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The RESTORE trial's implications on the future of blood transfusions

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NHS Blood and Transplant (NHSBT) and the University of Bristol are working together on the first ever clinical trial for transfusing red blood cells developed *in vitro*. This seminal study is called 'Recovery and survival of stem cell originated red cells' (RESTORE), and it compares how long lab-made red blood cells can survive in the body compared to donated red blood cells[4]. The trial started in August 2018 and is projected to last until May 2024[2]. The RESTORE clinical trial has been planned meticulously. It is a phase one randomised, single blind clinical trial: the participants do not know whether they are in the control group or the experimental group receiving the lab-grown red blood cells [2]. This clinical trial is a true multicentre effort, with input from experts at three different centres (Figure 1).

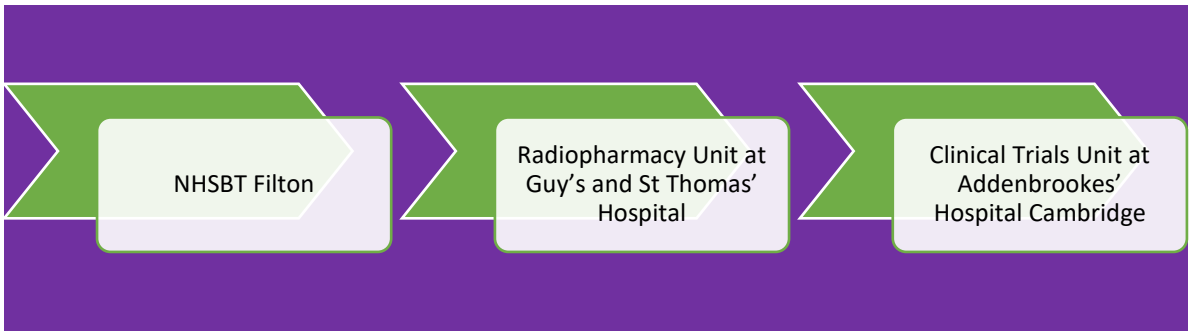

Figure 1. The mRBCs journey starts at NHSBT Filton with haematopoietic stem cells from the initial blood donors making its way to the participants in Addenbrookes' Hospital[4].

NHSBT supply the blood donors, and their Advanced Therapies Unit in Filton make the red blood cells using CD34+ cells isolated from the donors' blood[4,5]. Then the Radiopharmacy Unit at Guy's and St Thomas' Hospital labels the manufactured red blood cells (mRBCs) with a tracer element to help keep track of the cells once they are transfused into the participants[4]. Finally, at the Clinical Trials Unit at Addenbrookes' Hospital Cambridge, the mRBCs are transfused into healthy participants sourced through the NIHR BioResource[4]. Two small transfusions of around 10 mL were made with a gap of at least four months between the first and second transfusion[4,6]. As of November 2022, two people have received the lab-made blood transfusions and no adverse effects have been observed. No further transfusions have been publicly reported, but the researchers are hoping to perform these transfusions on at least 10 participants[4].

Manufactured red blood cells have the potential to change how blood is sourced for transfusions. The immediate aim for the researchers is for mRBCs to be used for patients with rare blood types and patients with blood disorders who require regular transfusions[2]. For rare blood types, finding a donor can be difficult especially when looking worldwide[3]. While Bristol is also home to the International Blood Group Reference Laboratory which can aid in this search, there are instances when a donor cannot be found[3]. Similarly, with patients who require regular blood

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transfusions, the chance of developing antibodies against different blood types increases each time they have a blood transfusion which can lead to the donor pool becoming narrow[1]. While this clinical trial is important with many benefits if the initial findings are positive, the researchers believe that this technology can only really be used in complex scenarios meaning blood donors will still have a significant role to play in saving lives[4].

Previous research suggests that it takes about 21 days to make red blood cells from haematopoietic stem cells using various growth media[7]. Combined with the fact that the number of haematopoietic stem cells being isolated from donor blood is low, it means that it is difficult to scale up the production of red blood cells[7]. There are alternative sources of stem cells like induced pluripotent stem cells and embryonic stem cells. These alternatives are different due to their relatively infinite supply which means that they could be more scalable[7].

With the ongoing research in this area of transfusion science, the possibility of a future with blood transfusions without donors feels more probable day by day. However, in the meantime life-saving blood transfusions are needed every day, so signing up to become a blood donor is something you can do today to help. The link below can provide more information on how to donate: https://www.blood.co.uk/.

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