Joint Meeting of the UKBTS/NBSC Standing Advisory Committees on Blood Components and Care and Selection of Donors.
MRC Clinical Trials Unit, 17th May 2002

1) Present

Rekha Anand	Michelle Ashford	Cynthia Beatty
Neil Beckman	Sylvia Benjamin	Frank Boulton
Rene Braithwaite	Rebecca Cardigan	Tom Crusz
Steve Devereux	Khalid El-Ghariani	Joan Fitzgerald
Terry Flood	Katy Forman	George Galea
Moji Gesinde	Rachel Green	Jean Harrison
Catherine Howell	Jane Butler	Saber Bashir
David Hutton	Sheila MacLennan	Ellen McSweeney
Yvette Makar	Edwin Massey	Brian McClelland
Morris McClelland	Mike Murphy	Alec Mijovic
Gordon Nicholson	Derwood Pamphilon	Lizanne Page
Rachel Pawson	Chris Prowse	Graham Rowe
Nigel Russell	Josie Scally	Neil Smith
Janet Sutherland	Clare Taylor	Craig Taylor
Tim Wallington	Lorna Williamson	Keith Wilson
April Totham	Cristina Navarrete	

2) Introduction and Chair for morning session - Lorna Williamson

Aims of the day: LW had previously circulated a series of questions / issues related to both donors and patients (attached). The aim of the day was to try and agree a clear way forward for each of them.

3) Questions/Comments on Tim Wallington's Presentation: Quality Assessment

Key points: Numbers of granulocytes are most important in determining outcome, but if we feel that granulocyte transfusion is clinically important we must be able to quality control the components.

Q: S MacLennan - Where does Red Book specification come from?
A: S Devereux and D Pamphilon - work extrapolated from work in dogs that suggests this is dose required.
A: J Harrison - yield is not related to starting count.

Q: G Galea - how well do markers reflect numbers of intact neutrophils?
A: T Wallington - thinks they do.

4) Questions/Comments on Joan Fitzgerald's Presentation - Overview from the Literature on Granulocyte Efficacy

Key points: Review of studies of the use of granulocyte transfusions with and without the use of donor priming with GCSF / steroids. Benefit appears to be related to dose, which in turn is related to the use of priming agents. Use of GCSF frequently causes minor and occasionally severe symptoms in donors. Steroids have been associated with development of posterior subcapsular cataract.

Q: L Williamson - Study by Peters with range of granulocyte doses – is there a correlation between dose received and patient response?
A: J Fitzgerald – There was no correlation in outcome between patients receiving donations from GCSF-stimulated donors compared with those receiving predisolone (dose is more important than agent used)

Q: J Harrison - Were donor and patient white cell antigen matched?
A: J Fitzgerald – no.
Comment: C Navarrete - Depends on whether HLA or granulocyte antibodies are present as to whether matching is necessary.

Q: L Williamson – Regarding the donors developing cataract - how many donations did they give and how much prednisolone were they exposed to?
A: J Fitzgerald - No correlation between amount of prednisolone exposure or number of procedures and presence/absence of PSC. All donors exposed had >15 doses of 60mg at time of examination. Mean no of granulocyte donations (therefore doses) =26, median 23, range 17-46, carried out over mean length of time 8.5 years. Although the donor who received the highest total dose of prednisolone developed a PSC the other 3 donors with PSCs received the lowest cumulative dose.

Comment: E Massey - Germans exclude donors incompatible by XM - have not being doing so in UK.
A: C Navarrete - Will depend on whether patient is alloimmunised.

5) Questions/Comments on Rachel Green' presentation - Experience with buffy coat granulocytes

Key points: Presentation of the recent experience in Scotland of providing buffy coats instead of apheresis granulocytes.

Q: K Wilson - Were components supplied on consecutive days?
A: R Green - Yes

Q: C Navarrete - Did the patients develop antibodies?
A: R Green - None were screened (but were not refractory to platelet transfusion)

Q: K Forman - What would your response be to a request for granulocytes for a patient with no focus of infection?
A: R Green - Would supply.

Q: A Mijovic – Did you select CMV negative components?
A: R Green - Matched components for patient's CMV status.

Q: S Bashir - Were buffy coats irradiated?
A: R Green - Yes.

Q: L Williamson – Was a red cell crossmatch performed?
A: R Green - Done by hospital lab with buffy coat pool. Antibody screen alone is preferable.

Q: N Smith – Were there any problems with high Hb?
A: R Green - No, but the red cell content tended to replace sampling loss.

Q: S Devereux - What was the time from collection to time of infusion?
A: R Green - Most < 6 hours but some supplied to hospitals further away probably longer.

Q: L Williamson – Was the HCV NAT test done retrospectively?
A: R Green - Yes, none found to be positive (tended to be 'old' donors).

Comment: R Cardigan - Maybe it is not a bad thing that there is no rise in WCC as white cells being used up?

Q: L Williamson – Did you notice a difference in pattern of fever following transfusion, i.e did the component itself cause fever?
A: R Green - Not really.

Comment: J Harrison - Should be giving high doses collected by apheresis, but she thinks not possible in practice if buffy coats are shown to be efficacious as not enough donors. L & SE receive a lot of requests currently for which there are not enough apheresis donations and buffy coats are supplied instead - this year already at least 9 requests for BCs. Should think of yields as per m^2. If have to select recipients to receive apheresis components should choose children.

J Harrison presented slides on difference between apheresis granulocytes and BCs.

Key points: Thinks will always need both. May be able to improve granulocyte yield in BCs. We should aim to select product according to patient characteristics.

Comments:

M Ashford - Agrees about feasibility of working to optimise yield of BCs. May also be able to use starch sedimentation in vitro.

C Navarrete - Antibody status of patient is important. If negative, could use BCs. If Ab positive then should have selected apheresis product.

L Page - When supplying granulocytes current practice is to select apheresis donors during the working week but use BCs at weekends.

C Navarrete - That is a separate issue - providing on-call.

J Harrison - If red cell antibodies are present then need to use BCs as apheresis donors not red cell phenotyped.

A Mijovic - Likes idea that scope for more products - should take further and think of partnership with hospitals - some may be able to produce granulocytes having given GCSF to donors.

J Harrison - Reiterate that still not enough donors.

A Mijovic - May be able to use family/friends too.

6) Questions/Comments on Derwood Pamphilon's Presentation Prophylactic Granulocytes for High Risk Bone Marrow Transplant Patients

Key points: Presented the cases of 2 patients undergoing BMT who were at high risk for fungal infection, who received prophylactic granulocyte transfusions.

Q: L Williamson - How many components did each patient receive?
A: D Pamphilon – One 5, the other 4.

Q: M Murphy – Did the neutrophil count remain high at 24 hours?
A: D Pamphilon - No

Q: M Murphy - Did the worst response correlate with worst post transfusion course?
A: ??

Q: K Forman - Any information on monocyte content?
A: D Pamphilon - No

Q: C Prowse – What was the size of the patients?
A: D Pamphilon - all 50 -70 kg.

Q: N Russell - How easy it is to organise to collect the donations?
A: D Pamphilon - Pre-planned so easier than ad-hoc. Sometimes problem if Bristol unit busy. If believe worth doing then need to be able to.

Comment: N Russell – It is a logistical problem just screening potential donors.

Q: S Devereux – Did the components immunise against minor HLA Ags?
A: D Pamphilon - Didn't give this much thought. Patients were probably severely immunosuppressed anyway.

Q: R Pawson - Could granulocytes contribute to 'cytokine storm' and lead to worsening GVHD?
A: D Pamphilon – Not seen. Very little bacterial infection in these patients. Some reactivated CMV.

Q: L Williamson - Were all components CMV negative?
A: D Pamphilon - CMV matched.

7) Question/Comments on Terry Flood's Presentation
Experience in Congenital Disorders of Granulocytes

Key points: Presented problems associated with the care of these patients. He and his colleagues are keen to be able to get GCSF stimulated apheresis granulocytes to support patients with Chronic Granulomatous Disease during the aplastic phase of bone marrow transplantation.

8) Questions/Comments on Rachel Green's Presentation
Review of German Trial Protocol

Key points: This study has now started. Entry criteria and protocol were outlined.

Q: M Murphy – Do we have any information on numbers so far recruited?
A: R Green - No.

Q: B McClelland – Is there any attempt to blind the study?
A: R Green - No.

Comment: J Harrison - Not very high number of granulocytes - i.e. $2x10^{10}$ 3x weekly. Need to know what dose is actually given.

Q: S Devereux – Are steroids being used?
A: R Green - No.

Comment: E Massey - Donor complications are planned to be reviewed either very early or very late – there should also be an aim to collect data on medium term complications.

Q: S Benjamin – Is patient consent being obtained?
A: R Green - Yes.

Comment: S Benjamin - Visits of donors appear excessive - 4 in total per donation.

9) Questions/Comments on Professor Nigel Russell's presentation
Experience with G-CSF in Unrelated PBSC Collections

Key points:

Q: C Navarrete - Are donors quoted just from Anthony Nolan panel?
A: N Russell - Yes

Q: C Navarrete - How many?
A: N Russell - Around 180 donors in last year.

10) Questions/Comments on Derwood Pamphilon's Presentation Use of G-CSF in BBMR PBSC Donors

Key points:

Q: N Russell - Do you mention risk of splenic rupture on information sheet?
A: D Pamphilon - Yes

Q: L Williamson - What happens if a donor reports splenic pain?
A: D Pamphilon - Ultrasound and have discussion on whether to proceed.

Q: D Hutton - Would spleen size decrease if the patient undergoes leucopheresis?
A: D Pamphilon – One can use a formula to work out size of decrease.

Comment: D Hutton – You could measure splenic volume before/after.

11) Questions/Comments on Dr Steve Devereux's Presentation Experience in Recruiting Volunteer Donors to a Trial of G-CSF Mobilised Granulocytes.

Key points:

Comments:

L Page - Approached 50 donors. All said no, mostly because of travel to UCH which included taking 2 days off work. Four donors went to discuss with their GP and two were advised that they should not go in a drug trial.

J Harrison - If doing again could make more convenient e.g. do at Edgeware Clinic, use Care at Home to give G-CSF.

L Page - Most stressed that would consider again if more convenient.

12) Questions/Comments on Sylvia Benjamin's Presentation NBS Experience with Granulocyte Collections from Family/Friends

Key points:

No questions.

Chair of afternoon session: Frank Boulton

DISCUSSION OF QUESTIONS ON WHICH DECISIONS ARE NEEDED.

Patient-related

1. Is there a place for therapeutic granulocytes for the management of infected patients with dis-orders of neutrophil number/function?

C Navarrete - Not convinced that we have demonstrated a place for therapeutic granulocytes.
Are further steps needed before deciding?

J Fitzgerald - Look at situation to use in. What overall survival in particular conditions - need to confine indications to proven/definite indications.

F Boulton - Indications possible - focus on actively infected patients.

J Harrison - Don't know whether effective. Need to do trial - still anecdotal.

J Fitzgerald - What do we say to family and relations who want to donate?

S Devereux - Heard about potential problems during meeting. Should not consider introducing extension to provision of apheresis granulocytes without 'proof'. Should we collaborate in other trials or set up our own?

E Massey? –Should we refer to NICE?

F Wilson - Agrees that not sure whether granulocyte transfusion is effective. Prof. Alan Burnett would be interested in adding a granulocyte 'arm' to one of the MRC adult leukaemia studies. It needs to be shown if they are useful in prophylaxis and/or proven infection.

B McClelland – The UKTS already has some experience. Can we make progress in defining clinical indications for trial?

D Pamphilon - Don't need to reinvent the wheel. A group have already devised a section for Red Book on how to approach donors – this is written but not published and covers situations where it is reasonable to provide granulocytes. (DP can circulate)

F Boulton – Agreed. Need to recover and circulate. **Action: DP send to FB**

B McClelland - Are the reasons for providing granulocytes 'political' or because there is proven efficacy?

R Green - Need to choose condition which is likely to benefit and look at e.g prophylaxis.

L Williamson - Could you do randomised trial of acutely ill patients anyway?

F Wilson - Induction therapy AML - approx 10% will die. If randomised up front may be able to see difference.

T Wallington - Most dangerous immune deficiency does not have granulocytes. How can you carry these patients through BMT?

S Devereux - Can learn from way news drugs introduced - compassionate use or all other use in trial only.

D Pamphilon - Agreed - already supplying grans for clinical use but if withdraw may need to be able to use too.

F Boulton - Feeling that trial should be done but need compassionate use meantime.

T Wallington - Most of what is done now is 'lip service' only.

J Harrison - Currently only providing for compassionate use only.

F Boulton - What are the best indications which should be considered for trial?

J Harrison - Trial set up by SD good - now may be able to do it. If recruitment were to be attempted again making donation more convenient may be able to. Also include BCs.

K Forman - Conditions for compassionate use need to be rigid - if clinicians already using either apheresis granulocytes or buffy coats it will be difficult. Need to state in which conditions components will not be provided.

D Pamphilon - In BBMR have adjudication panel for DLI - ? something similar?

L Williamson - Cannot design trial here. But if group of people could collaborate would be good. One of questions would be what components to include. Need to include BC - "challenging" to meet every request with apheresis. Should UKTS apheresis donors be approached in advance and signed up - or family/friends?

B McClelland – Advancing of knowledge will be iterative. Should decide that if legitimate trial then should ask donors to do. Unless there are very good reasons not to we should use donors.

T Wallington - Should look for trials to test efficacy of different components too. Not necessarily in same trial.

D Pamphilon - Useful group would be BSBMT to include David Marks (Chair).

F Boulton – Suggest DP and SD get together with BSBMT to consider trial.

L Williamson - Could be in collaboration with MRC/NBS Clinical Studies Unit.

2. Assuming availability of pooled buffy coats, non-stimulated apheresis granulocytes and G-CSF stimulated granulocytes, what is the optimum product and dose?

F Boulton - "Unethical" almost to get family/friends.

S Devereux - Should not exclude. If managed properly can be done (done through Blood Service).

N Smith – Family and friends may be motivated for wrong reasons.

S Devereux - Why?

N Smith - Same reason as other directed donations. Thinks we have enough donors.

L Williamson - Have we got enough?

M Gesinde - Donors to be used to collect granulocytes are platelet donors. Not adequately resourced - would take time to get proper panel.

C Beatty - If decide that they do work no danger to donor from BCs but is for apheresis.

F Boulton - Need to look at both routes. If using BCs will have to adjust processing.

G Nicholson - 10 years since we started making BCs on purpose. Currently BC is a 'by product'.

F Boulton - WP of UKBTS may be required to look at processing.

M Ashford - What will be release criteria e.g. mandatory, NAT?

F Boulton - Time problem same for both components. Apheresis donors may have been tested more recently.

D Hutton - Existing risks of micro transmission are extremely small.

F Boulton - Clinicians need to understand that components will be released only after testing.

S Benjamin - If can show that BCs work should donors be exposed to extra risks?

L Williamson - One question is how many times can a donor donate and what would be impact on production of other components e.g platelets.

J Harrison - At moment not using stimulated volunteer donors but are using non-stimulated donors and BCS. Which patients should we allocate apheresis donors too?

L Williamson - Could provide different components from different sites.

J Harrison - Could use apheresis for paediatrics.

J Fitzgerald - Tried BCs in small baby and had problem with erythrocytosis.

N Smith - Could starch sediment BCs.

T Wallington - Don't know how granulocyte function affected by all these manipulations - may be able to assess in vitro.

F Boulton - Buffy coats - regarding treating BCs should be looked at - ? future WP.

B McClelland - ? Is composition of BCs same as apheresis granulocytes. BCs are "white cell enriched bags of blood".

F Boulton - Agree that needs better understanding of what is in the bags. Probably different between apheresis machines. Need to look at this. **Action Tech WG.**

L Williamson- Need to get assays to monitor function sorted out first.

R Cardigan - Don't know what assays mean - need to be set up and validated first.

D Pamphilon - Group should look at storage too.

S Devereux - In-vitro testing and function - if incubate grans with G-CSF looks like function increased but not comparable to in-vivo.

M Gesinde - Question on whether we should collect from family/friends - need consensus.

F Boulton - "Absolutely". Services to Donors does not want this service dismissed. Families need very sensitive handling. May need to identify liaison teams.

E Massey - At Bristol, the family organise potential donors who have blood taken pre-counselling.

D Pamphilon - Hospitals don't like doing it. Need to assess our role.

J Fitzgerald - Who should obtain consent to G-CSF?

S Benjamin - Part of the reason why hospitals will go along with using family donors is that they are clinicians too and see the need.

C Howell - Amount of time/resourcing should not be under-estimated.

L Williamson - Confirmed AM's view that NBS and hospitals are all part of NHS. Really resource problem currently.

A Totham - Developed clearly defined roles at Bristol. 4 steps to assessment/donation.

F Boulton - Some of pressure is because there is a severe condition which is difficult to treat.

C Navarrete - Who takes responsibility for friends - other parts of NBS/NHS get strict consent for allowing donation.

F Boulton - If donor presents it is responsibility of NBS to get proper consent. Some of donors may be paid. Donor/family may not be being truthful but this may not be apparent.

T Wallington - Could give apheresis group responsibility for formulating set of rules.

J. Butler – May be able to use platelet donors who don't meet platelet specs.

R Green - SNBTS ventures hospital based - would provide grans if asked. Don't ask family to provide blood and also not grans.

T Wallington - If there is a service for grans don't need to use family / friends.

R Green - Would turn away volunteers if did not meet donor criteria, not otherwise.

G Galea - Issue of directed donor - needs to be balance.

E McSweeney - Irish have done grans on stimulated donors from friends/family. Unrelated donors - ? insurance for them. Tried to set up Ethics Committee which was not successful because of lack of appropriate insurance.

L Williamson - Don't have UKTS Ethics Committee but indemnity for clinical trials provided by UKTS.

Clinical situations in which granulocytes should be considered – Chair L Williamson

All – need to define those situations for which we do not provide granulocytes.

B McClelland – What are our duties? There may be a problem about us saying no.

F Boulton – There are areas where we say no if deleterious to donor - also offer opinion as to other components.

S Benjamin - Need to have unified view.

D Pamphilon - Adjudication panel would be useful.

T Wallington - Should not allow situation where "anyone" can transfuse grans in hospitals.

K Wilson - BCSH are asking for any ideas for guidelines.

L Williamson - Suggest to BTBMT and BSH (Transfusion Task Force and Haematology Task Force) that look at guidelines.

C Navarrete – Guidelines should include the need for patients to be tested for antibodies.