Topics in Regenerative Medicine
Kings College London
21/01/2011

ANTHONY NOLAN
BE A MATCH, SAVE A LIFE

CORD BLOOD BANKING

OPTIMISING INVENTORIES

PUBLIC vs PRIVATE

Anthony Nolan Cell Therapy Centre
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ANTHONY NOLAN
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CORD BLOOD APPROACH

The first cord blood transplant was performed on a 5 year-old Parisian boy who was suffering from Fanconi's anaemia, using his newborn sister's HLA-matched umbilical cord blood. To date, the recipient is alive and well and free of disease. This achievement began an new era in umbilical stem cell transplantation.

E. Gluckman, H.E. Broxmeyer, A.D. Auerbach, H. Friedman, G.W. Douglas, A. DeVergie, H. Esperou, D. Thierry, G. Socie, P. Lehn, S. Cooper, D. English, J. Kurtzberg, J. Bard and E.A. Boyse (1989).
Hematopoietic reconstitution in a patient with Fanconi anemia by means of umbilical-cord blood from an HLA-identical sibling, N Engl J Med 321, p. 1174.

After the first sibling-donor cord blood transplant, performed in 1988, the National Institute of Health (NIH) awarded a grant to Dr. Pablo Rubinstein to develop the world's first cord blood programme at the New York Blood Centre (NYBC) in order to establish the inventory of non embryonic stem cell units necessary to provide unrelated, matched grafts for patients.

Rubinstein P, Rosenfield RE, Adamson JW, Stevens CE. Blood. 1993 Apr 1;81(7):1679-90.
Stored placental blood for unrelated bone marrow reconstitution.

Kurtzberg J, Graham M, Casey J, Olson J, Stevens CE, Rubinstein P. Blood Cells. 1994;20(2-3):275-83
The use of umbilical cord blood in mismatched related and unrelated hemopoietic stem cell transplantation.

CORD BLOOD APPROACH

- Today global network of public cord blood banks - 500,000 cord blood units.
- 20,000 transplants reported to WMDA to date
- 2009 cord blood became second most common source of transplant stem cells.
- Clinical trials using UCB Stem Cells
  - - wide variety of conditions including stroke, spinal injuries, cerebral palsy and a wide variety of other degenerative conditions.

WHY CORD BLOOD?

Pablo Rubinstein, Human Immunology 67, 398 – 404 (2006)

a) the logistic advantage avoiding the uncertainties and delays

b) the better long-term prognosis for well-matched cord blood graft

c) the larger and ethnically more diverse inventories,,

d) the accreditation and government regulation assuring improved and standardized quality

e) potential of improvement by the use of two-unit transplants and possibly by new cell expansion technologies

(f) more direct collaboration between the banks and the transplant centers.

Cord blood is increasingly replacing donated adult haematopoietic stem cells for unrelated recipients.

Using unrelated, HLA-well matched cord blood eliminates the unpredictable delays that cause many patients to loose the opportunity of actually receiving a transplant.

The manifest destiny of cord blood is the replacement of the need for adult unrelated bone marrow donors.

STEM CELL SOURCES: COMPARISON

N=20	MO	SPM	SCU	SPA
%CD34	1.28±0.55	0.19±0.10	0.30±0.21	0.02±0.02
CN/µl	29600±12000	43500±21000	16300±6200	7000±3000
CD34/µl	378±162	82±43	49±32	1.4±1.4
CFU-GM/µl	39±23	18±10	16±11	0.2±0.1
BFU-E/µl	29±17	11±9	5±4	0.2±0.1
CFU-Mix/µl	9±8	5±5	6±4	0.1±0.1
CLONE-CFU (%)	20±6	41±14	55±22	36±30
CFU-Mk/µl	15±6	2±2	2±1	ND
BFU-Mk/µl	6±4	0.5±0.7	2±2	ND
CFU-GEMM/µl	2±2	2±2	2±2	ND
CLONE-Mk (%)	6±2	6±3	12±5	ND

CORD BLOOD CELLS: A NEW PARADIGM

- New way in allogeneic haematopoietic stem cell transplantation:

  Towards GVL with less GVHD

- New way in regenerative

  Off-the-shelf natural multipotent embryonic-like stem cells and naïve regulatory T cells

CORD BLOOD PROS AND CONS

- Advantages:
  - Donor safety/attrition
  - ‘Off-the-shelf’= time
  - Reduced match stringency= equitable access
  - Long-term Sustainability
- Disadvantages:
  - (Speed) Engraftment
  - DLI

FACTS

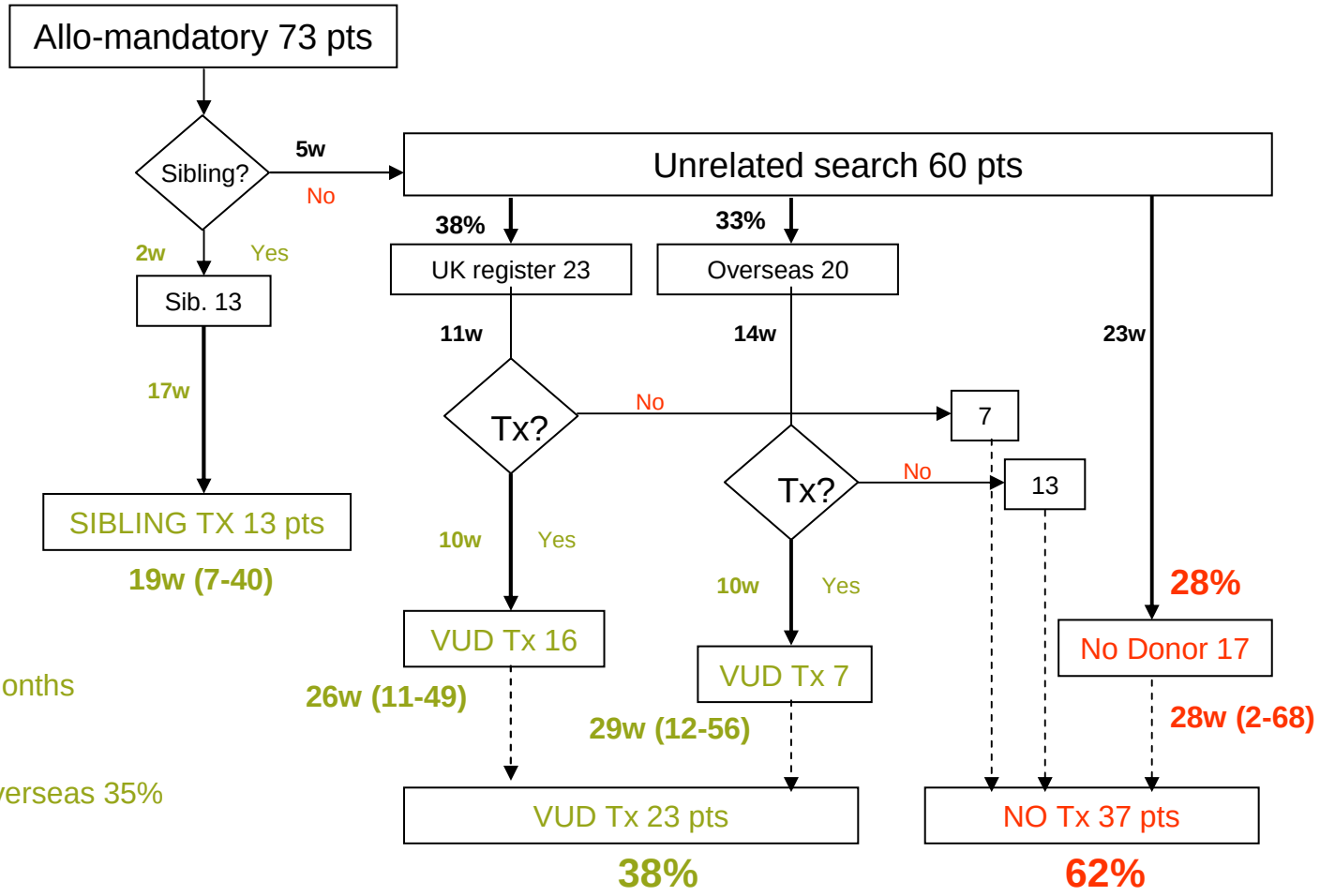
Cord blood is a naturally discarded tissue…

That contains a high proportion of circulating haematopoietic stem cells…

Able to reconstitute the haematopoietic tissues…

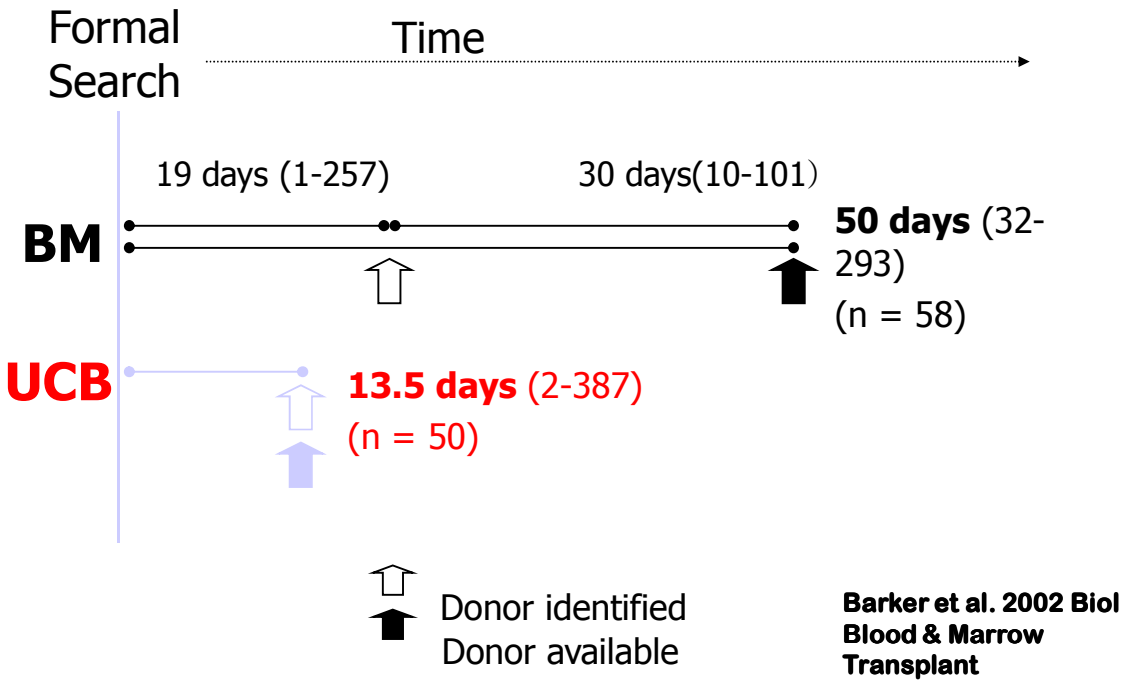
This properties suggested the development of relatively large inventories of ready-to-use, fit-for-purpose tissue products for bone marrow transplantation: CORD BLOOD BANKS

SOME PATIENTS DO NOT HAVE SUITABLE ADULT DONORS



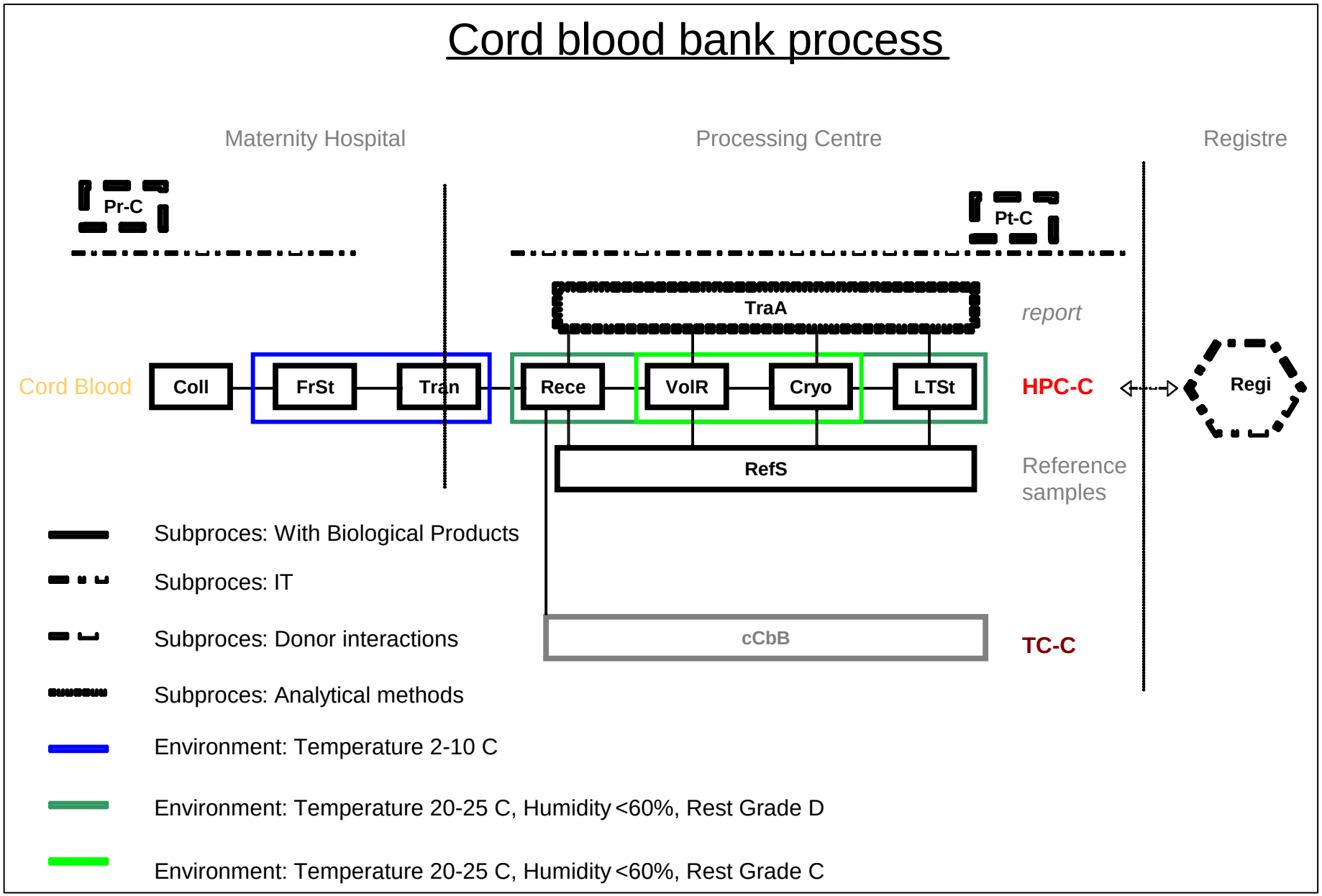
- Estimated time delay: 2 months
- Access failure: 28%
- UK self-sufficiency: 38%
- Efficiency: UK 70% vs. Overseas 35%
- Total allo-therapies: 38%

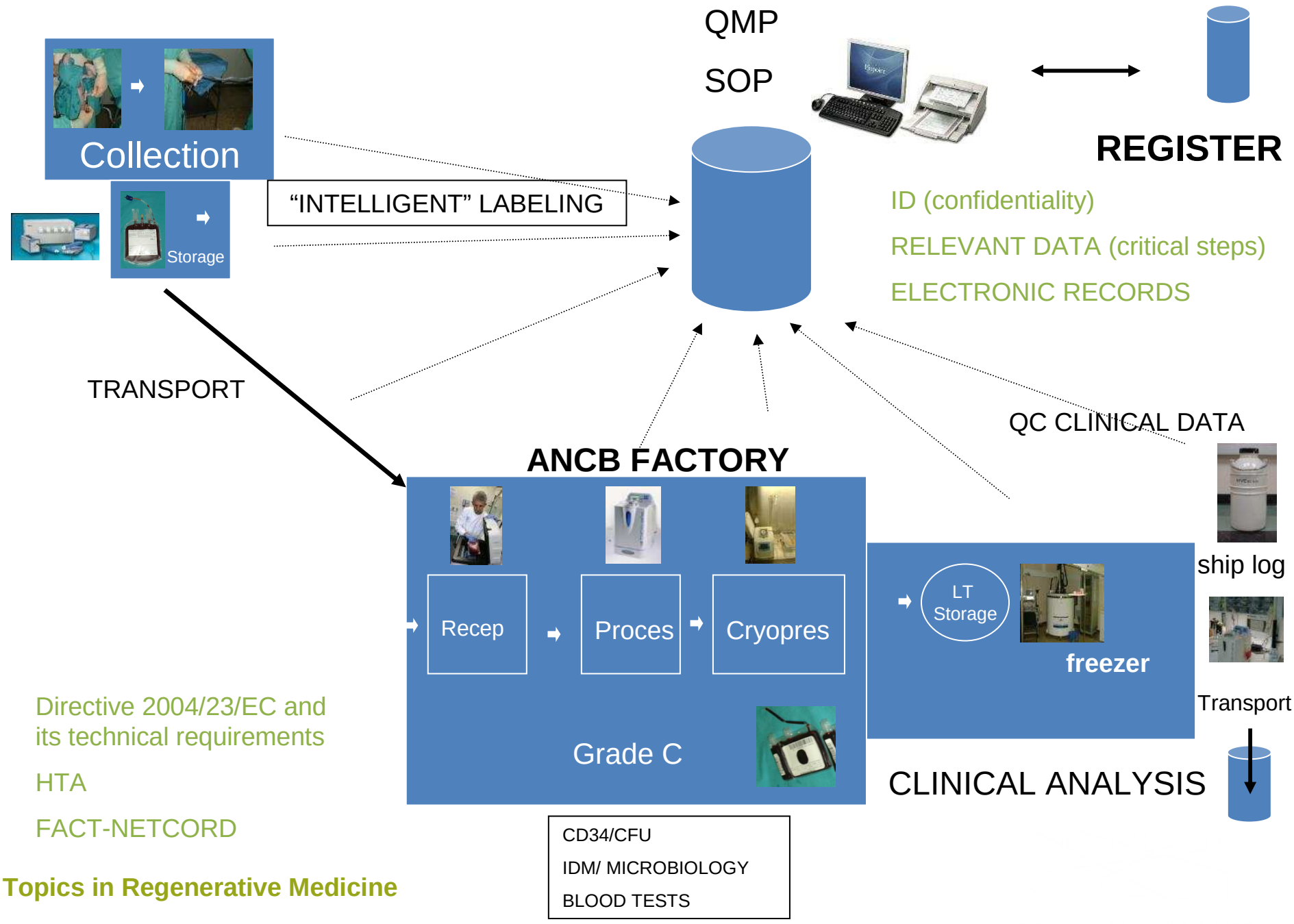
Rapid Availability



Barker et al. 2002 Biol Blood & Marrow Transplant

Cord blood bank process





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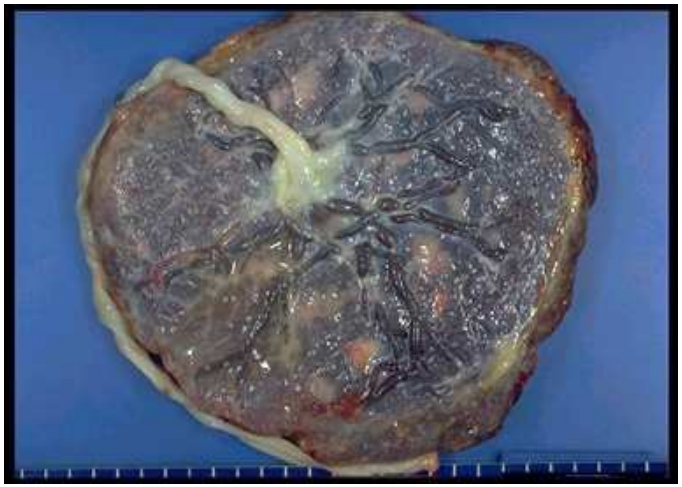
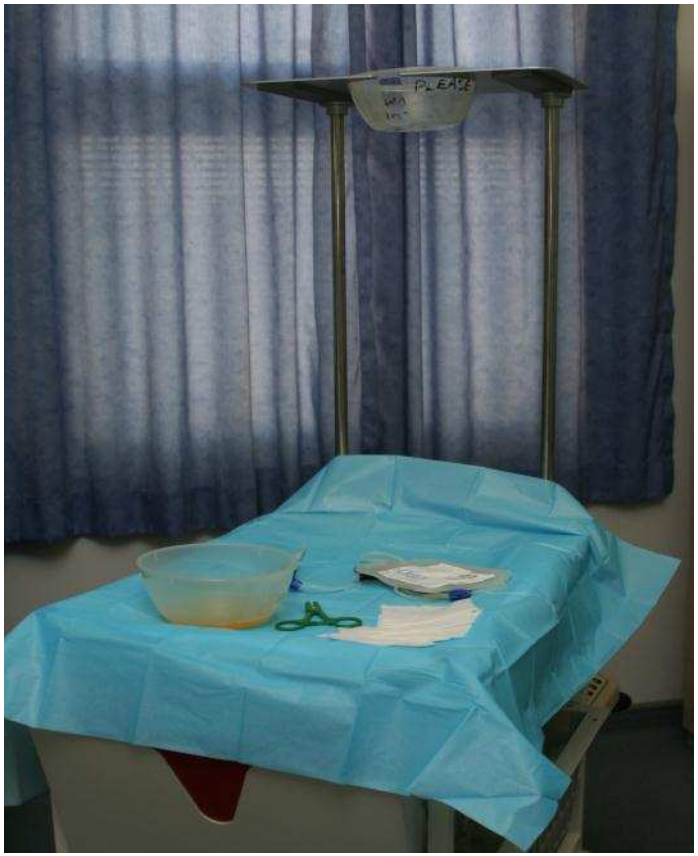
COLLECTION



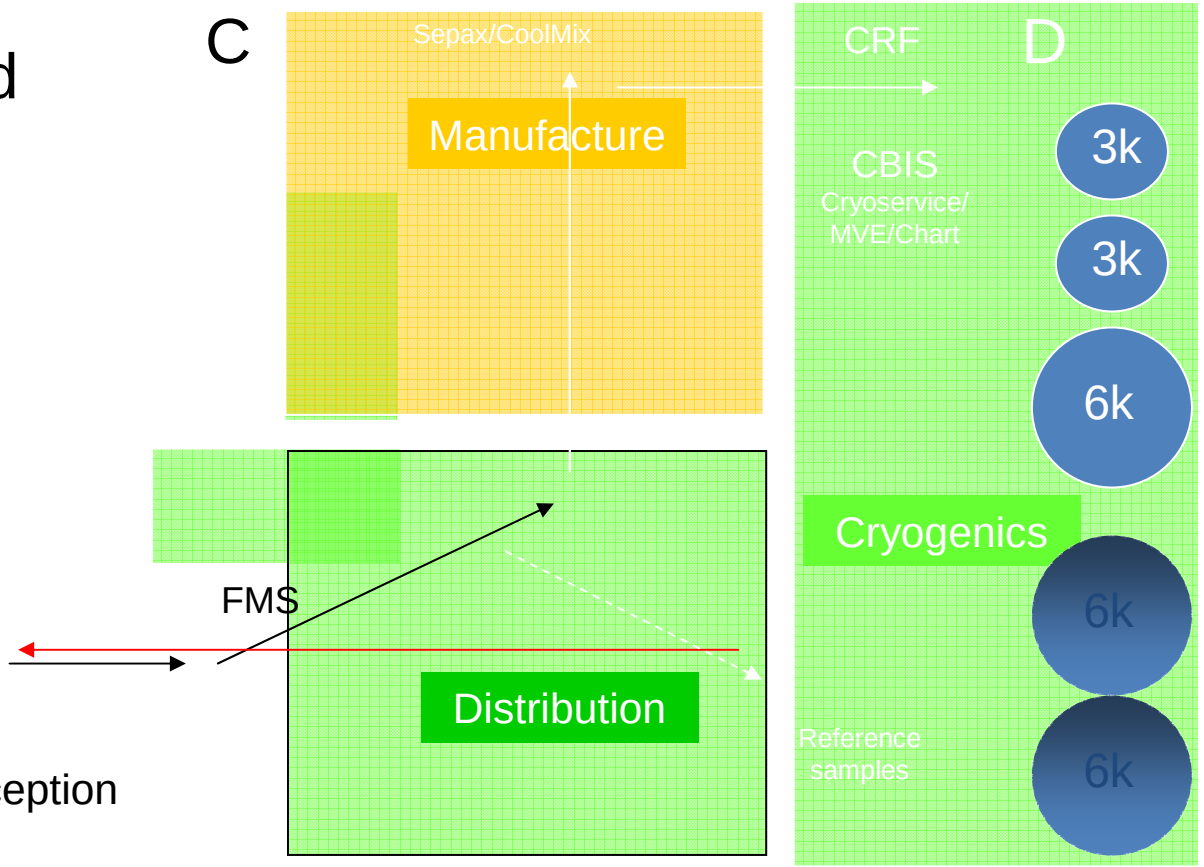


STEM CELLS ARE CLEARED FROM PERIPHERAL BLOOD AFTER DELIVERY

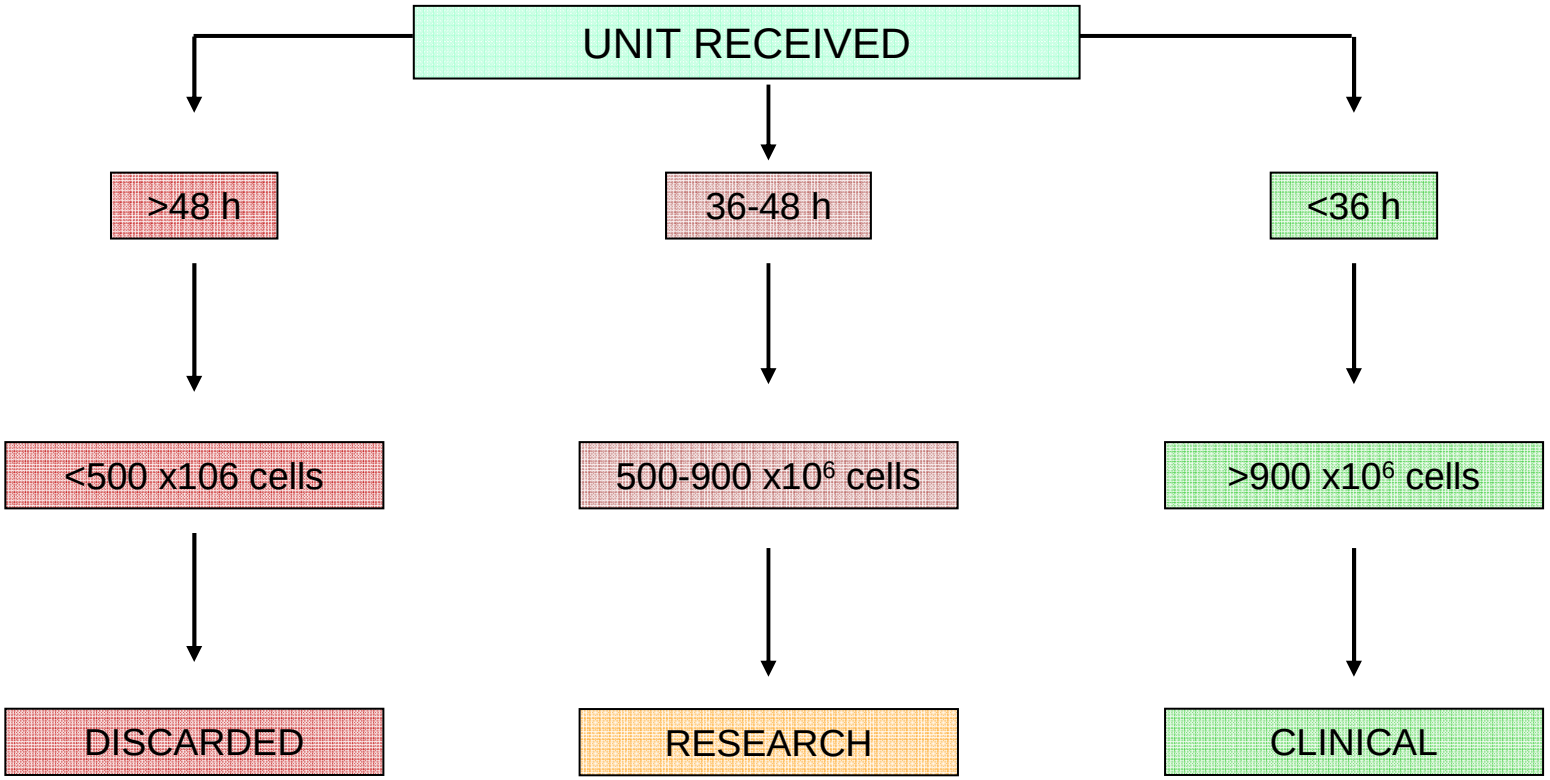
N=30	**%CD34**	**CFU-GM/ 10^5 CN**	**BFU-E/ 10^5 CN**	**CFU-Mix/ 10^5 CN**
Cord blood Time 0	0,25±0,13	75±37	23±15	49±32
Newborn 3 h.	0,19±0,12	51±31	16±13	34±20
Newborn 12 h.	0,11±0,07	28±17	10±13	23±18
Newborn 30 h.	0,06±0,04	21±15	9±12	17±18
Newborn 60 h.	0,05±0,03	15±16	8±8	13±12

PROCESSING FACILITY

Ground floor:



DECISSION FLOW CHART



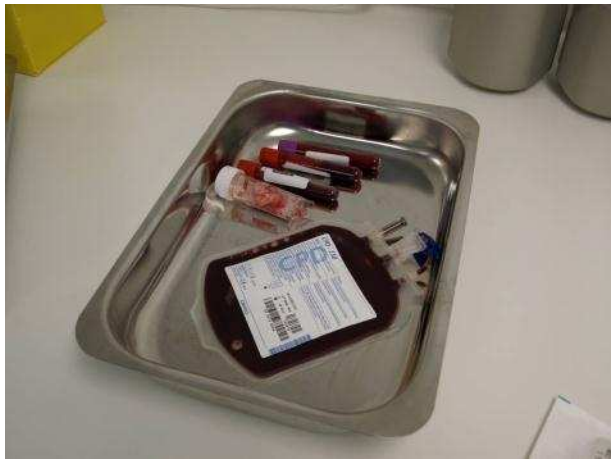
RECEPTION

The sample is received in the cord blood bank.

The paperwork and sample are checked.

Check none of the packs are leaking

Monitor the data logger



PROCESSING

The cord blood bag is attached to SEPAX® kit using a sterile connection.

All the procedure is performed in a close system.

PROCESSING

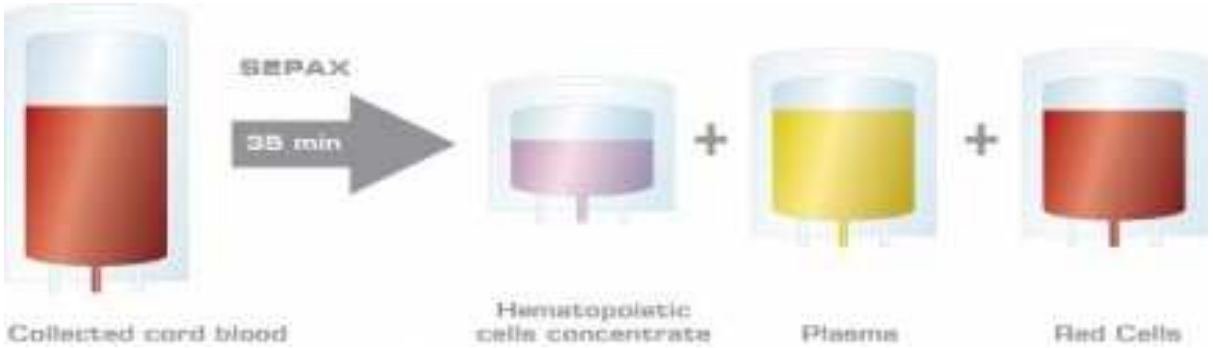
Place the kit on the SEPAX® machine and select the proper programme to perform a volume reduction

The SEPAX® process takes approx. 35 minutes.

PROCESSING

The UCB protocol is designed for routine processing of umbilical cord blood (UCB) to concentrate the buffy-coat fraction that is rich in hematopoietic stem cells. Highly efficient separation and TNC recovery is achieved without addition of any sedimentation agent.

The UCB protocol allows a volume reduction of UCB in approximately 35 min to a predetermined fixed volume ranging (21 ml). The input volume range is 35 to 290 ml.

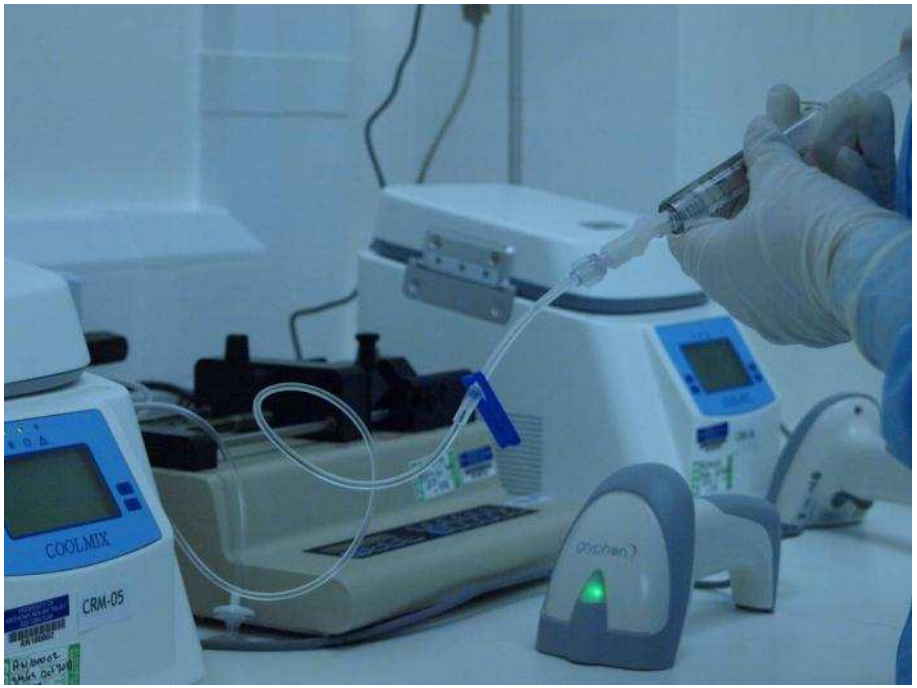


PROCESSING

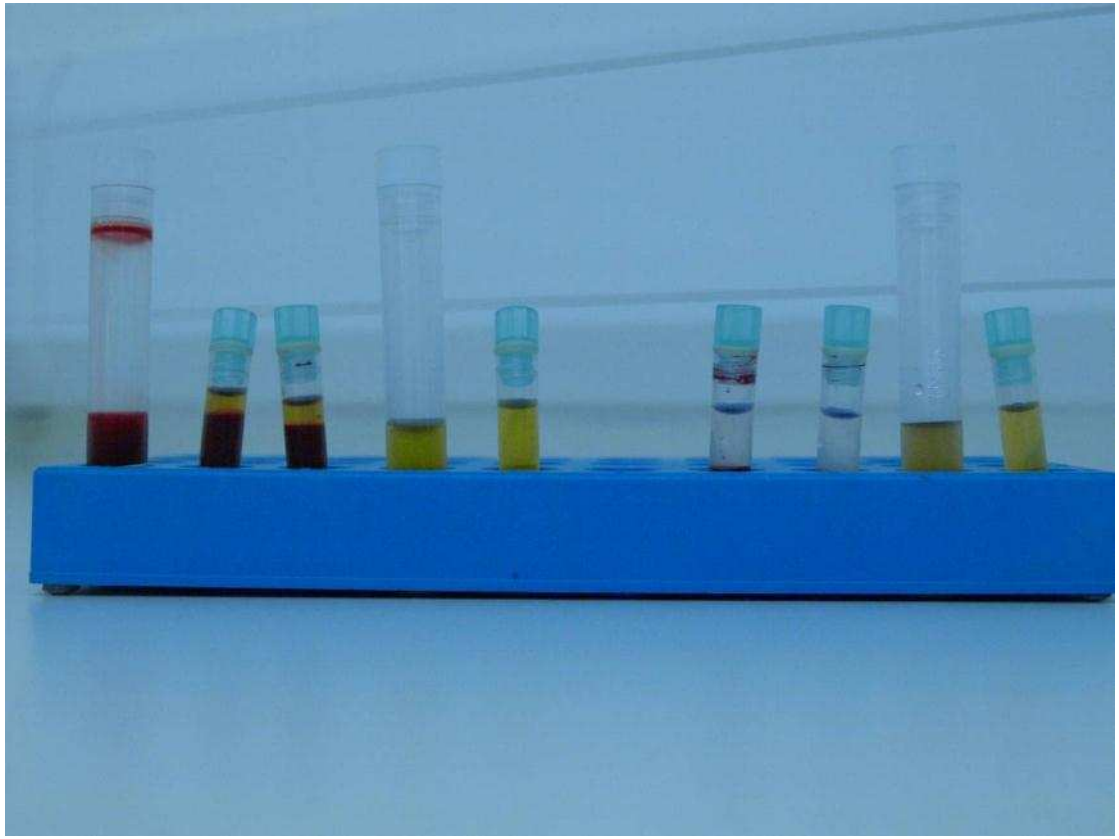
ADDING DMSO

Precooling and mix the product for 10 mins.

Add the DMSO-dextrane (5ml) with a syringe pump fro 10 mins.

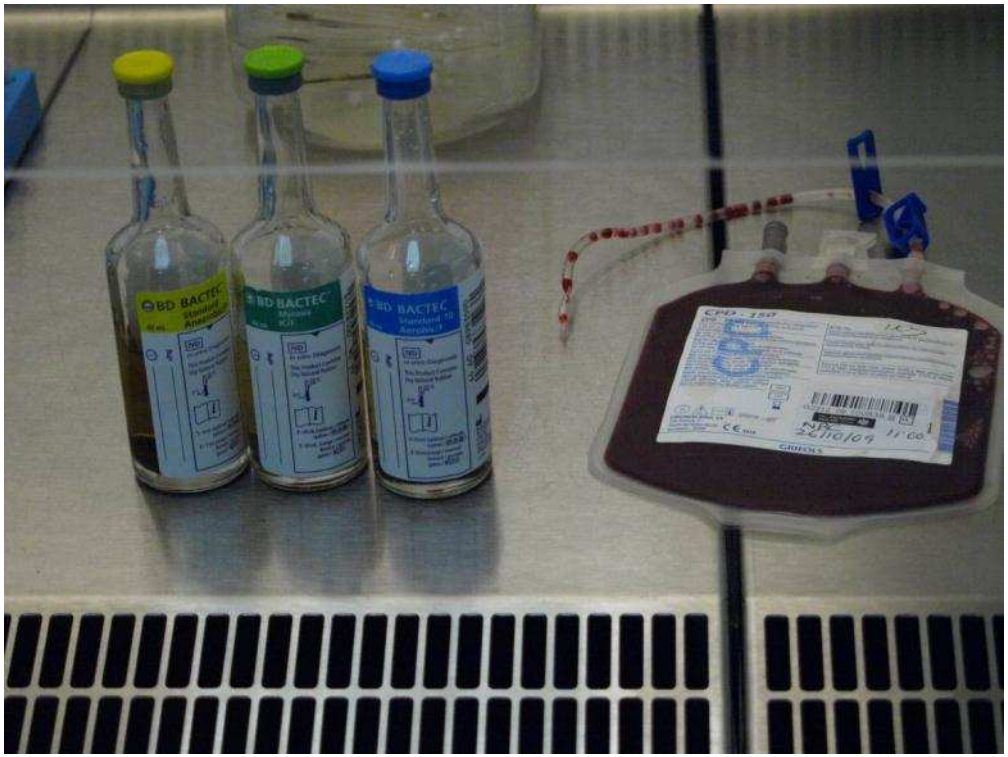


DIAGNOSTIC SAMPLES

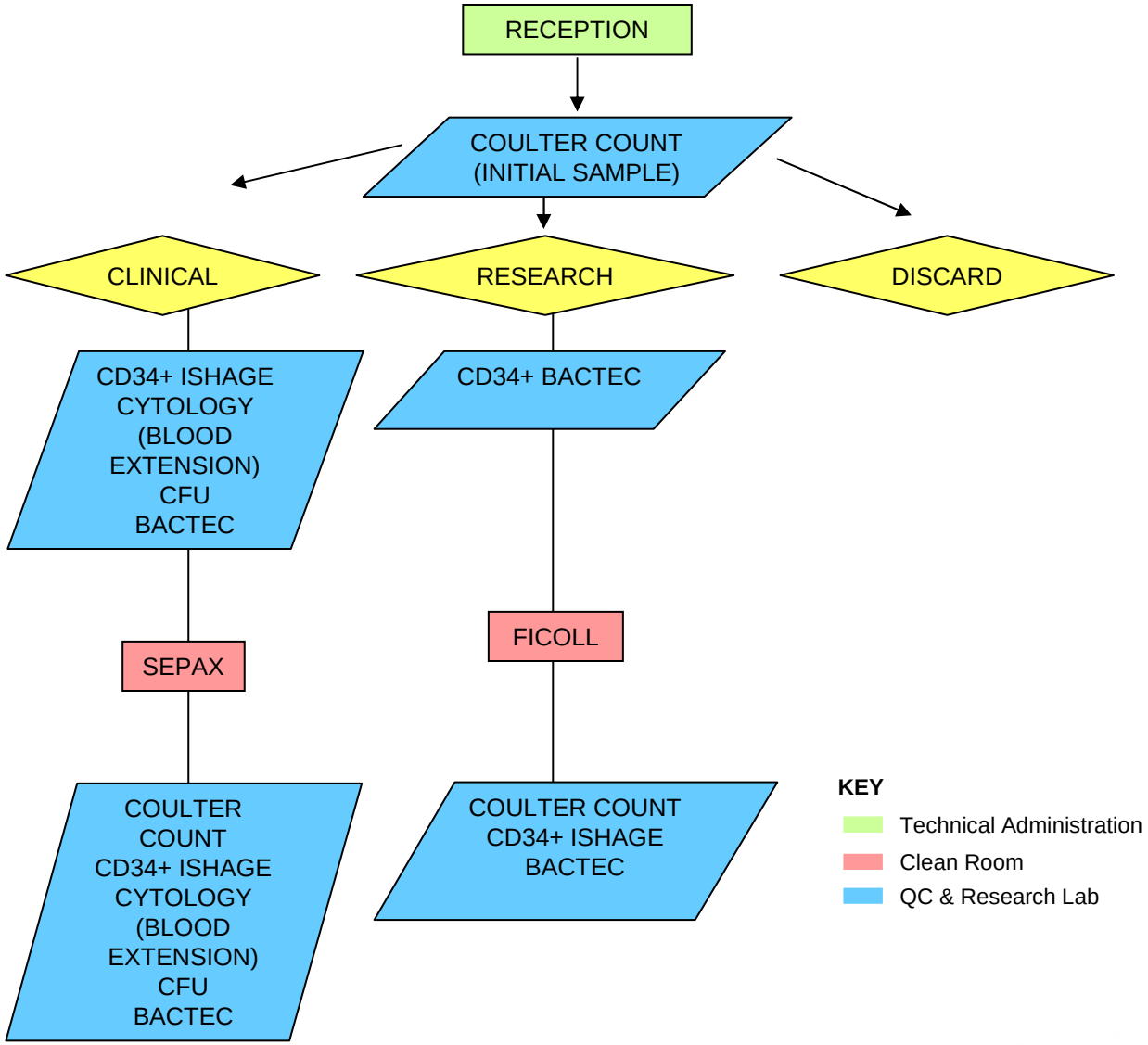


BACTERIOLOGY

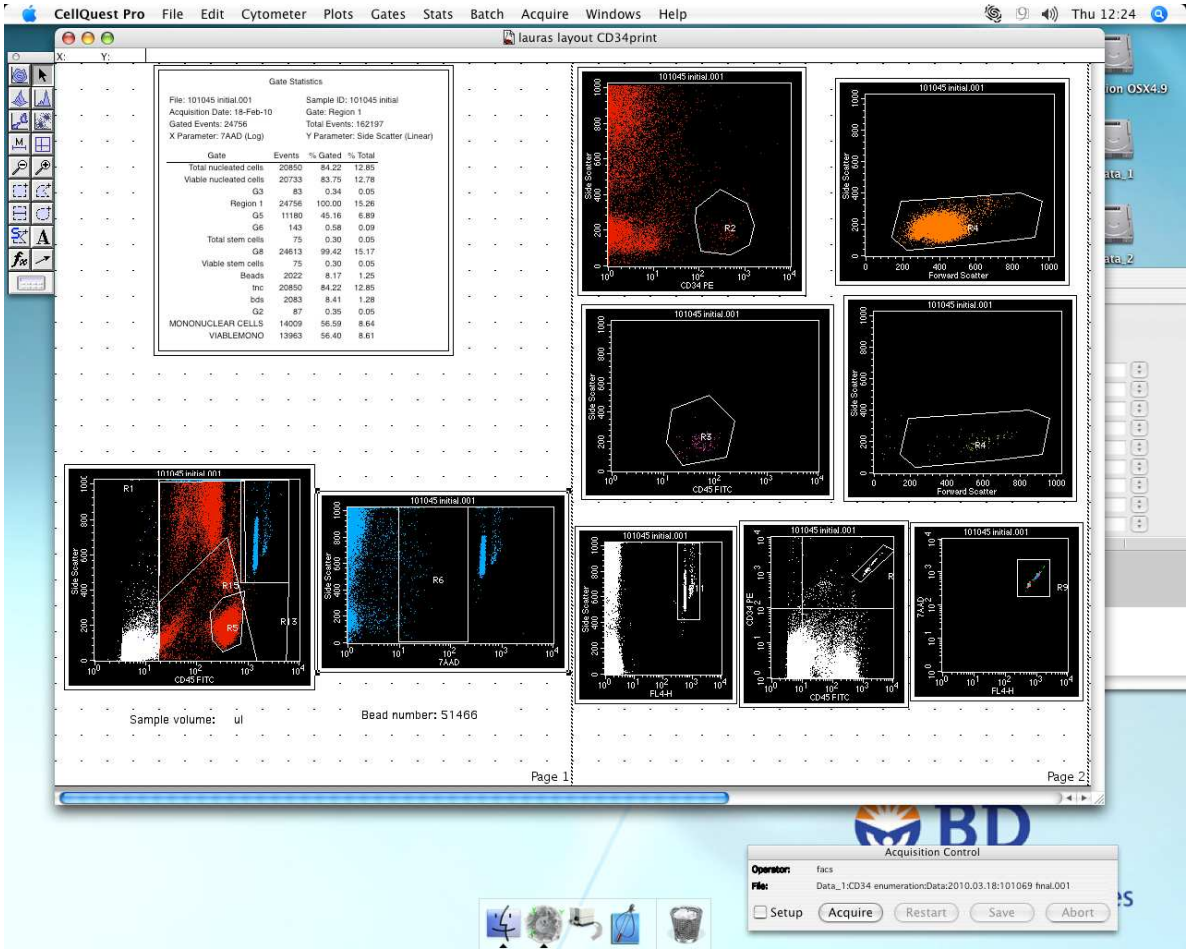
From cord plasma and red blood cells (waste product) inoculate volume to perform bacteriology tests.



QUALITY CONTROL ASSAYS



FLOW CYTOMETRY-CD34+



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QUALITY CONTROL ASSAYS

Virology:

Hep B, Hep C, HIV, HTLV I-II, Syphilis, CMV, Toxo

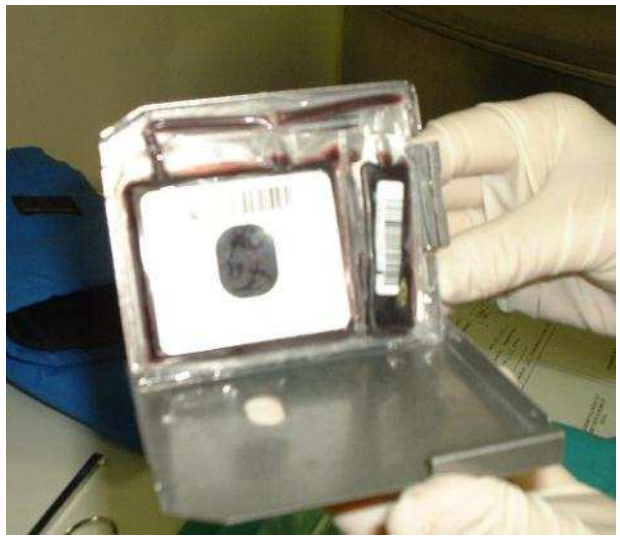
HLA typing & blood group

Haemoglobinopathies

RELEASING TESTS

QUALITY:

- Safety
- Identity
- Potency



What to do:

- Built quality in front
- Verify: releasing tests

Safety:

-*Serology on cord blood*

Identity:

-HLA

-Blood group and gender

- *Maternal haplotype*

Potency:

-CFU/CD34/CLONE

-Viability

-NC recovery

-Volume

NEEDS AND REQUIREMENTS OF USERS

Table 2 Required and recommended tests and test results according the US FDA for cord blood and HPC-C (final cord blood product)[46]

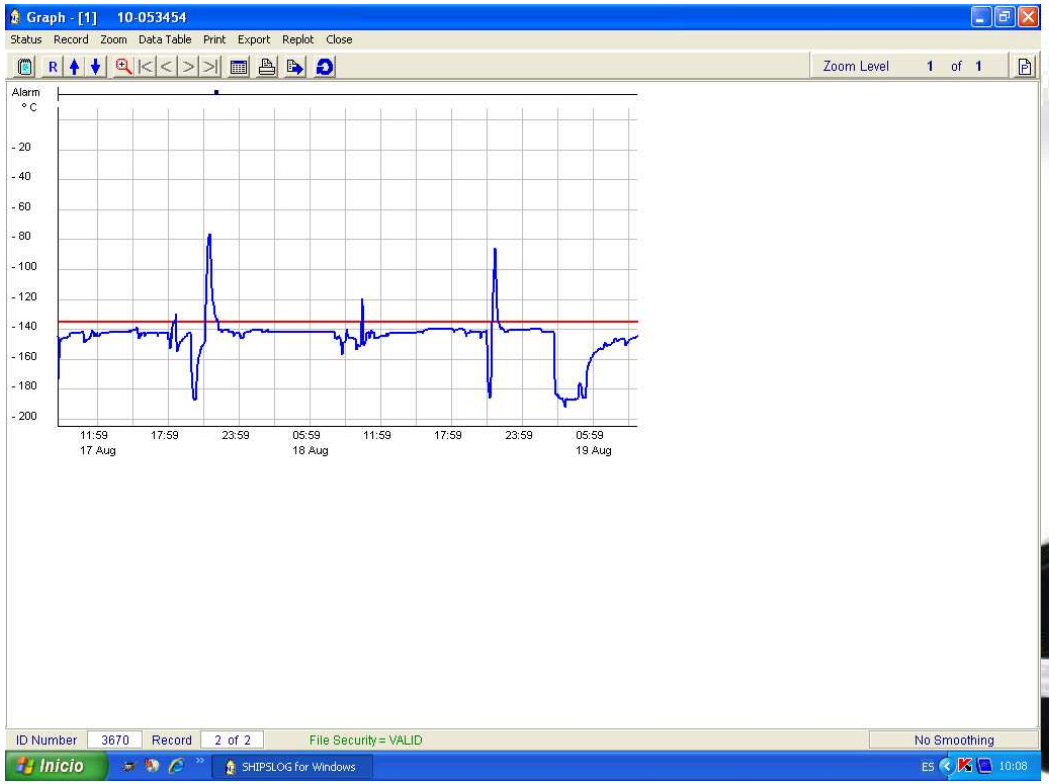
Product characteristics	*Testing*	*Sample (type and timing)*	*Results of product testing*
Safety	Infectious diseases—testing required (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 days of cord blood collection—type and timing required. (21 CFR 1271.80(a) and (b))	All tests negative except non-treponemal test for syphilis when confirmatory test is negative. CMV results are recorded). CMV report
	Sterility—bacterial and fungal cultures—testing required. (21 CFR 211.165(b) and 21 CFR 610.12)	HPC-C [a](pre- cryopreservation)	No growth
	Haemoglobin	Cord blood[b] or appropriate donor sample obtained at time of cord blood recovery	No homozygous haemoglobinopathy
Purity and potency	Total nucleated cells (TNCs)	HPC-C (pre-cryopreservation)	$\geqslant 5.0 \times 10^8$ TNC[c] per unit HPC-C
	Viable nucleated cells	HPC-C (pre- cryopreservation)	$\geqslant$85% viable nucleated cells
	Viable CD34+ cells (flow cytometry)	HPC-C (pre-cryopreservation)	$\geqslant 1.25 \times 10^6$ viable CD34+ cells[d] per unit HPC-C
Identity	HLA typing	Cord blood	Report
	Confirmatory HLA typing	Attached segment of HPC-C	Confirms initial typing
	Blood group and Rh type	Cord blood	Report

Abbreviation: FDA = Food and Drug Administration.
[a]Sample may be obtained before or after addition of the cryoprotectant.
[b]Cord blood = cord blood before undergoing volume reduction.
[c]Based on 20 kg recipient, a target dose of $\geqslant 2.5 \times 10^7$ nucleated cells per kg and 70% post-thaw recovery = 1.7×10^7 nucleated cells per kg.
[d]Based on CD34+ cells $\geqslant$0.25% of TNC before freezing.

QMS: CONTINOUS IMPROVEMENT:

i.e. Bag issues

i.e. Transport issues

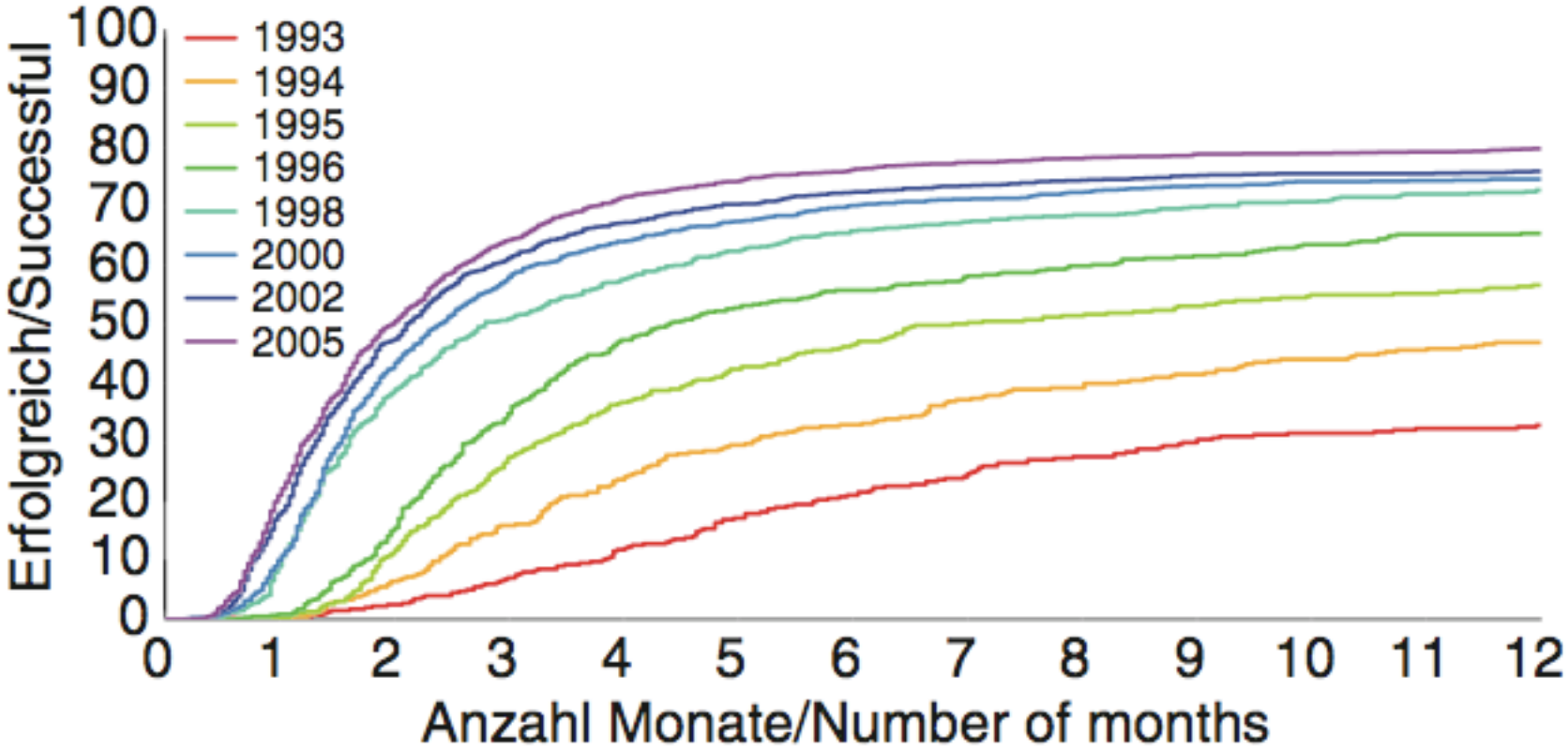


- Limitations of adult registries
  - Non-equitable / Imbalanced access to the therapy
    - Repertoire
    - Time
- Cord blood could be a complementary tissue for haematopoietic stem cell transplantation:
  - Impact of accessing non predominant population
  - Less HLA stringency due to immunological naiveté
  - Keeping goals:

    Reconstitution of a healthy haematopoietic system

    Cellular immunotherapy against malignancies

LIMITATIONS OF THE ADULT BONE MARROW REGISTERS: ACCESS AND TIME



Querol S, Rubinstein P, Marsh SG, Goldman J, Madrigal JA. Cord blood banking: 'providing cord blood banking for a nation'.

Br J Haematol 2009;147(2):227-35

TRANSPLANT AND ETHNICITIES

Ethnicities*	Census 2001	ANT Donors	Searches for UK Patients	Transplants per searches	Cords per transplants
Black	2.2	3.7	2.5	22	40
Asian	4.3	3.1	4.5	12	40
Oriental	0.4	0.2	0.4	n/a	n/a
NWE	88.8	91	86.9	34	7
n-NWE	2.6	n/a	5.3	n/a	n/a
Other	1.7	2	0.4	n/a	n/a

*16% of unknown ethnicities were excluded in the percentage assignment within 1079 searches performed during 2005

Querol S, Rubinstein P, Marsh SG, Goldman J, Madrigal JA. Cord blood banking: 'providing cord blood banking for a nation'.

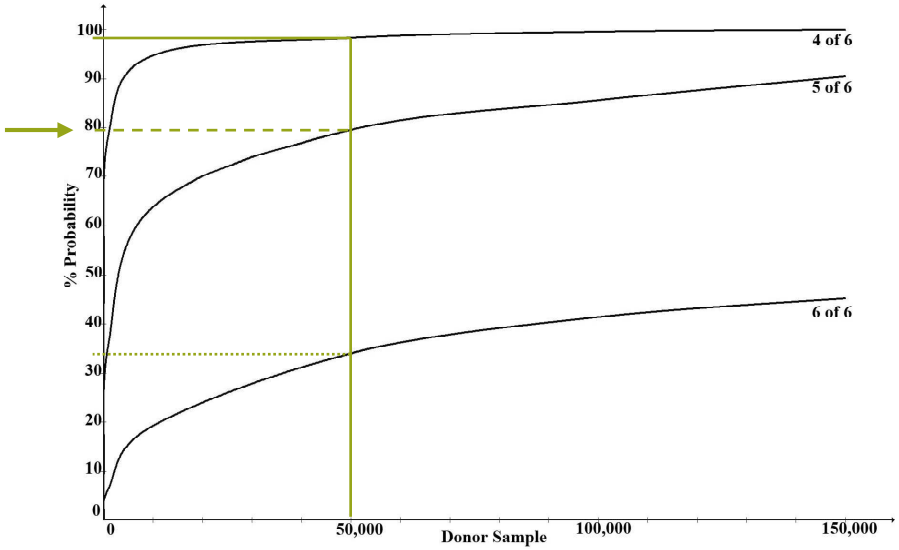
Br J Haematol 2009;147(2):227-35

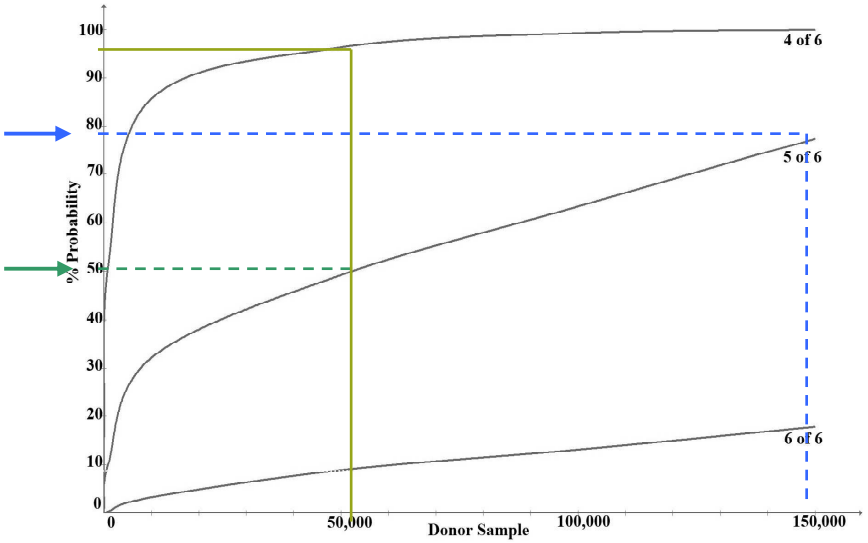
Ethnicities	Census 2000	NMDP Donors	Searches for US Patients	Estimated donor available
Black	12%	14%	7%	34%
American Indian	1%	2%	0.3%	n/a
Asian/Pacific	4%	11%	5%	44%
Hispanic	12%	15%	6%	47%
White	71%	58%	82%	65%

Source: Transplantation, Volume 78(1), 15 July 2004, pp 89-95

SIZE FOR UK

Probability to find a least 1 HLA-A,B low and DRB1 high match





All patients

2,000

Against 150,000 Anthony Nolan Donors

Non north western european patients

722

80% chance for 5/6 (50% non-predominant)

≈ 50,000

Raise to 80% chance for 5/6 to non-predominant

≈ 150,000

Querol S, Mufti GJ, Marsh SG, Pagliuca A, Little AM, Shaw BE, Jeffery R, Garcia J, Goldman JM, Madrigal JA. Cord blood stem cells for hematopoietic stem cell transplantation in the UK: how big should the bank be? Haematologica. 2009, 94(4):536-41

DOSE

- Preference of bigger units make obsolete many units stored in the cord blood banks (internal competition)
- Prospective thresholds could raise until a level that makes new units highly competitive:
  - NC12x10^8 and CD34 4x10^6
- Unfortunately, this makes necessary large collection programmes that are highly inefficients (up to 80% of units are discarded)

WHY NATIONAL PROGRAMMES?

- Meeting National Regulations
- Pre-defined Quality
- Easy Logistics
- Better Feedback
- R&D using CB surplus
- Economic control (auto-sufficiency)

PRIVATE vs PUBLIC CORD BLOOD BANKS

Same concept but different targets:

- Public CBB: A new allogeneic network, focused in the product and in the recipient safety

- Private CBB: First speculative application of the Regenerative Medicine principle, focused in the donor

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 3828–3832, May 1989
Medical Sciences

Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells

HAL E. BROXMEYER*†‡§, GORDON W. DOUGLAS¶, GIAO HANGOC*‡, SCOTT COOPER*‡, JUDITH BARD‖, DENIS ENGLISH*‡**, MARGARET ARNY¶, LEWIS THOMAS‖††, AND EDWARD A. BOYSE‖

Departments of *Medicine (Hematology/Oncology), †Microbiology and Immunology, **Pathology, and the ‡Walther Oncology Center, Indiana University School of Medicine, Indianapolis, IN 46223; ‖Memorial Sloan–Kettering Cancer Center, New York, NY 10021; ¶Department of Obstetrics and Gynecology, New York University Medical Center, New York, NY 10016; and ††Cornell University Medical Center, New York, NY 10021

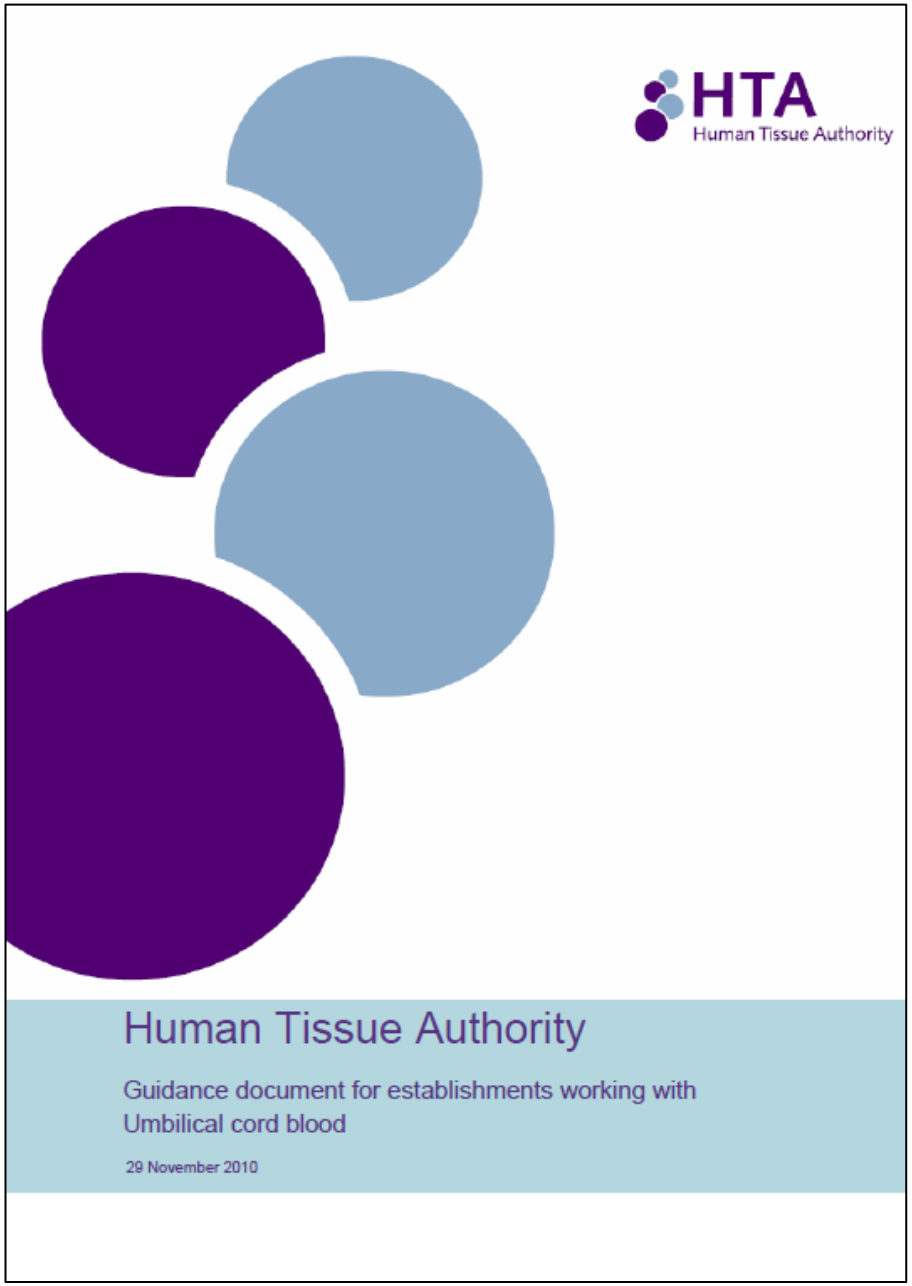
Contributed by Edward A. Boyse, February 9, 1989

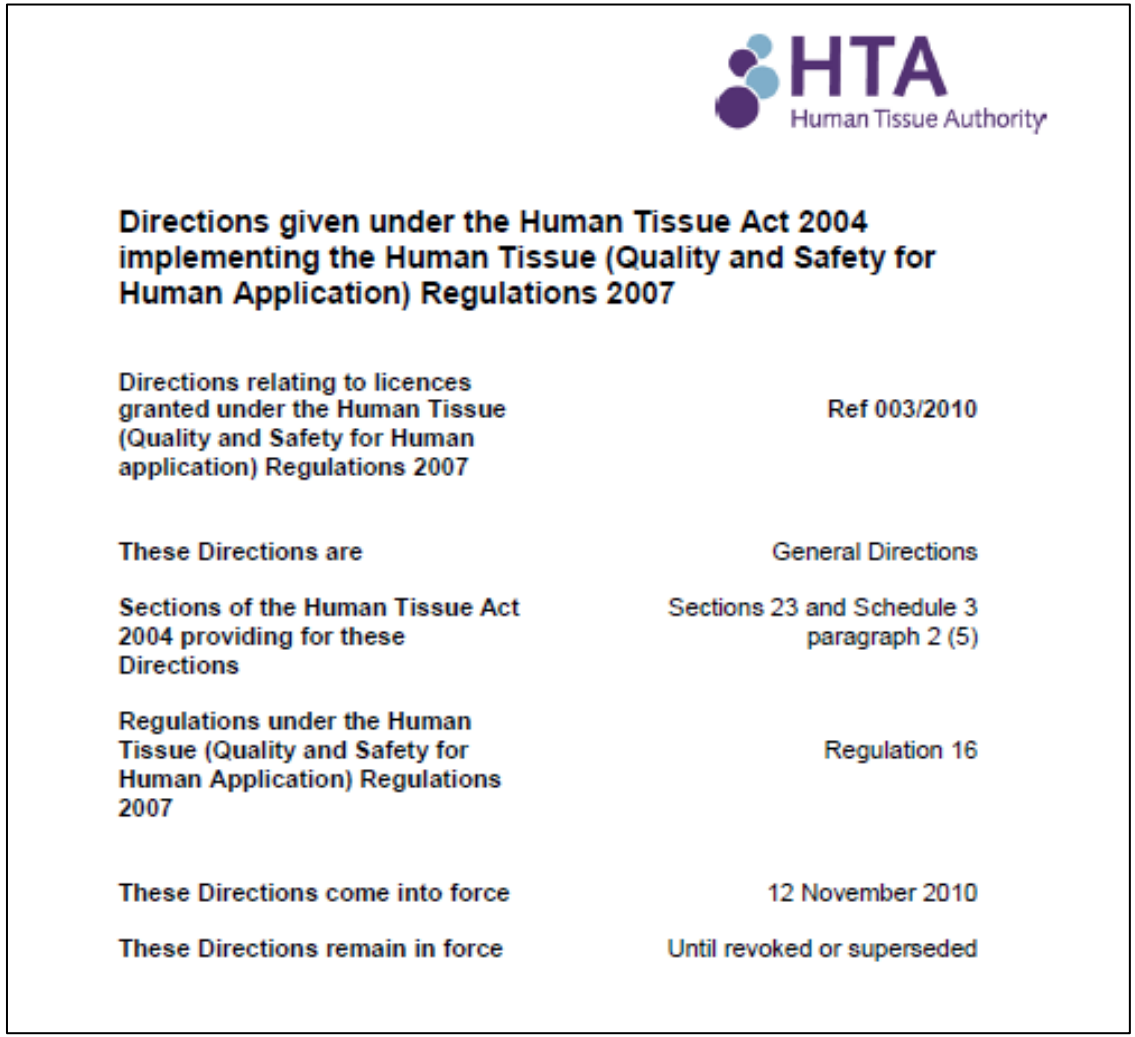
blood infused into donors immediately after thawing would not present serious problems.

The final question of whether human cord blood cells can successfully reconstitute a human subject is the subject of an international and multiinstitutional collaboration (E. Gluckman, H.E.B., A. D. Querbach, H. S. Friedman, G.W.D., A. Devergie, H. Esperou, D. Thierry, G. Socie, P. Lehn, S.C., D.E., J. Kurtzberg, J.B., and E.A.B., unpublished research).

We thank Linda Cheung for typing the manuscript. These studies were supported by a grant from the Biocyte Corporation (New York, NY) and by Public Health Service Grants CA36464 and CA36740 (to H.E.B.) from the National Cancer Institute.

E. Gluckman, H.E. Broxmeyer, A.D. Auerbach, H. Friedman, **G.W. Douglas**, A. DeVergie, H. Esperou, D. Thierry, G. Socie, P. Lehn, S. Cooper, D. English, J. Kurtzberg, J. Bard and **E.A. Boyse** (1989).
Hematopoietic reconstitution in a patient with Fanconi anemia by means of umbilical-cord blood from an HLA-identical sibling, N Engl J Med 321, p. 1174.


HTA
Human Tissue Authority
Human Tissue Authority
Guidance document for establishments working with Umbilical cord blood
29 November 2010



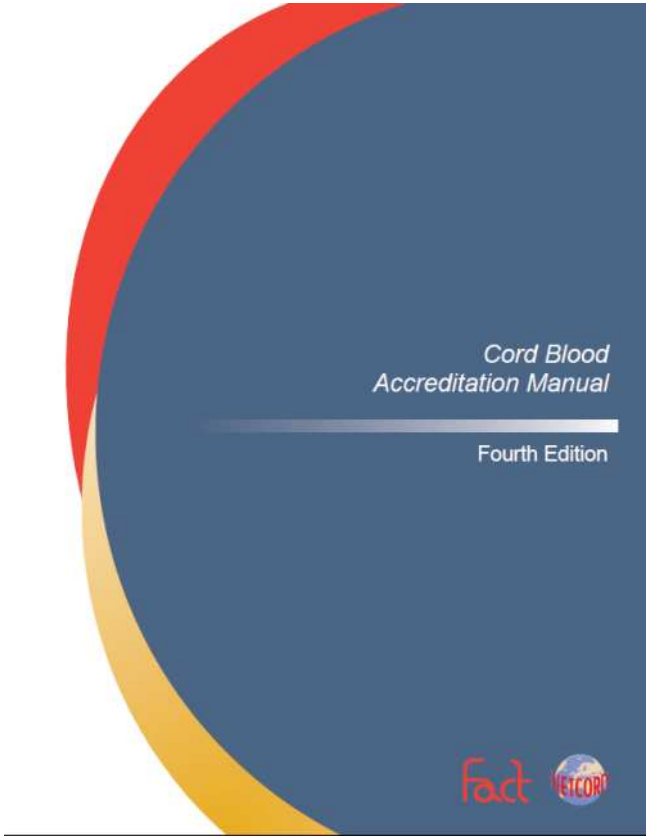
HTA
Human Tissue Authority

Directions given under the Human Tissue Act 2004 implementing the Human Tissue (Quality and Safety for Human Application) Regulations 2007

Directions relating to licences granted under the Human Tissue (Quality and Safety for Human application) Regulations 2007	**Ref 003/2010**
These Directions are	General Directions
Sections of the Human Tissue Act 2004 providing for these Directions	Sections 23 and Schedule 3 paragraph 2 (5)
Regulations under the Human Tissue (Quality and Safety for Human Application) Regulations 2007	Regulation 16
These Directions come into force	12 November 2010
These Directions remain in force	Until revoked or superseded

BUT, WHAT IS A CORD BLOOD BANK?

2010: Standards for Cord Blood Services



INTERNATIONAL STANDARDS FOR CORD BLOOD COLLECTION, BANKING, AND RELEASE FOR ADMINISTRATION
ACCREDITATION MANUAL

Guidance to Accompany the NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration, Fourth Edition

Fourth Edition
January 2010

NOTICE

These Standards are designed to provide minimum guidelines for Cord Blood Banks, facilities, and individuals performing cord blood collection, processing, testing, banking, listing, search, selection, reservation, release, and distribution, or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a Cord Blood Bank, facility, or individual should implement if the standard of practice in the community or Applicable Law establishes additional requirements. Each Cord Blood Bank, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. The Foundation for the Accreditation of Cellular Therapy and NetCord disclaim any responsibility for setting maximum standards and expressly do not represent or warrant that compliance with these Standards is an exclusive means of complying with the standard of care in the industry or community.

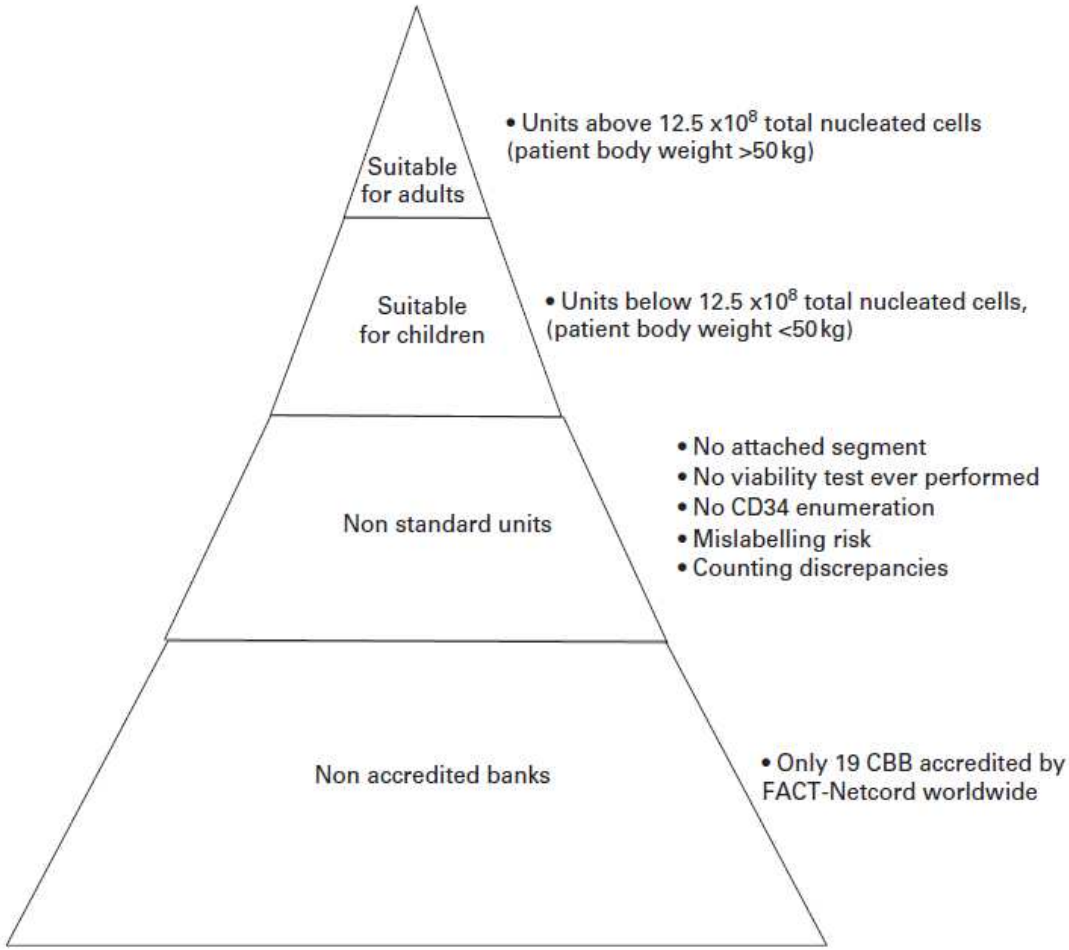


Figure 1 Figurative representation of the quality of the international cord blood inventory (400 000 Units from 107 cord blood banks according to www.bmdw.org) and suitability for adult and paediatric transplantation on the basis of accreditation, administrative and quantitative factors—The Iœberg effect.

JAMA. 1995 Dec 13;274(22):1783-5.

Ethical aspects of banking placental blood for transplantation.

Sugarman J, Reisner EG, Kurtzberg J.
Program in Medical Ethics, Duke University Medical Center, Durham, NC 27710, USA.

Transplantation of blood cells harvested from the umbilical cord immediately after birth has been effective in repopulating the bone marrow. These placental blood transplantations may be safer than conventional bone marrow transplantations and may suspend the need to harvest bone marrow, a process fraught with difficulties. Further understanding and advancement of this emerging technology require developing large banks of placental blood. In this article, we examine some of the ethical issues associated with placental blood banking, including (1) questions about **ownership** of the tissue, (2) the necessity and nature of obtaining **informed consent** from parents for harvesting placental blood and the information-gathering process associated with it, (3) **obligations to notify parents** and children of the results of medical testing for infectious diseases and genetic information, (4) matters of **privacy and confidentiality** related to such information, and (5) the need for fair and **equitable harvesting of and access** to placental blood.

RECOMMENDATIONS OF EXPERTS IN BIOETHICS

European group on ethics in science and new technologies to the European commission published on 2004

- 1) On commercial cord blood banks: as they sell a service, which has presently, no real use the activities of these banks **should be discouraged**.
- 2) On collection: The collection must **not disturb the process of delivery** and should **not present any risks**.
- 3) On directed cord blood banks: It should be proposed to them that **storage should be by public cord blood banks.**
- 4) On **promoting public cord blood bank**
- 5) On autologous collection in public cord blood banks: In the future, should the development get to the point where the use of one's own cord blood cells may be of value, the **storage should not be a service left to commercial banks but should be taken over by the public sector** in order to ensure fair access to healthcare services for everybody.
- 6) On encouragement of a **single point of access** between adult registries and cord blood banks

BIOETHICS AND CORD BLOOD

- AUTONOMY: Each individual has the **right to freely choose their own course of action** and to choose what happens to them.
- **NON-MALEFICENCE: Do not harm!**
- BENEFICENCE: Actions taken should **do good**

LEGAL RATHER THAN ETHICAL ISSUES

N. Engl. J. Med. 1999 May 13;340(19):1521-4.

Waste and longing--the legal status of placental-blood banking.

Annas GJ.
Health Law Department, Boston University School of Public Health, USA.

- Legal Model: Solid Organ vs Blood
- Legal issues: Ownership, Consent and Privacy

THE WOMEN'S DILEMMA

To release or to maintain ownership?

THE WOMEN'S PROBLEM

Universal access to private donation but 2000€

Reduced access to public donation (0.1% population)

The role of perinatal care providers

J Perinat Med. 2007 May 21 (on line). Umbilical cord blood collection: do patients really understand?

Fox NS, Stevens C, Ciubotariu R, Rubinstein P, McCullough LB, Chervenak FA.
Department of Obstetrics and Gynecology, Weill Medical College of Cornell University, New York, USA.

Women are poorly informed about cord blood banking. The **decision making process** should be conducted with the goal of ensuring every pregnant woman the opportunity to make a well informed decision about cord blood banking

COMMERCIAL BANK PITFALLS

(Fox et al, 2007)

1) Commercial CBB should not represent the service they sell “doing everything possible”
2) More than 95% allogeneic searches find a potential donor
3) Few cases of really autologous transplantation has been reported (mainly there are related)
4) If stored publicly, 90% of units are available after a 10-years period
5) Collection in a non-trained environment could increase the risk of neonatal anemia (early clamping)
6) Collectors should disclose any benefit received from the company
7) Commercial bank for Regenerative Medicine relies on expansion technology still unsuccessful

FACTS

- Cord blood is a natural cellular product, extensively harvested in a Cord Bank
- More than half of the donated products are disposed in spite having substantial numbers of functional cells
- An effort must be done to develop clinical and research applications for these products that maintain the altruistic will of the donors such is to be transplanted to any patient in need

CONCLUSION:
THE CORD BLOOD MOVEMENT

- Cord blood represents an actual (real) product (not virtual lists)
- Ethical (naturally discarded product)
- Cost-benefit (lower inventories, less maintenance, highest efficiency and self-sufficiency)
- Potential to expand access, improve outcomes and open new doors in therapy (new paradigm)
- Potential to develop a biotechnological and biopharmaceutical platforms (biotechnology/biopharmacy)
- Reconcile public and private interests (same answer to different questions)

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Daniel Gibson

Pam Sami

Chris Leonforte

Laura Fry

Kieran Herrity

Guy Parkes

Terie Duffy & dedicated collectors at Kings

Linda Moss & dedicated collectors at Leicester

All Anthony Nolan Cord Blood Programme donors

Topics in Regenerative Medicine
Kings College London
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