

REPORT OF MEETING

Convalescent plasma and Ig-based therapies for influenza treatment Monday 7th September 2009, The Wellcome Trust, London

1. On 7th September 2009, the Wellcome Trust held a meeting of experts from the scientific and clinical communities to discuss and explore possibilities for conducting a trial of convalescent plasma and/or Ig-based therapies in the near term for seriously ill patients hospitalized with pandemic H1N1 illness. The meeting was convened by Jeremy Farrar, David Menon, Gail Thompson and Fred Hayden. Preliminary discussions were held among interested parties on Friday 4th September to address issues related to procurement, storage, and distribution of relevant blood products and on Saturday 5th September to work up a draft outline protocol in preparation for the main meeting on the 7th September. A list of meeting participants can be found in Annex A.

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SUMMARY OF PRESENTATIONS

Introduction - Frederick Hayden

2. Fred Hayden welcomed all to the meeting and summarised the rationale for holding the meeting. Information was presented on various studies describing the experience of protocols using sera in patients during the 1918 influenza pandemic. A literature review¹ of the use of convalescent blood products in treating pneumonia patients hospitalised in 1918-20 yielded eight studies containing a total of 336 treated patients, with 1,219 controls receiving supportive care. None of these studies were blinded, randomised or placebo controlled. Patients usually received 100-250ml doses of convalescent serum or plasma, given 1-7 times a day over 1-3 days, with the majority having received only two doses (500 ml). Overall findings indicated a positive outcome on mortality (i.e. overall crude mortality reduced from 37% to 16% in six studies). The mortality benefit appeared to be limited to those treated within 4 days of a pneumonia diagnosis. Of note, initial clinical improvement was often prompt occurring within 1-2 days. While the mechanism of action was uncertain, no benefit was reported in studies using non-immune blood products, an observation which suggested that passive transfer of specific immune factors was important. In any case the apparent mortality benefit warrants further investigation in the contemporary situation.

Recent papers describing monoclonal antibody (mAb) treatment for H5N1 infections were also outlined. In mice, mAb treatment was seen to decrease morbidity and mortality when used either prophylactically or post-infection². Several case reports have also described survival with convalescent plasma therapy of H5N1-infected patients who had clinical progression despite oseltamivir treatment³

Background to concept - David Menon

3. David Menon summarised the critical care background of the current pandemic situation. In summary:
 - Pandemic A/H1N1 will impose a substantial burden on ICUs across the world, with demand exceeding resources even with optimistic current estimates. This burden is worsened by the need for more complex ICU interventions (advanced ventilation, ECMO, renal replacement therapy). In developed countries between 10-25% of hospitalized patients have required ICU care.
 - Modelling has indicated⁴ that predicted peak critical care bed occupancy in the UK would be 160% of total capacity, and predicted peak ventilator utilisation 78% of total capacity (assuming an attack rate of 61% for <15 years old and 29% for >15 years old; hospital admission rate of 0.25%; an ICU admission rate of 36% and a ventilated admission rate of 18%), with significant variations between parts of the UK.

¹ Luke *et al.* 2006 Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment. *Ann Intern Med.* Oct 17; 145(8):599-609.

² Simmons *et al.* 2007. Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza. *PLoS Med.* May;4(5):e178; Prbakaran *et al.* 2009. Combination therapy using chimeric monoclonal antibodies protects mice from lethal H5N1 infection and prevents formation of escape mutants. *PLoS ONE* May 22;4(5):e5672; Throsby *et al.* 2008. Heterosubtypic neutralizing monoclonal antibodies cross-protective against H5N1 and H1N1 recovered from human IgM+ memory B cells. *PLoS ONE* 3(12):e3942

³ Zhou *et al.* 2007. Treatment with convalescent plasma for influenza A (H5N1) infection. *N Engl J Med.* Oct 4;357(14):1450-1.

⁴ Ercole *et al.*, 2009. Modelling the impact of an influenza A/H1N1 pandemic on critical care demand from early pathogenicity data: the case for sentinel reporting. *Anaesthesia* 64: 937-41.

- Outcome in the severely affected is surprisingly good with aggressive intensive care, but there continues to be significant mortality. There is a strong case for maximising ICU resource utilisation, so that these benefits of aggressive critical care are widely available.
- Any intervention that reduces mortality directly is clearly desirable, but an intervention that reduces ICU length of stay and ICU resource utilisation would likely save lives by making ICU resources available for more patients.
- Many patients who improve slowly or die despite critical care and antiviral therapy, particularly oseltamivir, show evidence of continued viral excretion, whereas clearance of virus has been associated with survival in limited studies of pandemic A/H1N1. However further data is needed to fully describe correlations between patient viral load kinetics and clinical outcomes. This information will help indicate if plasma therapy is likely to be effective when administered at different time points after infection.
- It would be imprudent to rely on currently available drugs – there are increasing concerns about antiviral resistance – and therefore interventions that might more rapidly terminate lung viral replication and perhaps modulate inflammatory responses need prompt study.
- In addition to the UK, convalescent plasma would be accessible as a therapeutic option in many parts of the world.

Update on UK pandemic H1N1 experience in hospitals - Gail Thomson

4. Gail Thompson provided an update on the UK pandemic H1N1 experience in hospitals from the Health Protection Agency's viewpoint. Key points included:
 - When the UK stopped community testing on 3rd July, there were 7904 laboratory confirmed cases in the UK, 123 confirmed cases requiring hospitalisation (rate 1.6%, CI[1.3-1.9%]), and 20 cases in ICU, yielding an intensive care admission rate (as a percentage of proven cases) of 0.25% overall. or 17%(CI[10-25%]) of hospitalised cases requiring ICU. The age distribution of illness was predominantly in school age children, though this is probably biased by the effect of transmission in schools.
 - England is currently experiencing a decline in numbers of cases; as of 2nd September there were 159 hospitalised patients with suspected pandemic influenza, around 20% of which were in intensive care. The highest hospitalisation rate has consistently been in those aged under 5 years, and rates in all age groups have been fairly stable in past two weeks. There have been 71 deaths in the UK, 21% of which occurred in previously healthy persons.
 - It was noted that criteria for admission to ICU varied between countries, and that being in ICU does not always mean that the patient is ventilated. Comparing rates of admission across countries is therefore difficult.
 - ICU units in the UK have essentially coped well with the extra demand resulting from the pandemic to date, although prolonged stays have led to high occupancy. The length of stay of patients in ICU has varied from 5-28 days, with one ICU in England holding a patient for 40 days. Renal replacement therapy has been used in 10% of cases, with one unit using it in around half of cases.
 - ICU planning assumptions were discussed. In summary, current assumptions to mid-May 2010 suggest a worst case scenario of x3 normal capacity.

Overview of antibody therapies - Antonio Lanzavecchia

5. Antonio Lanzavecchia provided an overview of antibody therapies. Key points included:
 - Current understanding of neutralising antibodies (Abs) was reviewed. In short, classical studies have emphasised the role of antibodies against the globular head of the haemagglutinin (HA) that show potent neutralizing activity but limited breadth of cross-reactivity against multiple strains or HA subtypes. Recent studies have described heterosubtypic neutralizing Abs that can bind multiple group 1 HA subtypes (H1, H2, H5,

H6, H9) – these exhibit considerable breadth, but lower potency. Most of these Abs are directed to highly conserved epitope(s) in the HA stem region and are present in very low concentrations in human sera, even in those who have experienced multiple influenza infections. Both Abs reactive to the globular head and stem regions were discussed, along with the prospect of a pan-influenza A neutralising Ab.

- Challenge studies of *H5N1-specific neutralising Abs* in ferrets have demonstrated that a 'cocktail' of antibodies recognising non-overlapping epitopes effectively transferred passive immunity and could reduce problems with escape mutants.
- In response to seasonal influenza vaccination (H1/H3) some individuals produce IgG *heterosubtypic neutralising Abs*, which show broad neutralizing activity *in vitro* (and *in vivo*) against group 1 viruses (H1, H2, H5, H6, H9). Human monoclonal antibodies (mAbs) with such activity have been derived from human B cells. Most (but not all) of these mAbs utilize VH1-69, recognize an acid labile epitope in the HA stem region and inhibit fusion (as contrasted with attachment inhibition observed with mAbs directed to globular head). Most Abs that bind to the stem region, have low neutralizing activity on infectious virus (but high binding to pseudotype viruses), and protect mice. Some recognize epitopes in the globular head. Attempts to select escape mutants using heterosubtypic antibodies that bind to the stem region have been unsuccessful, but escape mutants were readily isolated using antibodies that bind to the globular head. It was noted that the length of time these Abs endure is currently unknown.
- A proof of principle study investigating the isolation of a *pan-influenza A neutralizing monoclonal antibody* was described. In short, this involves isolating plasma cells from seasonal influenza vaccinees and screening for relevant, pan-influenza A antibodies with multiple parallel assays. The paired VH/VL genes can then be rescued by single cell RT-PCR, and the antibody produced in recombinant form. A human mAb isolated from plasma cells (FI6) was found to bind group 1 (H1, H5) and group 2 (H3, H7) influenza HAs.

Broadly reactive anti-HA mAb - Ronald Kompier

6. Ronald Kompier outlined broadly-reactive mAb production and studies carried out by Crucell. Briefly, main points included:
 - mAb production at Crucell involved the production of heterosubtypic anti-HA mAbs against group I HAs through binding primarily to a conserved epitope on the HA2 stalk. These mAbs were produced from phage display libraries constructed from human memory IgM+ cells and can be produced in high concentrations in PER.C6 cells.
 - Initial mouse studies⁵ using a high affinity mAb (designated CR6261) showed 100% protection when a minimum dose of 5mg/kg mAb was administered prophylactically 24hrs before infection with H5N1 virus (10 LD50 of A/Vietnam/1194/04). mAb treatment (15mg/kg) was also given at 3, 4, 5 or 6 days post infection with 25 LD50 A/Hong Kong/156/97. Successful survival and reversal of weight loss was seen for treatments given up to 3 or 4 days post-infection. These observations were mirrored by pathology data that showed decreased leukocyte infiltration into the lung on histopathological slide specimens. There was no beneficial effect of mAbs administered 6 days post-infection.
 - CR6261 neutralizes the pandemic H1N1 virus. Overall, in their experiments mice tended to die after approximately 8 days. Beneficial effects of mAb treatments were seen when administered 5 days post infection or less, whereas oseltamivir showed little effect at 4 days post challenge.
 - No toxic or adverse events were seen in mice or ferrets during mAb treatment. Analysis of the immune response after mAb therapy shows virus specific responses, indicating that natural immunity is still generated during mAb therapy and virus infection.

⁵ Throsby *et al.*, Heterosubtypic neutralising monoclonal antibodies cross-protective against H5N1 and H1N1 recovered from human IgM+ memory B cells. PLoS ONE 3(12):e3942

- Escape variants have not been observed in the animal studies to date. Serial passage of virus *in vitro* to select escape mutants required 10 such passes.
- Clinical grade CR6261 Ab is expected to be available soon for toxicologic studies. Crucell have recently received funding to the amount of US\$ 40.7 million from NIAID/NIH to develop monoclonal antibody therapies for influenza.

Blood product production for clinical trials – Lorna Williamson, Tim Wallington, Richard Tedder

7. The meeting attendees from the NHS Blood and Transplant (NHSBT) noted that the NHSBT would be supportive of an early trial, and presented an overview of considerations from their viewpoint. Key points included the following:
 - During initial discussions, NHSBT attendees were of the view that a pilot trial should be two armed: (1) pandemic H1N1 ‘flu recovered’ fresh frozen plasma (FFP) versus (2) pandemic H1N1 naïve FFP, with around 40 patients in each arm.
 - Highlighted areas for consideration included quantity of FFP; whether to use male or female plasma donors (male FFP is preferred due to the risk of anti-HLA Abs causing transfusion related acute lung injury – TRALI – which are more prevalent in females); ABO blood group considerations; how to screen for convalescent (immune) and non-immune FFP; and requirement for blinding.
 - The need for a suitable, rapid screening test for the quantities of donor plasma was also discussed; it was noted that the service has commissioned Richard Tedder to develop such a test which will most likely be an ELISA. HAI assays would then be performed on seropositive samples to determine Ab titres.
 - Calculating from the existing literature, it was suggested that around 800ml of FFP would be required for an adult (70kg), meaning 320 treatment packs (each pack containing 200ml) and 320 control packs would be required for a study involving 80 subjects. At a rate of 1% suitable donations, 32,000 donations will be required for screening purposes. Targeting donations from donors who know they had laboratory proven pandemic A/H1N1 could reduce this number.
 - Logistical areas for consideration noted included operation resource requirements, including availability of trained staff; storage requirements for plasma; and full cost recovery for NHSBT.
 - The possibility of a larger trial was discussed following a pilot study, including how to control such a trial following mass pandemic influenza vaccine uptake, when naïve FFP will be more difficult to obtain.
 - Ethical considerations were also discussed – including whether specific consent for donation will need to be obtained or whether results have to be reported back to donors. These would not be possible due to the increased logistical burden this will place on the ‘collection’ arm of NHSBT. Anonymisation is not an option, as according to regulations a component to be transfused must have traceability. It was suggested that we should assume that the current level of consent is sufficient – as there is a precedent from other studies for testing to define a component that is not reported back to the donor or acted upon – and early guidance could be sought from COREC (Central Office for Research Ethics Committees).
 - As the POC study would be limited to adults, vCJD is not an issue as study meets current UK transfusion standard.

Procurement, safety and distribution issues discussion

8. Following these presentations, the group discussed issues relating to procurement, safety and distribution. Key points emerging from the discussion included:

- The issue of unselected screening versus advertisement or traceback of volunteers for donation was a major area of discussion. Suggestions included sourcing plasma from areas of the UK such as London and Birmingham, where the pandemic H1N1 epidemic has been strongest and its estimated that 25-50% persons are seropositive in some areas. The blood transfusion service in Scotland has already begun thinking about asking blood donors if they have experienced ILI symptoms recently in order to gauge whether questioning at point of donation could help identify hyperimmune plasma. Another method of identifying persons with immune plasma might be to trace laboratory-confirmed cases identified during the 'containment' phase. It was noted that once mass vaccination begins, it may be difficult to distinguish between vaccinees, recovered patients and controls. The age of donors was also raised as a consideration due to observations that a proportion of persons born before 1950 harbor pre-existing, cross-reactive antibodies⁶. Possibilities for sourcing plasma from other countries more heavily affected by pandemic H1N1 were discussed but rejected because of likely time delays in near term.
- Use of FFP, fresh plasma or fractionated Igs – and furthermore, whether to use convalescent or post vaccine sera – were discussed. It was realized that using fractionated Igs or mAbs would be optimal to address questions regarding the therapeutic effects of antibodies alone, however, due to cost, time and safety constraints these were not considered viable options for a timely clinical study for the upcoming flu season. It was noted that using sera would have the possible advantage over manufactured mAbs of ensuring that antibodies are closely matched to the circulating strains. It was noted that the Medicines and Healthcare Regulatory Authority (MHRA) does *not* allow UK plasma to be fractionated for products, due to concerns around vCJD prion contamination of fractionating equipment (N.B. Elaine Gadd, Department of Health, summarised the current UK situation regarding vCJD and blood – see Annex B) . Pooling of plasma may also raise concerns (regarding adventitious agents) which should be checked with MHRA.
- A key issue for many participants was standardization of the intervention product. It was noted that FFP contains a large number of potentially confounding substances such as allo-Abs and cytokines, and specific immunoglobulin concentrations would vary between donors. Any increased volumes administered could potentially affect lung function. Screening for and standardizing Ab levels could perhaps be creating 'minipools' of plasma might help in this regard but would require regulatory approval. Others argued that the available data and the medical need were sufficient to proceed with a proof-of-concept (POC) study with convalescent plasma.
- It was stressed that the blood collection arm of NHSBT is currently heavily in demand in preparation for the pandemic, and would prefer not to receive additional demands on its services. It was noted that only a few weeks' worth of FFP is stored by NHSBT, and for regulatory reasons this is sourced from abroad. However, if appropriate, storage facilities are available: FFP can be stored up to two years.
- Although a risk, it was emphasised that TRALI is still a relatively rare occurrence. The increased risk of TRALI from female plasma, though still relatively small, could potentially be mitigated through screening if necessary.

Presentation of draft protocol and discussion

9. David Menon presented the outline study protocol drafted at the pre-meeting held on Saturday 5th September. The proposed study aims to define the safety, tolerability, efficacy and pharmacokinetics of immune plasma therapy in critically ill patients with severe influenza A (H1N1) infection. The short title of the proposal was suggested as Swine flu IMMune PLasma Evaluation, or SIMPLE.

⁶ Hancock *et al.*, (2009) Cross-Reactive Antibody Responses to the 2009 Pandemic H1N1 Influenza Virus. *N Engl J Med*; published at www.nejm.org on September 10, 2009

Proposed objectives and outline of the study were given as follows:

- *Primary objective* - to assess the impact of immune plasma therapy on viral clearance and surrogate clinical outcome measures in patients with severe pandemic H1N1 disease. Proof of concept was suggested as the ability of the intervention to accelerate viral clearance; whereas proof of mechanism was suggested as whether this accelerated viral clearance would improve pulmonary gas exchange.
- *Secondary objectives*: safety and tolerability of IV immune plasma therapy; PK of IV plasma therapy in pandemic A(H1N1)-infected adults; antiviral efficacy of plasma therapy in controlling viral replication; impact on survival, clinical course, SOFA severity scores over time.
- *Tertiary objectives*: correlations between virological and PK and clinical responses; antigenic characterization of the infecting virus and last isolate on therapy to look for evidence of antigenic escape variants; viral susceptibility to oseltamivir (and other antivirals) before and in last positive sample during or after therapy; correlations between changes in viral replication markers and host inflammatory responses.
- *Study design*: it was proposed that the trial be a multicentre, three way, partially blinded, randomized study. The proposed three arms of the study were (i) FFP obtained from donors immune to A(H1N1) as signified by Ab titres; (ii) non-immune FFP; and (iii) 0.9% saline. A dose of 200ml every 12 hours for 48 hours was suggested.
- *Endpoints*: primary endpoints were suggested as (i) viral clearance from LRT, ascertained through PCR and viral culture, and tracheobronchial suction specimens; and (ii) changes in pulmonary function: PaO₂/FIO₂ ratio, oxygenation index (PaO₂/FIO₂/mean airway pressure). A number of secondary endpoints were suggested for example, clearance of virus from the respiratory tract and ventilator free days.
- *Funding*: grant funding, reallocation of existing resources and CLRN funding were suggested as possibilities.

10. Key points emerging from the discussion were as follows:

- There was a broad consensus that an initial study of this nature was very timely and it was therefore right to take forward quickly during this unique pandemic situation to investigate the effectiveness of the treatment as a therapy for severe influenza. It was commented that the UK is perhaps one of a few countries with the capacity to integrate clinical/intensive care blood services, virology and immunology expertise quickly to undertake such a study. In addition to reducing mortality, a positive outcome of using convalescent sera for treatment would also be reducing the length of stay in ICU.
- Obtaining convalescent plasma for study and funding were identified as the major rate limiting logistical steps.
- **Intervention and Controls**: appropriate control group(s) was a major topic of discussion. Some participants suggested that administering no intervention as a control (i.e. using 'standard of care') may be more appropriate than using either non-immune sera or saline or albumin because of the possibility of confounding variables inherent to sera, such as cytokines and allo-antibodies and fluid administration considerations. The dose of convalescent plasma to be administered was discussed in the context of those used in past studies and uncertainties regarding the anticipated neutralizing antibody levels to pandemic H1N1 virus in convalescent plasma. In animal models using mAb repeated doses (days 1 and 3) showed more rapid elimination of virus than single doses. A dosing regimen of 2 to 3 days has been used in most clinical reports to date. Based on plasma volume of ~2.5L in a 70 kg patient, a preliminary estimate was that 800 ml of plasma (sourced to have HAI titre of 1:256) would provide a therapeutic titre of 1:32. This would require FFP from 4 donations.
- **Design**: Some intensivists suggested that the study should be simplified in order to be feasible in a resource-limited pandemic setting, where demands placed on ICU facilities

would be extremely high. It was thought that a three-armed study may be overly complex, and a two-armed study comparing intervention (convalescent plasma) to standard of care was ultimately agreed. One suggestion was the inclusion of unbalanced randomization with more patients in the intervention rather than control arm (e.g., ratio 2:1 for intervention versus control). Some participants advocated including dose escalation in the study and commented that the relatively small number of participants could potentially make the study insufficiently powered. It was suggested that the study should aim to incorporate as many patients as possible, and that the 80-90 patients discussed could be viewed as an initial target based on feasibility rather than a fixed number. In any case, an independent data safety and monitoring board would be needed to review adverse events and outcomes as the study proceeds. The MRC Biostatistics Unit could help with the complex issues of randomisation.

- **Endpoints and follow-up:** whether endpoints should be clinical or virological in nature was discussed. While duration of viral replication has not been well-studied in seriously ill pandemic H1N1 patients, initial reports from a Scottish ICU did see a correlation of sustained viral titre with poorer outcome. Sustained viral detection in seriously ill patients has been reported from several clinical groups, and multiple animal model studies show increased pathogenicity with increased lower respiratory tract viral replication compared to seasonal influenza viruses. Overall, more virological data from hospitalised patients was needed to fully determine the relationship between viral dynamics and clinical disease progression and that the proposed study would help to provide such information. The duration of follow-up was generally agreed to be relatively brief (e.g., 28-25 days post enrolment) to capture key data quickly but avoid over-burdening the research staff and investigators.
- **Inclusion criteria:** it was agreed that patients included in the study should be verified H1N1 positive, especially as a viral clearance endpoint was planned and concerns were expressed about administering plasma to non-H1N1 patients. While testing for pandemic H1N1 could slow down the enrolment process, it was commented that many hospitals currently expedited testing and rapid testing would be possible. It was agreed that patients with various co-morbidities should be included in the study, for example, transplant recipients and HIV positive patients (interestingly the UK has not seen an increase in HIV positive patients admitted to ICU upon pandemic H1N1 infection). Because of the important effect of time to treatment on outcomes, stratification on duration of illness was recommended.
- **Sites for study:** Some participants, particularly those from the intensivist community, that the number of participating centres should be reduced (from perhaps 10-20 to 5-10 larger units in more densely populated areas) to make the study less logistically complex. However, ensuring a reasonable geographical coverage even in a pandemic situation was considered important for adequate enrolment, since it is impossible to predict 'hotspots' in advance. It was noted that the FluCIN study is currently collecting data on around 100 hospitalised influenza cases to present to SAGE, and that SwiFT, a DH-funded study involving the clinical scoring of ICU patients, might be a good platform for this intervention study to be based on. It was thought that the SwiFT study would be able to identify ten sites in its existing framework for this convalescent sera study.

Summary of action points from the meeting:

11. The following points were agreed during the afternoon discussion:

- The broad consensus was that the study should be an initial feasibility study with two arms to assess the potential effectiveness of convalescent (immune) FFP versus standard of care. The study should initially aim for 80-90 patients, with a view to including more if possible. The meeting organisers agreed to make contact to begin to revise the proposal following comments from this meeting.

- There was broad agreement that the study should go ahead as soon as possible. This is especially the case given the recent apparent increase in pandemic cases now observed in some parts of the world, and increasing reports of oseltamivir resistance. However, it was important that the protocol was scientifically robust and capable of producing meaningful results.
- NHSBT would seek advice from MHRA as to whether minipooling (i.e. plasma pooled from several donors) plasma is possible to allow for standardisation, and whether testing of imported plasma for pandemic H1N1 antibodies would be possible in the near-term. As fractionation of UK-derived plasma to isolate immunoglobulins will *not* be possible in the UK, it was decided that this would not be explored further at this stage. Future studies could investigate the possibility of acquiring plasma from outside of the UK for fractionation within the UK, however, this would be too difficult to implement in time for this proposed study. NHSBT will also investigate the possibility of 'outreach' to those with documented pandemic A/H1N1 infection to source hyperimmune plasma more effectively.
- Recruitment of a part- or full-time project manager for this study should be investigated. Obtaining early input from regulatory authorities was considered to be priority for such a person.
- Contact should be made with other groups abroad (e.g., Dr. Anand Kumar, Winnipeg Manitoba; Dr. Elizabeth Higgs, NIH, Bethesda) who are apparently involved in sourcing pandemic A/H1N1 immune blood products and considering conducting similar studies. This would facilitate possible collaboration, sharing of protocols and results, and possibly access to convalescent blood products for any future IgG study – including the likely time delay in obtaining these products.
- Contact will be made with Janet Darbyshire at the MRC Clinical Trials Unit for her input and advice.
- Since no animal model studies with convalescent plasma for pandemic A/H1N1 virus have been reported, the possibility of undertaking such studies should be explored, in parallel to the propose clinical study due to time constraints.
- If this proof of concept study of convalescent plasma provides encouraging results, future possibilities include a larger Phase III study in severe A/H1N1 infection and exploratory studies in other geographic locations, patient groups, of levels of disease severity (paediatrics, hospitalised patients, other countries). Subsequent studies might also investigate (i) the effectiveness of convalescent FFP versus naïve FFP to examine non-specific effects of plasma (ii) specific hyperimmune anti-H1N1 IgG, fractionated from sera sourced from abroad or (iii) the efficacy of neutralizing mAb therapy.
- Future discussions should primarily take place by teleconference, with those not wishing to participate in future proceedings given the option to opt-out.

ANNEX A – DELEGATE LIST

John Bleasdale	Sandwell & West Birmingham NHS Trust
Ruth Branston	Wellcome Trust
William Carman	West of Scotland Specialist Virology Centre
Kenneth Douglas	SNBTS Clinical Apheresis Unit
David Evans	Wellcome Trust
Jeremy Farrar	Hospital for Tropical Diseases, Vietnam
Elaine Gadd	Department of Health
Fang Gao Smith	Warwick Medical School
Nick Gent	HPA
Fred Hayden	Wellcome Trust
Wendy Howard	Wellcome Trust
Ronald Kompier	Crucell Holland BV
Peter Lachmann	University of Cambridge
Antonio Lanzavecchia	Institute for Research in Biomedicine/ETH Zurich
David Menon	University of Cambridge
Karl Nicholson	University of Leicester
Jerry Nolan	Royal United Hospitals NHS Trust, Bath
Charles Penn	World Health Organisation
Barbara Philips	St George's University London
Jim Robertson	NIBSC
Michael Rogers	Department of Health
Jonathan Salmon	Oxford Radcliffe Hospitals NHS Trust
Richard Tedder	UCL/HPA/NHSBT
Gail Thompson	HPA
Guy Thwaites	Imperial College
Alain Townsend	WIMM and NDM Oxford
Hien T Tran	Hospital for Tropical Diseases, Vietnam

Tim Wallington	NHSBT
Tim Walsh	Lothian University Hospitals Division and Edinburgh University
Lorna Williamson	NHSBT
Tom Woodcock	Southampton University Hospitals NHS Trust
Duncan Wyncoll	ICU Guy's & St Thomas NHS Foundation Trust

Apologies:

Libby Higgs	NIH
Danny McAuley	Intensive Care Society

ANNEX B – SUMMARY OF vCJD AND BLOOD: MEASURES IN PLACE

The United Kingdom blood services have taken a number of precautionary measures to protect the blood supply and associated plasma products. Since the theoretical risk of vCJD transmission through blood was first considered, precautionary measures have been introduced to minimise the risk, including:

Applicable to all blood/blood products

- From December 1997, blood components, plasma products or tissues obtained from any individual who later develops vCJD, have been withdrawn/recalled to prevent their use.
- From October 1999, white blood cells (which may carry a significant risk of transmitting vCJD) have been reduced in all blood used for transfusion, a process known as leucodepletion or leucoreduction.
- Following the report of the first possible case of transmission of vCJD by blood transfusion in December 2003, it was announced in March 2004 that individuals, who had themselves received a transfusion of blood components since January 1980, would be excluded from donating blood.
- In July 2004, the exclusion criteria for blood donation were extended to include two new groups, who had received transfusions of blood components since 1980:
 - Previously transfused platelet donors,
 - Donors who were unsure if they had previously had a blood transfusion. This now applies to donors who have been transfused anywhere in the world.
- In July 2005, the Department of Health announced further precautionary measures for around 100 individuals who donated blood to three people who later developed vCJD. The notified people have been asked not to donate blood, tissues or organs and to inform health care professionals so extra precautions can be taken when they have surgery or other invasive procedures.
- In November 2005, the Department of Health announced an extension of the July 2005 notification exercise. A further 50 people who had received blood from some of the 100 or so donors notified since July 2005 were traced and notified of their potential exposure to vCJD.

Platelets

Collection of platelets by apheresis continues to be extended where possible. This reduces the need to pool donations to produce platelet doses, thus reducing donor exposure.

Plasma

- In July 1998, it was announced that plasma for the manufacture of plasma products, such as clotting factors, would be obtained from non-UK sources.
- In August 2002 it was announced that fresh frozen plasma for treating babies and young children born on or after 1 January 1996 would be obtained from the USA.
- Fresh frozen plasma for treating babies and young children born on or after 1 January 1996 is obtained from the USA, and from July 2005 its use was extended to all children up to the age of 16.
- The NHS has been instructed to purchase imported solvent detergent FFP for adult patients with thrombotic thrombocytopenic purpura (TTP), although there is some doubt about the effectiveness of this measure, and further advice is being sought from the Advisory Committee on the Safety of Blood, Tissues and Organs.

Cryoprecipitate

- Cryoprecipitate produced from methylene blue treated-plasma imported from the USA is being implemented for children up to the age of 16.

Additionally, considerable effort is being extended to promote appropriate use of blood throughout the NHS, to target blood use to where it is clinically essential. This work has already achieved notable successes, especially in reducing the use of blood in surgery.

vCJD AND BLOOD – MEASURES PENDING

At their July 2009 meeting, SaBTO (Advisory committee on the Safety of Blood, Tissues and Organs) recommended the following:

At least 80% of **platelets** should be collected by apheresis by all the UK Blood Services.

Use of UK-derived **fresh frozen plasma (FFP)** should be ceased, and replaced by imported FFP for all recipients. Source countries of plasma should show an estimated subclinical vCJD prevalence of at least 3 log below that of the UK (but in principle the lower the better). Use of pooled FFP is acceptable where a combination of sourcing and processing results in a 4-5 log decrease in relative risk compared with UK-derived FFP.

A DH decision on implementation has yet to be formally agreed.