NHS Blood and Transplant

NHS Blood and Transplant (NHSBT) Board
25 January 2018

Understanding the implications of the INTERVAL and COMPARE studies

1. Status – Public

2. Executive Summary

The results of the INTERVAL and COMPARE studies have shown that some donors (5% of men and up to 14% of women) are being accepted with lower haemoglobin results than regulatory limits, for most donors this is not a clinical concern as the results are only just below this level. However, 1.1% male and 2.8% female donors had levels below 125g/l and 115g/l respectively and thus were already anaemic prior to donating, albeit healthy. More importantly, there are very small numbers of donors (approximately 0.1% donors) who were accepted with significantly low haemoglobin results. The COMPARE study was devised and set up as soon as these results were known, this sought to establish the optimal method of haemoglobin screening. The unpublished data shows that non-invasive methods are not suitable for implementation and that other methods have similar acceptability to the current copper sulphate and venous HemoCue method (post donation strategy) or are safer (capillary HemoCue) but the latter also inappropriately defers large numbers of donors which would have big impacts on the sufficiency of supply, operational efficiency and costs.

The implications of these results are that there is a risk that, without changing our processes, we could inadvertently bleed a donor, who is already anaemic, resulting in harm to them. We have considered a number of options to mitigate this risk. Some of these options could introduce a new risk, namely of increasing the numbers of donors failing the haemoglobin screening test resulting in a future reluctance to donate and hence a loss of donors, which in turn would result in costs being incurred to recruit more donors to stabilise the donor base.

The initial options appraisal has now been completed and the following actions are recommended;

a) Immediate action to improve practice in relation to the use of copper sulphate.
b) Action to move to testing of capillary samples across all donation environments as the secondary test in place of venous HemoCue.
c) Assess the impact of these changes before implementing anything else.
d) Pilot, alongside these changes, screening women under 50 with the capillary HemoCue as a first line test to assess the operational impact of this, in case we need to move to this.
e) Assess the potential for a post donation strategy with an incorporated algorithm as the preferred longer-term strategy

None of these first three options incur substantial costs, however we expect them to mitigate the risk to donors. If a significant risk to donors remains when we assess the impact of these changes, then we will look at this using the risk based decision making framework to assess the risk tolerability and understand the cost implications from the pilot of moving to screening women under 50 with a capillary HemoCue.

The option of moving straight to testing the haemoglobin level by capillary HemoCue in all donors has been excluded on the basis of too great an impact on the sufficiency of supply resulting in harm to patients.

3. Action Requested

The Board is asked to note the actions above and to discuss any concerns

4. Purpose of the Paper

This paper brings the Board up to date with the appraisal of the potential options for response to the INTERVAL and COMPARE study results.

5. Background

5.1 The INTERVAL study recruited nearly 50,000 donors who had a full blood count (FBC) and ferritin test done at first donation and then after two years on the study. They were accepted for donation using the routine gravimetric copper sulphate test for haemoglobin (Hb) with a secondary venous HemoCue test for donors who fail the copper sulphate test. The Blood Safety Quality Regulations (BSQR) (2005) specify a Hb level of 125g/L for women and 135g/L for men to be accepted for blood donation. Whilst most donors did not report any adverse symptomatic effects from more frequent donations over the two years of the study the results of the FBC tests done at entry to the study revealed that approximately 5% of men and up to 14% of women were being accepted based on the outcome of the routine screening but actually had haemoglobin levels below the BSQR limits according to the 'gold standard' FBC test. It should be noted that most of these donors have Hb levels that are just below the BSQR requirement and are still in the normal range for haemoglobin levels. There were however, 1.1% men and 2.8% women who had levels below 125g/l and 115g/l respectively and thus were already anaemic prior to donation and a very small number (below 0.1%) of donors who are significantly anaemic. These latter donors should be identified and appropriately referred to their GP, this. Whilst the numbers are very low it is concerning that they would have been accepted to donate blood.

As a result, the COMPARE study was performed to determine the optimal method of determining haemoglobin levels in donors. The standard process whereby blood from a capillary or finger prick test is put into copper sulphate is done first and, if a donor fails, then a second test is done. This is a more standard 'blood test' which uses venous blood tested on a HemoCue machine. This was compared with a capillary (finger prick test) on the HemoCue, two non-invasive devices and a FBC taken with the routine donation samples (eg venous sample) and tested post-donation on a laboratory-based Sysmex analyser. This 'post-donation' sample was used as the haemoglobin level to determine the eligibility to donate at the next donation attendance. For each method, the number of people who should have been bled or deferred according to the gold standard were calculated. The results are not yet peer reviewed or published and hence are not yet public.

Whilst it is evident that NHSBT has a duty of care to donors to ensure they are not bled with significantly low haemoglobin levels, the implications of these results need to be considered in the context of the sufficiency of supply, the current reducing demand for red cells; the size of the donor base; together with the operational impact and cost of any changes.

The unpublished results of COMPARE confirm the findings of the INTERVAL trial in the rates of donors accepted with a haemoglobin result below the BSQR limits and showed that almost no donors are deferred when they could have donated using our standard method. Additionally, the post donation strategy, as tested, performed to a very similar level to our routine method. The safest device, in terms of the fewest donors accepted below BSQR limits, was the capillary HemoCue but it would also have deferred up to 14% of donors who could have donated. The non-invasive devices have been discounted because of their variability and operational issues that were identified during the trial. They will not be discussed further in this paper.

The implications of these results are that there is a risk that, without changing our processes, we could inadvertently bleed a donor, who is already anaemic, resulting in harm to them. We have considered a number of options to mitigate this risk which are discussed below. Some of these options could introduce a new risk, namely of increasing the numbers of donors failing the haemoglobin screening test resulting in a future reluctance to donate and hence a loss of donors, which in turn would result in costs being incurred to recruit more donors to stabilise the donor base.

5.2 Options Appraised:

5.2.1 Methods of testing with copper sulphate; We have reassessed how we perform the copper sulphate testing to ensure that we are using best practice. We have gone back to the original paper and we feel that method used in NHSBT could be improved upon. For example, using a pipette rather than a capillary tube alone can indirectly influence results, and our pass criteria include a more liberal criterion than in the original paper, additionally whilst the method allows for a repeat test to be done if a bubble or splattering of the drop occurs, some teams are repeating tests in a larger cohort of donors than would be expected. Work has started already to standardise the testing and will be rolled out as soon as possible.

We expect that these changes will minimise donors who are accepted inappropriately through the copper sulphate test.

5.2.2 Change the secondary testing regime to capillary rather than venous HemoCue. Results suggest that this would lead to fewer donors being accepted with levels below BSQR however we would also expect some donors having the secondary to be deferred unnecessarily, the numbers of these are not clear as the study did not discriminate between donors who were accepted or deferred due to copper sulphate or the secondary venous testing as this was a composite measure and, arguably, the donors being inappropriately deferred probably had higher haemoglobin results in the first place. However, we expect that the introduction of capillary testing would have some advantages of improving safety and minimising the operational impact of deferrals if it was rolled out more widely. Additionally, this change would help the sessions to run more smoothly as the disruption of having to do a venepuncture as the second test can be significant, donor carers could do the capillary test very easily within the continuous care model. We expect that this change will further minimise any donors accepted with a low haemoglobin as the capillary test accepted very few donors inappropriately.

Irrespective of the other options appraised below it is recommended that these changes are made as soon as feasible and the impacts assessed before making any other changes.

5.3 The other interim options assessed were:

5.3.1 Continue two stage copper sulphate/ venous HemoCue testing with a longer deferral of donors who fail the current screening test.

This would extend the current deferral period from 3 months to 6 months which will allow deferred donors longer to replenish their Hb. This has little operational impact and additional lost donations could be absorbed within current business plan. However, whilst this option allows deferred donors a greater opportunity to replenish their iron stores and increase their haemoglobin, in those with a low 'normal' haemoglobin and normal iron stores this might not be the case. In addition, if a more accurate method of using copper sulphate together with a capillary HemoCue test was implemented then the benefit of a six-month deferral rather than a three month deferral is not clear. For this reason, we feel that this change is not required at the current time.

5.3.2 Stop copper sulphate testing and move to testing all donors using capillary HemoCue.

Capillary Hb testing on all donors would defer the majority of donors who we currently bleed with a Hb level of less than 125g/l (women) or 135g/l (men) and would resolve the donor safety risks. However, if we switch to this option, we anticipate that we would also inappropriately defer an additional 14% of women and 11% of men who could have been accepted for donation. This is in addition to a potential increase in baseline deferral rates (from the current 3.5% to a likely 10%). This option is therefore considered to be untenable from a sufficiency of supply perspective; particularly of vulnerable groups where we could not recruit for a loss of 11-14% of donors. Additionally, there would be a severe operational impact and a severe impact on the donor base.

It should be noted however, that some countries routinely do use this technology without issue. The problems described above arise as the donor base has to equilibrate between techniques and it is the change of technology whole scale that will have the impact on the sufficiency of supply. Once the donor population has equilibrated we would foresee that this technology would not give ongoing problems. However, even with a staged implementation plan, the costs and loss of donors remain too high.

5.3.3 Continue copper sulphate test as the primary test for the majority of donors and implement capillary HemoCue as a primary test for a sub group of donors most at risk of developing iron deficiency anaemia.

This option was assessed for groups as follows:

- 3a) New Donors
- 3b) Females under age 50 yrs

5.3.3.1 New Donors: Our data shows the proportion of new donors who are inappropriately selected for donation is lower than that of returning donors. In addition, any new donors in a demographic group would be automatically included within that group. Therefore this option has been ruled out.

5.3.3.2 Females under 50 years: Iron deficiency in donors is most common in women of child bearing age. Whilst most women are relatively unaffected by iron deficiency, pre-existing iron deficiency through blood donation may have an impact on increasing iron deficiency in pregnancy, with potential effects on the outcome of pregnancy. There is, for example, good evidence that iron deficiency in pregnancy is associated with lower birth weights. Generally, the chances of becoming pregnant are greatly reduced over the age of 50 and, indeed, data confirms that this group has the greatest risk of being inappropriately accepted for donation.

The impact of introducing this as a method of haemoglobin screening however means that that this approach could result in up to 23% of women being deferred but the impact of this will be highest in the first 16 weeks post implementation with a decreasing effect thereafter.

This option could be implemented in a phased way by age-range bands and as directed by demand requirements. The operational impact of this option is less than implementing for all donors. However, the cost and operational impacts require further assessment and this should be piloted on a session, it should then be put through a risk based decision making framework to understand the costs benefits and risk tolerability if the changes to copper sulphate testing and secondary testing with capillary HemoCue are not sufficient.

5.4 Optimal future testing strategy

In addition, at the beginning of the INTERVAL study around 8.5% men and 24.5% women donors had ferritin levels below 15µg/L (which is the lower limit of the normal range). We are working to understand the level in the healthy general population and hence the degree that blood donation impacts on this. Furthermore, there were significant reductions in donors' ferritin levels during the study which was greater with more frequent donation, with up to 26% of women and 21% of men ending the study with serum ferritin levels 15µg/L. Many international blood services are now either introducing ferritin testing to prevent donors becoming anaemic and/or are introducing iron supplementation for donors. Our strategy has been to use donation intervals to prevent anaemia from occurring, however it would be useful to have an assessment of iron stores in our donors. Ferritin testing is expensive but a parameter on some FBC tests, called reticulocyte haemoglobin, may be a good surrogate marker. An additional benefit to post donation testing is operational efficiency together with the fact that almost no donors have their time wasted for a haemoglobin deferral. If, by introducing an algorithm to the post donation strategy, we could show this is safer than current screening methods, gives an assessment of donor iron stores, particularly if this allows some donors to donate more frequently, and is operationally efficient then this would be an attractive proposal and we recommend further work is done on this alongside work to deal with donors differently to understand the overall cost benefits and operational implications. This would also require discussions with our regulator and would require CSM to be finished in order to implement.

5.5 Indicative costs:

The introduction of improved copper sulphate testing and capillary HemoCue can be done within current budgets. Options that would impact on deferral rates with the subsequent potential loss of donors and requiring significant donor recruitment will have a cost impact, particularly because of the need to recruit more vulnerable group donors. Projected figures

are based on the need to recruit ten new donors to get one lost O negative donor. Initial assessment of a change to capillary HemoCue screening of women under 50 suggests that this figure would be in the range of £2.3M to recruit sufficient new donors, based on current donor loss rates (40-50%) following a haemoglobin deferral. However, this does not consider alternative strategies to mitigate the loss of donors deferred and is projected from deferral rates in all donors, it should therefore be considered a worst-case scenario financially and would be further informed by the pilot prior to any plan to implement. If the proposed changes of improving copper sulphate methodology and using capillary HemoCue for secondary testing mitigate the risk to donors then no additional marketing costs will be incurred.

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