Azienda Ospedaliera San Gerardo

GITMO

SIdEM Società Italiana di Emaferesi e Manipolazione Cellulare

…Human progenitor cells are not like single-malt whiskey… they don’t get better with prolonged storage..

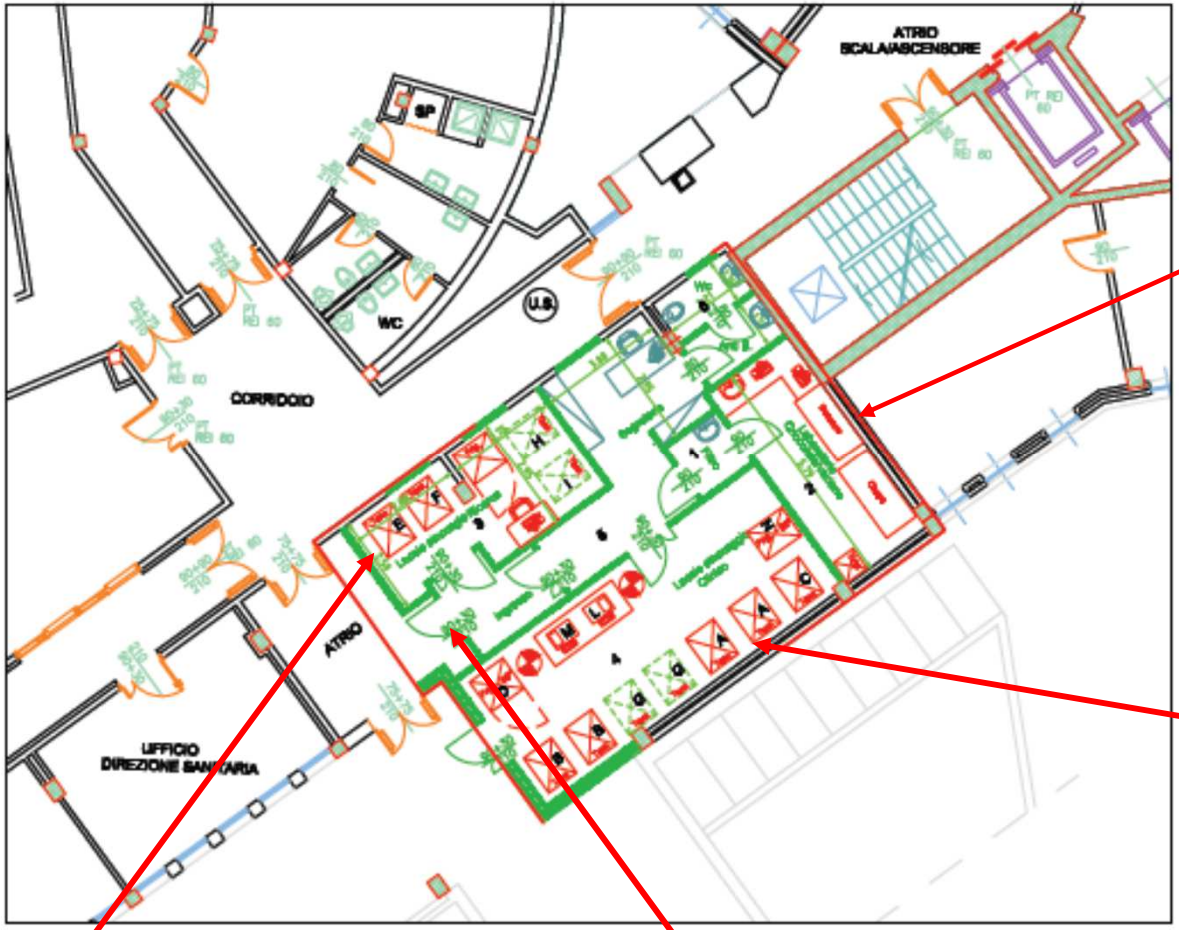
- **So far, there are no national and/or european regulation or rules which define criteria, modalities and timing for the disposal of residual HSC frozen**

AO S. Gerardo

UOS Aferesi e nuove tecnologie trasfusionali

Laboratorio di criobiologia

Locale Aferesi

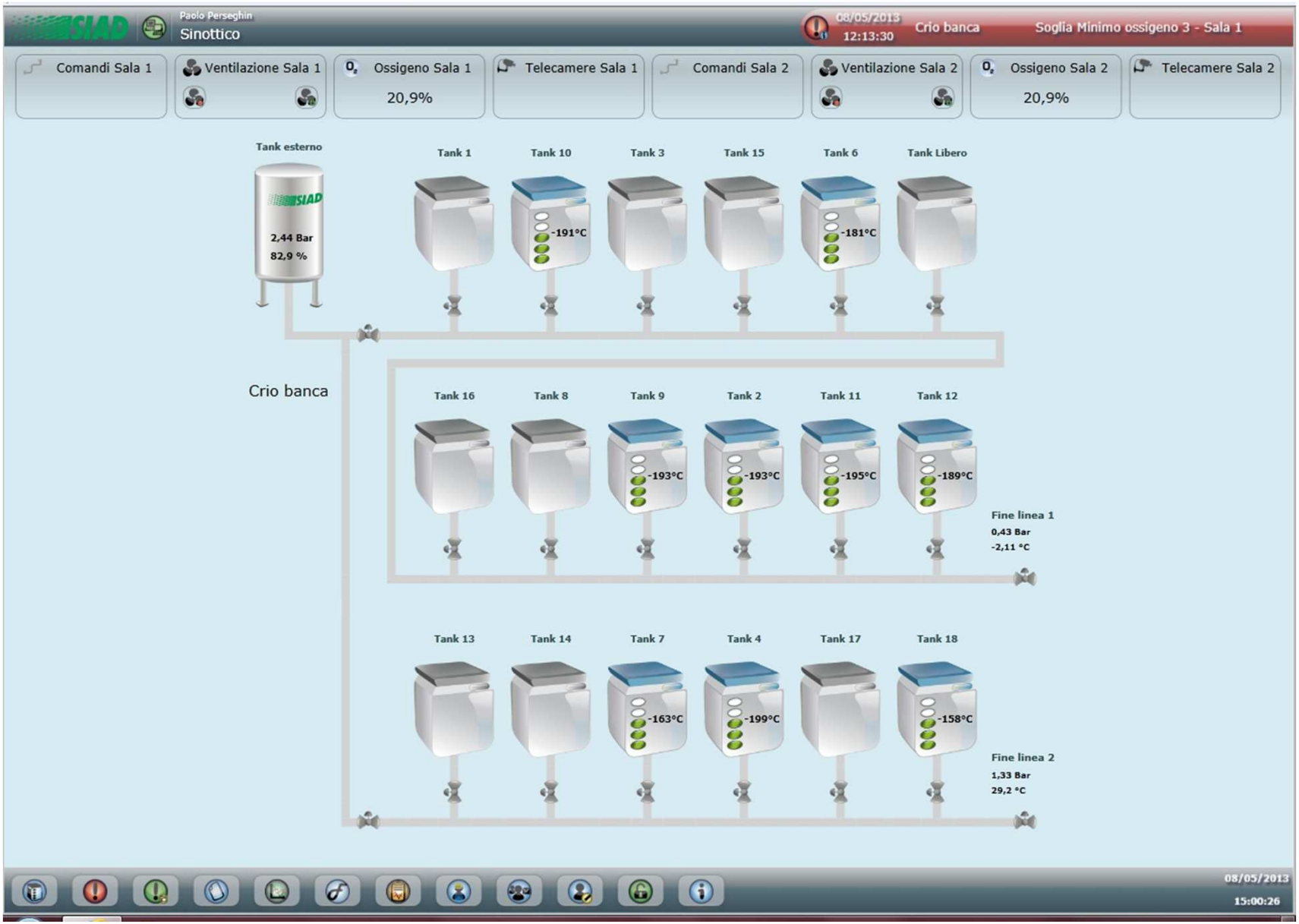


Lab. Classe D

Locale stoccaggio prodotti uso clinico

Locale stoccaggio campioni per ricerca

Ingresso operatori-controllo con badge


Paolo Perseghin
Sinottico
08/05/2013
12:13:30
Crio banca
Soglia Minimo ossigeno 3 - Sala 1
Comandi Sala 1
Ventilazione Sala 1
Ossigeno Sala 1
20,9%
Telecamere Sala 1
Comandi Sala 2
Ventilazione Sala 2
Ossigeno Sala 2
20,9%
Telecamere Sala 2
Tank esterno
2,44 Bar
82,9 %
Crio banca
Tank 1
Tank 10
-191°C
Tank 3
Tank 15
Tank 6
-181°C
Tank Libero
Tank 16
Tank 8
Tank 9
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Tank 2
-193°C
Tank 11
-195°C
Tank 12
-189°C
Fine linea 1
0,43 Bar
-2,11 °C
Tank 13
Tank 14
Tank 7
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Tank 4
-199°C
Tank 17
Tank 18
-158°C
Fine linea 2
1,33 Bar
29,2 °C
08/05/2013
15:00:26

Survey GITMO 2007-2008

1- number of stored units

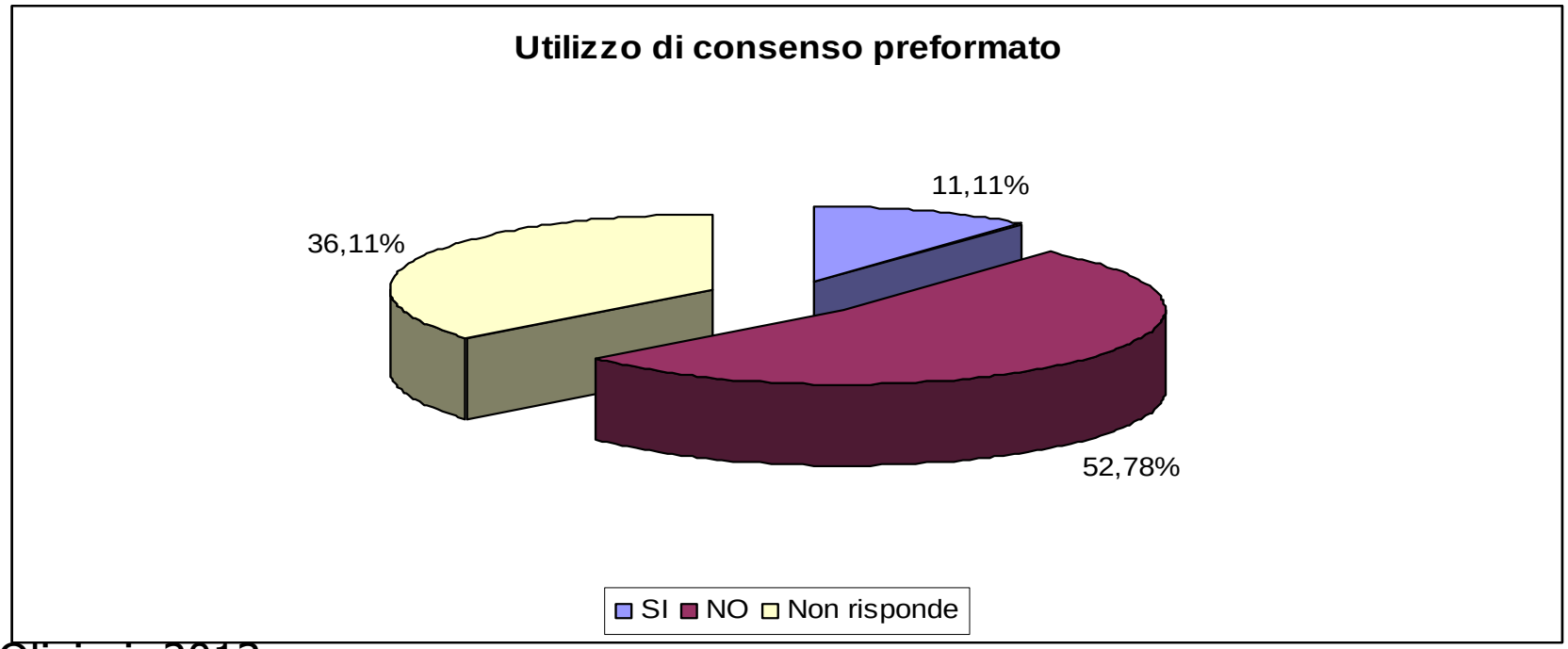
2- Local policies for disposal of residual HSC

3- Need for a national, agreed, policy

The results from the survey have been presented at GITMO 2008-Naples

Only 36 centers (out of 83) answered

- ALL centers had residual stored units (overall, 7097).
- 61% of those 7097 units frozen before 2005
- Only 11 % had requested a patient's signed informed consent for possible disposal of residual units



Olivieri, 2013

2013 Excellence in Science EBMT European Group for Blood and Marrow Transplantation

39th Annual Meeting of the European Group for Blood and Marrow Transplantation

7 – 10 April 2013 • London, UK

Long-term stored and never reinfused, cryopreserved Stem Cell Units (SCU) for Autologous Transplantation: a GITMO survey about the relevance and management of storage and discharge.

Attilio Olivieri, Alberto Bosi, Luca Pierelli, Marco Risso, Patrizia Accorsi, Martino Introna, Jacopo Olivieri, Stefania Mancini, Silvia Felicetti, Gerardo Catena, Clelia Musto, Ilaria Scortechini, Mauro Montanari, Pietro Leoni, Giuseppe Milone, Alessandro Rambaldi on behalf of the GITMO (Gruppo Italiano Trapianto di Midollo Osseo)

36 GITMO centers answered to a questionnaire about the amount of SCU stored for a long time (from 1990-2000 up to the end of 2007)*

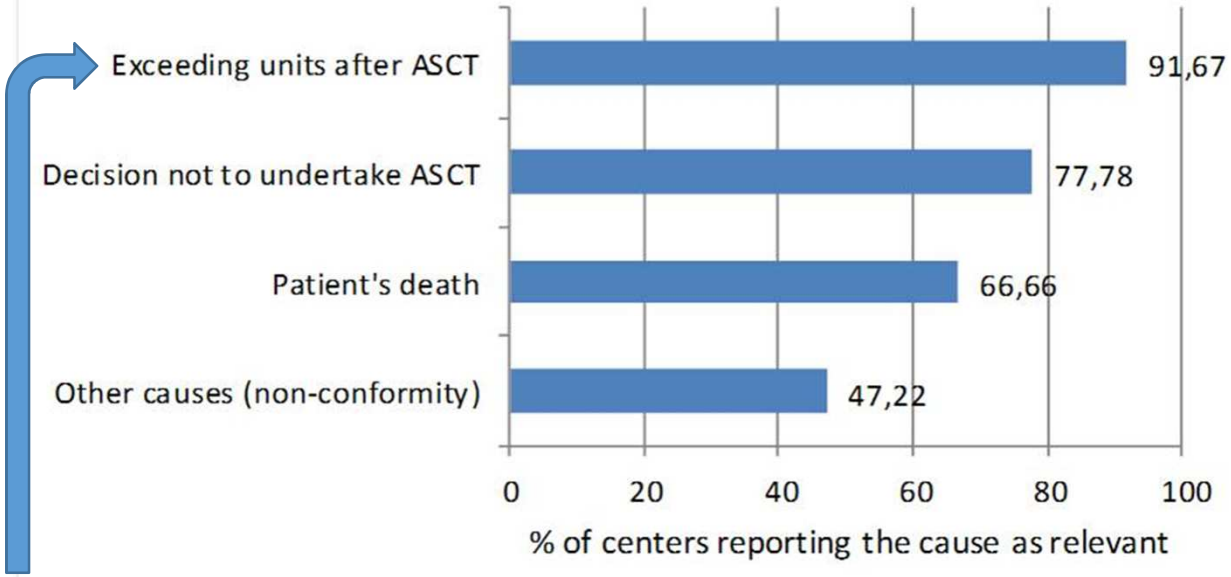


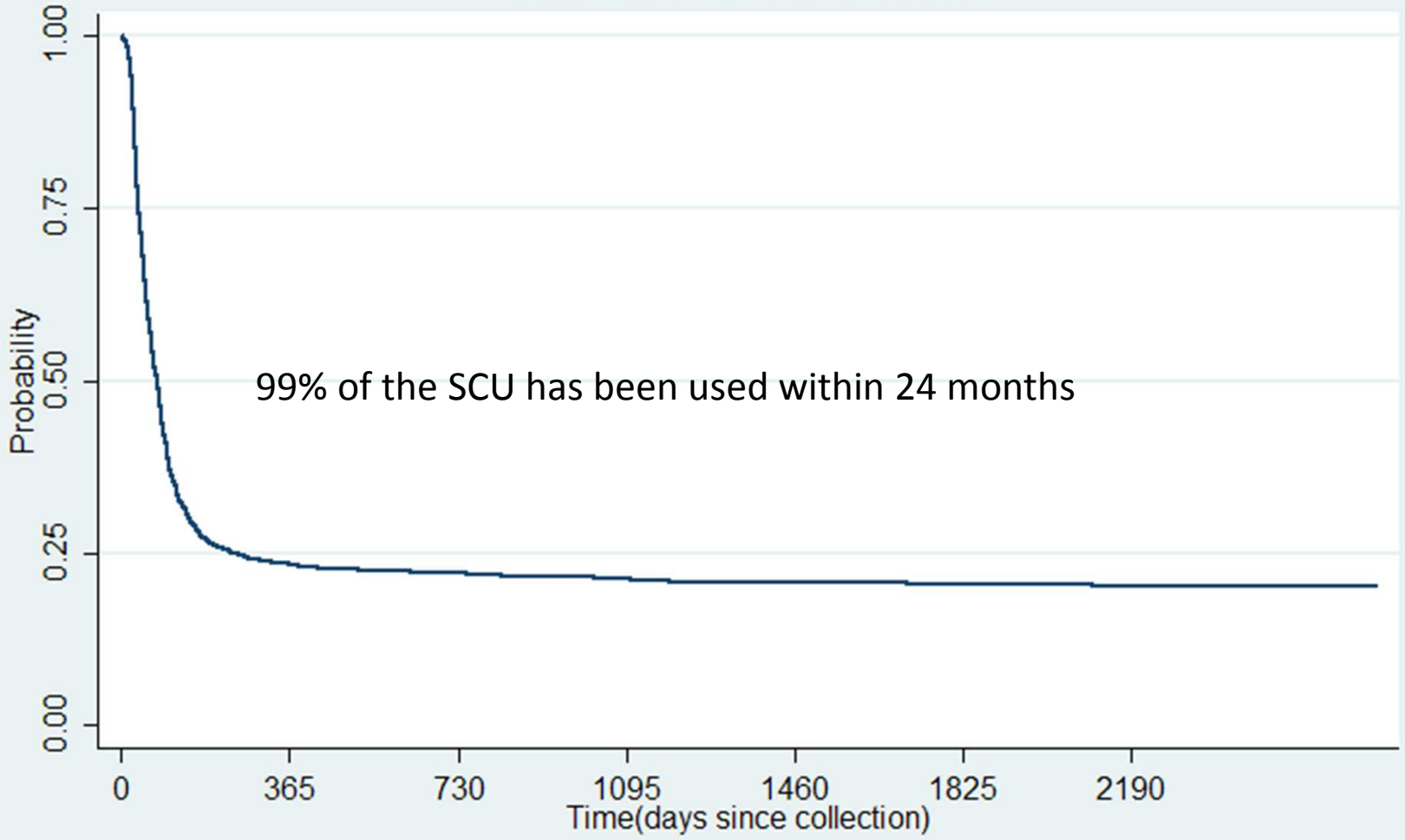
Fig.1 Relevant causes of non-use of SCU among 36 italian centers participating to the GITMO questionnaire

Interviewed centers represented about 30-40% of the Italian GITMO centers involved in the activity of cryopreservation for ASCT

Olivieri, 2013

GITMO ONLUS

Kinetics of reinfusion N°1

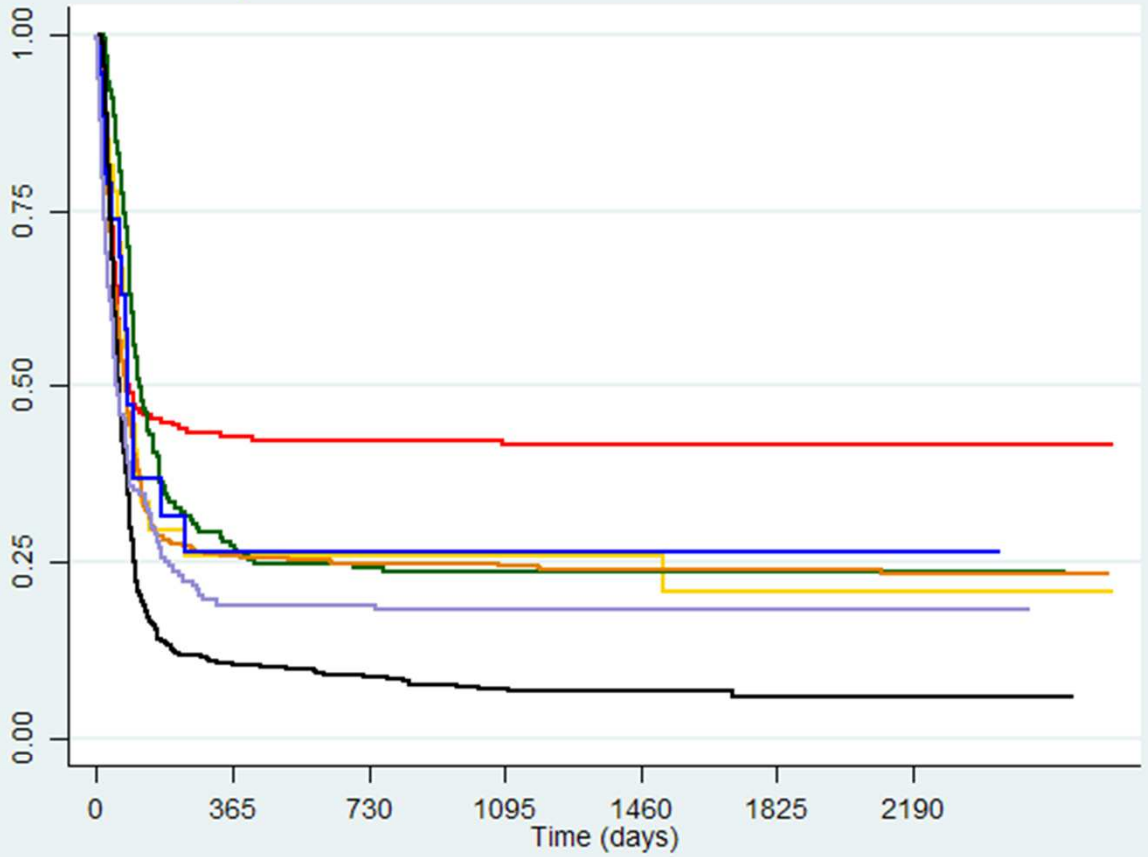


99% of the SCU has been used within 24 months

Pts still not reinfused (Reinfusions)

1585	(1212)	345	(18)	291	(10)	222	(3)	144	(2)	98	(1)	58

Kinetics of 1st reinfusion, according to the underlying disease



Number at risk

ALTRO	27	(20)	6	(0)	6	(0)	6	(0)	5	(1)	3	(0)	3
LA	213	(121)	82	(1)	67	(1)	51	(0)	34	(0)	23	(0)	13
LH	165	(120)	44	(5)	39	(1)	26	(0)	13	(0)	9	(0)	3
LNH	575	(425)	137	(5)	120	(2)	95	(2)	64	(0)	50	(1)	30
MISSING	19	(14)	5	(0)	5	(0)	5	(0)	5	(0)	2	(0)	2
MM	438	(392)	43	(7)	28	(5)	21	(1)	10	(1)	8	(0)	4
TS	148	(120)	28	(0)	26	(1)	18	(0)	13	(0)	3	(0)	3

Kinetics of the use of cryopreserved autologous stem cell grafts: a GITMO-SIDEM survey

JACOPO OLIVIERI[1], LUCA PIERELLI[2], MARTINO INTRONA[3], PATRIZIA ACCORSI[4], ALBERTO BOSI[5], PAOLO PERSEGHIN[6], MARCO RISSO[7], ANNINO PANDOLFI[2], STEFANIA MANCINI[1], MONIA MARCHETTI[8], SIMONE DAL POZZO[5], ELISA GOTTI[3], ALESSANDRO RAMBALDI[3], PIETRO LEONI[1] & ATTILIO OLIVIERI[1], ON BEHALF OF THE GITMO (GRUPPO ITALIANO TRAPIANTO DI MIDOLLO OSSEO)–SIDEM (SOCIETÀ ITALIANA DI EMAFERESI E MANIPOLAZIONE CELLULARE) WORKING GROUP ON SCU DISPOSAL

Cytotherapy, 2014; 16: 101–110

Table II. Outcome of HPC by patient according to disease categorization: patients undergoing HPC cryopreservation were followed from collection to seek the outcome of the autologous SCU.

	NHL	HL	AL	MM	ST	Other	Unknown	Total patients (%)
Disease category (%)[a]	35.9%	10.4%	13.4%	27.4%	10.0%	1.7%	1.2%	100%
Disease category (patients)	576	166	214	440	161	27	19	1603
Patients in each disease category, %								
Reinfusing (R)	75.7	76.5	57.9	92.7	83.2	77.8	73.7	1264 (78.9%)
Wholly reinfusing (WR)	38.2	34.9	29.9	49.3	41.0	18.5	57.9	641 (40.0%)
Partially reinfusing (PR)	37.5	41.6	28.0	43.4	42.2	59.3	15.8	623 (38.9%)
Disposed SCU (PR-S)	11.1	10.8	9.8	10.2	6.2	7.4	0.0	160 (10.0%)
Stored SCU (PR-D)	26.4	30.7	18.2	33.2	36.0	51.9	15.8	463 (28.9%)
Never reinfused (NR)	24.3	23.5	42.1	7.3	16.8	22.2	26.3	339 (21.2%)
Disposed SCU (NR-D)	5.2	1.8	16.8	1.8	3.7	3.7	5.3	85 (5.3)
Stored SCU (NR-S)	19.1	21.7	25.2	5.5	13.0	18.5	21.1	254 (15.9)

[a]The "Other" category includes idiopathic thrombocytopenic purpura, multiple sclerosis, systemic sclerosis and other autoimmune diseases.

- A huge amount of HPC are at present stored at Italian transplant centres: based on a previous audit including one third of Italian centers, more than 30,000 units are actually stored unused
- This amount if growing higher since 0.88 HPC units are stored and never used per each reinfusion/SCT procedure completed. This implies that further 15,000 autologous HPC units are uselessly stored in Europe each year (EBMT 2011 reports on 17.700/ASCT/year).
- Assuming that storing costs vary **from 65 to $100** per year/unit, as reported by several biobanks, we can easily calculate that unregulated long-term storing of useless autologous HPC actually burdens Italian Health Care Service with 3 million euro each year.

Criteri GITMO-SIDEM per lo smaltimento delle unità di HPC-A autologhe criopreservate

Marchetti Monia, Bosi Alberto, Perseghin Paolo, Olivieri Attilio, Risso Marco, Introna Martino, Lombardini Letizia, Accorsi Patrizia, Petrini Luca, Pierelli Luca

on behalf of the GITMO-SIDEM Working Group on SCU disposal

ANALYTIC HIERARCHY PROCESS

decision support tool usefully employed if quantitative data are lacking

quantitative method to share decisions by a group of experts (consensus support tool)

-- explicit statement of VALUES and of CHOICES

-- ranking of values

-- pairwise comparison of choices (per each value)

Examples:

1) definitions of response of Essential Thrombocytemia (Barosi)

2) definition of poor mobilizers (Olivieri)

5-10 yr elaapsed		OLD	DAM UNIT	FREEZE	Major COLD	CD34 <1	VITAL low	Major MICRO
Stable & complete engraftment	possible relapses manageable for SCT							
Stable & complete engraftment	not possible relapses manageable with SCT							

Grading: from 1 (minor importance) to 9 (high importance)

Decision criteria for the disposal of autologous HPC

MAJOR CRITERIA	DETAILS
Patient death^	Checked yearly by a specific SOP
Patient withdrawal of consent to SCT^	Written refusal of the patient to proceed to any SCT
Contraindications to SCT^	Severe not reversible organ toxicity or severe comorbidity that contraindicate high-dose chemotherapy: need to be checked yearly.
Damaged label^	Absolute impossibility to correctly identify the unit
Time since harvest longer than 10 years	
Loss of indications to SCT	SCT "Generally Not Recommended" according to the kind and phase of the disease (EBMT guidelines)
MINOR CRITERIA*	
Documented cold chain interruption	The unit is kept for more than 96 hours at a temperature higher than -80°C
Damaged unit	Loss of bag integrity with possible product spilling
Total amount of stored CD34+ cells lower than 1*10(6)/Kg	According to patient weight at the assessment of disposal (if harvested in pediatric patients)
Total amount of stored CD34+ cells lower than 2*10(6)/Kg in patients with successfully completed SCT program	
Low vitality at assessment of disposal according to the presence of one of the four above criteria	According to a specific institutional SOP
PROMP DISPOSAL§	
Abnormal freezing procedure causing highly reduced vitality	Documented according to a specific SOP
Major microbiology contamination	High-load (growth within 24 h) bacterial contamination

Minor criteria: each one allowed to anticipated disposal if concurrently viability was tested and showed impairment

- The Panel selected six major criteria that allow disposal:
- patient death
- withdrawal of consent to SCT
- contraindications to SCT
- loss of indications to SCT
- a damaged label that absolutely prevent from correctly identifying the unit
- time elapsed since harvest >10 years.

TABLE 1. Aims and values

AIMS

To identify the criteria for appropriate disposal of autologous HPCs

VALUES

To allow SCT program completion (including a second planned ASCT)

To allow a second unplanned ASCT or HPC support to intermediate- to high-dose chemotherapy for a relapse avoiding the risk of failure at remobilization

To allow alternative HPC use within protocols that are active at the moment disposal is assessed avoiding the risk of failure at remobilization

To limit costs and organizational burden of stocked HPCs

TABLE 2. Proposed conceptual criteria

	Conceptual criteria
Area: PATIENT	
Subarea: AVAILABILITY	1. Death
	2. Impossibility to recall patient
	3. Patient refusal of SCT
Subarea: INDICATIONS	4. Contraindications to SCT
	5. Loss of indications to SCT
	6. Completed SCT program
	7. Stable and complete engraftment after allogeneic SCT (back-up units)
Subarea: AGE	8. Age at mobilization
	9. Age at assessment of disposal appropriateness
Area: PRODUCT	
Subarea: IDENTIFICATION	10. Damaged labeling
	11. Availability of additional sample vials
Subarea: INTEGRITY	12. Damaged unit
	13. Interrupted cold chain during storage
	14. Major deviations in the freezing process
	15. Major microbiology contamination
Subarea: CONTENT	16. CD34+ cell content (of the unit)
	17. Viability
Area: TIME	18. Time since harvest

TABLE 3. Decision criteria for the disposal of autologous HPCs

PROMPT DISPOSAL‡	
Abnormal freezing procedure causing highly reduced viability	Documented according to a specific SOP
Major microbiology contamination	High-load (growth within 24 hr) bacterial contamination or presence of 1) Gram-negative bacteria or 2) highly pathogenic multiresistant bacterial species
MAJOR CRITERIA	DETAILS
Patient death†	Patient survival status checked yearly by a specific SOP
Patient withdrawal of consent to SCT†	Written refusal of the patient to proceed to any SCT
Contraindications to SCT†	Severe not reversible organ toxicity or severe comorbidity contraindicating high-dose chemotherapy: it needs to be checked yearly
Damaged label†	Absolute impossibility to correctly identify the unit
Time since harvest longer than 10 years	
Loss of indications to SCT	SCT "generally not recommended" according to the type and phase of the disease (EBMT guidelines):[37] it needs to be checked yearly
MINOR CRITERIA*	
Documented cold chain interruption	The unit is kept for more than 96 hr at a temperature higher than –80°C
Damaged unit	Loss of bag integrity with possible product spilling
Total amount of stored CD34+ cells lower than 1×10^6/kg	According to patient weight at the assessment of disposal (if harvested in pediatric patients)
Total amount of stored CD34+ cells lower than 2×10^6/kg in patients with successfully completed SCT program	
Low vitality at assessment of disposal according to the presence of one of the four above criteria	According to a specific institutional SOP (i.e., CD34+ cell viability should be at least 50%)

* Criteria that might help predating disposal (before 10 years since harvest) in patients lacking major criteria for disposal.
† Each one was judged to be sufficient to support a disposal decision at any time.
‡ Disposal of the HPCs is allowed only after successful patient remobilization.

TABLE 4. Key issues to be included in the consent form for disposal of autologous HPCs

Criteria for disposal	Criteria need to be listed along with the rationale for their application
Communication of disposal	The transplant institution proceeds to disposal according to the above criteria without recalling the HPC donor
Withdrawal of prior consent	At any time from disposal to the expiry date (10 years from harvest), the donor can request to transfer his or her HPCs to a specified laboratory*
Consent author	Adults patients are the authors of their consent. However, for teenager patients, both relatives and patients need to express their consent.

* Tissue and cell exchange for transplantation is regulated in Europe by law 23/2004 and in Italy by DL 191/2007: it imposes an exchange between same vale institutions. Such laws do not regulate cell and tissue exchange destined to non-transplant uses, such as those HPCs that cannot be used anymore within a transplant program.

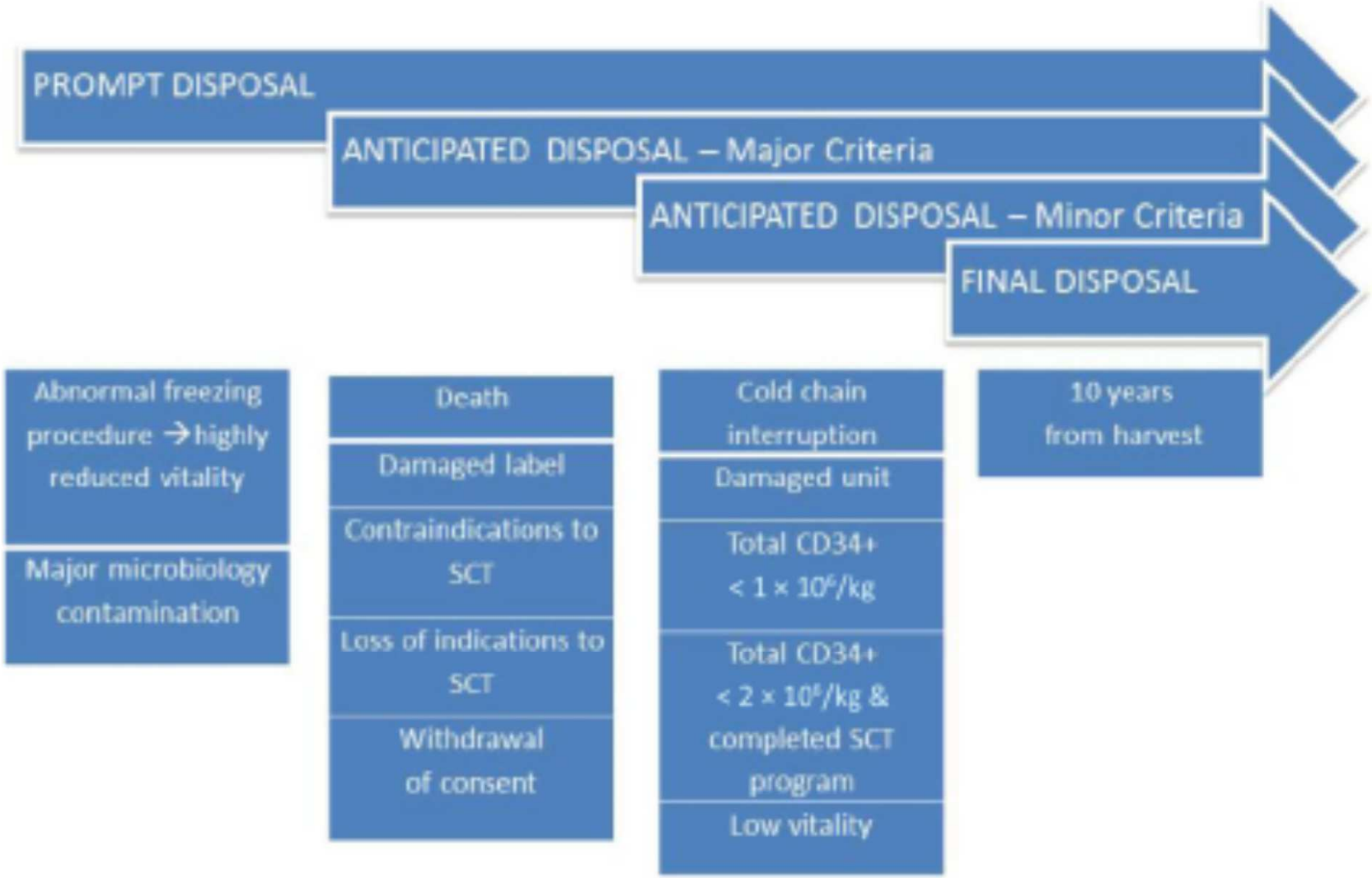


Fig. 1. Final decisional algorithm for autologous HSC disposal.

Key issues to be included in the Consent Form for Disposal of autologous HPC.

Criteria for disposal	**Criteria need to be listed along with the rational for their application**
Communication of disposal	**The transplant institution proceeds to disposal according to the above criteria without recalling the HPC donor**
Withdrawal of prior consent	**At any time from disposal to the expiry date (10 years from harvest), the donor can request to transfer his/her HPC to a specified laboratory^**
Consent author	**Adults patients are the authors of their consent. However, for teeneager patients, both relatives and patients need to express their consent.**

A policy for the disposal of autologous hematopoietic progenitor cells: report from an Italian consensus panel

Paolo Perseghin,[1] Monia Marchetti,[2] Luca Pierelli,[3] Attilio Olivieri,[4] Martino Introna,[5] Letizia Lombardini,[6] Patrizia Accorsi,[7] Carlo Petrini,[8] Marco Risso,[9] and Alberto Bosi,[10] on behalf of Società Italiana di Emaferesi e Manipolazione Cellulare (SIDEM), Gruppo Italiano Trapianto Midollo Osseo (GITMO) and Centro Nazionale Trapianti (CNT)

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EDITORIAL

Meeting the ethical promises of a policy regarding the disposal of autologous hematopoietic progenitor cells

Volume 54, September 2014 TRANSFUSION 2147

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Open issues

1. Patients advocate and more patient representative involvement
2. Possible loss of biological samples to be used for research. Need for appropriate patient informed
3. Field monitoring of policy application
4. A more "patient oriented" language with limitation of technical phraseology

Critical issues still pending

- Storage time for peculiar patients (i.e pediatrics, genetic diseases, etc)
- Administrative issues (how to contact patients whose units have been frozen before the publication of the policy)
- Patient advocate (informed consent form)

Survey 2016 SIDEM-GITMO-CNT

1) Awareness of SIDEM-GITMO CNT policy for residual HSCT units disposal y/n

2) Previous local residual HSCT units disposal policy y/n

3) Are you currently applying the SIDEM-GITMO CNT policy ? y/n

4) Do you apply all the criteria for disposal?

5) Do you apply SIDEM-GITMO CNT policy only for those residual units frozen AFTER the publication?

6) How many units have been eliminated since the publiication of the policy? How many patients?

7) Suggestion/comments

8) Do you know SIDEM-GITMO recommendation on HSC collection (published in 2012) ?

9) Are you applying in your center the above mentioned recommedation?

Question 2: Which is the target PBPC dose?

RECOMMENDATIONS. *The minimum PBPC dose to be collected and infused is 4.0 × 10⁶ to 4.5 × 10⁶ CD34+ cells kg/body weight of the recipient.*

In sibling myeloablative transplants the maximum PBPC dose to be collected and infused should not be higher th

Question 7: Which is the target PBPC dose?

ra

RECOMMENDATIONS. *The minimum PBPC dose to re be collected and infused to assure a low transplant-related do morbidity is 2 × 10⁶/kg/body weight CD34+ cells per pr planned transplant.*

The optimal PBPC dose to be collected and infused to Cl assure a prompt hematopoietic recovery is 5 × 10⁶/kg/body pr weight CD34+ cells per planned transplant.

The highest PBPC dose to be infused in patients with acute myeloid leukemia is 7 × 10⁶/kg/body weight CD34+ cells, due to a reduced event-free survival at higher doses.

Survey 2016 SIDEM-GITMO-CNT

Preliminary results (as April 24)

41 center out of 83 answered to the survey (49%)
Knowledge of GITMO-SIDEM-CNT policy: 38 out of 41 (92.6 %)
Previous local policies : 33 out of 41 (80.4 %)
Policy guidelines applied in 24 out of 41 (58.5 %) and 13 out of 24 (54.1 %) apply ALL the criteria
Policy applied only for those units frozen AFTER the publication of the policy : 4 out of 41 (9.7 %)

Total number of disposed units: 758 (from 371 patients)
-107: storage time > 10 yrs
-636 : major criteria
-15: minor criteria

Knowledge of SIDE-GITMO recommendation on HSC collection:
37 out of 41 (90 %), applied in 94.5 %

Courtesy of Daniel Lazslo and Letizia Lombardini

Italy in the Renaissance

Italy nowadays

Take-home message: working together gives rapidly better and more reliable results

Thank you!

SIdEM:

Luca Pierelli, Roma

Patrizia Accorsi, Pescara

Marco Risso, Genova

Paolo Perseghin, Monza

GITMO: Attilio Olivieri, Ancona

Martino Introna, Alessandro Rambaldi Bergamo

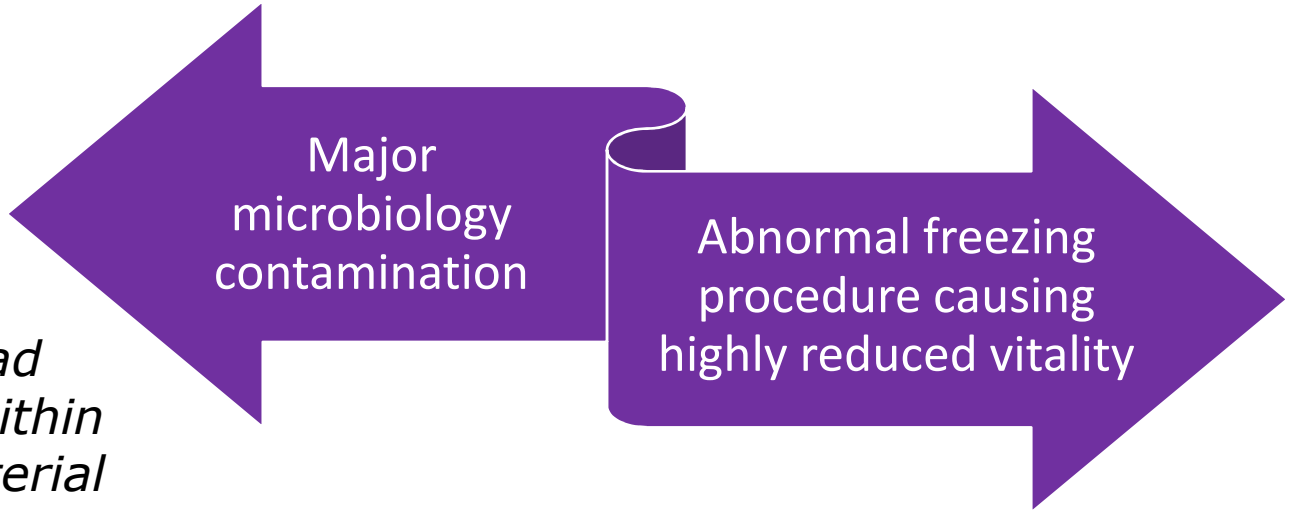
Alberto Bosi, Firenze

Monia Marchetti (methodologist), Asti

CNT: Letizia Lombardini, Roma

ISS: Carlo Petrini (bioetico), Roma

PROMPT DISPOSAL

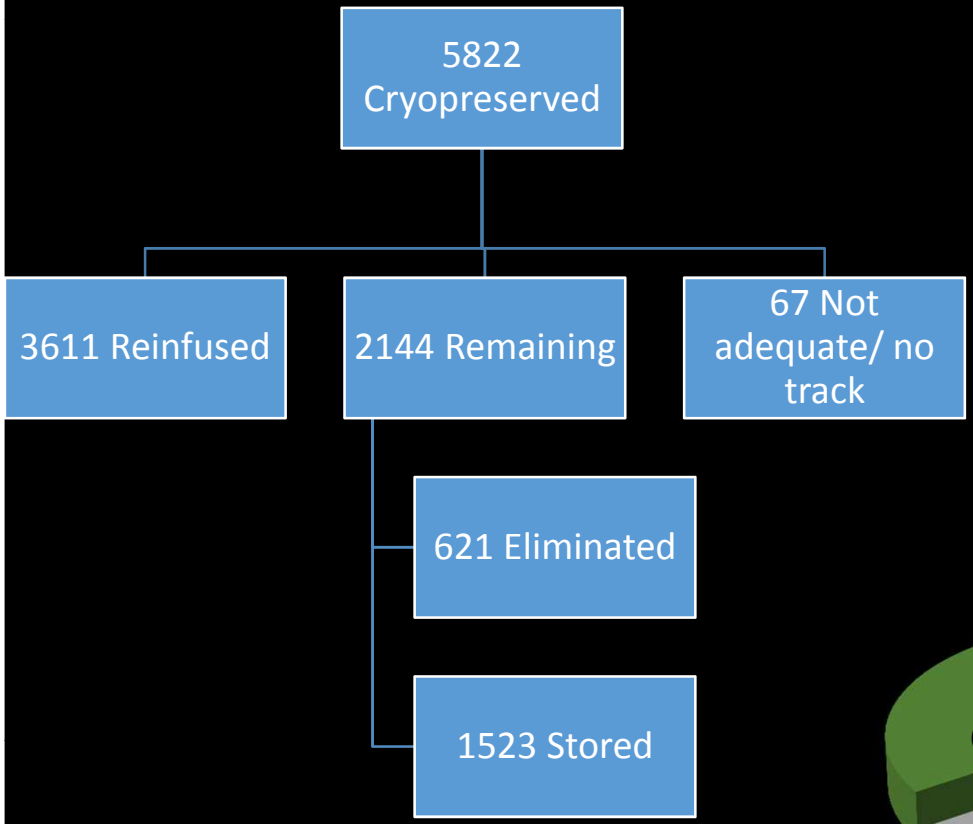


high-load (growth within 24 h) bacterial contamination

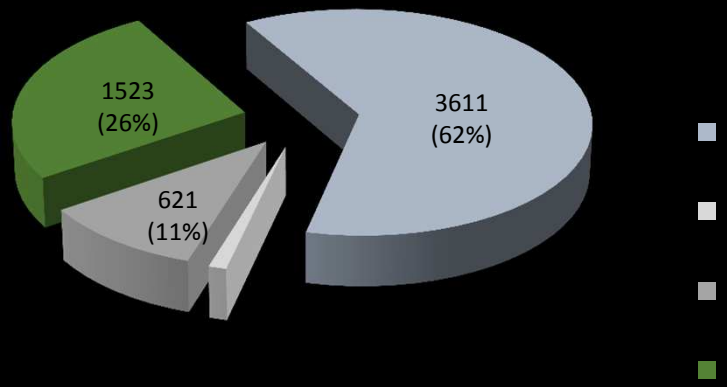
Documented according to a specific SOP

only after patient successful remobilization

Flow chart: fate of stem cell units



SCU	Total	Median SCU	%
Cryopreserved	5822	3.63	100
Reinfused	3611	2.25	62.0
Not adequate/ no track	67	.042	1.1
Eliminated	621	.39	10.7
Stored	1523	.95	26.2



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