NHS BLOOD AND TRANSPLANT BOARD MEETING

30 JANUARY 2020

CLINICAL TRIAL OF MANUFACTURED RED CELLS:

1. Status – Official

2. Executive Summary

A clinical trial of red blood cells manufactured in our laboratories was approved as the flagship project of the 2015 – 2020 R&D Strategy. This paper provides the Board with an update on the progress of this work. All the necessary regulatory approvals are now in place for the clinical trial to begin, with the first volunteers scheduled to receive red cells in March 2020.

Advanced cellular therapies are offering new treatments to patients who do not respond to traditional therapies or for whom suitable treatments do not exist currently. Manufactured red blood cells (mRBCs) grown in the laboratory offer several potential advantages over standard donated cells particularly for those patients difficult to provide blood for.

The RESTORE clinical trial is a first-in-human trial mRBCs which demonstrates our expertise in advanced manufacturing, research and clinical trials. The successful delivery of this trial will continue to generate experience and build credibility in the field of advanced cellular therapies.

3. Action Requested

This update is provided for information.

4. Background

Our research scientists in Filton have developed a method of culturing red blood cells in the laboratory from donated, whole blood derived, stem cells. Studies in mice show that these mRBCs survive longer than donated red blood cells and therefore offer potential advantages for patients. In addition, new techniques allow the creation of 'designer' red cells to be produced. There are also some other potential benefits which include reduced infection risk, controlled manufacturing process, better blood group matching with patients and the possibility of fewer transfusions and reduced complications (e.g. iron overload).

The next step in the development of mRBCs is a demonstration that they are safe and that they survive for longer in human volunteers. To that end, NHSBT agreed £1.77M transformation funding for a proof-of-concept clinical trial of mRBCs.

This is a complex and ambitious programme which is highly collaborative. Successful delivery involves expertise from across NHSBT (SCI, Blood donation, testing, manufacturing, transport and logistics, RCI, IBGRL, Quality, NTMRL, the Clinical Trials Unit, Microbiology Services and the Component Development Laboratory), as well as effective partnerships with Universities (University of Bristol and University of Cambridge) and other NHS organisations (Guy's Hospital Radiopharmacy and Addenbrooke's Department of Nuclear Medicine and NIHR/Wellcome Trust Clinical Research Facility).

5. The RESTORE Clinical Trial

The RESTORE first-in-human clinical trial will determine whether mRBCs survive longer post-transfusion than standard red blood cells. The trial will involve a total of 10 recipients who will receive both mRBCs and standard red cells.

The trial duration is 26 months with the first two standard RBC infusions scheduled for March 2020. We anticipate that all the recipients will have received both doses of red cells by the first quarter of 2021. An interim analysis, when the first 5 participants have received both mRBCs and standard RBCs, is scheduled for May 2021. Follow up of recipients to assess red cell survival and safety outcomes will continue until the first quarter of 2022.

In the trial each recipient receives standard donor red cells and mRBCs sequentially in a randomised order. Recovery and survival of the cells will be assessed. Each recipient will receive infusions of mRBCs and standard RBCs from the same donor to minimize any effect of donor variation.

The trial duration is determined by the cross over design which involves two separate infusions and a 180-day follow-up after the second infusion. Current production capacity allows for one RESTORE mRBC culture per month, with clean rooms being requalified every 6 months.

Completed milestones

The following milestones on the critical path for the trial have been met:

- The R&D manufacturing process has been translated into a Good Manufacturing Practice (GMP) compliant process to support production of clinical-grade mRBCs;
- The cell culture process has been transferred to the Advanced Therapies Unit (ATU) at Filton;
- Three successful GMP compliant validation production runs have been completed;
- The Investigational Medicinal Product Dossier (IMPD) and the Investigator's Brochure (IB) have been compiled and approved;
- The Trial Steering Committee has signed off the trial protocol and the NIHR BTRU's Public Advisory Group has reviewed the participant documentation for the trial;
- Applications to NHS Research Ethics Committee (REC), NHS Health Research Authority (HRA) and Administration of Radioactive Substances Advisory Committee (ARSAC) were submitted and approved. Further amendments were made and final approval for the RESTORE clinical trial has been obtained;
- 20 donors have been identified for invitation to participate in RESTORE and 197 blood group compatible volunteers invited to participate in the trial;
- Insurance and indemnity arrangements have been confirmed;
- An end to end test run with standard red cells was successfully completed. This tested production, logistics and change controls from donation to point of injection.

Governance

The delivery of the Clinical Trial is overseen by a Project Board, chaired by the Medical & Research Director, with membership including the Director of DTS and the Director of Quality. The Accountable Executive for the project is the Assistant Director – Research and Development. Progress has been reviewed on a monthly basis by the project board, with quarterly reporting to the Transformation Programme Board.

In October 2018, a request to change the scope of the original submission was approved by the Executive Team via the Transformation Programme Board (TPB). The approved changes were:

1. To extend project by 6 months, with the end date changing from Sept 2020 to March 2021;
2. To remove the planned trial of mRBCs produced from cord blood derived stem cells and focus on the adult trial only;
3. To confirm that the original budget of £1.775M was available to complete the adult trial;

We will be seeking a further change via TPB to extend the project to March 2022 to complete the project.

The Research and Development Committee has reviewed progress at each of the nine Committee meetings held since funding was approved by the Board on 28th May 2015. At each review they confirmed their support for the trial, seeking and obtaining further reassurance on two occasions:

In accordance with Good Clinical Practice, the supervision of RESTORE is overseen by a Trial Steering Committee (TSC). This includes independent investigators, clinicians and patient group representatives. Professor Irene Roberts (Professor of Paediatric Haematology, University of Oxford) chairs the TSC which monitors trial progress and conduct and advises on scientific credibility.

The RESTORE clinical trial also underwent independent expert review as part of the Quinquennial review held in June 2019. This confirmed the need for and continued support of this important project in order to realise any potential commercial exploitation of intellectual property.

6. Current status of work compared to competitors

The clinical trial will be the first of its kind to determine the utility of mRBCs compared to donor derived standard cells in an allogeneic study. Other groups around the world are attempting to produce RBCs from a variety of stem cell sources, but to date, and to the best of our knowledge, only our scientists in Filton have demonstrated the ability to reproducibly produce the quantity of cells required for such a trial.

We are aware of two planned Phase 1 clinical trials of *in vitro* produced reticulocytes. However, these are not as advanced as the RESTORE trial and have different objectives.

7. Benefits of the RESTORE Clinical Trial

As the major UK Blood Service, a national provider of stem cell immunotherapies and the UK's largest contract manufacturer of cell therapies, we are uniquely placed to carry out the RESTORE clinical trial and supporting research. A key goal of the current strategy is to strengthen our position in the development, assessment and clinical delivery of advanced therapies. The completion of such a complex and logistically challenging trial will significantly enhance our reputation and promote our expertise.

Data obtained from RESTORE will be crucial for the design of future dose escalation trials and second-generation products that are in development by us and others. The trial represents an important step on the path to substantial commercial investment. In support of this, there is already commercial interest in licensing the trial data.

Currently, mRBCs are more costly than blood obtained from donors and it is therefore anticipated that the initial clinical use of mRBCs will be for patients who have no compatible donor. We anticipate that the cost of mRBC production will decrease with further process development and optimisation (e.g. using automation and bioreactor technology). Further clinical development of mRBCs beyond the trial is likely to require investment from commercial partners, hence to 'spin out'. We are currently exploring commercialisation opportunities.

£3.7M funding from external bodies, including the Wellcome Trust, MRC and DSTL, has already been obtained to develop additional advanced blood products, including platelets, neutrophils and novel RBC-based therapeutics. Our investment in RESTORE has provided a strong foundation on which to develop a programme in cultured blood component and cellular therapies and we have learned a significant amount from transferring this ability from research bench to the GMP environment. Once complete, RESTORE will inform the production of novel therapies that use RBCs as delivery vehicles, particularly if it demonstrates the expected increased survival.

8. Financials

Developing advanced therapies is expensive – each mRBC production run now costs approximately £57,000. In order to reduce our financial exposure in supporting this trial we have used a mixed funding model that splits expenditure across multiple funding sources.

The NIHR BTRU in red blood cell products at the University of Bristol (Director: Dr Ashley Toye) provides essential infrastructure for the trial as well as parallel research (£3M over 5 years). An application has been submitted to extend the NIHR BTRU to March 2022 (£900k). Due to the challenges and delays experienced, it is unlikely that the project will be delivered to the original phasing of the budget, however, TPB expenditure is forecast to remain within agreed tolerances (< 10%). We are not seeking approval for any additional funding. The inclusion of a contingency for two additional production runs provides some level of flexibility as the trial commences.

The £1.77M TPB funding approved by the Board in 2015 supports:

- The costs of developing therapeutic grade mRBCs;
- Manufacturing costs for the mRBCs;
- Clinical trial infrastructure;
- Delivery of the clinical trial;

Several unforeseen issues have affected the cost for delivering the trial, the original costings were based on estimates, prior to the methodology being fully developed:

- The actual costs of transferring and validating the production process to the clean rooms was significantly higher than the original estimate (£736k vs £214k);
- A loss of yield was observed when transferring the manufacturing process to the clean rooms and therefore an additional donor screening and optimisation step was introduced to produce a sufficient quantity of cells;
- The finalised GMP manufacturing costs for each batch of mRBCs and standard red cells are higher than the original estimate (£57k vs £41k).
- The total GMP production costs include an element to retain NHSBT Regulatory Lead / Qualified Person time (£35k) for the project;
- The costs for an end-to-end production run to test systems prior to injecting mRBCs and contingency of two additional production runs to mitigate against failures during the trial have been added.

9. Timelines and Next steps

With all the regulatory approvals in place, the trial is scheduled to commence in March 2020. Final selection of donors and recipients has begun, and eligibility screening is planned for early February. The first two recipient injections of standard red blood cells are planned for March. The first mRBC manufacturing run is scheduled for July 2020. We anticipate that all the recipients will have received both doses of red cells by the first quarter of 2021. Follow up of recipients to assess red cell survival and safety outcomes will continue until the first quarter of 2022.

Authors: Nick Watkins, Assistant Director – R&D, Ruth Allen, Operations Manager NIHR BTRU, Ash Toye, NHSBT PI and NIHR BTRU Director on behalf of the RESTORE team.

Responsible Director: Dr Gail Miflin, Chief Medical Officer