower infection risk • Potentially improved event-free survival (lower relapse?)

What about the Donor?

Hematopoietic Cell Sources

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Risks to donor	• General anesthesia • Anemia • Pain	• G-CSF related pain • Possible need for central line
Benefits to donor	• ???	• ???

BM vs PBSC:
Donor Adverse Events

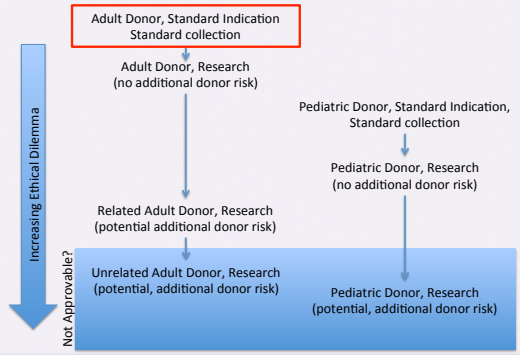
- Serious events similar: BM slightly more (~1.5% vs 0.8%)
- Mild events frequent (70-80%) but generally transient with full recovery in 1 month in most (80% BM vs 90+% PBSC)
- Pain, fatigue, anemia
- Very small percentage experience long-term complications (pain in BM, GCSF?)
- Ref:
  - Favre et al, BMT 2003 (retrospective, related)
  - Miller et al, BBMT 2008 (retrospective, related)
  - Siddiq et al, Cochrane Database Syst Rev, 2009 (retrospective, related)
  - Halter et al, Haematologica 2009 (severe events)
  - Pulsipher et al, Blood, 2009 (prospective, unrelated, PBSC only)
  - Pamphilon et al, BJH, 2009 (Review and general donor advice)
  - Pulsipher et al, Blood 2013 (prospective, unrelated, BM vs PBSC)
  - RDSafe trial ongoing (CIBMTR DS05-02, 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?

Pot-Mees and Zeitlin, J Psychosoc Oncol, 1987
Wilkins and Woodgate, Cancer Nur, 2007
Wiener et al, J Psychosoc Oncol, 2007
Pachman et al, BMT, 2010

Ethics of HSC Donation



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

From: National Marrow Donor Program® 21st Edition Standards October 1, 2011

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

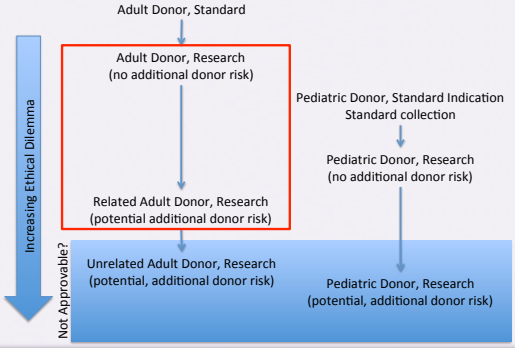
B6.3 Donor Evaluation: Criteria and evaluation procedures in place to protect the safety of donors

- 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



Is the Donor a Research Subject?

- FDA: Donor would be a research subject if they are recipient of test article or control (21 CFR §5033(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?

45 CFR 46.102(f)(1), (2)
21 CFR 812.3(p)
21 CFR 56.102(e)

Document Title: Donors as Research Subjects – Algorithm Analysis Worksheet
Document Number: F00602 revision 3
Also: King et al, BMT 46(1): 10-13, 2011

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.

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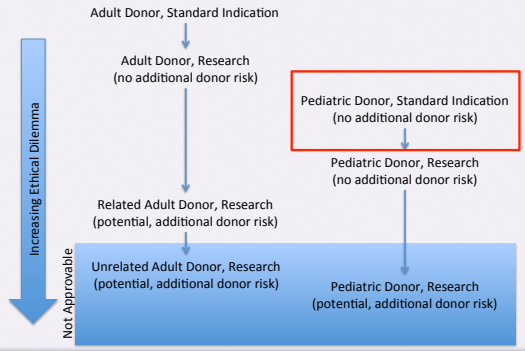
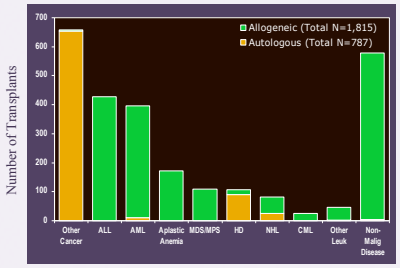
Ethics of HSC Donation



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

CIBMTR Summary Slides, 2011

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

Styczynski et al. Blood 2012
(Editorial by Pulsipher)

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

PEDIATRICS®
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Children as Hematopoietic Stem Cell Donors
COMMITTEE ON BIOETHICS

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

Pediatrics 2010

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- A donor advocate, independent of the team responsible for the recipient, should be appointed for all minor donors and be involved from the onset (prior to HLA testing)
- Minor donors should be included in all stages of the decision making process to the extent that they are capable and assent should be obtained when possible (starting at age 9)

Pediatrics 2010

COMMENTARY

A Parent's Point of View on the American Academy of Pediatrics Policy Statement: Children as Hematopoietic Stem Cell Donors

LETTER TO THE EDITOR

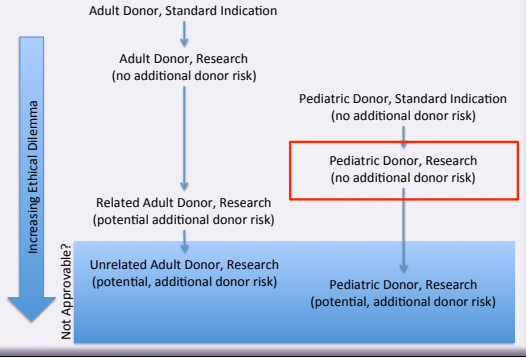
The American Academy of Pediatrics Policy Statement—Children as Hematopoietic Stem Cell Donors

(1) the AAP guidelines were not acceptable and (2) that it was important that the objections to these guidelines were documented in the medical and bioethics literature so that the AAP guidelines did not appear to be accepted by acclamation by the pediatric, pediatric hematology oncology, or transplantation communities.

In our view, the AAP's policy errs in failing to weigh the medical, emotional, financial, and symbolic burdens of the donor advocate requirement against the scope of the problem it purports to solve and the magnitude of the benefits it offers to prospective donors.

Pediatric Blood Cancer, 2011

Ethics of HSC Donation



STUDY CHAIR

Stephan A. Grupp, MD PhD
Director, Stem Cell Biology
Children's Hospital of Philadelphia

CHILDREN'S ONCOLOGY GROUP

COG ASCT0631
PBMTC STC051

CureSearch Children's Oncology Group

2007

A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation

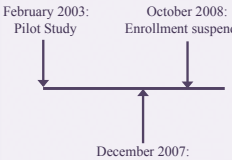
Primary Objective:

- 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:

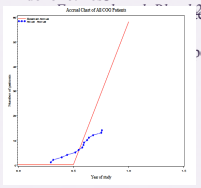
- Evaluate the incidence and time to engraftment.
- Evaluate rates of acute and chronic graft-versus-host disease (GVHD).
- Evaluate short- and long-term toxicities of G-CSF mobilized bone marrow vs. standard bone marrow donation. (donor)
  - Experimental arm: G-CSF 5 mcg/kg/day x 5 days prior to harvest

ASCT0631 Timeline



PBMTC STC 0233 (Pilot study)

- G-CSF mobilized bone marrow
- 42 sibling donors
- Protocol opened at 25 sites
- Total enrollment: 44 recipient donor pairs
- Median age 9
- All received G-CSF
- No complications



Federal Risk-Benefit Regulations Governing Pediatric Research

Subpart D

Prospect of Direct Benefit	Direct Benefit:	Minimal Risk:
Yes Prospect of Direct Benefit	• Arising from receiving the intervention being studied • Those that accrue directly in a proximate manner to the subject or as result of participation. *(not in federal guidelines)*	• When the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves that those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. *(in federal guidelines)*
No Prospect of Direct Benefit		

Federal Guidelines: Summary

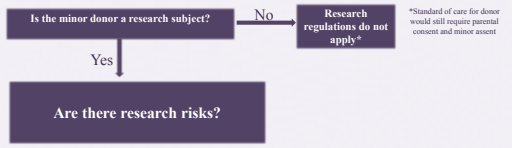
- Research intervention that does not offer the prospect of direct benefit must expose a child to either:
  - No greater than minimal risk, or
  - To only a minor increase over minimal risk, if the child has the disorder or condition that is the object of study.

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

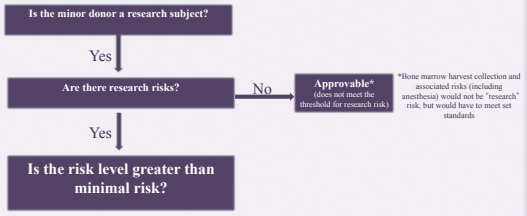
Are there Research Risks?

- 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)

- 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)



Step Assessment of Risk to Minor Donors

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.
- Institute of Medicine (IOM):
  - Should be based on the risks <u>average, healthy, normal</u> 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.

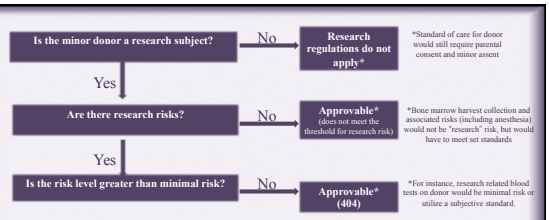
Research Risks: Minimal Risk
Subjective Standard

- 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 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 recipient, the disease-specific indication is irrelevant and thereby ok 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)



Step Assessment of Risk to Minor Donors

Research Risks: Increase over Minimal Risk

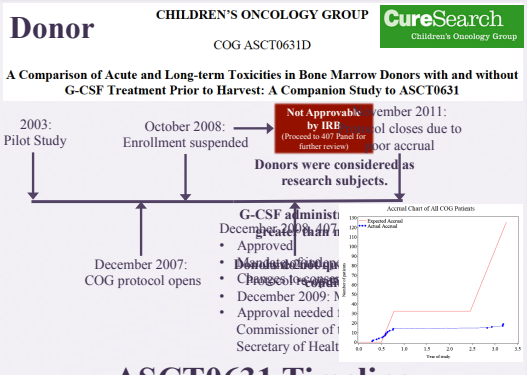
- If no direct benefit:
  - Can be approved by an IRB only if a "minor" increase over minimal risk—AND—
  - Yield generalizable knowledge about the subject's disorder or condition. (CFR §46.406/50.53)

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.

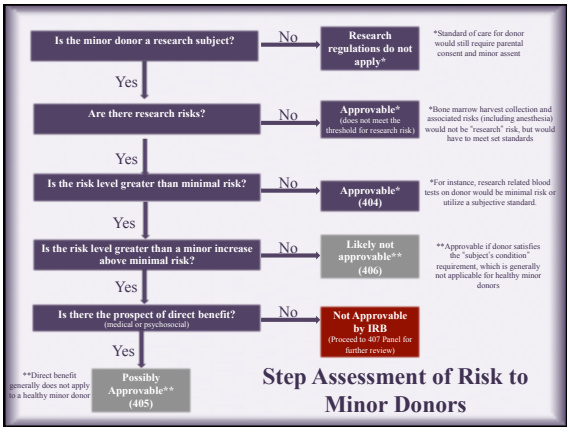


ASCT0631 Timeline

"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."*

ASCT0631 Fall 2011 Progress Report



Step Assessment of Risk to Minor Donors

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