

## Minutes

XXXIInd Meeting of the Biomedical Excellence for Safer Transfusion Collaborative  
Cape Town, South Africa  
September 1-2, 2006

*These minutes represent presentations and discussions at the BEST meeting on September 2 as well as a synopsis of the team meetings held immediately before. They include some detail and discussions that occurred only in the team meetings in order to provide all members with as much information as possible about past and planned studies. Additional details can be obtained from the leader of each team, who prepared the summary of the team's activity given below, often with assistance from presenters.*

Jim AuBuchon opened the meeting with a welcome to all attendees. First-time attendees and guests were welcomed.

A photo tribute to Scott Murphy was offered in his memory. AuBuchon announced that the *Transfusion* Supplement on platelet radiolabeling would be published with the November issue and dedicated to Scott.

Nancy Heddle had agreed to serve as the Interim Treasurer when Scott was no longer able to perform this function. There were no questions on the financial report in the BEST book. It was noted that MacoPharma's dues payment for 2006 had been inadvertently omitted from the records.

AuBuchon mentioned recent updates of the website, including new login and roster routines. He encouraged the submission of comments for improvements.

The Puzzler, created by Ron Sacher, was then explained. (See website presentations for answers.) AuBuchon thanked Sacher for an interesting and educational challenge.

Hans Gulliksson was thanked for his excellent leadership of the Conventional Components Team over 7 years. He was presented with a plaque to commemorate his contributions.

After the summarizations of the team meetings were offered, AuBuchon offered a brief summary of the last four years. (See presentations on website.) He thanked all for a very productive cycle. He then turned the chair over to Lorna Williamson. She thanked AuBuchon for his leadership and showed a photo of an antique nautical chart of the waters of Maine that had been given to him as a thank you gift. She also thanked Susie AuBuchon for her management of BEST affairs and meetings, and presented her a thank you gift of a carved bird. Both gifts were greatly appreciated, and thank yous were offered. AuBuchon unveiled and distributed lapel pins of the BEST logo.

Williamson engaged the group in discussions of plans for the next cycle of BEST. Paolo Rebullia suggested that efforts be directed toward establishment of a database of data from all BEST studies for future data mining. Mo Blajchman suggested that BEST direct efforts to assist improvement in transfusion practices, such as determination of appropriate transfusion

triggers. Ron Sacher suggested that the group might profitably spend some time in a strategic planning mode to define its future directions. Marcela Contreras suggested that BEST should investigate how it might assist the improvement of transfusion practices in developing countries. AuBuchon noted that this had been discussed previously, such as in Vienna, which led to the creation of the Transfusion Safety Team; however, there was not a readily identifiable means of taking an organization created to push the boundaries of knowledge to improve hemotherapy in low development index countries. Cees Smit Sibinga noted that Transfusion Safety Team had generated improvements that could indeed be implemented in developing countries. Sherrill Slichter suggested that a personnel exchange might be established or that BEST might make its personnel available for assistance in developing countries. Williamson indicated that this discussion could be continued at BEST XXXIII.

Williamson announced that the next meeting would be BEST XXXIII in Amsterdam April 27-28 at the SAS Radisson. Further details will be forthcoming.

She closed the meeting by thanking all for their support, contributions and participation.

### **Report: Cellular Therapy Team**

*H. Eichler, Z. Szczepiorkowski*

#### **Participants**

Team Members: Anneke Brand, Hermann Eichler, Shuichiro Inadome, Derwood Pamphilon, Paolo Rebulli, Jo-Anna Reems, Ronald Sacher, Cees Smit Sibinga, Ziggy Szczepiorkowski, Majid Zia.

Hermann Eichler and Ziggy Szczepiorkowski welcomed all participants of the Cellular Therapy team meeting and gave an overview of the agenda listing current CT team projects.

#### **1. Administrative Issues and Update on Manuscripts (Eichler)**

The manuscript of BEST study #15 entitled “Multi-laboratory evaluation of procedures for volume reducing cord blood: influence on cell recoveries” has now been published (*Cytotherapy* 2006;8:254-264). The manuscript containing the results of the first part of BEST study #28 entitled “Multi-center study on in vitro characterization of dendritic cells” has been finalized and submitted for publication in *Cytotherapy* end of July (the submitted manuscript is posted on the BEST website). In addition, a ‘letter to the editor’ on the results of BEST 30.1 was submitted (see below).

#### **2. BEST #28: Inter-laboratory Study on Quality Characteristics of Dendritic Cells (DCs); discussion on how to proceed with functional DC testing (Eichler)**

Dr. Hermann Eichler briefly summarized the history and the current status of the BEST 28 DC study. At the Barcelona meeting a discussion was initiated about possible functional DC testing procedures that could be incorporated into the project. A summary slide from Dr. Celluzzi’s presentation at the Barcelona meeting was shown listing different functional DC tests with their advantages and disadvantages. Hermann mentioned that there is a number of

remaining vials of cryopreserved DCs and lymphocytes from the three volunteer donors still stored in the participating laboratories. The initial plan was to use these cells to perform a multi-center analysis of their functional characteristics, e.g. by implementing two different assay procedures in each of the eight BEST 28 labs following defined test protocols. On the other hand, because the cells were processed in Nov/Dec 2004 and are now stored frozen in LN<sub>2</sub> for nearly two years, DC viability and/or functional properties could be negatively affected. During the discussion of how to proceed with the DC study a couple of substantial problems were identified including an assumed high intra-laboratory as well as inter-laboratory variability of the result of functional testing techniques. Moreover, even simpler tests such as cell counting and viability testing are so far lacking standardization. As a next step the CT team decided to identify intra-laboratory variability in selected functional test systems by collecting data from the study participants. In parallel, test protocols from different labs should be compared to each other to generate standardized protocols for the functional assays to be used. At the same time as the cells will be tested in functional assays, it should be considered to repeat some of the tests of the first part of BEST 28 to get information about the impact of the prolonged storage time of more than 2 years on the results. The team suggested that the participants should discuss these issues during a conference call after this meeting. Results of these efforts will be shared before the Amsterdam meeting.

### **3. BEST #30: Cord Blood Assay Study – Results with Frozen/Thawed Samples (Brand)**

Dr. Anneke Brand presented an update on this project. In the first part of the study (BEST 30.1) aliquots of cryopreserved cord blood were sent around to eight laboratories using a dry ice as a coolant. The final analysis showed reasonable viability of the thawed cells but no proliferative potential as measured using the CFU assay. A letter to the editor entitled ‘Viability does not necessarily reflect the hematopoietic progenitor cell potency of a cord blood unit; results of an interlaboratory exercise of in vitro assays on frozen/thawed UCB containing no viable hematopoietic stem cells’ describing this highly interesting observation was submitted to *Bone Marrow Transplantation* in July 2006. The reviewer’s comments and editor’s decision to reject the manuscript were sent out on August 22. After short discussion it was decided to send the manuscript to another suitable journal after revision.

In the second part of her talk Anneke presented the results of BEST 30.2 as a follow-up study of BEST 30.1 (for details see the presentation on the BEST website). All eight participating sites were provided with frozen CB samples delivered in a temperature-controlled dry shipper device. Compared to study 30.1, higher CVs for the percentages of recovered NC after thawing were observed ranging from 17.9% to 24.1% (CVs in study part 30.1: <7%). WBC differentials of the thawed cells showed huge differences between sites depending on the type of hematology analyzers used. Six centers reported data on counting of nucleated red cells resulting in overall not comparable values (CV: 59%-91%). Counting results of CD34+ cells, measured either with or without 7-AAD, also proved to be highly different between sites. On the other hand, intra-laboratory variability for repeated testing of the samples was low for this parameter. At best only a low correlation of CD34+ cells and colony forming progenitors could be observed ( $R^2$ : ~0.4). Finally, viability testing resulted in CVs ranging from 27.6%-30.1%.

During the discussion of how to proceed with this BEST study #30, Anneke suggested to test the performance of different electronic cell counters for NC and WBC differentials of fresh and frozen cells on same sample for centers with access to more than one cell counting device. In addition, transient thawing of deeply frozen samples could be simulated as it actually may happen. She mentioned that each center could compare fresh with appropriately frozen and transiently thawed (10, 20, 30, 60, and 120 min exposure to 10% DMSO) and refrozen CB cells. To discuss these suggestions and to develop a study design, a conference call of the participating laboratories could be arranged after the Cape Town meeting. Results will be presented at the next meeting at Amsterdam.

#### **4. BEST #32: Transient Warming Events - Impact on the quality of frozen stem cell transplants (Reems)**

At the beginning of her presentation, Dr. Jo-Anna Reems stated that no clear definition of a transient warming event (TWE) of stored frozen stem cell products exists. A TWE might happen if a cryopreserved product is exposed to ambient temperature for longer than one minute. Jo-Anna presented own data on the thaw rate of a standard UCB unit (~30 ml) when placed at room temperature. These experiments showed a linear warming of the frozen product of nearly 19°C per minute. Therefore, a critical temperature limit of over -135°C is reached within less than two minutes (for more details see the presentation on the BEST website). To investigate TWEs and their impact on cryopreserved stem cell products in more detail, it was decided that, as a first step, a pilot study should be performed in one site (Puget Sound Blood Center, Seattle). Dr. Reems made suggestions of a draft study design that would be slightly modified based on the input coming from the team members. Multiple variables were identified possibly impacting the quality of products exposed to a TWE, such as DMSO concentration and other pre-freezing variables, or handling conditions of the frozen cryobag. Jo-Anna will provide the data from this initial study at our next meeting in Amsterdam. The CT team further agreed to investigate the feasibility of similar studies for other cryopreserved components to analyze the influence of external factors on cell proliferative capacity. Especially, the limitations of existing “read out” assays such as the CFU assay should be addressed, e.g. by investigating new test systems or by efforts in the standardization of already used QC test systems.

#### **5. BEST #29 B: Survey on transportation/shipping (Pamphilon/Szczepiorkowski)**

At the end of our last meeting in Barcelona, Dr. Pamphilon suggested a survey on transportation/shipping. Drs. Pamphilon and Szczepiorkowski have prepared a first draft of this survey in early July. This survey was piloted among the CT team members in the paper version. The median time for filling out the survey on paper was found to be approximately 15 minutes. There were several comments regarding the survey and some of them have been implemented prior to forwarding it to Ms. Eileen Selogie. Ms. Selogie prepared the first draft of web based survey prior to this meeting. During the meeting the group was able to review the survey live on line and made a number of very thoughtful suggestions. It was noted that the web design survey needs to be piloted again prior to wide distribution due to multiple suggestions. There was also a discussion on how to reach the largest number of responders without too much duplication. There was a sentiment that approaching FACT, AABB, ISCT,

JACIE could be sufficient, however, some suggested also forwarding it to national organizations to get a better representation. For this reason it was also argued that a paper copy of the survey (PDF format) should be also made available to improve participation from non-English speaking individuals.

Drs. Pamphilon and Szczepiorkowski will compile all the comments, some of which would be useful in the design of BEST 29 (see below), and implement them. After all the changes are made the survey will be piloted once again among the BEST CT team members (late September) and widely distributed afterwards (approximately early to mid October).

#### **6. BEST #29: Release Criteria Utilized with Cellular Therapy Products (Szczepiorkowski/Sacher)**

Dr. Szczepiorkowski presented the progress of the project. Similarly to BEST #29B the project has a corresponding timeline. The pilot paper survey was distributed for comments in early July. A number of comments have been made and some of them immediately implemented. A draft version of web based survey was prepared by Ms. Selogie in a week preceding the meeting. Dr. Szczepiorkowski presented a web based survey on line for comments. Some of the suggestions were similar to the ones discussed above. The survey will be updated with these comments and piloted among the CT team members prior to distribution. The timeline is similar to BEST 29B above. There was also a strong sentiment that a PDF format for the survey should be made available to responders so a copy of the submitted responses can be retained by the participants. The full presentation is available on the BEST website.

#### **7. Presentation of members' preferences for future cellular therapy projects (Szczepiorkowski)**

At the Seattle meeting the group reviewed the preliminary results of the survey on new projects. Ideas and suggestions were summarized in a PowerPoint presentation posted on the BEST website. Prior to the meeting in Barcelona the results were distributed and this time an additional scoring sheet was distributed as well. The team members were encouraged to score the level of enthusiasm and willingness to participate in several projects (see the BEST web site for details). The summary of the votes was presented by email after the Barcelona Meeting.

The results were discussed in Cape Town. The members of the group agreed to focus on projects which scored at least 70% in category 1 and 2 (i.e. an important topic and the members are either interested (1) or possibly interested (2) in participation.). There were four categories of projects; studies, survey/reviews, cellular therapy product source, and miscellaneous. The groups of projects were briefly discussed. The team members present agreed to, first, send around the selected projects and ask for suggestions to these projects. This will be followed by discussion (by email and conference call) of the most important projects. A number of projects (3-5) will be selected and leaders for each of these projects identified prior to next meeting. The plan is to have draft projects for discussion at the Amsterdam Meeting in April, 2007. The discussion also yielded two other observations: first,

the group would consider projects from collection to administration of cellular therapy projects and second, the main focus of our projects would be on standardization and analysis of methods and assays.

It was noted that the meeting was less well attended than the most recent meeting in Barcelona. The project plan will be submitted to the team members by email. It was also the last meeting with Dr. AuBuchon as a chair so it was announced that members of the CT team will be elected on Saturday afternoon. Dr. Lorna Williamson will send invitation letters to renewing and new members of the CT team.

The meeting was adjourned at 17:30.

### **Report: Clinical Studies Team**

*L. Williamson, N Heddle*

#### **Meeting Summary**

There were three topic areas that were discussed by the Clinical Studies Team. The first involved three presentations related to possible studies associated with dosing red cell transfusions. The second was quality monitoring related to plasma. The third topic area involved a number of studies related to platelets. At the end of the meeting there was also a discussion and presentation of possible future topics that the Clinical Studies Team could address. A summary of each of these areas is provided below. Each of the presentations referred to in this summary have been posted on the BEST website.

#### **1. Red Cell Dosing**

There were three presentations related to red cell dosing. All revolved around the issue of whether dosing red cells based on the hemoglobin content of the red cell unit would be a more effective way to provide red cell transfusions. The concept for this study arose from the paper published in *Transfusion* by Dr. Arslan and from the presentation that he gave at the Barcelona BEST meeting.

The first presentation involved a literature review related to this issue provided by Dr. Chris Prowse. It was noted that there appeared to be at least three different methods for calculating body surface area which is necessary to provide a red cell dosing approach. A recent study by Slight et al. which is published in *Transfusion* provides yet another method for calculating the body surface area. It was suggested that a comparison of all three methods could be done if some data were available. A summary slide of eleven studies that had been published was provided. Nine of the studies measured the hemoglobin content in grams per deciliter per unit. Two of the studies measured the volume of red cells transfused in milligrams per kilogram for one gram per deciliter. There were no studies that provided information on hemoglobin in grams per kilogram except for the information provided by Dr. Arslan. This review indicated that there is opportunity to explore further the issue of dosing red cells based on grams of hemoglobin per kilogram.

Since the Barcelona BEST meeting a small working group (Prowse, Hervig and Heddle) explored the feasibility of collecting some information to bring this idea to the Cape Town BEST meeting. A survey was sent to BEST members to determine what information was readily available both from Transfusion Services and from Blood Centers and the level of interest among BEST members to potentially participate if a pilot study was performed. This survey was performed using Survey Monkey and N. Heddle presented the results of the survey. There were twenty-eight responses to this survey with approximately half of the responses coming from Blood Centers and the other half involving Blood Centers and hospital Transfusion Services in the same location. Thirty-nine per cent of the Blood Centers who responded collected red cells using whole blood collections and forty-seven per cent used both apheresis and whole blood collection techniques. Most of the blood centers (sixty-one per cent) had information on the donor's hemoglobin value at the time of donation. The most frequent technique used to determine this hemoglobin was using HemaQue being performed on either venous or capillary blood. Most Blood Centers did not perform an actual hemoglobin value from the blood unit that was collected. When a hemoglobin value was performed on the blood unit, it was usually performed after the unit was manipulated (pathogen inactivated or leukoreduced), and was usually performed using an automated counter. All of the hospital Transfusion Services responding to the survey indicated that they did not receive a hemoglobin value from the Blood Supplier on units of red cells that were sent to their Transfusion Service. None of the hospitals routinely measured the hemoglobin value; however, approximately half of the hospitals would be able to measure the hemoglobin value as part of a BEST study. If measurements could be performed they would be done using an automated cell counter and performed after the concentrate was manipulated. Only forty-three per cent of the hospitals actually captured the indication for the red cell transfusion. Hospitals were asked to indicate whether they had pre- and post-transfusion hemoglobin levels on transfused patients and the weight and height of the patient that could be used to calculate blood volume. Hospitals indicated that pre- and post-transfusion count information was available either on all or some patients; however, the majority of hospitals did not have the height and weight of the patient for all transfusions. Of the seven transfusion services that responded, six indicated that they would be interested in participating in a BEST protocol if developed.

The third presentation in the Red Cell Section was by Dr. Tor Hervig. Tor presented a draft of a possible pilot BEST study to look at hemoglobin dose and patient matching. The draft protocol for this study was published in the Cape Town book and is available on the website along with the presentation by Dr. Hervig. The members of BEST provided some excellent feedback on the draft proposal and a small working group was formed to look at the feasibility of moving such a project forward. The individuals who indicated they would be interested in working on such a protocol were: Williamson, Lozano, Wendel, AuBuchon, Prowse, Hervig and Heddle. Some of the feedback received from the group during the discussion at the meeting included the following issues:

- exclusion criteria
- use of erythropoietin
- clarify which drugs would be included as exclusion criteria
- clarify thrombophilic disease (could this be taken out?)
- remove temperature?

- keep it simple
- splenomegaly should be included?
- ? positive DAT
- suggest that coagulation disorders be taken out

The group also discussed the values of limiting inclusion criteria versus an all-inclusive approach and the working group will give consideration to this. The group also discussed the objective of the study, whether it was related to improving stock management or improving patient outcome. There was a suggestion that children could also be included. It was suggested that baseline information should be collected on transfusion triggers and policies used for red cell transfusion. The measuring of hemoglobin value using the automated instruments does not appear to be an issue as there is slight variation between instruments on hemoglobin values. Optimal time for sampling was discussed:

- fifteen minutes versus twenty-four hours (if feasible 15 minutes would be good for outpatients)

It was also mentioned that two Canadian studies had addressed the issue of red cell dosing (TRICC Study and PINT Study); however, these were not addressed in the same manner that the draft protocol is suggesting. The question of when to standardize hemoglobin measurements was raised. Overall the working group received excellent feedback and all of these suggestions will be considered in any future protocol that is brought forward.

## **2. Plasma**

Dr. Dana Devine led a discussion related to possible options for BEST moving forward with performing some plasma studies. At the previous meeting it was determined that any members who had ideas for quality monitoring studies should contact Dana; however, no contacts to-date had been received. It was also re-emphasized that the Clinical Studies Team should liaise with the Safety Team to ensure there is not overlap between the survey being developed by Tinmouth and Stanworth. Dr. Devine summarized some of the possible questions that BEST could address such as:

- linkages to TRALI Studies/monitoring
- age of product at use
- survey of manufacturers' practices for frozen plasma and fresh-frozen plasma, including: standardized quality control; monitoring measures; pathogen reduction, etc.

A pre-survey survey was also suggested to understand the range of practices among BEST members who manufacture plasma products and blood banks that use them. Members were asked to think about the top three plasma-related issues that "keep them awake at night". It was also mentioned that there may be a possibility to link the plasma products with other studies which are being proposed (see Antibody Titration Study: AuBuchon) under the Section: Future Studies.

Other issues that came up in the discussion included: studying how long blood could be held before plasma is made; the ratio of red cells to plasma; issues around antibody titer in the plasma; what to do with cryoprecipitate if it is thawed and not used; a survey of indications for products; and the use of O plasma to Group A individuals.

There were a number of individuals on BEST who indicated that they would be interested in pursuing and working with Dr. Devine related to a plasma project. This included: Cardigan, AuBuchon, Elfath, Wendel, Hervig. Others that are interested are asked to contact Dr Devine directly.

### **3. Platelets**

The next presentation revolved around platelet studies which have been ongoing for several meetings.

#### Buffy Coat Survival Study

Dr. Williamson reported on the recovery and survival of autologous buffy coat platelets stored for seven days. They have done six determinations of recovery and survival of single buffy coat platelets stored in plasma/CLX. There were three of the six determinations where the recovery of fresh platelets was less than forty-three per cent. All six buffy coat platelets stored for seven days indicated that recoveries were all below thirty per cent. The survival studies on all six single buffy coat platelets at day 7 also showed significant variation, ranging from a survival on the fresh platelets of 134.8 hours to 214.6 hours. Percentage F/S ranged from twenty-eight per cent up to sixty-three per cent. Six studies have also been done with single buffy coat platelets stored in plasma/ELX. Variability still existed; however, it appeared to be less than the variability seen with plasma/CLX. (See presentation on BEST website.) Further work being done in this area is to look at platelets stored in Composol and to date 4 single donor buffy coat platelets have been evaluated

Dr. Slichter indicated that she is also interested in doing the studies. A company has agreed to supply bags and equipment; however, in return the company would like to use the information for FDA licensing purposes. The following discussion related to that issue occurred amongst the BEST members:

The clinical studies team had a discussion related to the role of BEST in conducting studies where the data may be used by manufacturers for regulatory submissions and product approvals (e.g., licensing). Manufacturers generally expressed their view that BEST could conduct studies which may be supportive of a specific manufacturer's regulatory submissions as long as the studies were not solely directed at work to support only one manufacturer's objectives and interests. BEST studies should continue to be directed at the development of common methodologies and/or approaches that may be generalized to other devices and applications. Data gathered during such a study will be available to the manufacturers for their use in regulatory applications, but on a non-exclusive basis. BEST will own the data and have all publication rights. It was recognized that specific projects will not always align perfectly with every individual manufacturing member's business objectives, but BEST activities will bring a general advance to the field of transfusion medicine which will be of benefit to all members.

#### BEST 33 Study

This study involves the comparison of radiolabelling and flow cytometry for calculating recovery and survival of platelets in patients. Ongoing work has been done related to this technique by both Williamson and Brand. The technique is based on HLA disparity between

donor and recipient and determining if this disparity can be used to identify the transfused patient population using flow cytometry and how it relates to radiolabelling studies. The purpose of the studies to-date are to validate in vitro detection of HLA-A2 discordant platelets; develop a method for absolute quantitation of transfused platelets using calibrant bead; compare the increment count in patients; and compare recovery and survival as assessed by indium labeling in patients.

Dr. Williamson provided an update of the studies to-date and these are summarized in her presentation on the website. Currently work includes: selecting the HLA-A2 monoconals to be used; use of other HLA monoconals provided by Dr. Brand; addressing the issue of “cross talk”; determine whether COST can handle flow cytometry data using events instead of gamma counts; and then present any progress made at the next BEST meeting. Once some of these issues have been worked out, Dr. Slichter is also interested in participating in studies to validate this approach. Dr Dumont is also very interested in participating.

#### Update on SToP Study

N. Heddle provided an update on the SToP Study. Recruitment has increased since Toronto has starting enrolling patients. At the time of the presentation, there were 98 patients who had been randomized. The group is still exploring the possibility of adding new sites to the study. It appears that Cincinnati may be able to participate as well as possibly another site in California. The Data Safety Monitoring Board is up and running. To date there have been ten serious adverse events reported and eight of these have been reviewed by the Data Safety Monitoring Board and reports issued. Two adverse events are still pending; however, the Data Safety Monitoring Board has not identified any issues. The adjudication process for bleeds is almost ready to be started through a web-based system and it will be tested by a few BEST members initially to determine if there are any other issues that need to be addressed. Canadian Blood Services was acknowledged for their ongoing support related to this study as they have committed funding for another year for the Canadian sites and with a review after a year in terms of continuing funding. Once approximately two hundred patients have been randomized onto the study a statistical sample size using the recurrent event analysis will be determined and at that time a decision will be made as to whether the original sample size of 550-600 patients can be decreased.

#### **4. Future Studies**

##### Reduction in Variation of Performance of Antibody Titration (AuBuchon)

Dr. AuBuchon presented a possible study to determine whether it is possible to standardize titration measurements. There have been a number of surveys in various countries including CAP surveys which have shown wide variation between laboratories when titrating the same antibody. Dr. AuBuchon presented a possible study design that could be used to address this issue. The details of such a study design are included in the presentation which is on the website.

##### Other Studies

Dr. Lozano raised the issue of doing studies in the area of treating thrombotic microangiopathies and microangiopathies; looking at alternatives to transfusions such as tranexemic acid, and wondered about the status of the Age of Blood study that was presented several meetings ago by Drs. Tinmouth and Hebert. There were discussions around all of these issues. Mo Blajchman reminded the group that there was a BARD study which is a multicentre clinical trial looking at four different alternatives to reduce blood loss and minimize transfusion.

N. Heddle provided an update on the Age of Blood study being conducted by Dr. Hebert . There was recently a meeting held in Toronto bringing together a group of international people to try and move this study forward. There are still numerous issues to resolve before the study will get off the ground, including obtaining appropriate funding for the study. One of the issues that may be presented at a future BEST meeting is the concept of looking at red cell inventory age distribution amongst different countries. N. Heddle suggested a potential future project related to the classification of acute transfusion reactions. A group at St. Jude's Children's Hospital has submitted a manuscript where they reviewed almost 600 transfusion reactions, classifying them both by the AABB classification and the common terminology criteria for adverse events (NCI). This group does not appear to be carrying this work any further but would be very happy and willing to participate with BEST if BEST was interested in looking at further standardization of acute reaction classification. The value of having a classification tool which is reproducible would allow for future comparison of studies performed in different centres in different countries.

### **Report: Transfusion Safety Team**

*S. Dzik, M. Murphy*

### **Report: Transfusion Safety Team**

*S. Dzik, M. Murphy*

Mike Murphy hosted the team meeting as Sunny Dzik was unable to attend the meeting. This was the first Transfusion Safety team meeting he had not attended, and his input was greatly missed.

#### **1. Bacterial Detection Survey; C Prowse & S Wendel**

Chris Prowse introduced this topic, and reminded the team that the objective of the survey was to determine what Blood Centers have done in terms of implementing bacterial detection strategies and what outcomes they had observed.

Silvano Wendel presented the data. The following conclusions were made:-

- There was no standardization for the method for skin disinfection
- Diversion methods were used by 37% of centers for sampling
- Automated culture methods were used by most centers
- Aerobic cultures were generally used

- The combination of aerobic and anaerobic methods provided a higher level of bacterial detection
- The use of sample diversion reduced the difference in bacterial detection between aerobic methods alone and combined aerobic and anaerobic cultures

*Next steps*

Silvano and Chris to:

1. Prepare a manuscript for publication.
2. Devise revised survey tool for application to a smaller group of transfusion services on a regular basis. The survey tool should ideally include collection of data on pathogenicity and patient outcome.

**2. PROBE-TM: Mike Murphy**

Mike Murphy indicated that the manuscript in the book for the BEST meeting was under consideration by *Transfusion*.

There was further discussion of the results of this study and agreement that the methodology would prove useful for future studies of the bedside transfusion process.

Nancy Heddle suggested that a follow up study could be a qualitative focus-group research study involving the participating nurses at PROBE-TM sites. A 3 step plan was suggested: 1) to develop a structured survey tool regarding the bedside check; 2) to review the results of the PROBE study with the nurses; and 3) to elicit nurses opinions on how the process could be improved.

*Next steps*

The team to consider by conference call the follow-up project suggested by Nancy.

**3. Statistical Process Control (SPC): Neil Beckman**

Neil Beckman updated the group on the SPC project. Following on the Collection of Blood Samples (COBS) study, the SPC project seeks to offer blood banks a user friendly validated tool for monitoring the performance of their sample labelling process. Real data obtained from hospitals in the UK, Canada (Nancy Heddle) and USA (Sunny Dzik) were plotted using control charts and these charts used with local boundary limits for the plotting of additional data.

Some important questions about the scope of the project were discussed:-

Question 1. Should the project focus only on mis-labeled samples; or should we focus on both mis-labeled and Wrong Blood in Tube samples ?

	Mis-labeled only	Mis-labeled & WBIT
Pro	* easy	* builds on prior BEST paper * more comprehensive * promotes regional hemovigilance
Con	* limited in scope * not highly novel	* requires more work to complete * need to develop logical approach to 'pooling' data

		among 'like hospitals'
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Question 2. Which SPC software tool should we plan to recommend?

A. Our own "home made" Excel-based SPC software tool?

B. A public domain free-software, which the end-user needs to configure in order to “set it up” for monitoring sample collection?

C. A “hybrid”? This might be a public domain free-software to be configured for the purpose of monitoring the sample collection process—in the form of a “template”

	Home-made	Public domain Free-ware	Hybrid
Pro	* already done	* no maintenance by BEST * better graphics	* very limited maintainence * advantages of commercial software * easier for hospitals since template is “ready to go” * capitalizes on our public web site
Con	* are instructions truly adequate for novice? * who will maintain, respond to questions	* requires additional work-- need to select and test out a program	* need to select a Free-ware program

*Next steps*

1. Produce a spreadsheet for distribution to those, who have already contributed data, to submit retrospective data on both mislabelled samples and WBIT.
2. Source and format an alternative, more robust software package.
3. Where appropriate i.e. where there are common practices for sample collection, pool data from multiple centers on WBIT, and obtain upper control limits for comparison.
4. Complete manuscript for publication.
5. Make methodology and software available on BEST website.
6. Consider establishing user group to support users and further developments.

**7. Joint Conference of America’s Blood Centers and the European Blood Alliance: Mike Murphy**

Mike Murphy drew the attention of the team to a joint conference organised by America’s Blood Centers and the European Blood Alliance on 13<sup>th</sup> and 14<sup>th</sup> November in London. Much of the program is of interest to the team. There are sessions on:-

1. New technology for prevention of mis-transfusion
2. Influencing blood usage
3. Managing the relationship between blood centers and hospitals
4. Improving blood availability

## **6. Assessing the decision to transfusion: Simon Stanworth**

Simon Stanworth presented a revised survey instrument designed to explore the methods by which hospitals connected to BEST collect information on the appropriateness of transfusion in hospital, specifically on RBCs, FFP, Plts, IVIG and recombinant VIIa.

### *Next steps*

1. Make final minor revisions to the survey tool.
2. Pilot before making available for BEST members and hospital contacts to complete.
3. Mo Blajehman suggested that the collection of guidelines for blood use from participating centers be considered. Future work could involve an analysis of whether these guidelines were evidence-based.

Mike Murphy closed the session with an open invitation to any BEST members to contact him or Sunny Dzik in order to discuss projects related to the overall theme of the proper use of blood transfusion and transfusion safety. Ziggy Szcapiorkowski suggested the team consider developing performance measures for key aspects of hospital transfusion practice, giving an example of their development for monitoring therapeutic apheresis services; this will be a major item for the agenda for the next team meeting.

## **Report: Conventional Components Team**

*H. Gulliksson, J. Hess*

Presentations from the team meeting are available at the BEST Collaborative Home Page, "Members only, Meeting presentations, Cape Town, South Africa, September 2006, Conventional Components". Please notice that these presentations are the sole property of the creator(s) of the slide set and are not for reproduction or distribution.

Hans Gulliksson welcomed the team, opened the meeting of the Conventional Components Team and chaired the first part of the team meeting focusing on red blood cells (RBC).

### **RBC Section Presentations:**

1. Hans Gulliksson gave a talk on the effects of whole blood (WB) storage overnight before the preparation of blood components. This technique is used in several countries and is associated with a number of logistic advantages, e.g. (1) All WB blood units will be available in the following morning allowing a very effective routine production, thus avoiding periods of waiting for WB to be supplied from different blood collection sites. (2) The staff for blood component preparation basically will be needed only during business hours and the workload can be evenly distributed over time. (3) The number of transports of WB from collection sites may be significantly reduced. (4) Furthermore, platelet yield from buffy coat (BC) for the preparation of pooled BC-derived platelet concentrates may be improved. He presented studies performed in two different sites, viz. Stockholm, Sweden (Gulliksson) and Amsterdam, the Netherlands (van der Meer). (See BEST book for

details.) Four different blood containers were used, either Terumo (Stockholm and Amsterdam), Fresenius or Gambro Atreus (Amsterdam) with inline leukocyte reduction red cell filters for the preparation of RBC, BC and plasma or alternative Baxter with WB filters for the preparation of RBC and plasma. Standard CPD solution and SAGM solution (100 ml) in one of the transfer packs were used as additives for RBC. All WB units were stored at room temperature, either overnight for 18-24 hours (test groups) or for up to 8 hours (reference groups). The only exception was a number units in one of the WB filtering test groups that were stored at +4°C overnight. Specific cooling plates were used to rapidly reduce the temperature from 37°C to room temperature after blood collection. Generally, the results from Stockholm and Amsterdam indicated significantly reduced levels in test groups (overnight storage at room temperature) of extracellular potassium, 2,3-DPG and pH. On the other hand, increased levels of ATP were seen in all test groups. When WB was stored overnight at +4°C before WB filtration, higher levels of ATP and hemolysis were noticed. The levels of extracellular potassium, 2,3-DPG and pH were similar to those of the reference. He also showed some very preliminary data after WB storage overnight using the ErythroSol red cell additive solution instead of SAGM as the storage environment.

2. Rebecca Cardigan presented a summary of studies performed by the Components Development Laboratory, National Blood Service, UK on effects associated with whole blood (WB) storage overnight before the preparation of blood components. (See BEST book for details.) This study included four arms, viz. (1) Reference units stored for up to 8 hours at room temperature (RT). Storage overnight for 24 hours without active cooling either at +4°C (2) or at RT (3). (4) storage overnight for 24 hours at RT with active cooling. The main significant differences in red cell quality when WB was stored overnight related to levels of 2,3 DPG and ATP. 2,3 DPG was best preserved if blood was processed on the day of collection or after storage at 4°C. However, it was not clear what, if any, clinical significance this would have, since 2,3 DPG is thought to be regenerated 48-72 hours following transfusion of red cells. By the end of red cell storage, levels of ATP were not significantly different between WB storage methods. All units in this study had a red cell ATP content of >2 umol/gHb. It has been suggested by others that a red cell ATP that meet that criterion is associated with good recovery of red cells in vivo.
3. AuBuchon and Dumont presented an update on BEST #37. (See BEST book for details.) They noted that obtaining complete data sets was very difficult, and that this would impeded analysis according to the proposed FDA criteria. Instead, they proposed a bootstrap approach and illustrated how that would work. The group was supportive of applying this method. They will next contact study sponsors to verify the data that has been received and discuss the proposed analytic approach with the FDA before actually proceeding to an analysis. They also discussed the comparison of single- and double-label calculation methods. With large data sets, a statistically significant (although small) difference can be seen between the calculation methods, particularly at the extremes of results. Further analysis of the difference will be undertaken when the data set is completed.

4. Seghatchian followed with a presentation entitled “BEST pilot study on new platelet storage lesion index, evaluated by changes in platelet cellular indices, using the paired (+/-EDTA) sampling protocol: comparison with changes in the pH, swirling score and the in-vivo response.” This presentation replaced “Status of frozen RBC and new equipment”, since neither Hess nor Popovsky could attend the meeting. Seghatchian described studies from two different laboratories using platelet concentrates (PC). (See BEST book for details.) The French group (Cazenave) focused on pooled buffy -coat -PC stored in T-Sol and Intercept -treated -PC stored for 7 days using two different cell counters, based on impedance and optical principles. The Canadian Group (Heddle) investigated random donors -PRP-PC before and after pooling, using coulter LH 750 (samples required predilution) and assessed the clinical response in patients. He conclude that: (1) The absolute values of the fresh citrated samples are usually less consistent and much lower than platelet counts values obtained using EDTA -added samples. (2) The impedance technique, used in this study gives a lower absolute value than the optical method on the same samples and in the same laboratory. (3) The average dMPV value of INTERCEPT at day 2 is equivalent to that of day 3 in T-Sol, suggesting that INTERCEPT had a limited effect on platelet quality. (4) Some very low values were observed in citrated pooled PRP-PC samples, whereas the EDTA added samples values were acceptable. (5) The patterns in changes of the proposed new platelet storage lesion index ( dPLT, dMPV, dPDW) parallel changes in pH & swirling and possibly 24 hours CCI. (6) Due to the limited number of data points it is difficult to predict the accuracy of each individual parameter and their relationship with in vivo outcome, requiring more data. For this reason, an additional preliminary evaluation will be performed in one site (Hervig in Bergen, Norway).

### **Granulocyte and Platelet Section Presentations:**

Granulocyte concentrates are regaining interest for treatment of neutropenic patients with persistent bacterial or fungal infections that do not react to antimicrobial agents. Two presentations were given covering the topics of producing, storing and determining quality of granulocyte concentrates.

1. Cardigan gave an overview of the in vitro tests that could be used to investigate the quality of granulocytes, in the light of collecting and storing granulocyte concentrates. A number of tests are commercially available, but they have been designed for whole blood, not for granulocyte concentrates. Important tests are determination of viability, chemotaxis, phagocytosis and oxidative burst/killing. Flow cytometric methods are usually applied. As in vivo tests, count increments can be used, although the granulocytes quickly migrate to the tissues. Other methods are radiolabeling studies, ‘skin windows’, and counting granulocytes in mouth washes. The pro’s and con’s of the procedures were discussed. Cardigan also shared data of obtaining granulocyte concentrates from buffy coats. The background is that in the UK, undirected donors cannot be stimulated with G-CSF in order to collect sufficient granulocytes from one donor. Ten buffy coats need to be pooled to obtain a sufficient number of neutrophils.

- Viability and phagocytosis capacity were maintained for 42 hours, but chemotaxis declined over time. It was acceptable for up to 18 hours after donation. An observational clinical study is currently ongoing, studying increments, infection markers, and adverse events, including alloimmunization.
2. Van der Meer then continued describing their efforts to obtain granulocyte concentrates from G-CSF stimulated (family) donors to treat pediatric patients. Stimulation leads to a 10-fold increase in neutrophil count. He noted that there are very few specifications for granulocyte concentrates, only volume and number of cells, though the number of red cells and platelets in the concentrates is high. A number of centers is optimizing collection of granulocyte concentrates, and a survey is to be conducted amongst these centers to determine the state of the art with respect to collection, storage and QC.
  3. At the Barcelona meeting, the results were presented for the platelet send around study (BEST #35). Some concern was expressed about sample stability; a send around with fresh unfixed samples will be performed using the same platelet levels as in the BEST-NEQAS send around to determine if sample stability is of concern. When these data are evaluated, a manuscript will be drafted. Based on ICH guidelines, Van der Meer is writing a platelet counting guideline. A proposed draft procedure has been developed, and a number of BEST centers have been asked to perform this procedure. Fifteen centers responded, and in general, the procedure seemed doable and the proposed acceptance criteria seemed adequate. Loose ends were discussed, and the most important item was development of a 'gold standard' platelet counting procedure to obtain an accurate platelet count. After initial problems in setting up this flow cytometric counting procedure, the latest results from the Groningen center are encouraging. The group emphasized that the guideline should not be too specific; it should be useful for a number of years to come. A final draft will be in the next BEST book.

### **Brief summary the last term of four years:**

Since this was the last meeting with Gulliksson as the team leader, he summarized the studies performed in the Conventional Components Team during 2002-2006 by presenting a list of publications from the team. He also thanked the members for the past years, their outstanding contributions and the excellent co-operation within the team.

### List of publications:

1. BEST #17 (A). Storage of platelets in additive solutions: A pilot in vitro study of the effects of potassium and magnesium. Gulliksson, AuBuchon, Vesterinen et al. Published in Vox Sanguinis 2002;82:131-136.
2. BEST #17. Storage of platelets in additive solutions: A multi-center study of the in vitro effects of potassium and magnesium. Gulliksson, AuBuchon, Cardigan, van der

- Meer, Murphy, Prowse, Richter, Ringwald, Smacchia, Slichter, de Wildt-Eggen.  
Published in *Vox Sanguinis* 2003;85:199-205.
3. BEST #17. The influence of platelet additive solutions on cytokine levels and complement activation in platelet concentrates during storage. Cardigan, Sutherland, Wadhwa, Dilger, Thorpe. Published in *Vox Sanguinis* 2003;84:28-35.
  4. BEST #17. Storage of platelets in additive solutions: The effects of magnesium and potassium on the release of RANTES, beta-thromboglobulin, platelet factor 4 and IL-7 during storage. Shanwell, Falker, Gulliksson. Published in *Vox Sanguinis* 2003;85:206-212.
  5. BEST #20. Effect of interruption of agitation on in vitro quality of platelet concentrates: Van der Meer, Gulliksson, AuBuchon, Prowse, Richter, de Wildt-Eggen. Published in *Transfusion* 2004;44:69A.
  6. BEST #20. Interruption of agitation of platelet concentrates: effects in vitro parameters. Van der Meer, Gulliksson, AuBuchon, Prowse, Richter, de Wildt-Eggen. Published in *Vox Sanguinis* 2005;88:227-234.
  7. BEST #20. Interruption of Agitation of Platelet concentrates – A multi-center in-vitro study by the BEST Collaborative on the effects of shipping. Dumont, Gulliksson, van der Meer, Nixon, de Wildt-Eggen, VandenBroeke, Liefing, Herschel, Roger, AuBuchon. Manuscript.
  8. BEST #21. Platelet storage solution effects on the accuracy of laboratory tests for platelet function – A multi-laboratory study. VandenBroeke, Dumont, Hunter, Nixon, Murphy, Roger, Herschel, AuBuchon, Gulliksson, Dengler, Hornsey, Prowse. Published in *Transfusion* 2002;42:53-S-54S
  9. BEST #21. Platelet storage solution effects on the accuracy of laboratory tests for platelet function – A multi-laboratory study. VandenBroeke, Dumont, Hunter, Nixon, Murphy, Roger, Herschel, AuBuchon, Gulliksson<sup>4</sup>, Dengler, Hornsey, Prowse. Published in *Transfusion* 2004;86:183-188.
  10. BEST #23. In vitro pH effects on in vivo recovery and survival of platelets: an analysis by the BEST Collaborative. Dumont, AuBuchon, Gulliksson, Slichter, Elfath, Holme, JM Murphy, Rose, Popovsky, S Murphy. Published in *Transfusion* 2006;46:1300-1305.
  11. BEST #26. Interlaboratory comparison of red-cell ATP, 2,3-diphosphoglycerate and haemolysis measurements. Hess, Kagen, van der Meer, Simon, Cardigan, Greenwalt, AuBuchon, Brand, Lockwood, Zanella, Adamson, Snyder, Taylor, Moroff, Högman. Published in *Vox Sanguinis* 2005;89,44-48.

12. Platelets from pooled buffy coats: an update. S. Murphy for the BEST Collaborative. Published in Transfusion 2005;35:634-639.

### **Minutes of the Meeting of the Executive Committee**

September 2, 2006  
Cape Town, South Africa

The Executive Committee convened immediately after the BEST XXXII meeting. Present were J. AuBuchon (chair), L. Dumont, H. Eichler, H. Gulliksson, N. Heddle, M. Murphy, Z. Szczepiorkowski, P. van der Meer, L. Williamson and S. AuBuchon (staff).

The outgoing chair, Jim AuBuchon, thanked the Team Leaders for their diligent efforts and strong support over the past four years. He indicated that he would “wrap up” the details from this meeting and then turn over the chair functions to the incoming chair, Lorna Williamson.

Williamson opened the discussion of future planning by continuing the discussion that occurred in the BEST meeting about whether and how BEST might facilitate improvement of transfusion services in developing countries. This was part of a larger consideration of a review of strategic directions. The group was of the general opinion that BEST performed optimally when it was attempting to extend knowledge. Further consideration will occur at the next meeting.

Time was also given to considering how to organize BEST meetings in the future. One approach considered was to have the Executive Committee convene at lunch before the BEST meeting itself and then announce the new studies and publications at the subsequent, afternoon BEST meeting along with, perhaps, a guest speaker. This speaker might be accorded an honorific title related to Scott Murphy. The team meetings would occur with the same pairings as at present.

The majority of the meeting was spent assessing the membership list for the next round of BEST. Most slots were filled, but Williamson was going to follow up with several team leaders as they finalized their choices.

The new administrator for BEST will be Gill Cook, Williamson’s PA. She will be engaged on a self-employed basis using her current salary schedule, with periodic invoices to be paid. The Executive Committee agreed to provide her a laptop computer. Williamson thanked Susan AuBuchon for her assistance in the handover.

AuBuchon reviewed several financial matters. The Executive Committee agreed to increase Manufacturer Member dues for 2007 to \$20,000, thought to be the first increase in dues in 15 years.

There was agreement that team minutes would be provided by the end of the month to AuBuchon. New studies that were assigned numeric designations included:

- 40: Reduction in variation of performance of antibody titrations (AuBuchon)
- 41: Whole blood overnight storage (Gulliksson/van der Meer/Cardigan)
- 42: TM-PROBE survey (Murphy)

Study #32 was redesignated as Transient Warming Effect on Stem Cells (Reems). A second part was added to Study #29, the Transportation/Shipping Survey (Pamphilon/Szczepiorkowski). Study#30 was re-assigned to Brand.

The Executive Committee agreed to support the Pathogen Reduction Consensus Conference with a donation of \$5,000. Williamson and Dzik will represent BEST on the steering committee.

Williamson shared details of the BEST XXXIII meeting scheduled for Amsterdam, April 27-28, 2007. BEST XXXIV would be scheduled in conjunction with the AABB Annual Meeting in Anaheim, California in October, 2007. The Spring, 2008 meeting (XXXV) was tentatively slated for Cambridge, and thought was given for BEST XXXVI to be held in Montreal in conjunction with the AABB meeting there in October, 2008.

There being no further business to conduct, the meeting was adjourned at 6:15 pm.