Outline

1. Pathogen Reduction Overview
   - What is Pathogen Reduction?
   - PR Effectiveness
   - Layers of Safety
   - PR Technologies
   - Mechanism of Action
   - Where is PR Used?
   - Selecting a PR

2. PREPAReS Clinical Trial Overview
   - Study Description
   - Participating Countries
   - CBS’ Objectives
   - Study Design
   - Study Objectives
   - Inclusion Update
   - Next Steps
Pathogen Reduction Overview
What is Pathogen Reduction?

It is an approach for the prevention of transfusion-transmitted diseases that is both **broad-spectrum** and **proactive**.

**Broad-spectrum**
Because it effectively inactivates almost all viruses, bacteria and parasites (not prions) that may be present in a unit.

**Proactive**
Because it removes the necessity of developing specific assays for each pathogen and because it is applied regardless of the infectivity status of the unit.
Pathogen Reduction Overview

Pathogen Reduction Effectiveness

**Viruses**
- CMV, HIV
- HAV, HBV, HCV
- WNV, B-19
- Chikungunya
- Rabies virus
- Influenza A ...

**Bacteria**
- *S. aureus*
- *S. epidermidis*
- *S. pyogenes*
- *S. mitis*
- *Escherichia coli*
- *K. pneumoniae*
- *Y. Enterocolitica*
- ...

**Parasites**
- *Plasmodium falciparum*
- *Trypanosoma cruzi* (Chagas’ disease)
- *Leishmania major*
- *Babesia microti* ...

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Canadian Blood Services
*it’s in you to give*
Pathogen Reduction Effectiveness

In the context of the blood system, Pathogen Reduction allows:

- Protection against bacterial contamination that may be missed by BacT/Alert screening in platelets
- Inactivation of viruses in their incubation phase
- Inactivation of white blood cells
- Protection against pathogens that are not tested for
- Probable protection against Emerging pathogens
Layers of Safety

Safety measures that made a difference:

- Donor deferral policies for risks related to travel, behaviour, family history, etc.
- Nucleic Acid Testing (NAT) for HIV, HCV, WNV and HBV
- Bacterial reduction & detection
- Chagas’ Disease testing

Next logical step: Pathogen Reduction?
### Pathogen Reduction Technologies

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>System</th>
<th>UV (nM)</th>
<th>Photo-sensitizer</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerus</td>
<td>Intercept</td>
<td>320-400</td>
<td>Psoralens</td>
<td>Plasma Platelets</td>
</tr>
<tr>
<td>MacoPharma</td>
<td>Theraflex</td>
<td>254</td>
<td>none</td>
<td>Platelets</td>
</tr>
<tr>
<td></td>
<td>Theraflex MB</td>
<td>Visible light</td>
<td>Methylene Blue</td>
<td>Plasma</td>
</tr>
<tr>
<td>TerumoBCT</td>
<td>Mirasol</td>
<td>280-360</td>
<td>Riboflavin</td>
<td>Plasma Platelets</td>
</tr>
</tbody>
</table>
Mechanisms of Action

Pathogens must be able to reproduce to be infectious

- Visible or UV light alone or in combination with an active ingredient cause damages to nucleic acids blocking further replication.
- Red Blood Cells and Platelets have little DNA/RNA – less impacted than pathogens
Where is Pathogen Reduction Used?

**Non-North America**

Pathogen Reduction is becoming standard of care

Overall 50% of European countries have implemented or are implementing some form of PR for plasma and/or platelets
Pathogen Reduction Overview

Where is Pathogen Reduction Used?

The Americas

Press Releases:

Feb. 9, 2016 Cerus Enters Multi-Year Agreement with the American Red Cross for the Use of INTERCEPT Platelets and Plasma

Jan. 14, 2016 AABB Authorizes Use of the INTERCEPT Blood System for Platelets to Reduce the Risk of Transfusion-Associated Graft Versus Host Disease

Jan. 7, 2016 Cerus and LifeShare Blood Centers enter into Agreement for the Use of INTERCEPT Platelets and Plasma

Jan. 5, 2016 Cerus Announces Agreement with Blood Systems, Inc. for the Use of INTERCEPT Platelets and Plasma
Choice of a Technology

• CBS has opted to first engage in a strategic partnership with Terumo BCT to participate in the evaluation of its Mirasol® Pathogen Reduction Technology

• This joint effort does not bind CBS to this technology

• Rationale:
  • Riboflavin (Vitamin B2) has fewer safety concerns, no need to remove
  • Process time is very rapid (approx. 12 minutes/unit)
  • We have an established working relationship with Terumo BCT
Pathogen Reduction Overview

Choice of a Technology

Connect & transfer product to Illumination bag
Add riboflavin solution
Illuminate (4-10 min)

Transfuse or store for up to 5 days
Total process time ~ 12 min

Mode of action: Causes irreversible alterations to nucleic acids (DNA, RNA)
PREPAREs
Clinical Trial
Overview
Pathogen Reduction Evaluation & Predictive Analytical Rating Score (PREPAREs)

• A prospective, randomized, single-blinded, multicenter non-inferiority trial for the side by side evaluation of Mirasol-treated and standard of care Pooled Platelet products in terms of bleeding complication in hematological patients.

• Initiated in the Netherlands in November 2010, the clinical trial will close on May 1st, 2016 😊
Pathogen Reduction Evaluation & Predictive Analytical Rating Score (PREPAReS)

• Sponsored by the Sanquin Blood Supply Foundation, the national blood operator in the Netherlands and financially supported by Terumo BCT.

• Canadian Blood Services’ role in this study is to produce, at its Ottawa manufacturing site only, the Mirasol-treated pooled platelets strictly for use in PREPAReS by the participating hospitals.
Who is Participating

Europe
- HaGa Hospital
- Leiden UMC
- Erasmus UMC
- Maastricht UMC
- Bergen Haukeland

Canada
- Hamilton Juravinski
- Sunnybrook HSC
- London HSC
- Ottawa General Hospital
- Kingston General
Canadian Arm of PREPAReS

- Terumo holds the Canadian Clinical Trial Authorization
- Prof. Nancy Heddle (McMaster University) is the principal investigator of the Canadian study
- CBS and each participating hospital have received approval from their local Research & Ethics Board.
CBS Objectives

• Contribute to expand knowledge about safety and efficacy of Mirasol®

• Gain valuable experience should we later implement this technology or a similar one

• Contribute to increase market availability (licensure) of Pathogen Reduction technologies in Canada
A study protocol for a randomised controlled trial evaluating clinical effects of platelet transfusion products:
the Pathogen Reduction Evaluation and Predictive Analytical Rating Score (PREPAReS) trial

Paula F Ypma, Pieter F van der Meer, Nancy M Heddle, Joost A van Hilten, Theo Stijnen, Rutger A Middelburg, Tor Hervig, Johanna G van der Bom, Anneke Brand, Jean-Louis H Kerkhoffs for the PREPAReS Study Group


http://bmjopen.bmj.com/content/6/1/e010156.full.pdf+html
Objectives of the Clinical Trial

• To assess the non-inferiority of Mirasol-treated pooled platelets compared to standard pooled platelets in terms of % of patients with WHO bleeding complications ≥ grade 2 in hemato-oncological patients
• Assess predictive value of lab tests on platelet recovery
• Determine level of alloimmunization
• Others
PREPAReS Clinical Trial Overview

PREPAReS Study Design

Target: 578 patients in total

Patient eligibility criteria:
- Age ≥ 18 years
- Expected ≥ 2 platelet transfusions
- Hematological-oncological disease
- Treated as an in-patient (need daily bleeding assessments)
- Informed consent
PREPAReS Clinical Trial Overview

PREPAReS Study Design

Study period  (treatment period)

- 6 weeks (42 days) after the first transfusion OR
- Transfusion independency (7 days without transfusion) OR
- Hospital discharge OR
- Patient withdrawal OR
- Death
Objective - Clinical effectiveness
Objective - Clinical effectiveness

- Daily bleeding assessment => physical assessment, patient input, chart review.
  - Performed daily by study coordinator on weekdays
  - Patients complete a diary on weekends/holidays and this is supplemented by a chart review and consults with nurses on Mondays
Objective - Clinical effectiveness

• Standardized report is used to collect raw bleeding data daily

• These reports are sent to the Netherlands for adjudication of bleeding grade (blinded)
PREPARES Clinical Trial Overview

**Objective - Clinical effectiveness**

- The grade of bleeding is assigned by three independent adjudicators based on the specified WHO bleeding scale (Blinded to treatment allocation).

<table>
<thead>
<tr>
<th>WHO Bleeding Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No bleeding</td>
</tr>
<tr>
<td>1</td>
<td>Minor bleeding</td>
</tr>
<tr>
<td>2</td>
<td>Mild blood loss, (clinically relevant)</td>
</tr>
<tr>
<td>3</td>
<td>Gross blood loss, needing transfusion (severe)</td>
</tr>
<tr>
<td>4</td>
<td>Debilitating, death</td>
</tr>
</tbody>
</table>

Miller, Cancer 1981;47:207
Objective - Clinical effectiveness

Other parameters for the evaluation of clinical effectiveness:

- the frequency of 1h and 24h post-transfusion platelet increment failures (CCI),
- the percentage of days that bleedings ≥WHO grade 2 occur,
- the incidence of adverse reactions,
- the transfusion requirement of red cells and platelets, and the platelet concentrate transfusion interval.
Objective - In vitro platelet quality testing
Objective – In vitro platelet quality testing

Other than pH \((\text{pH}_{22^{\circ}} > 6.2)\), what in vitro measurements could accurately predict platelet recovery, survival or haemostatic function \((1\ h\ and/or\ 24\ h\ CCI)\) in platelet concentrates?

– **CD62P** expression, an activation marker, on the platelet surface. A higher CD62P expression has been associated with enhanced platelet clearance from the circulation.

– apoptosis marker **annexin A5** binding was found to be associated with impaired platelet survival in animals.

– **lactate** concentration (as surrogate for lactate production) as a low lactate production rate is considered a good indicator of mitochondrial function.
Objective - Assess alloimunisation
Objective – Assess alloimmunisation

Could Mirasol play a role in reducing alloimmunisation and induce tolerance to a subsequent allograft in humans?

– Samples are obtained from patients who are negative for HLA antibodies prior to transfusions and collected weekly up until day 28, and then on day 56, and tested for presence of HLA antibodies.

The potential reduction of alloimmunisation through the use of Mirasol-treated platelets would be of additive beneficial value, potentially even more clinically significant in comparison to the reduction of transfusion transmitted infectious diseases.

Where are we at?
Where are we at?

- 548 patients out of 578 were enrolled to date
- Approx. 2,000 platelet transfusions
- Close to 240,000 days of follow-up
- Clinical trial will close for enrolment on May 1, 2016
What is next?

• Results will be compiled and analyzed to verify if the objectives were successfully met
• The data collected on the Mirasol technology may then be submitted by Terumo BCT to Health Canada for market approval
• Canadian Blood Services could then decide on whether or not to seek approval from Health Canada to implement
• ... A very long process!
The CBS Team at the completion of Mirasol process validation in 2012

Many Thanks to:

Pieter van der Meer and Jean-Louis Kerkhoffs at Sanquin
Peter Schubert, CBS Vancouver
McMaster Transfusion Research Program
The Production and QA teams at the Ottawa CBS Site
The participating hospitals
The Patients

Clinical trial partners visiting the Ottawa CBS site in 2015
Questions?
Canadian Blood Services

it's in you to give
Manufacturing Process

Whole Blood Extraction

Legend
WB: Whole Blood
BC: Buffy Coat
LP: Liquid Plasma
RBC: Red Blood Cell
Current Buffy Coat Process (4 BC)

- Centrifuge
- Extract using on Compomat (settings differ between 4BC and 5BC)

Add all volume of the largest compatible male plasma

Pool

Plt. Pool

Ready for transfusion

Clinical Trial Process (5 BC)

Add a portion of a compatible male plasma

Pool

Plt. Pool

Ready for Mirasol treatment
Mirasol Treatment of the 5BC Pooled Platelet

- 5BC Transfer Plt. Pool and Riboflavin into UV Illumination/Storage bag
- UV light

Ready to issue to the participating hospitals
(Strictly for use in the clinical trial setting)