Dried Plasma Data and Products in Development

Tom Woolley

The Duck Test

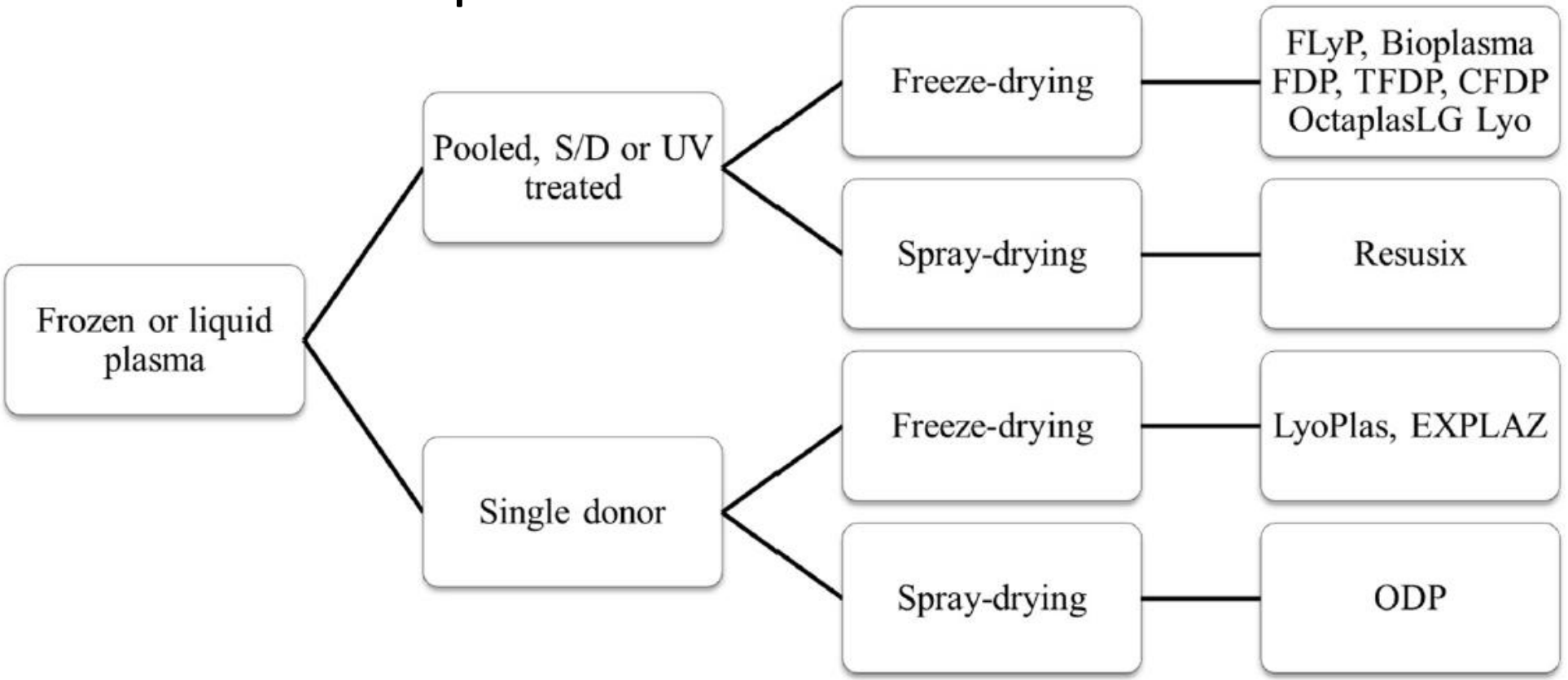
If it looks like a duck, swims like a duck, and quacks like a duck,

Then it probably *is* a duck

Dried plasma sources

- You can buy the product
  - Lyoplas
  - Flyp
  - Octaplas LG
  - Bioplasma
- You can buy the redistributed manufacturing system
  - Velico

Different source plasmas



Review
Dried Plasma for Major Trauma: Past, Present, and Future
Henry T. Peng [1,*], Kanwal Singh [1], Shawn G. Rhind [1], Luis da Luz [2] and Andrew Beckett [3,4]

Is Dried Plasma…. Plasma?

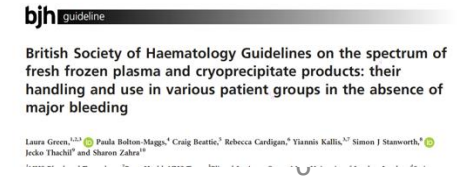
What is plasma?

It is the liquid part of blood that is not cells (RBC, WBC, platelets). Apart from all sorts of proteins there are also lots of cell microparticles. FFP and never frozen are not the same thing and this is why they are labelled differently. Whether any of these differences in the lab matter in vivo less clear. This is a topic in its own right.

Is Dried Plasma…. Plasma?

Table I. Typical values for fresh frozen plasma and cryoprecipitate in the UK.

	FFP	MB FFP	Octaplas LG‡	S
Volume (ml)	267 ± 17	229 ± 12	200	4
FVIII	0·96 ± 0·27 iu/ml (average 256 iu/unit)	0·68 ± 0·23 iu/ml (average 156 iu/unit)	Group O: 0·53 (0·52–0·53 iu/ml) Non-O: 0·71 (63–84) 106 (iu/unit)	1
Fibrinogen (Clauss)	2·57 ± 0·48 g/l (on average 0·69 g/unit)*	1·70 ± 0·15 g/l (on average 0·39 g/unit)†	2·31 (2·21-2·41) g/l (on average 0·46 g/unit)	(
UK specification for FVIII / fibrinogen	>75% units >0·70 iu/ml FVIII	>75% of units >0·50 iu/ml FVIII	European Pharmacopoeia requires FV, FVIII and FXI >0·50 iu/m	:


bjh guideline

British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding

Laura Green, Paula Bolton-Maggs, Craig Beattie, Rebecca Cardigan, Yiannis Kallis, Simon J Stanworth, Jecko Thachil and Sharon Zahra

Is dried plasma safe and effective? Animal studies

- 15 studies
  - 2 mice , 13 swine
  - 2 studied Entegrion spray dried plasma (1 mouse, 1 swine)
  - 13 freeze dried
- Potter et al: effect of Entegrion spray dried plasma (a single donor SDP) on systemic vascular stability and inflammation
  - both FDP and SDP similarly modulate pulmonary vascular integrity, permeability, and inflammation in vitro and in vivo whereas saline did not
- Alam et al: Entegrion spray dried plasma (a single donor SDP) to investigate the long-term survival and organ function after polytrauma
  - Colloid resus had 25% 7 day survival, SDP 83% survival

Is dried plasma safe and effective? Human volunteer

- Entegrion:
  - Phase 1 trial
  - 1 thromboembolic event
  - Phase 2 trial ran out of money?
- Replas/Ezplas
  - Dose escalation
  - No SAE’s
- HemCon
  - Dose escalation
  - No SAE’s
- Octapharma: Equivalence

Is dried plasma safe? Human volunteer

- Velico Phase 1 trial
  - 24 healthy volunteers
  - Dose escalation
  - No SAE
  - Awaiting unblinding

Is dried plasma safe and effecive? Clinical studies

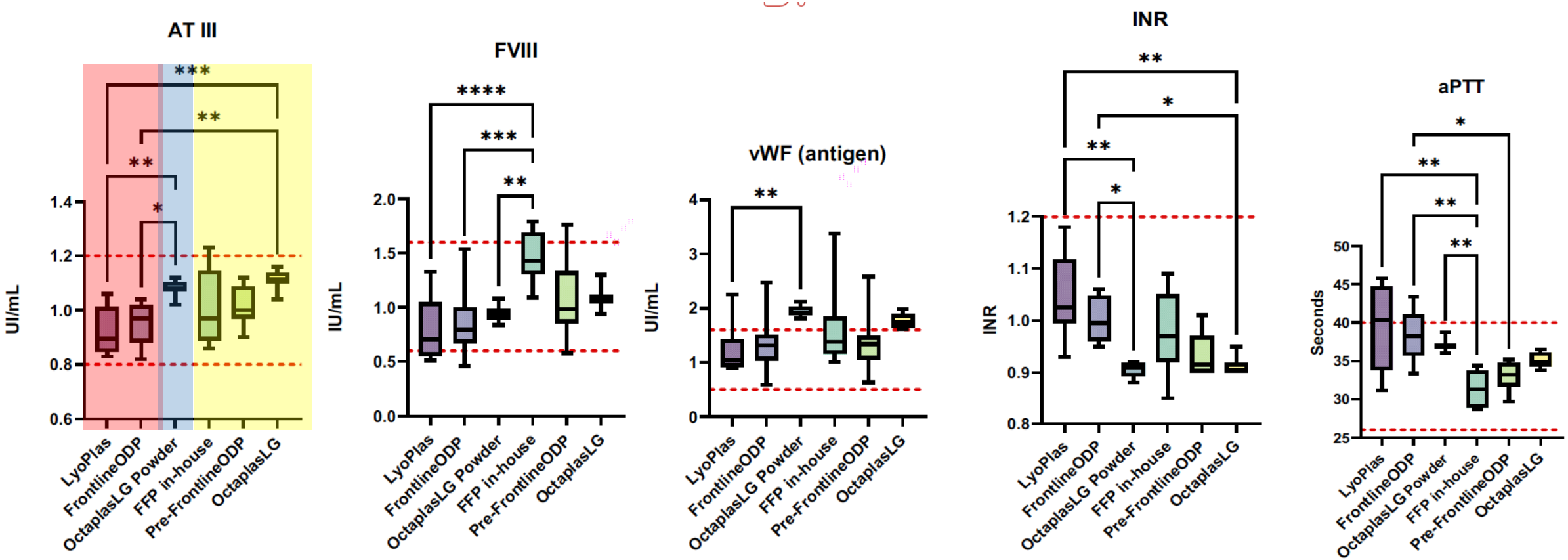
- Spray dried =0
- Freeze dried = lots
  - 7 Million units in WWII
  - 300 000 Lypolas
  - 300 000 Biopharma
  - 9000 FLYP
- Good safety record
- Mok et al systematic review, 30 day mortality no difference between FDP and FFP
- FLYP vs FFP in trauma: better fibrinogen levels in FLYP arm at 45 mins (TrauCC)
- Octapharma post marketing surveillance Data soon.

How do the plasma's compare?

An experimental comparison and user evaluation of three different dried plasma products

Kristina Ehn[1,2] | Gabriel Skallsjö[3,4,5] | Birgitta Romlin[6] | Göran Sandström[3,7] | Per Sandgren[1,2] | Agneta Wikman[1,2]

- Compared Dried plasma (Octaplas LG Lyo, Lyoplas, frontline ODP) with FFP
- Lab tests
  - Fibrinogen, FVIII, Protein C, ATIII, vWF, FXII, INR, aPTTR
  - ROTEM (mixed with red c ells and platelets)


AT III
UI/mL
1.4
1.2
1.0
0.8
0.6
***
**
**
*
FVIII
IU/mL
2.0
1.5
1.0
0.5
0.0
****
***
**
vWF (antigen)
UI/mL
4
3
2
1
0
**
INR
INR
1.2
1.1
1.0
0.9
0.8
**
*
aPTT
Seconds
50
45
40
35
30
25
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**
**
LyoPlas
FrontlineODP
OctaplasLG Powder
FFP in-house
Pre-FrontlineODP
OctaplasLG

TABLE 2 Thromboelastography: Citrated rapid thromboelastography and citrated functional fibrinogen (mean ± SD).

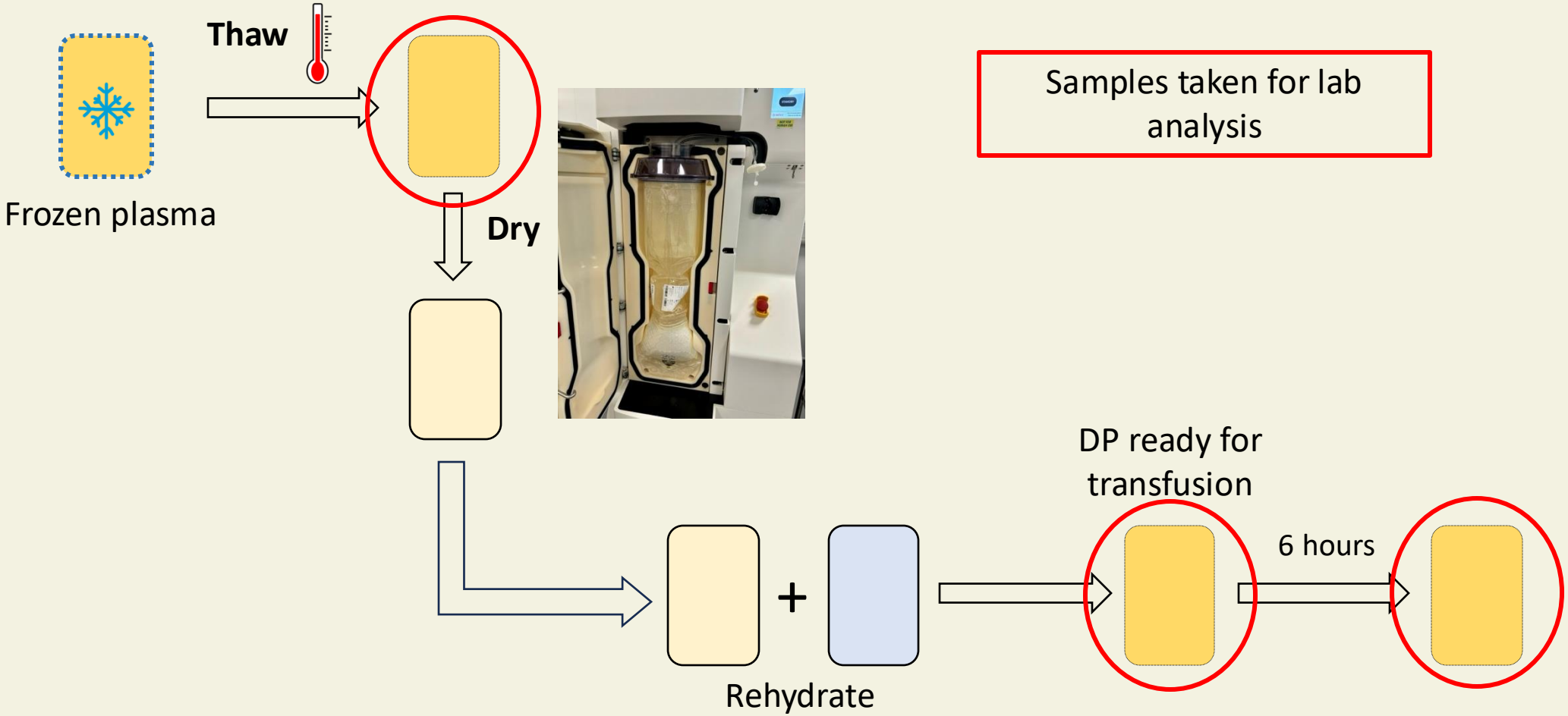
	Ref. values	LyoPlas	FrontlineODP	OctaplasLG Powder	FFP	Pre-FrontlineODP	OctaplasLG	*p*-Value
CRT	*R*, 0.3–1.1 min	0.6 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	ns
	K, 0.8–2.7 min	1.0 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	ns
	Angle, 60°–78°	76.2 ± 1.0	74.9 ± 2.0[a]	75.9 ± 0.8	77.0 ± 0.5[a]	76.7 ± 1.7	75.3 ± 1.3	<0.05
	ACT, 82–152 s	103.0 ± 10.5	97.4 ± 9.4	96.1 ± 8.7	85.6 ± 13.8	98.4 ± 7.3	93.8 ± 14.8	ns
	A10, 44–67 mm	60.4 ± 1.8[b,c]	62.3 ± 2.5	62.3 ± 1.3	64.6 ± 1.2[b]	63.9 ± 2.5[c]	62.5 ± 1.8	<0.01
CFF	A10, 15–30 mm	22.6 ± 1.2	23.1 ± 2.6	22.8 ± 0.8	23.6 ± 1.1	23.5 ± 2.3	22.8 ± 1.5	ns

Basically No Difference

UK Standing Advisory Committee on Blood Components (SACBC)

- Provisional specification for dried plasma for a phase 2 trial - Validation of Velico Medical FrontLine On Demand plasma (ODP) System for Manufacture of Dried Plasma Components in the UK
- Loss of <20% comparable to plasma
- Minimum absolute level
- 90% should be greater than xxx

Laboratory evaluation



Results table

Coagulation		Whole Blood (n=16)						Apheresis (n=15)						Should meet the specified values below		
		Pre mean (SD)		DP Mean (SD)		Mean % loss pre to post (SD)		Pre mean (SD)		DP Mean (SD)		Mean % loss pre to post (SD)		Mean loss due to treatment process (%; pre v post or control v test)	Mean in final component	90% of units should be above
Basic	Volume (mL)	**274.7**	(2.4)	**229.1**	(6.7)	n/a		**271.7**	(6.4)	**227**	(2.6)	n/a		NA	To meet spec	
Coagulation	PT ratio	**0.99**	(0.03)	**1.1**	(0.05)	n/a		**1.04**	(0.06)	**1.14**	(0.07)	n/a		NA	NA	NA
screening tests	APTT ratio	**1.23**	(0.08)	**1.35**	(0.10)	n/a		**0.94**	(0.08)	**1.03**	(0.09)	n/a		NA	NA	NA
Global tests	Thrombin Generation (1 or 5pM TF)	Data ready for JPAC meeting												NA	NA	NA
Coag.	Fibrinogen (Clauss) (g/L)	**2.68**	(0.42)	**2.27**	(0.36)	**15.2 %**	(5.2)	**2.67**	(0.57)	**2.35**	(0.49)	**12 %**	(3.6)	≤40	≥1.70g/l	1.50g/l
factors (U/mL)	Fibrinogen antigen	Data next week												<5%	≥ 2.50g/l	2.00g/l
	Factor II	**1.05**	(0.08)	**0.92**	(0.10)	**12.4 %**	(5.2)	**1.03**	(0.08)	**0.88**	(0.07)	**15.1 %**	(2.4)	≤20	≥0.8 U/ml	0.70 U/ml
	V	**0.76**	(0.12)	**0.74**	(0.11)	**3.1 %**	(5.7)	**0.97**	(0.12)	**0.78**	(0.13)	**19.1 %**	(7.3)	≤20	≥0.7 U/ml*	0.60 U/ml
	VII	**1.01**	(0.16)	**0.88**	(0.14)	**12.7 %**	(5.6)	**0.86**	(0.17)	**0.77**	(0.16)	**10.3 %**	(4.1)	≤20	≥0.8 U/ml	0.60 U/ml
	VIII**	**0.87**	(0.21)	**0.72**	(0.16)	**16.6 %**	(7.2)	**0.87**	(0.22)	**0.72**	(0.18)	**17.8 %**	(5.0)	≤30	≥0.5 U/ml*	0.50 IU/ml
	IX	**0.90**	(0.14)	**0.74**	(0.14)	**17.6 %**	(4.9)	**1.03**	(0.18)	**0.88**	(0.15)	**13.7 %**	(5.0)	≤20	≥0.8 U/ml	0.70 U/ml
	X	**1.04**	(0.12)	**0.88**	(0.11)	**15.4 %**	(5.3)	**1.04**	(0.11)	**0.89**	(0.09)	**15.1 %**	(2.5)	≤20	≥0.8 U/ml	0.70 U/ml
	XI	**0.63**	(0.13)	**0.56**	(0.12)	**11.3 %**	(5.6)	**1.07**	(0.13)	**0.96**	(0.12)	**9.6 %**	(6.0)	≤40	≥0.6 U/ml	0.60 U/ml
	XII	**1.01**	(0.17)	**0.87**	(0.14)	**13.3 %**	(5.2)	**1.06**	(0.23)	**0.93**	(0.20)	**12.1 %**	(3.1)	≤20	≥0.8 U/ml	0.60 U/ml
	XIII	Data ready for JPAC meeting												≤20	≥0.8 U/ml	0.70 U/ml
vWF (U/mL)	Ag	Data next week												≤20	≥0.8 U/ml	0.70 U/ml
	RiCof/CBA	**0.88**	(0.28)	**0.39**	(0.15)	**55.6 %**	(4.8)	**0.75**	(0.29)	**0.41**	(0.17)	**46 %**	(7.1)	≤20	≥0.50 U/ml	0.40 U/ml
	Multimers	See Velico data (appendix 3)				-	-	-	-	-	-	-	-	NA	NA	NA
	ADAMTS-13	Data next week												≤20	≥0.8 U/ml	0.70 U/ml
Inhibitors (U/mL)	AT III	**0.98**	(0.06)	**0.89**	(0.09)	**9.0%**	(6.4)	**1.13**	(0.12)	**1.06**	(0.11)	**6.6 %**	(3.2)	≤20	≥0.8 U/ml	0.70 U/ml
	Prot C	**1.09**	(0.10)	**0.99**	(0.11)	**9.3 %**	(5.5)	**1.12**	(0.16)	**1.02**	(0.14)	**9.1 %**	(2.3)	≤20	≥0.8 U/ml	0.70 U/ml
	Prot S Activity	**0.98**	(0.13)	**0.84**	(0.11)	**13.6 %**	(7.6)	**0.84**	(0.16)	**0.70**	(0.11)	**16.2 %**	(5.6)	≤20	≥0.8 U/ml	0.60 U/ml
	Prot S free	**0.99**	(0.11)	**0.91**	(0.11)	**8.4 %**	(4.5)	**0.94**	(0.14)	**0.90**	(0.13)	**4.0%**	(2.8)	≤20	≥0.8 U/ml	0.60 U/ml
	Alpha-2 antiplasmin	**0.94**	(0.05)	**0.88**	(0.06)	**6.4 %**	(5.2)	**0.98**	(0.09)	**0.90**	(0.10)	**7.7 %**	(2.4)	≤20	≥0.8 U/ml	0.70 U/ml
Activation	FPA	Data ready for JPAC meeting												NA	NA	NA
	S2302	Neg	N/A	Neg	N/A	N/A	N/A	Neg	N/A	Neg	N/A	N/A	N/A	NA	NA	NA
	C1 Inhibitor	See Velico data (appendix 3)				-	-	-	-	-	-	-	-	≤20	≥0.8 U/ml	0.70 U/ml

Results table

NHS Blood and Transplant

Coagulation		Whole Blood (n=16)			Apheresis (n=15)			Should meet the specified values below		
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Basic	Volume (mL)	274.7 (2.4)	229.1 (6.7)	n/a	271.7 (6.4)	227 (2.6)	n/a	NA	To meet spec	
vWF (U/mL)	Ag	Data next week						≤20	≥0.8 U/ml	0.70 U/ml
	RiCof/CBA	0.88 (0.28)	0.39 (0.15)	55.6 % (4.8)	0.75 (0.29)	0.41 (0.17)	46 % (7.1)	≤20	≥0.50 U/ml	0.40 U/ml
	Multimers	See Velico data (appendix 3)		- -	- -	- -	- -	NA	NA	NA
	ADAMTS-13	Data next week						≤20	≥0.8 U/ml	0.70 U/ml

What's with the vWF

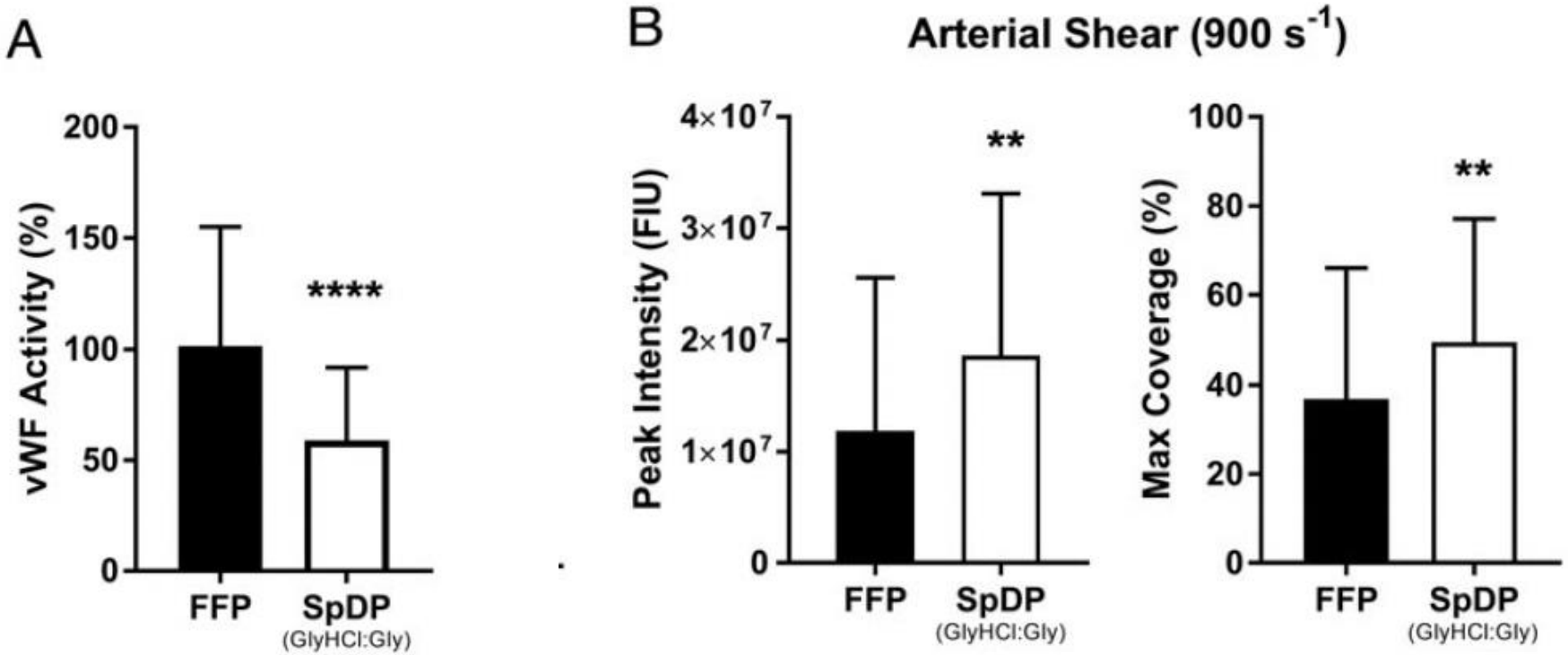
- We know spry drying removes the large multimer vWF
- ristocetin co-factor (RiCof) activity in spray dried plasma is reduced
- RiCOF test reliant on HMWT mulitmers

- What about vWF activity?
  - In trauma there is masses

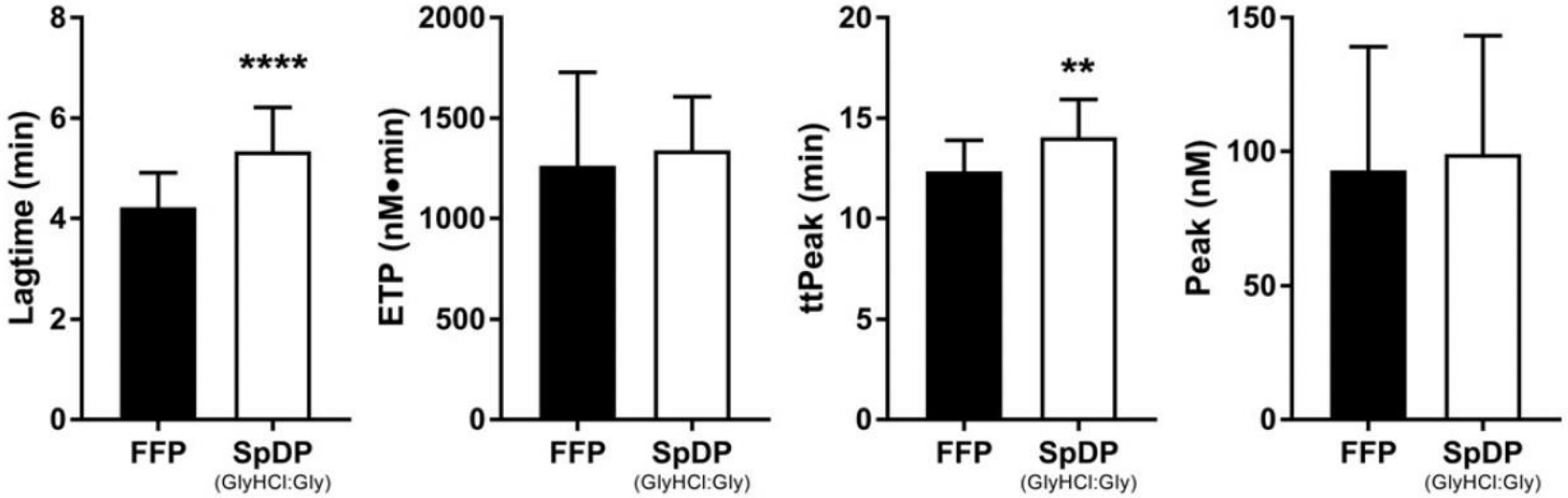
Spray-dried plasma deficient in high-molecular-weight multimers of von Willebrand factor retains hemostatic properties

Michael Adam Meledeo[1] *Qiyong Peter Liu*[2] *Grantham C. Peltier*[1]
Ryan C. Carney[2] *Colby S. McIntosh*[1] *Ashley S. Taylor*[1] *James A. Bynum*[1]
Anthony E. Pusateri[1] *and Andrew P. Cap*[1]

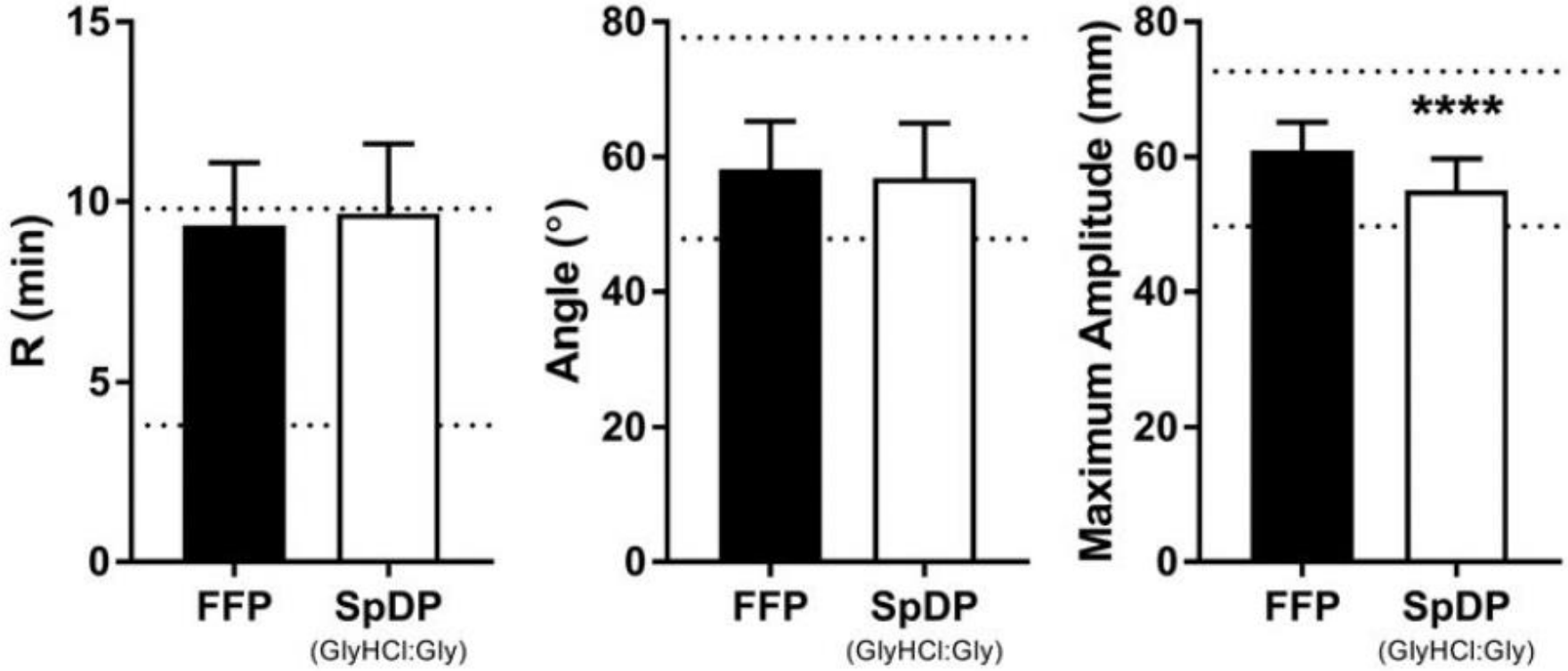
Test vs reality



Thrombin generation



ROTEM


R (min)
15
10
5
0
FFP
SpDP
(GlyHCl:Gly)
Angle (°)
80
60
40
20
0
FFP
SpDP
(GlyHCl:Gly)
Maximum Amplitude (mm)
80
60
40
20
0
****
FFP
SpDP
(GlyHCl:Gly)

CONCLUSION: Comparable coagulability was observed in FFP and SpDP. The apparent paradox between vWF–ristocetin cofactor assay and vWF-mediated platelet adhesion may be explained by the increase in smaller multimers of vWF in SpDP, producing different outcomes in these assays.

Data summary

- Few specification failures
  - Final values (impacted by starting values, not drying)
  - No “% loss pre to post drying” specification failures (except vWF)
- All coagulation factors within +/- 20% pre to post drying (except vWF)
- vWF activity:
  - Approx 50% decline (expected from manufacturers' data)
  - Breakdown of protein into smaller multimers
  - Not concerned:
    - further work ongoing (clot structure and literature review)
- Biochemistry data shows minimal changes pre to post drying (not shown)
- Externally tested specialist coagulation data and moisture content still to come

Is dried plasma a duck?

Do I care what sort of duck it is?

Future Developments

Uk clinical trial

- Spray dry plasma versus fresh frozen plasma for traumatic haemorrhage: a multicentre randomised control trial.
- Parallel, randomised, controlled, non-blinded, non-inferiority, multi-site trial, with internal pilot and cost-effectiveness embedded.
- **Primary outcome**
- Total blood component requirement (number of units) in first 24 hours after admission to hospital with traumatic haemorrhage.
-

- Inclusion criteria
- Patient (age ≥16) who have suffered a traumatic injury.
- Require plasma transfusion to treat major haemorrhage
- Exclusion criteria
- No intravenous or intraosseous access (should be assessed prior to opening box
- Knowledge that patient will object to being given blood transfusion for any reasons.

- Patients with traumatic bleeding, and for whom clinician requests plasma transfusion to treat the bleeding will be randomized to Spray dry plasma or standard plasma:

- Spray dry plasma, intravenously: 4 units (max 2 doses)

- Fresh Frozen Plasma or LG-Octaplas: 4 units

Ministry of Defence

velico

NHS Blood and Transplant

Real-world military storage study for SDP

- Current high temp validation for DP used static 40^{0}C incubator[1] to inform shelf-life
- Only 1 paper (n=25) analysed LyoPlas after military deployment, but no temp data[1] provided from deployment. No data available for SDP
- Disregards thermal stress of diurnal temperature variation, humidity changes etc. No data at all < 4^{0}C.
- Hence real-world storage assessment needed for SDP validation in military environments

1. Zur M, Glassberg E, Gorenbein P, Epstein E, Eisenkraft A, Misgav M, Avramovich E. Freeze-dried plasma stability under prehospital field conditions. Transfusion. 2019 Nov;59(11):3485-90.

Caring Expert Quality

Ministry of Defence velico NHS Blood and Transplant

Plan

Send units of SDP out with deploying CMTs (n=24)

Units to have temperature and humidity tracker

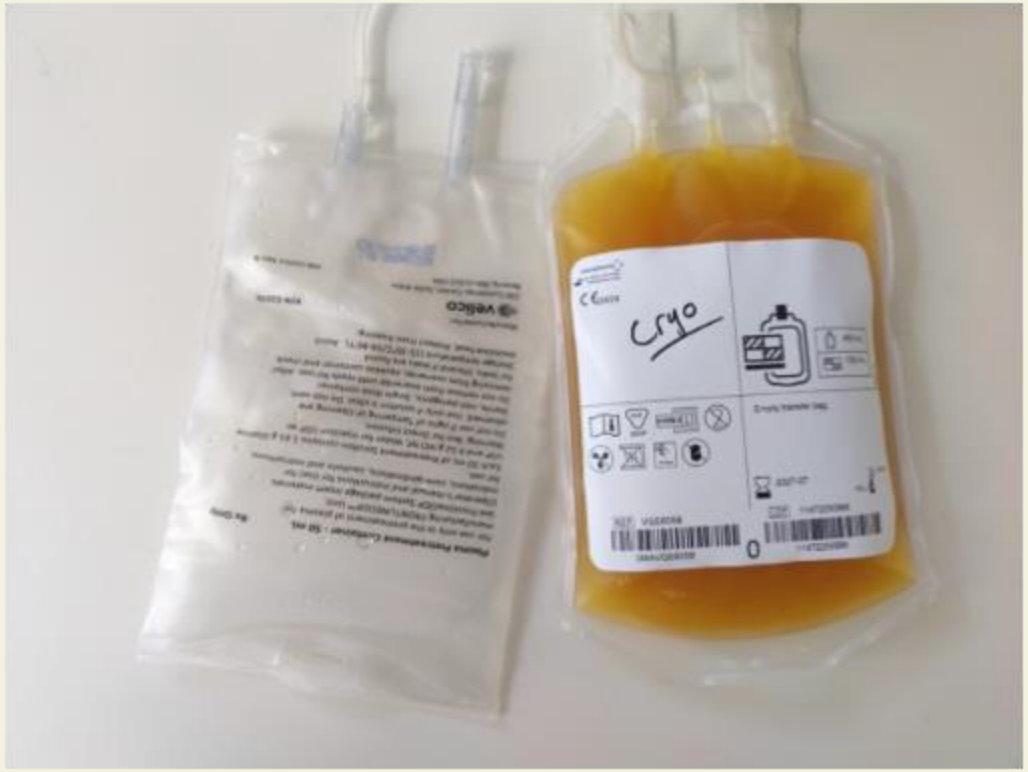
Analyse temp and SDP on return

Ministry of Defence velico NHS Blood and Transplant

Cryo Feasibility update

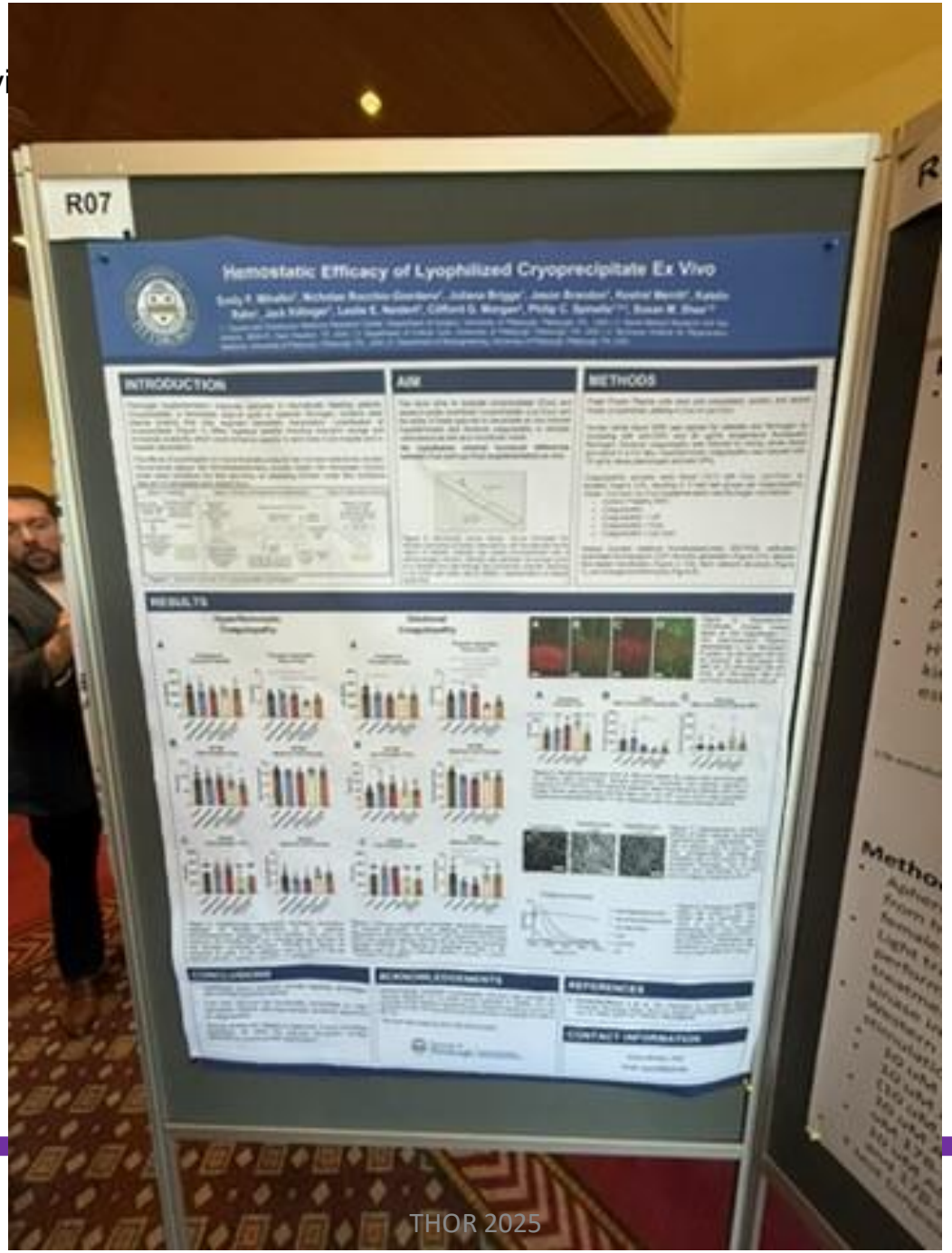
280 g / 271 mL
Fib – 6.1 g/L
FVIII – 2.598 IU/mL
pH 7.05

No precipitation observed up to 60 minutes



UK pooled Cryo (n=18)	Mean (range)
Fg	6.26 (4.99-7.94)
FVIII	2.28 (1.6-2.9)
FII	1.15 (0.97-1.35)
FV	0.91 (0.66 – 1.2)

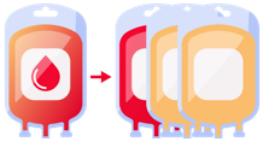
Caring Expert Quality


R07
Hemostatic Efficacy of Lyophilized Cryoprecipitate Ex Vivo
INTRODUCTION
AIM
METHODS
RESULTS
REFERENCES
CONTACT INFORMATION

The Nordic Dried plasma project

AIM:

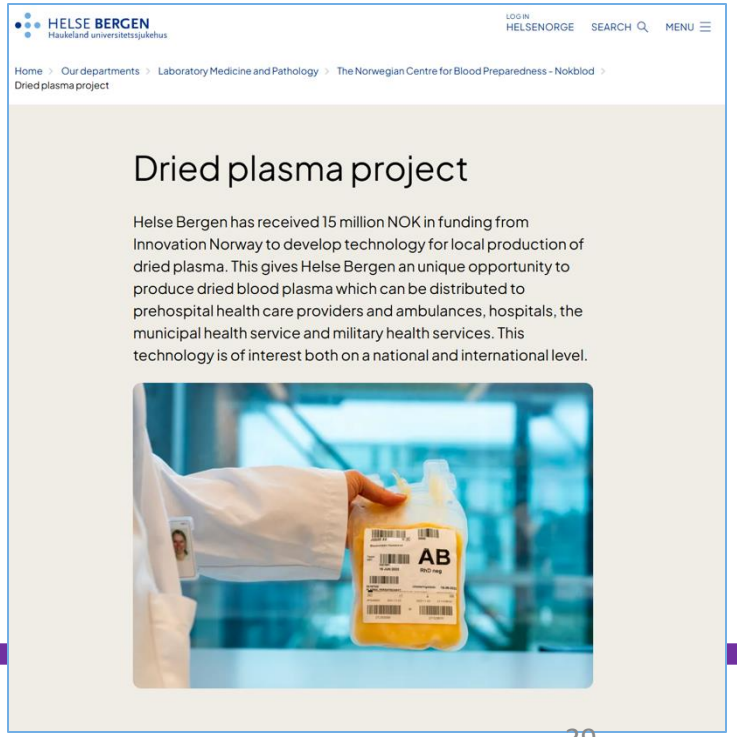
Establish local production of dried blood plasma



Be self-sufficient and meet national demand

Ensure preparedness and stable access to dried blood plasma

- Military-civilian Nordic Collaboration
- Project managing site: Norwegian Center for Blood Preparedness (Nokblod), Bergen, Norway
- Funding: Innovation Partnership Program (Innovation Norway)
- Status: Development phase
- Final testing phase and application of approval: 2026



More information: https://www.helse-bergen.no/en/avdelinger/laboratorieklinikken/nokblod/dried-plasma/

Thank You