SAFE PLASMA PRODUCTS FOR LOW RESOURCE COUNTRIES
Experience with Riboflavin/UV Plasma

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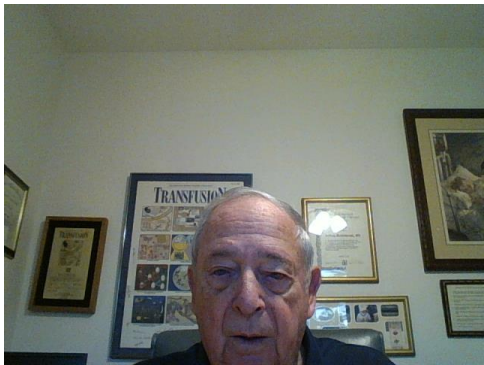
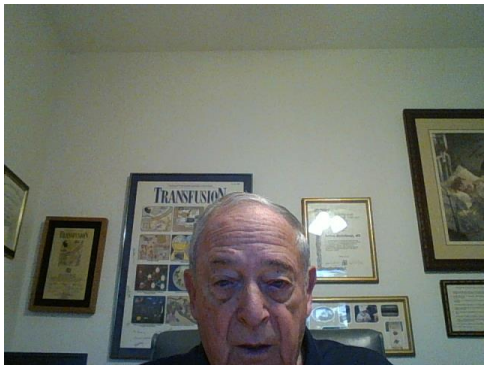
DISCLOSURES

- TerumoBCT – Advisor
- Fresenius Kabi – Scientific Advisory Board



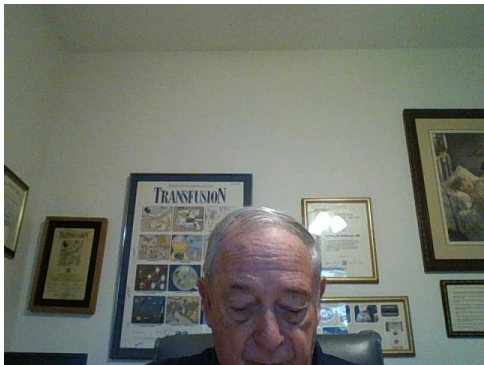
AGENDA

- STEPS TO PROVIDE SAFE BLOOD
- PATHOGEN REDUCTION USING RIBOFLAVIN AND UV LIGHT
- PATHOGEN REDUCTION CAPACITY OF RIBOFLAVIN/UV LIGHT
- EFFECT OF RIBOFLAVIN/UV ON PLASMA PROTEINS
- CLINICAL USE OF RIBOFLAVIN/UV TREATED PLASMA
- LABORATORY METHODOLOGY OF RIBOFLAVIN/UV FOR PATHOGEN REDUCTION
- ESTABLISHING THE RIBOFLAVIN/UV TECHNOLOGY
- ONGOING OPERATION OF THE RIBOFLAVIN/UV PROCESS



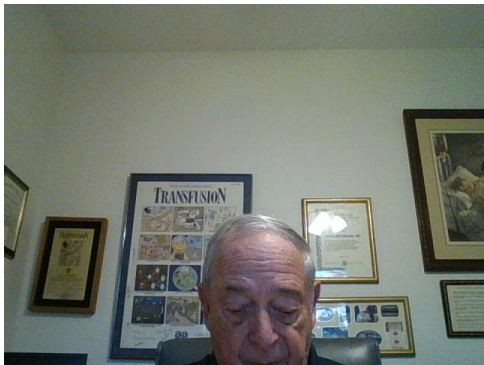
STEPS TO PROVIDE SAFEST POSSIBLE BLOOD

- Donor population
  - Volunteer
- Medical history
  - Risk behaviors
- Physical exam
- Donor deferral registry
- Laboratory testing
  - Retrospective
- Confidential unit exclusion
- Donor call back



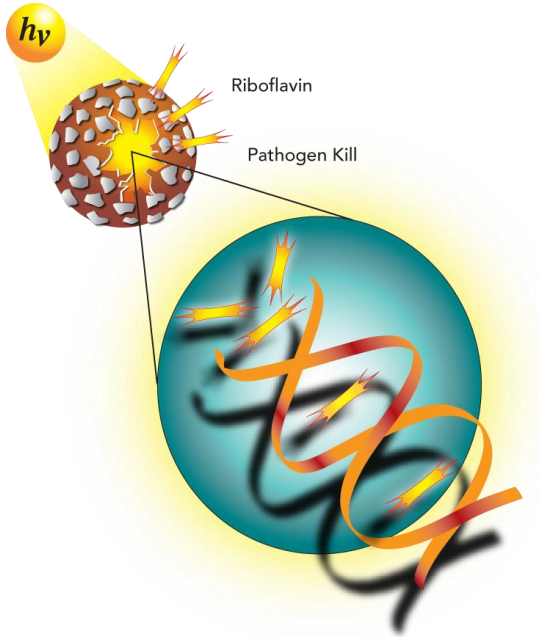
LIMITATIONS OF PRESENT PARADIGM TO DECREASE TRANSFUSION-TRANSMITTED DISEASES

- Applies only to known pathogens
- Reactive to new pathogens
- Accepts that patients may be harmed
- Does not prevent bacterial contamination
- Causes deferral of suitable donors
- **TREAT THE BLOOD PRODUCT TO MINIMIZE RISKS**



Mirasol System Primary Modes of Action

The Mirasol system inactivates disease-causing agents by altering their nucleic acids in two primary ways:[1,2]



1. UV light only: reversible inactivation
   - UV light alone breaks chemical bonds in the nucleic acids of pathogens

2. UV light + riboflavin: irreversible inactivation
   - Riboflavin molecules form complexes with nucleic acids
   - UV light from the Mirasol Illuminator activates the riboflavin molecule in the complex
   - Photoactivated riboflavin induces a chemical alteration to nucleic acids, making pathogens unable to replicate

The Mirasol PRT system

An Overview

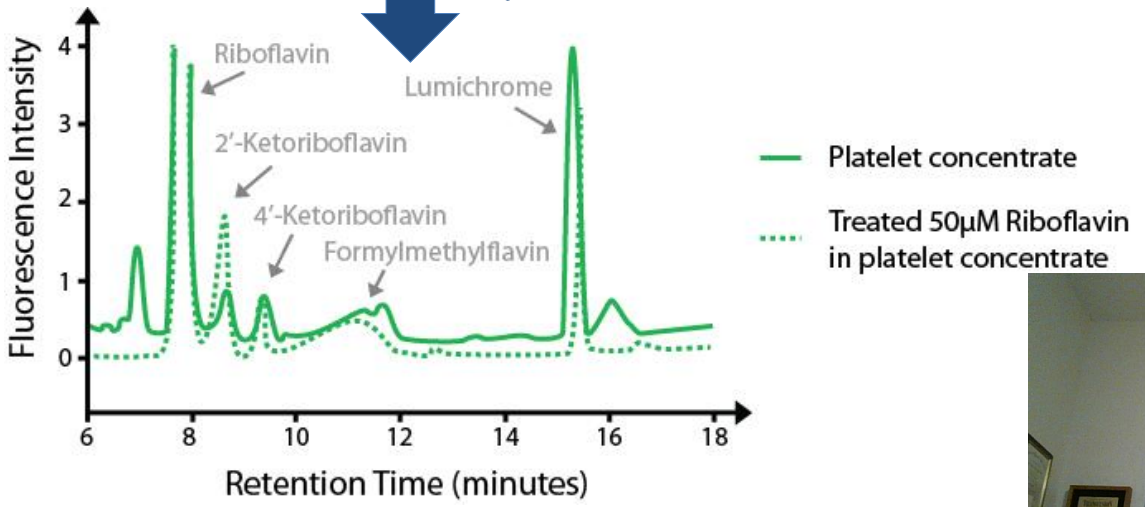
Blood product

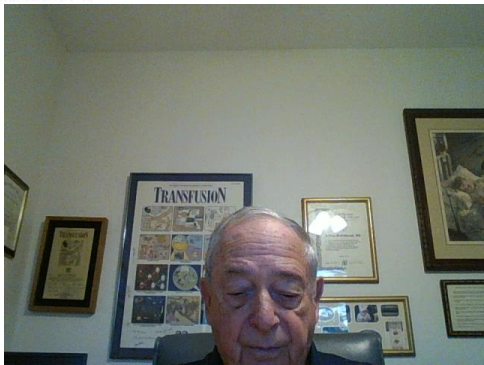
+

Riboflavin (vitamin B2) solution

+

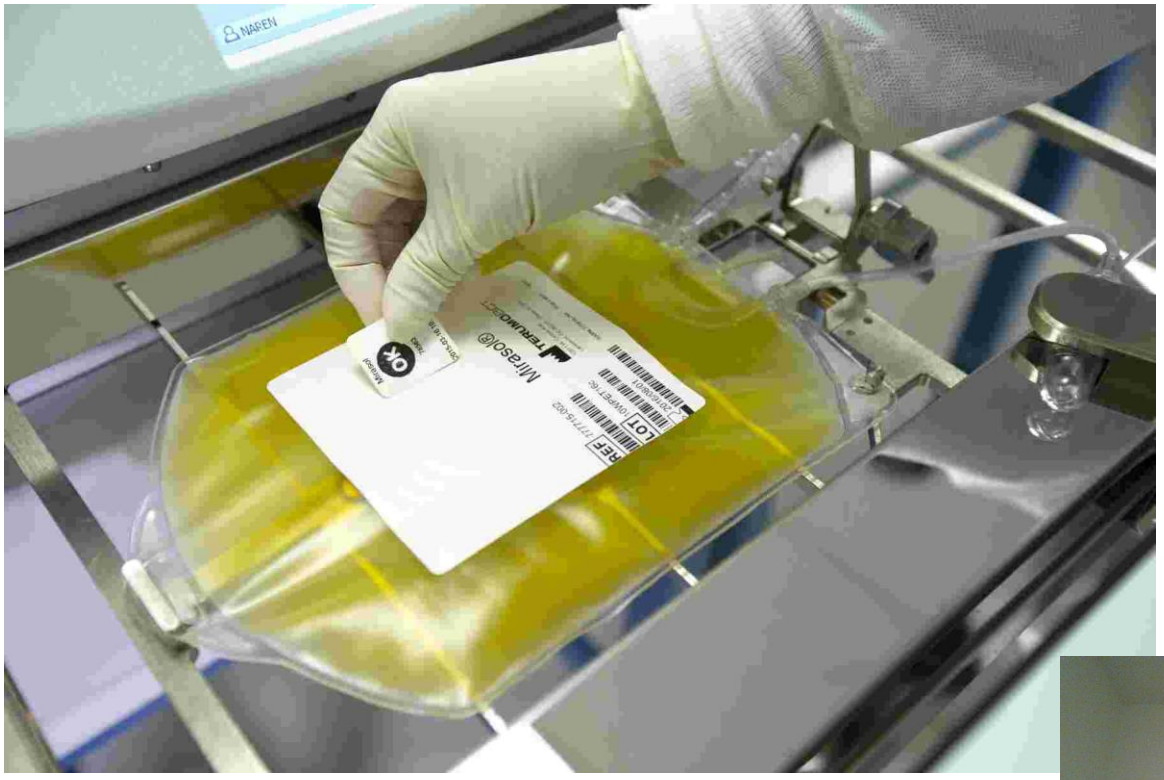
UV light

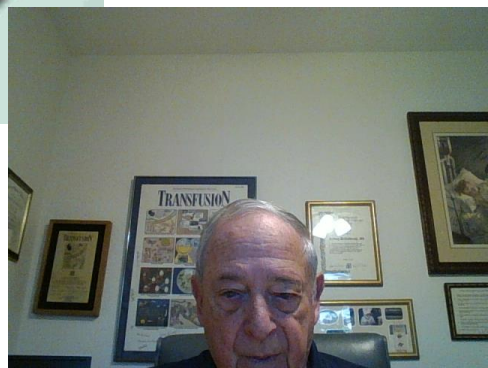




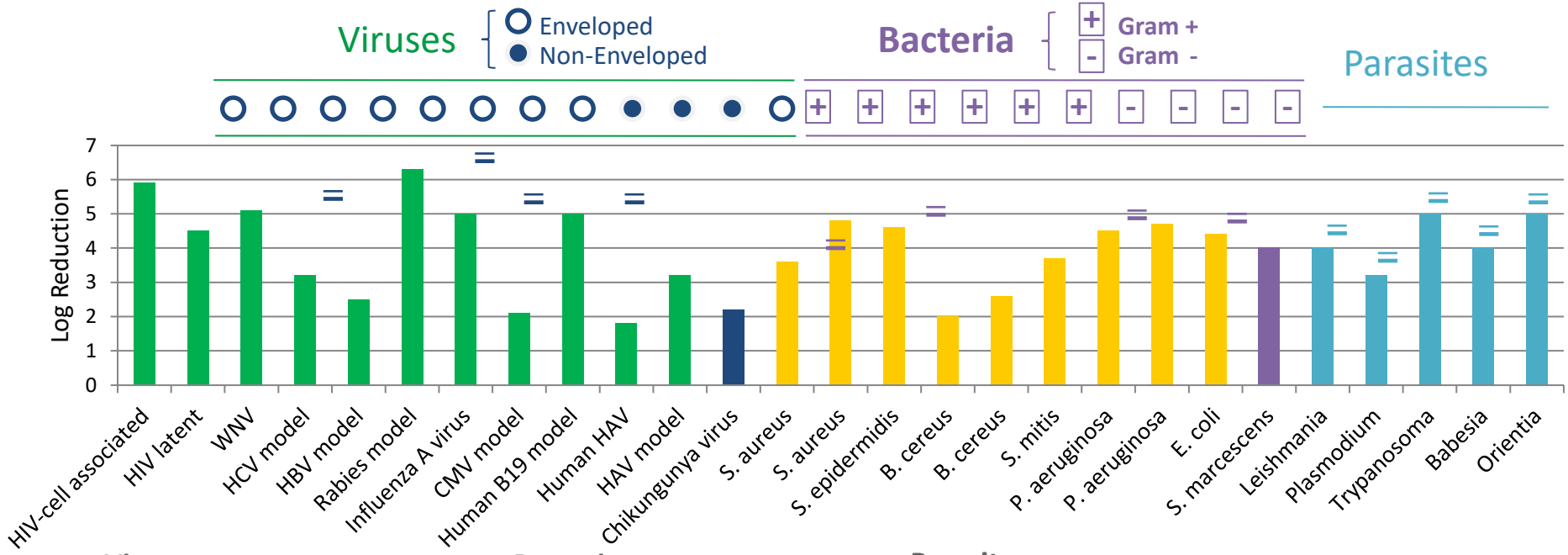
DEVICE FOR RIBOFLAVIN/UV PATHOGEN REDUCTION

UNIT OF PLASMA BEING PREPARED FOR RIBOFLAVIN/UV TREAMENT





Mirasol System Effectiveness Against Pathogens – Summary



Viruses:

~2 to 6 log reduction (99.0% to 99.9999%) demonstrated by infectivity assay ($TCID_{50}$)

Mirasol system shown to **prevent** transfusion-transmitted **CMV** in mouse model

Bacteria:

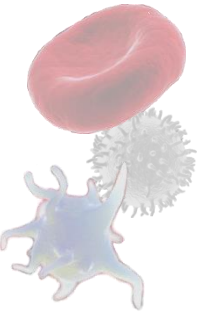
~2 to 5 log reduction (99.0% to 99.999%) demonstrated by high titer studies

Mirasol system shown to be **at least as effective as bacterial culture** methods at clinically relevant contamination levels

Parasites:

≥3 to ≥5 log reduction (≥99.9% to ≥99.999%)

Factors that Influence Infectivity of Blood Product



- Virus
  - Circulating Level
  - Ratio of infectious particles to genome equivalents
  - Replicative capacity of the agent
  - Genotype of the agent
- Donor
  - Stage of infection
  - Presence of antibody against the agent
- Transfusion
  - Blood component – volume of plasma = dose
  - Duration of storage of component
- Patient
  - Immune status – natural immunity or compromise due to underlying disease
  - Viral receptors - resistant to infection
  - Body size – relates to component and volume of plasma transfused

ISSUES IN ESTABLISHING THE RIBOFLAVIN/UV TECHNOLOGY FOR PATHOGEN REDUCTION

- FACILITIES –
  - Review space and arrangement of laboratory and benches
- ENVIRONMENT
  - Temperature, air flow, similar to general laboratory
- POWER
  - Type, dependability
- SPACE
  - Total amount, Bench space, location of centrifuges, location of freezers
- EQUIPMENT
  - centrifuges. Freezers, plasma separation devices; heat sealers, sterile connector
- STAFFING
  - qualifications, number, work schedules
- TRAINING
  - type of training, training materials, trainers, ongoing refresher training
- ESTABLISHING QC PROGRAM
  - test capability ; acceptable limits of results; frequency and number of samples to be tested, responsibility for monitoring

IMPORTANCE OF ADEQUATE AND CONTROLLED STORAGE SPACE FOR SUPPLIES

DR. MCCULLOUGH WITH DR. GOODRICH INVENTOR OF RIBOFLAVIN TECHNOLOGY WITH DEVICE IN UGANDA
Note window above devices

ONGOING OPERATION OF RIBOFLAVIN/UV FOR PATHOGEN REDUCTION

- BLOOD COLLECTION PLANNING
  - Collection time and location to enable blood to be transported to laboratory for time requirements for processing into FFP
- PROJECT PRODUCTION BASED ON USEAGE AND PATIENT NEEDS
- STAFFING
  - Have staff available when whole blood arrives
- EQUIPMENT MAINTENANCE
  - manufacturer vs blood center responsibility
- CLINICAL FEEDBACK
  - product effectiveness, adverse events
- MONITORING QUALITY CONTROL DATA
  - Equipment monitoring. Product monitoring - test systems in place with agreed acceptable boundaries

LEVELS OF COAGULATION PROTEINS IN PLASMA AFTER TREATMENT WITH RIBOFLAVIN FOR PATHOGEN REDUCTION

% Retention

FACTORS	Hornsey	Rock
Fibrinogen	78.8	77
F II	86	82
F V	78.9	73
F VII	79	85
F VIII	68.5	77
F IX	79	71
F X	79.7	82
F XI	67.7	67

FACTORS	Hornsey	Rock
Protein C	83.6	79
Protein S	98	91
Antithrombin	98.3	100
Plasmin inh.	92.5	84
VWF	85.5	114
ADAMS13	73.3	96

Hornsey et al Transfusion 2009

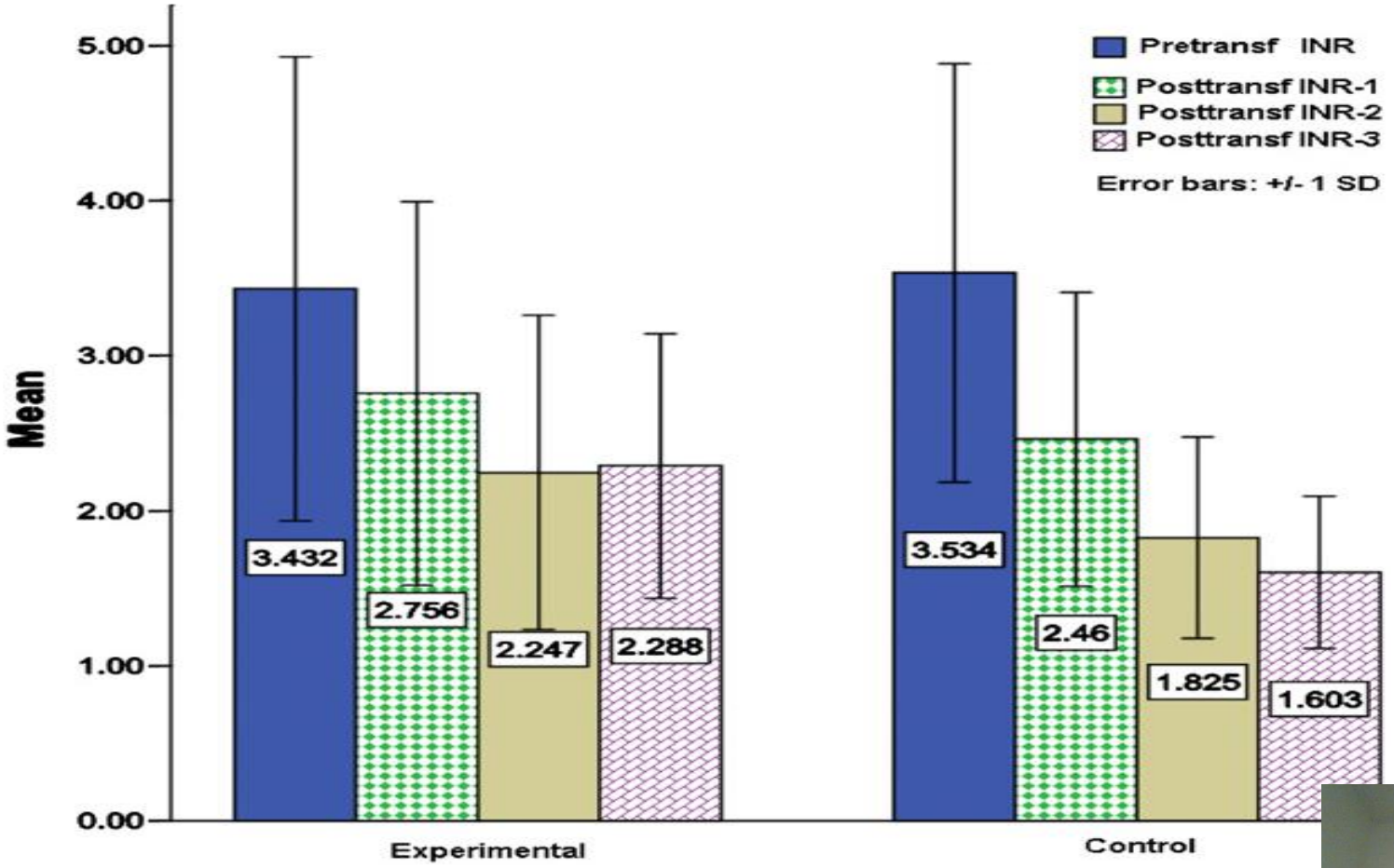
Rock Vox Sang 2010

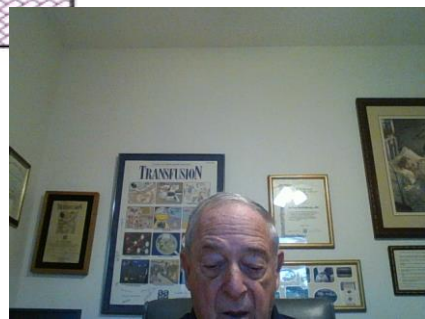
TRANSFUSION OF RIBOFLAVIN FFP TO 60 PATIENTS WITH COAGULOPATHY

Patients	Mirasol	Control
Bleeding with high INR	18	20
Correction of coag	12	10
Pre transfusion INR	3.4	3.5
Units FFP total	84	68
Units FFP per patient	2.8	2.2
Units per patient range	1-5	1-4
Improvements INR per 2 FFP	.66	.83
Stanojkovic et al Transf and Apheresis science 2012		

INR FOLLOWING TRANSFUSION OF RIBOFLAVIN FFP TO PATIENTS WITH ACQUIRED COAGULOPATHY

Stanojkovic et al Transf and Apheresis Science 2012





COAGULATION FACTOR CONTENT OF MIRASOL CRYOPRECIPITATE

Ettinger et al Transf and Aphereis Science 2012

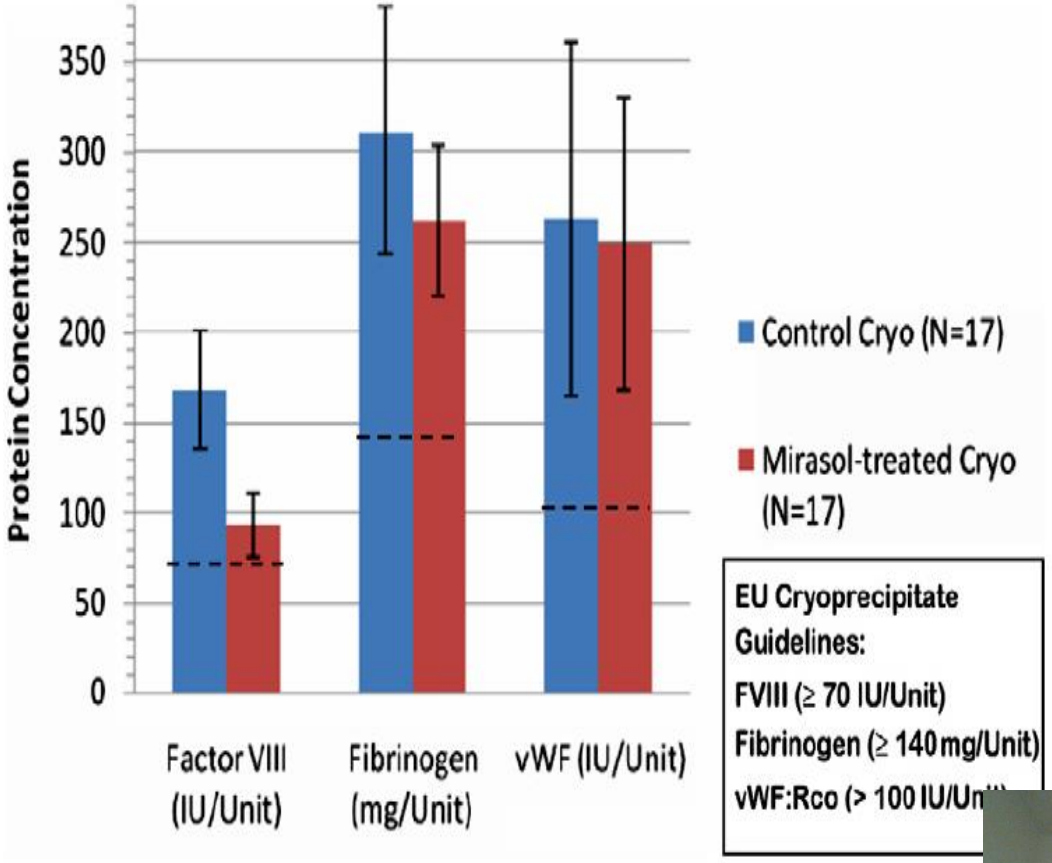
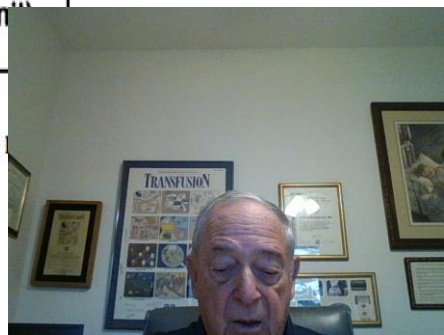


Fig. 1. Protein quality in cryoprecipitate units made from FP24 ($N = 17$). Dotted lines indicate protein levels
cryoprecipitate.



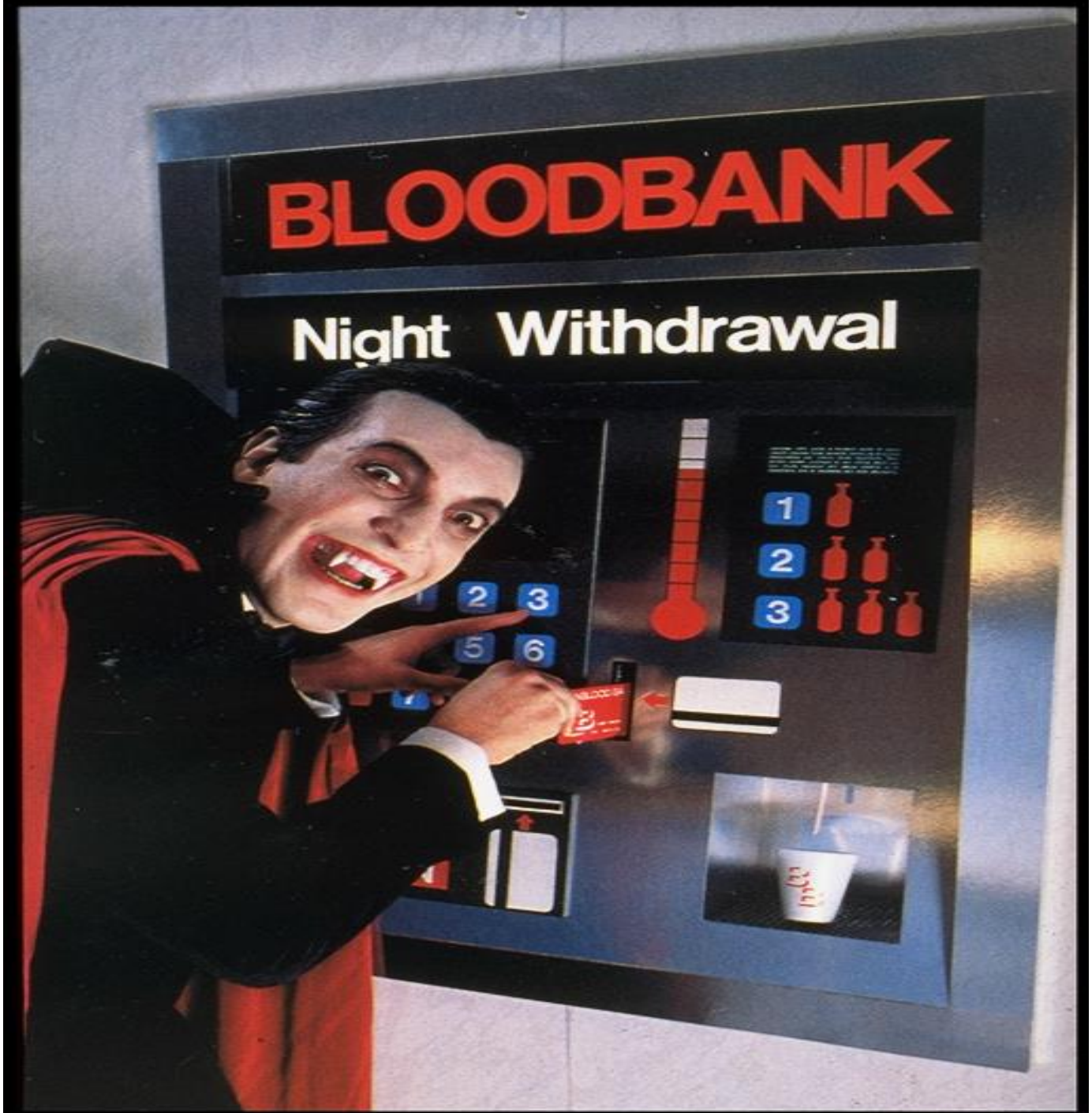
RIBOFLAVIN/UV DEVICES FOR TREATMENT OF WHOLE BLOOD IN UGANDA NATIONAL BLOOD CENTER

CARRYING OUT MIRASOL TREATMENT OF WHOLE BLOOD IN UGANDA

COMPANY POTENTIAL SUPPORT **

- Planning meeting
- Implementation planning assistance
- Advice regarding facilities
- Installation of equipment and software
- Training of staff on operation of the device and use of software and basic maintenance
- Validation of device and operation
- Review and advise about necessary changes to donor scheduling to assure arrival of blood to meet time requirements for treatment
- Routine preventive maintenance of equipment

- ** Authors opinion; not a company approved list


BLOODBANK
Night Withdrawal
1
2
3
2 3
5 6