The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

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20th ISCT Annual Meeting, Paris, France

Quality & Operations Track 1: Cord Blood Infusions: Current Gold Standards in Preparing and Testing of Cord Blood Products for Transplantation

April 24, 2014





Creating a cancer-free world. *One person, one discovery at a time.*

Impact of Cord Thaw Method on Processing and Clinical Outcome:

Why Choosing the Right Thaw Method Could Save a Patient's Life

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OSU-James BMT Program – Cord Blood Transplants

- Approximately 250 transplant / year
- Late entry into cords – first patient **March 2008**
- Only 4 patients transplanted off-study first year, then opened two clinical trials and accrual picked up
  - BMT CTN 0604 / CIBMTR 05-DCB – adult, nonmyeloablative, double cord transplant
  - BMT CTN 0501 – pediatric, myeloablative, randomized single vs. double cord transplant
- RBC-replete (containing) CBUs were initially preferred due to higher TNC dose
- **April 2009:** Our 2nd patient on 05-DCB experienced SAE and 9 days later the 3rd did as well

OSU-James BMT Program – Cord Blood Serious Adverse Events (SAEs)

- Both experienced sudden development of chest pain, shortness of breath, respiratory failure and pulmonary edema associated with severe heart failure (EF to 10-25%, elevated troponin), along with hematuria and acute renal failure requiring dialysis
  - Expedited reporting to CTN and NMDP
  - 1st patient felt to be chemo toxicity, patient recovered fully; 2nd raised red flags to all but unfortunately died d23 of cardiac failure
  - Both patients received 1 RBC-depleted and 1 RBC-replete CBU and both were diluted 1:1 but not washed (**NOTE** - Washing cords was actually not allowed on 05-DCB)
- May 7, 2009 – CIBMTR issues safety notice requiring notification of enrollment using RBC-replete CBUs, validation of wash method and signed acknowledgement by site PI, study coordinator, and processing lab

NMDP Investigation of SAEs

- **Spring 2009:** NMDP / CIBMTR performed a retrospective review of adverse reactions ***reported to*** NMDP looking for similar cases associated with cord blood infusion
  - 13 cases of caridomyopathy: 4 considered severe (including our 2)
  - 12/13 were associated with RBC-replete CBUs
- **Summer 2009:** multiple reports, memos & notifications
  - CTN to 0501/0602 and all PIs, clinical/regulatory/lab coordinators – requiring washing of RBC-replete CBUs
  - NMDP to cord IND PIs, TC Medical Directors & coordinators – explaining SAEs, investigation & ***recommending*** that transplants under NMDP BB-IND-7555 "comply with thaw, dilution and washing procedures set forth in Section 6.13.7 of the IND" but still allowing for provisions to eliminate washing if felt to have adverse impact.
  - NMDP to FDA
- **Summer-Fall 2009:** NMDP working group, detailed data for 6 of the cases: Cord info, Recipient info, Thaw & Infusion info, and Recipient Symptoms – Unsure of output status

Despite these efforts …

- Patient died of cardiac arrest within hours of bedside thaw of 2 RBC-replete CBUs
- As of March 2013, 8 reports to NMDP, 2 fatalities, all received at least 1 RBC-replete CBU, all (?) not washed

NATIONAL MARROW DONOR PROGRAM

Entrusted to operate the C.W. Bill Young Cell Transplantation Program, including Be The Match Registry®

March 27, 2013

Celia Witten, Ph.D., M.D.
Office Director, OCTGT
Center for Biologics Evaluation & Research
Food & Drug Administration
1401 Rockville Pike (HFM 700)
Rockville, MD 20852-1448

RE: BB-IND#: 7555-0095
IND Safety Report
NMDP Recipient Identification Number 616-970-3

Dear Dr. Witten:

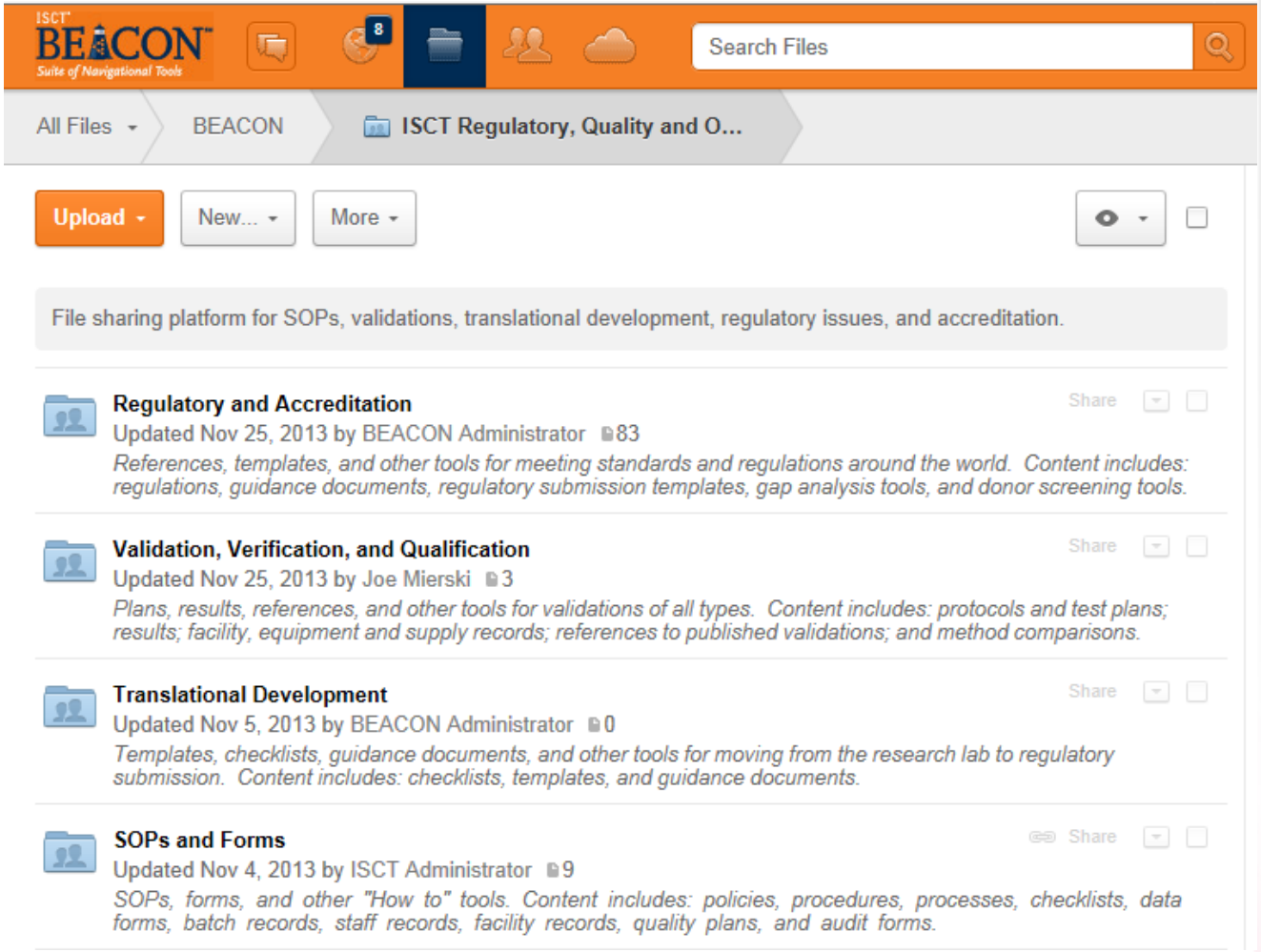
This is to inform you (in triplicate) of a fatal adverse event which occurred with a cord blood transplant recipient through the National Marrow Donor Program® (NMDP) participating in the NMDP protocol under IND#7555: *"A multicenter access and distribution protocol for unlicensed cryopreserved cord blood units (CBUs) for transplantation in pediatric and adult patients with hematologic malignancies and other indications (10-CBA)"*. This recipient experienced a cardiac arrest following double cord blood unit infusion and was not able to be resuscitated.

FACT / JACIE Standards – 5th Edition

- **STANDARD:** *B7.4 There shall be a policy addressing safe administration of cellular therapy products.*
  - **Guidance:** "For cord blood units, the NMDP recommends the washing procedure in Appendix F of the 0501 protocol, available at www.bmtctn.net, and requires washing of red cell replete CB units due to unexpected adverse events."
- **STANDARD:** *B7.4.1.1 Cord blood units that have not been red cell reduced shall be ~~diluted and/or~~ washed.*
- **STANDARD:** *B7.4.1.2 Cord blood units that have been red cell reduced should be diluted ~~and~~/or washed.*
  - **Guidance:** "There have been documented adverse events related to the administration of cord blood units containing red blood cells. Clinical Programs need to determine the appropriate volume, DMSO (and other additives), and red cell load for recipients. These Standards require dilution and/or washing of cellular therapy products that have not been red cell reduced, and this practice is also recommended for products that have been red cell reduced."

Better Dissemination to Key Individuals is Needed !

- Plan to post Safety Alerts on Beacon™ along with other materials from this session (pending NMDP authorization)
- Attend the Beacon™ session – QOps #9 Saturday 0730-0830



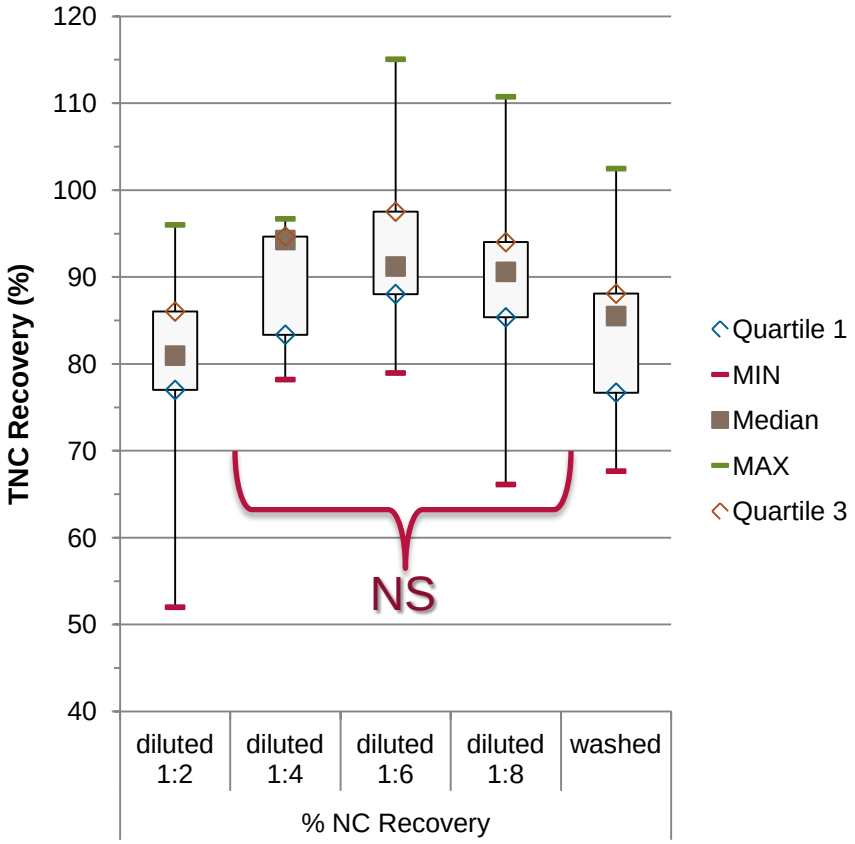
OSU Cell Therapy Laboratory (CTL): Cord Blood Processing at Thaw

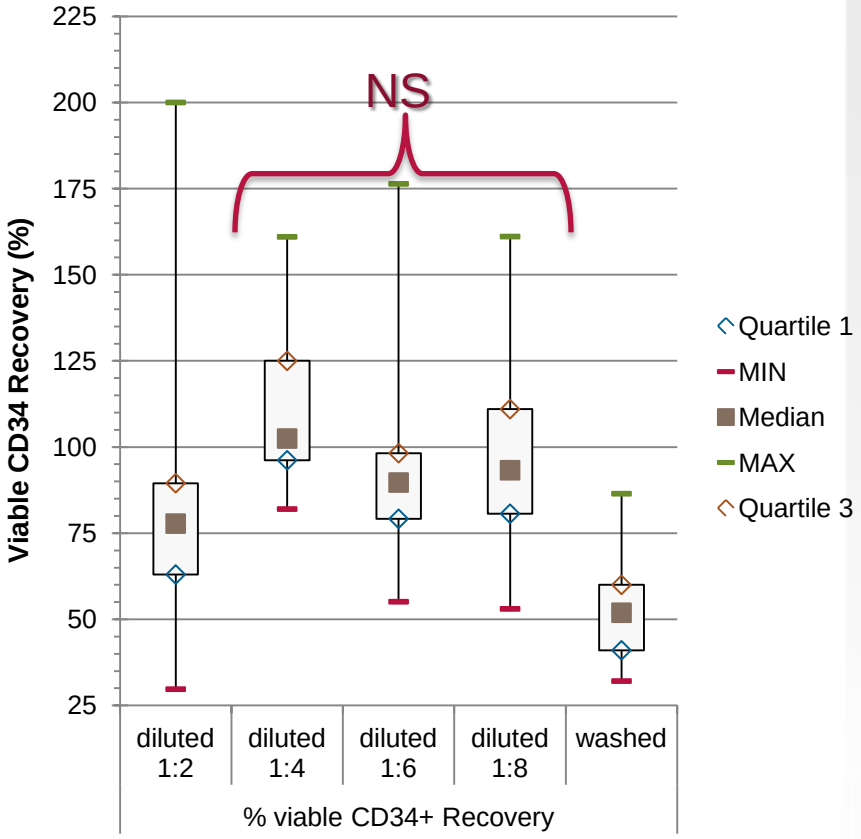
- Different options for thawing cords – Goal to minimize exposure of fragile cells to DMSO to minimize cell death, to remove or dilute potential toxic molecules (RBC stoma, free hemoglobin, other)
  - Bedside thaw – no longer done at OSU (pre-2007)
  - Thaw and dilute into iso-osmotic solution (Dec 2007-current, but fold-dilution has varied over time)
  - Thaw and dilute into iso-osmotic solution, followed by centrifugation, removal of supernatant and resuspension (Dec 2008-current)
- Both cord blood banks and transplant centers need to validate thaw methods – sometimes these will conflict
- CTL sets processing targets (“criteria”) that we use in real time to inform physicians of product quality
- The true quality is in engraftment data, but this can get complicated

OSU CTL: Cord Blood Thaw Methods – Processing & Clinical Outcomes

		ALL	Diluted 1:2	Diluted 1:6	Diluted 1:8	Washed
n		119	35	17	49	13
dates		Dec07-Jun12	Dec07-Feb10	Feb10-Jun12	Feb10-Jun12	Dec08-Jun12
% TNC Recovery	(mean ±SD)	87±10	80±10	94±10	90±9	83±10
	(median)	87	81	91	91	86
TNC Failure Rate (< 60%)	(%)	2%	6%	0	0	0
% vCD34 Recovery	(mean ±SD)	88±29	79±29	96±31	97±22	54±17
	(median)	84	78	90	93	52
vCD34 Failure Rate (<35%)	(%)	2%	3%	0	0	8%
% Trypan Viability	(mean ±SD)	78±6	78±8	78±5	80±5	73±5
	(median)	79	78	77	80	71
Viability Failure Rate (<60%)	(%)	0	0	0	0	0
ANC Engraftment	(mean ±SD)	25±14	21±12	29±18	25±13	28±12
	(median)	21	21	21	21	24
Delayed Engraftment Rate (>d42)	(%)	33%	21%	44%	39%	42%
PLT Engraftment	(mean ±SD)	54±49	71±82	52±33	46±24	42±26
	(median)	41	42	46	41	40
Delayed Engraftment Rate (>d60)	(%)	25%	30%	36%	18%	18%
Adverse Reaction Rate	(%)	5.9%	11.4%	0	2%	7.7%

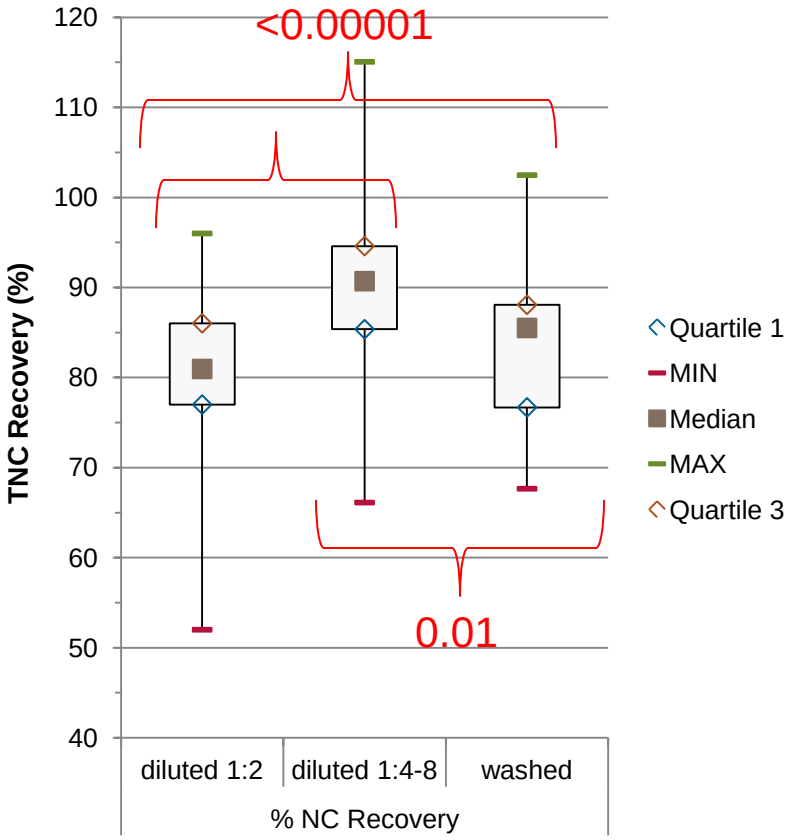
Comparison of All Thaw Methods – Cell Recoveries (includes pediatric patients)

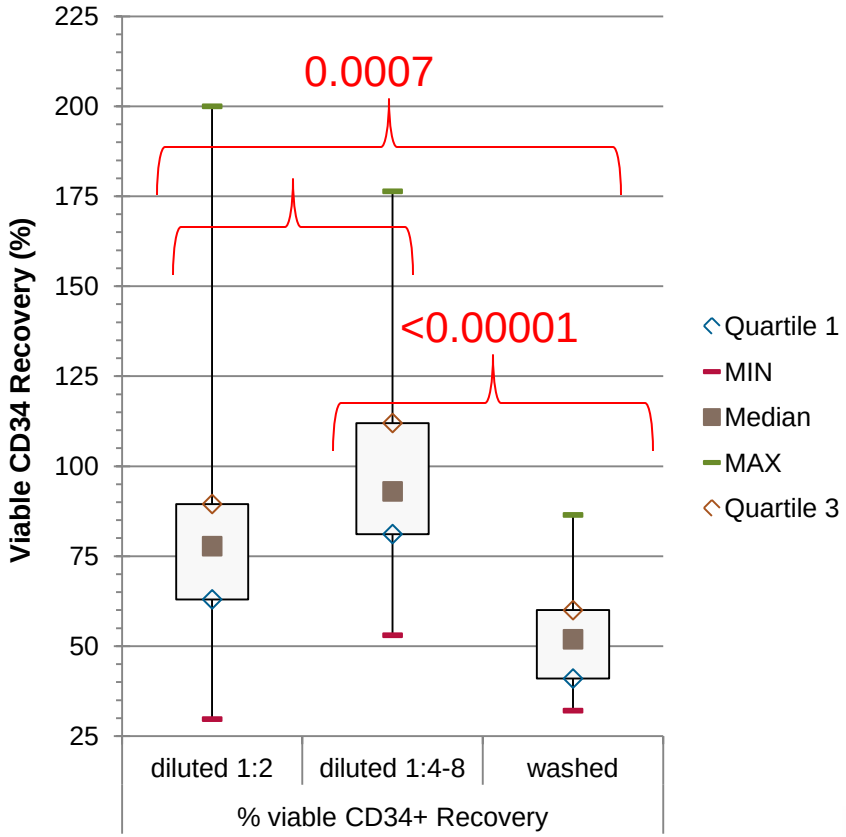




No statistically significant differences in means by t-test between 1:4, 1:6 and 1:8 dilutions (Hi-Dilute); many significant differences between these dilutions and washed or diluted 1:2 (Lo-Dilute).

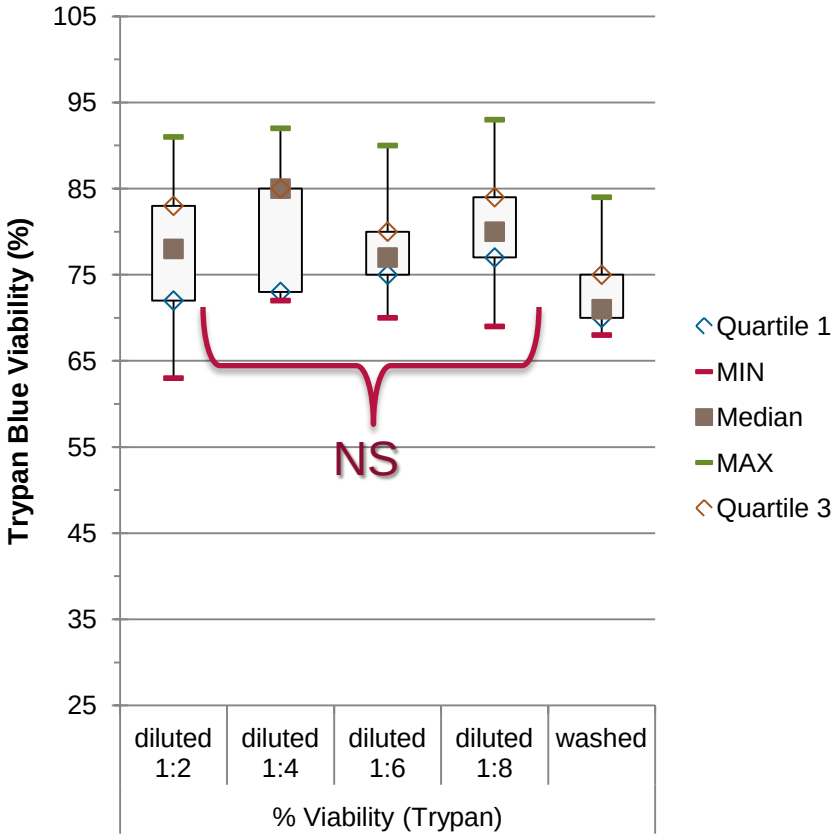
Comparison of Lo-Dilute, Hi-Dilute and Wash – Cell Recoveries (includes pediatric patients)

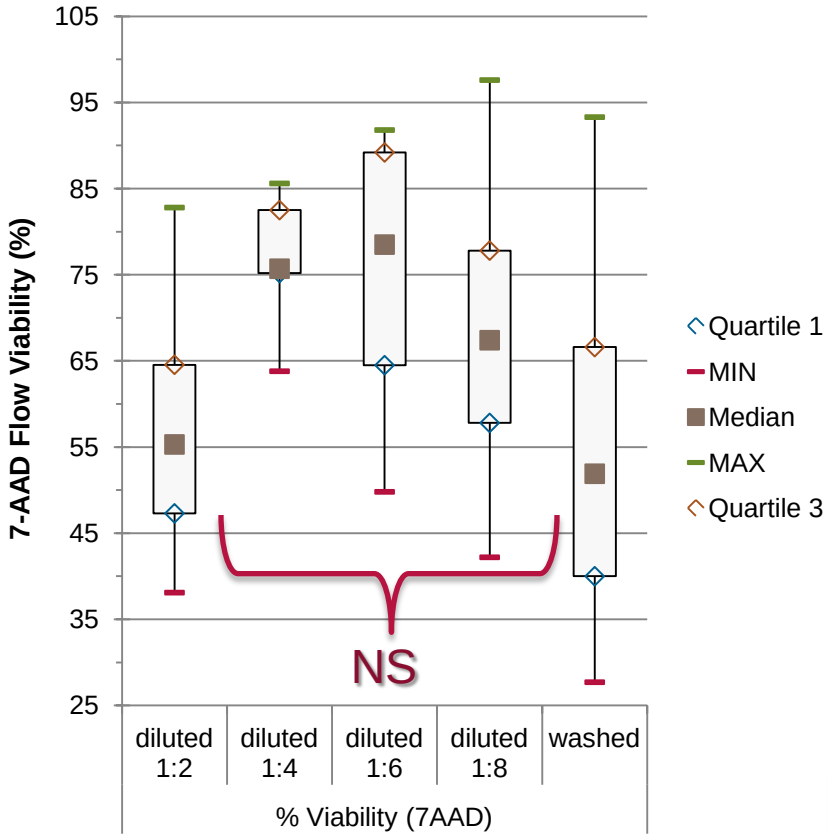




Statistically significant differences in means by t-test between all three methods. **Hi-Dilute thaw method gives best recoveries.**

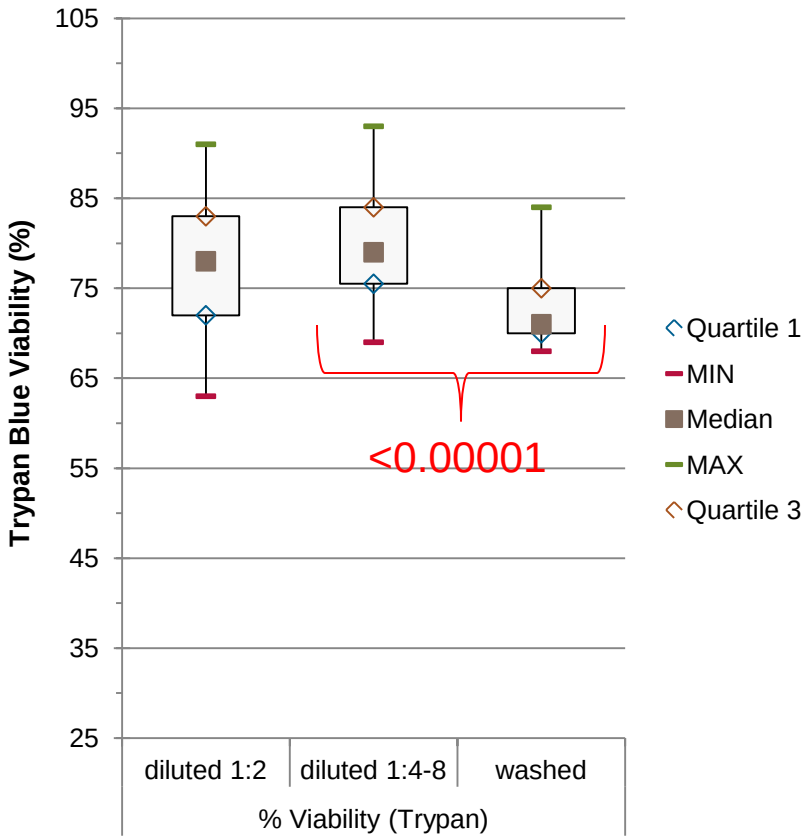
Comparison of All Thaw Methods – Cell Viabilities (includes pediatric patients)

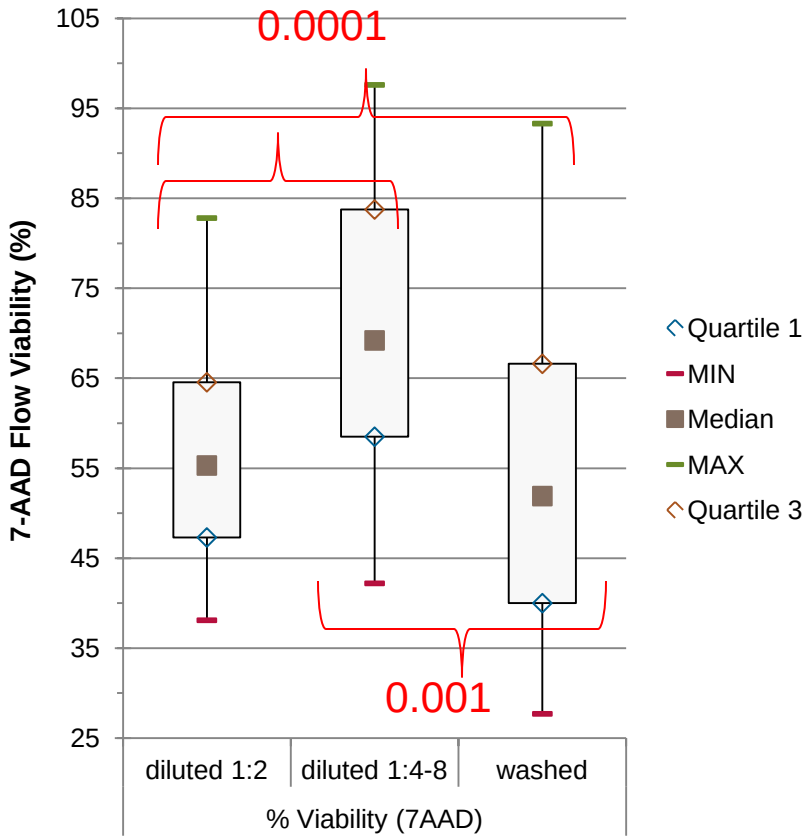




No statistically significant differences in means by t-test between 1:4, 1:6 and 1:8 dilutions (Hi-Dilute); many significant differences between these dilutions and washed or diluted 1:2 (Lo-Dilute).

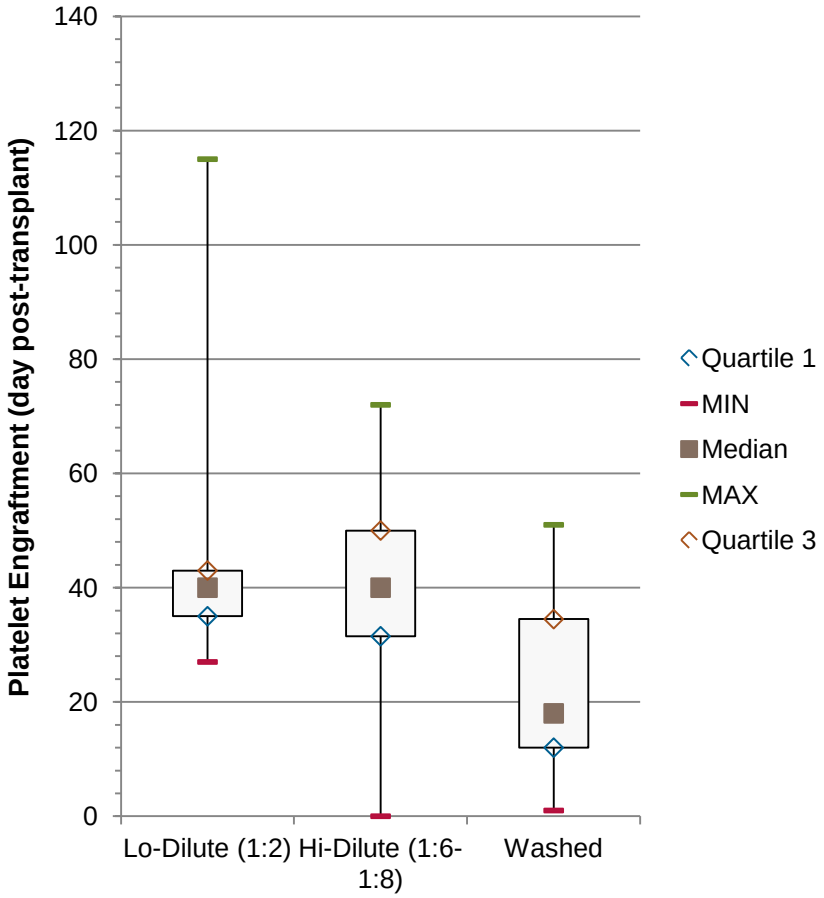
Comparison of Lo-Dilute, Hi-Dilute and Wash – Cell Viabilities (includes pediatric patients)

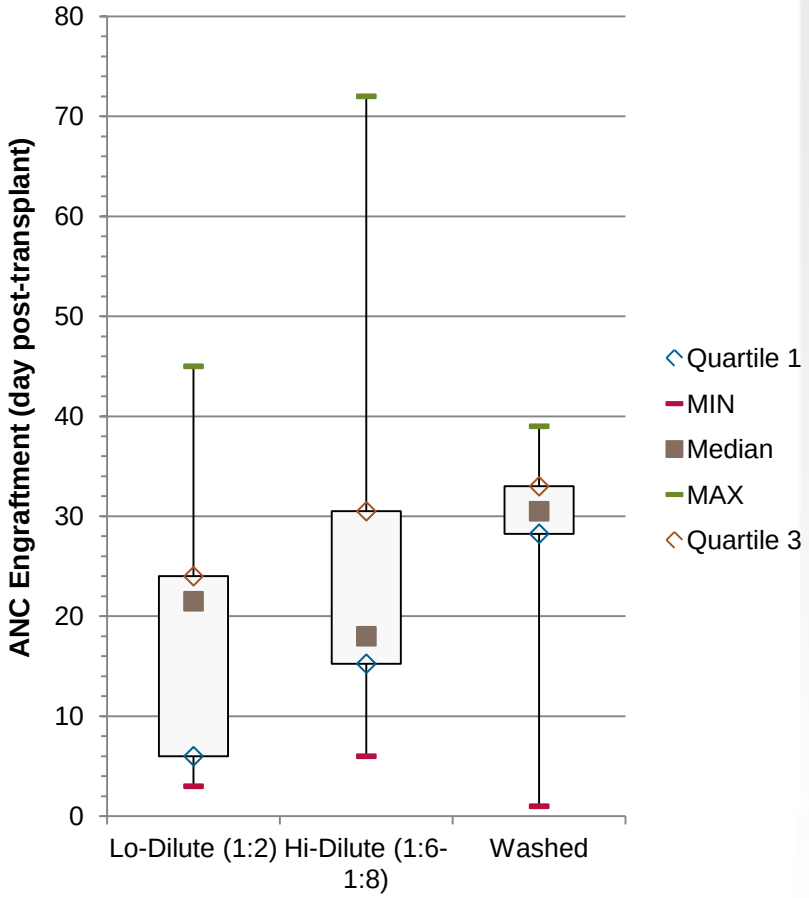




By trypan (light microscope) statistically significant difference in mean by t-test between wash and Hi-Dilute. Statistically significant differences between all three methods by flow. **Hi-Dilute thaw method gives best viabilities.**

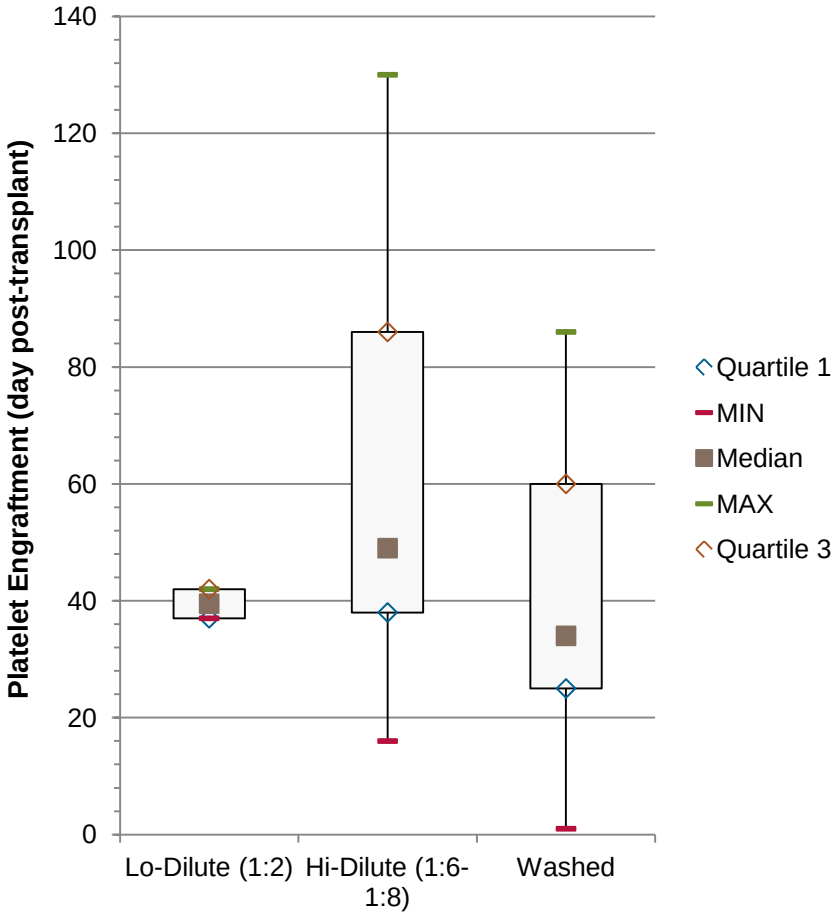
Comparison of Lo-Dilute, Hi-Dilute and Wash – Engraftment, Non-Ablative (EXCLUDES pediatric patients)

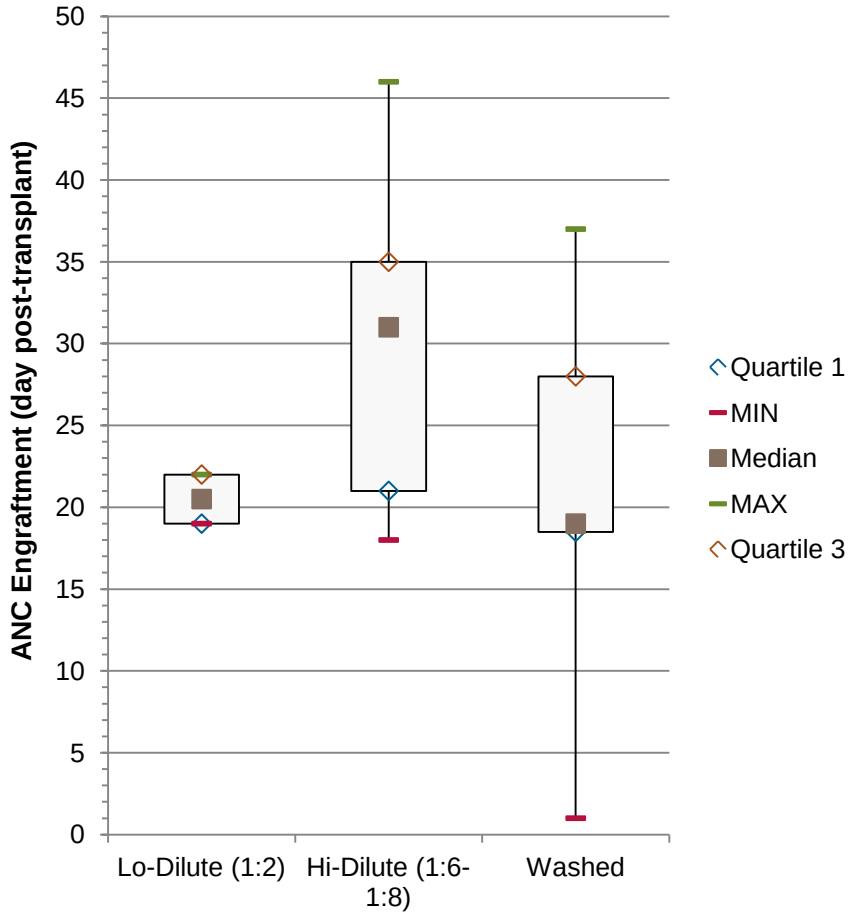




No statistics performed; patient numbers low – 11 Lo-Dilute, 30 Hi-Dilute, only 3 Washed;

Comparison of Lo-Dilute, Hi-Dilute and Wash – Engraftment, Ablative (EXCLUDES pediatric patients)





No statistics performed; patient numbers low – 3 Lo-Dilute, 18 Hi-Dilute, only 3 Washed

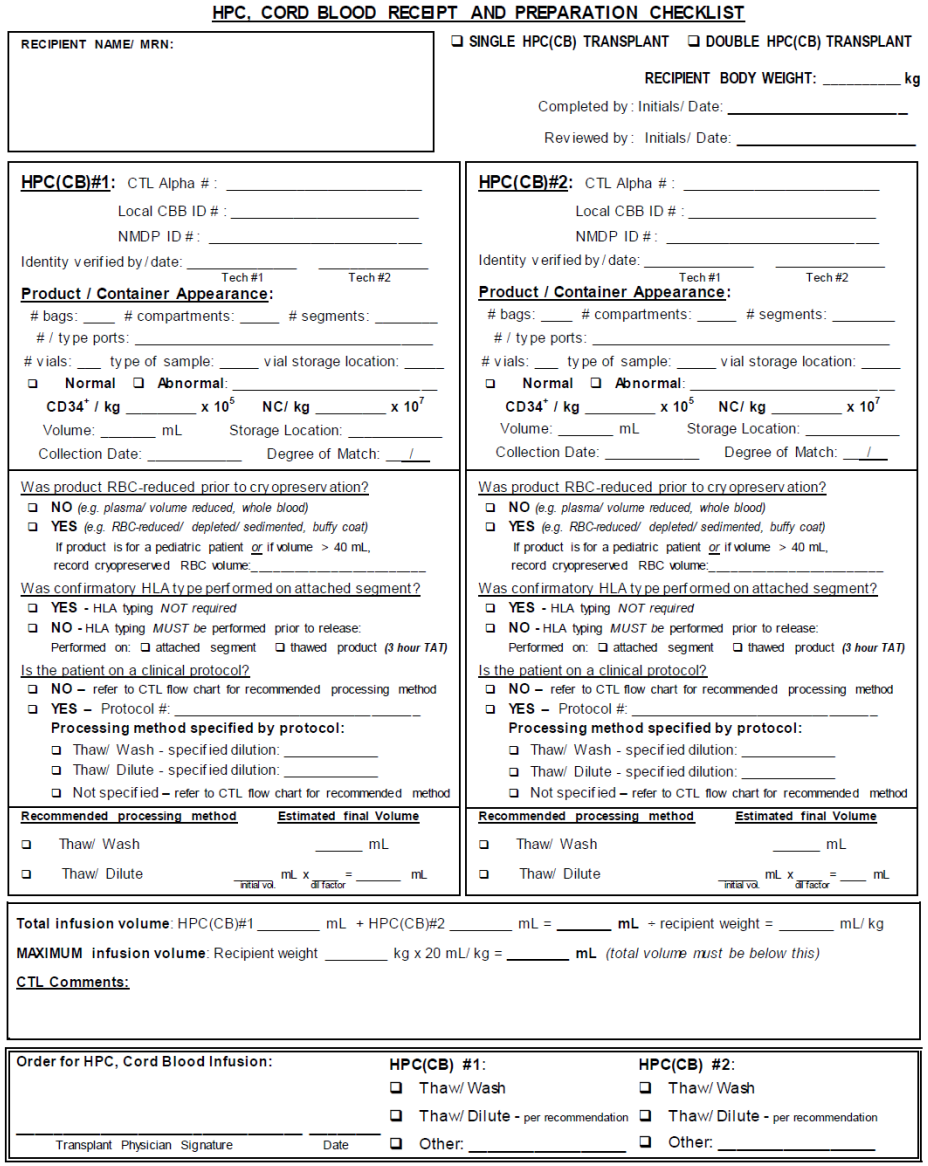
Upfront Communication with Cord Blood Banks

- Was the CBU RBC-depleted?
  - NO: “plasma-reduced”, “volume reduced” or “whole blood”
    → We **must wash** the CBU
  - YES: “depleted”, “reduced”, “sedimented” or “buffy coat”
    → We thaw/dilute the CBU – start with 1:8 dilution, but can reduce to 1:4 for larger CBUs / smaller patients or vol. overload
  - YES BUT some “buffy coat” CBUs still contain a high level of RBCs and high volume
    → For ALL pediatric patients or if CBU volume is >40mL, we record the RBC volume; often not available, request vol. or HCT from NMDP or bank → **must wash** if >2mL RBCs/kg (ped) or >20mL RBCs

- Was CT performed on an attached segment?
  - If this cannot be confirmed, repeat CT must be performed locally
  - If attached segments – done at receipt, prior to admission
  - If no attached segments – done at thaw – 3h TAT, 4h expiration

Upfront Communication with Transplant Physicians

- We allow different post-thaw processing based on the cord characteristics or patient status (size, volume overload, etc.)
- CTL makes recommendations, MD must approve them or modify based on patient status



HPC, CORD BLOOD RECEIPT AND PREPARATION CHECKLIST

RECIPIENT NAME/ MRN:

❑ SINGLE HPC(CB) TRANSPLANT ❑ DOUBLE HPC(CB) TRANSPLANT

RECIPIENT BODY WEIGHT: _____ kg

Completed by: Initials/ Date: _____

Reviewed by: Initials/ Date: _____

HPC(CB)#1: CTL Alpha # : _____
Local CBB ID # : _____
NMDP ID # : _____
Identity verified by/ date: _____ (Tech #1) _____ (Tech #2)

Product / Container Appearance:
bags: ____ # compartments: _____ # segments: _____
/ type ports: _____
vials: ___ type of sample: _____ vial storage location: _____
❑ Normal ❑ Abnormal: _____
$CD34^+$ / kg _____ x 10^5 NC/ kg _____ x 10^7
Volume: _____ mL Storage Location: _____
Collection Date: _____ Degree of Match: __/__

Was product RBC-reduced prior to cryopreservation?
❑ NO *(e.g. plasma/ volume reduced, whole blood)*
❑ YES *(e.g. RBC-reduced/ depleted/ sedimented, buffy coat)*
If product is for a pediatric patient or if volume > 40 mL, record cryopreserved RBC volume:_____

Was confirmatory HLA type performed on attached segment?
❑ YES - HLA typing *NOT required*
❑ NO - HLA typing *MUST be* performed prior to release:
Performed on: ❑ attached segment ❑ thawed product *(3 hour TAT)*

Is the patient on a clinical protocol?
❑ NO – refer to CTL flow chart for recommended processing method
❑ YES – Protocol #: _____
Processing method specified by protocol:
❑ Thaw/ Wash - specified dilution: _____
❑ Thaw/ Dilute - specified dilution: _____
❑ Not specified – refer to CTL flow chart for recommended method

Recommended processing method	Estimated final Volume
❑ Thaw/ Wash	_____ mL
❑ Thaw/ Dilute	_____ mL (initial vol.) x ____ (dil factor) = _____ mL

HPC(CB)#2: CTL Alpha # : _____
Local CBB ID # : _____
NMDP ID # : _____
Identity verified by/ date: _____ (Tech #1) _____ (Tech #2)

Product / Container Appearance:
bags: ____ # compartments: _____ # segments: _____
/ type ports: _____
vials: ___ type of sample: _____ vial storage location: _____
❑ Normal ❑ Abnormal: _____
$CD34^+$ / kg _____ x 10^5 NC/ kg _____ x 10^7
Volume: _____ mL Storage Location: _____
Collection Date: _____ Degree of Match: __/__

Was product RBC-reduced prior to cryopreservation?
❑ NO *(e.g. plasma/ volume reduced, whole blood)*
❑ YES *(e.g. RBC-reduced/ depleted/ sedimented, buffy coat)*
If product is for a pediatric patient or if volume > 40 mL, record cryopreserved RBC volume:_____

Was confirmatory HLA type performed on attached segment?
❑ YES - HLA typing *NOT required*
❑ NO - HLA typing *MUST be* performed prior to release:
Performed on: ❑ attached segment ❑ thawed product *(3 hour TAT)*

Is the patient on a clinical protocol?
❑ NO – refer to CTL flow chart for recommended processing method
❑ YES – Protocol #: _____
Processing method specified by protocol:
❑ Thaw/ Wash - specified dilution: _____
❑ Thaw/ Dilute - specified dilution: _____
❑ Not specified – refer to CTL flow chart for recommended method

Recommended processing method	Estimated final Volume
❑ Thaw/ Wash	_____ mL
❑ Thaw/ Dilute	_____ mL (initial vol.) x ____ (dil factor) = ____ mL

Total infusion volume: HPC(CB)#1 _____ mL + HPC(CB)#2 _____ mL = _____ **mL** ÷ recipient weight = _____ mL/ kg

MAXIMUM infusion volume: Recipient weight _____ kg x 20 mL/ kg = _____ **mL** *(total volume must be below this)*

CTL Comments:

Order for HPC, Cord Blood Infusion:	HPC(CB) #1:	HPC(CB) #2:
	❑ Thaw/ Wash	❑ Thaw/ Wash
	❑ Thaw/ Dilute - per recommendation	❑ Thaw/ Dilute - per recommendation
_____ Transplant Physician Signature _____ Date	❑ Other: _____	❑ Other: _____

Acknowledgements

- CTL staff
- BMT physicians & coordinators
- Patients

Questions? Comments?

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