Systematic Reviews Regarding Iron and Iron Supplementation in Blood Donors

by

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Submitted in partial fulfilment of the requirements for the award of the degree of Professional Doctorate in Health Science of the University of Portsmouth

September 2014
Abstract

**Background:** Blood donors are required to exceed a minimum haemoglobin level before they donate; those who fail are temporarily deferred from blood donation. In this way, donor health, and that of the recipient (patient), is assured and a drain on blood collection resource is avoided. Knowing what factors contribute to donors failing to reach these levels and whether provision of iron supplements decrease deferral rates would prove beneficial to blood collection agencies.

**Methods:** Two systematic reviews of available literature were conducted after searching on-line databases. The first looked at observational studies of demographic data, donation history and haematological and biological factors that might be associated with deferral from blood donation. The second review studied only randomised controlled trials and was carried out using the protocols and facilities of the Cochrane Collaboration to assess the efficacy and safety of iron supplementation to reduce iron deficiency and/or anaemia.

**Results:** Fifty-five studies met the inclusion criteria for the first review, thirty studies were included in the second. Key findings are:

1. Females show a significantly greater risk (11-fold) of donor low haemoglobin deferral as compared to males.
2. Higher deferral rates were also associated with increasing age, higher ambient temperature, lower body mass, shorter donation interval or being of certain ethnicity.
3. Donor deferral is reduced by taking iron supplements but the evidence is moderate.
4. Those taking iron supplementation are subject to more frequent adverse events.

**Conclusions:** These peer-reviewed and published works help define criteria that should be considered in large scale studies of donor deferral, especially any which attempt to address failure to meet low haemoglobin thresholds. Additionally, although donors may benefit from iron supplementation, the risk of side effects means it is unlikely to be a universal treatment. Together these reviews may help determine suitable donation intervals which decrease risk of donor iron-deficiency.
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Declaration

Whilst registered as a candidate for the above degree, I have not been registered for any other research award. The results and conclusions embodied in this thesis are the work of the named candidate and have not been submitted for any other academic award.

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<td>BCSH</td>
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<td>BMI</td>
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<td>MCV</td>
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<td>CD</td>
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<td>FBC</td>
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<tr>
<td>IPC</td>
<td>Iron(III)-hydroxide polymaltose complex</td>
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<td>Iron Supplement/ation</td>
<td>vCJD</td>
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<td>Intention To Treat</td>
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<td>Journal Impact Factor</td>
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<td>JPAC</td>
<td>Joint UK Blood Transfusion and Tissue Transplant Services Professional Advisory Committee</td>
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<td>LHD</td>
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Acknowledgements

I am grateful to Drs. Agnihotri, Arslan, Charles, Chaudhary, Custer, Hillgrove, James, Mustaffa, Kouao, Pandey, Sundar, and Shaz for the provision of additional information and data which has been included in the study in Chapter 2 and to Emma Sydenham and Dierdre Beecher (the Cochrane Collaboration) for their help and advice during the preparation of the Cochrane review.

I should like to thank Susan Brunskill of the Systematic Review Initiative (SRI) for her advice during the development of the protocols for these studies, my co-authors from SRI (Dr Carolyn Dorée) and NHSBT/ Oxford Biomedical Research Centre (Professor David Roberts, also my workplace supervisor) for their forbearance and guidance and most especially with Dr Sheila Fisher who patiently guided me through the systematic review process and helped me with general advice for my thesis.

I also wish to thank Wendy Slack, NHSBT R&D Business Manager and Carole Gill, University of Portsmouth (UoP) lecturer, who helped guide me through the vagaries of Word formatting before I deleted the whole project, and Dr Dave Allen and his daughter, Frances Allen, who kindly proof-read this dissertation. Any remaining errors are entirely my oversight.

Thanks go to Dr Sally Kilburn (UoP) who first suggested the possibility of systematic review for a doctorate project and who, with help and advice from Dr Amy Drahota (UoP), supervised me over the next three years.

Barnet and Chase Farm Hospitals NHS Trust and Surrey Pathology Services provided me with study leave to carry out the necessary meetings with members of SRI, related research groups and for supervisory meetings.

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or the UoP.

I should like to dedicate this thesis to my wife, Juliet, and my three boys, Nathaniel, Cameron and Joel, who had to endure my long absences during the research and especially during the writing of this project. I hope I can now spend the time with you that you deserve.
Dissemination

Two papers were published as a result of the research carried during the preparation of this thesis:


A more extensive discussion of the dissemination of this research is given in Chapter Four.
Chapter 1 – Introduction

This chapter introduces National Health Service Blood and Transplant (NHSBT) and describes their role in the supply of blood and blood products, their relationship with blood donors and the effect of donation on donor health. It will outline iron regulation and metabolism, what happens when the body experiences an iron deficiency and how iron supplementation is used to treat that deficiency.

Secondly, I will discuss the importance of evidence-based medicine (EBM), how systematic reviews contribute to EBM. Particular emphasis will be made of the Cochrane Review process.

Finally, I will give an overview of how NHSBT is committed to improve blood supply through a programme of research to produce an evidence base for new modes of practice. In this way I can demonstrate the origins of this project in the context of where it fits within the aims of the NHSBT and how it will help inform future practice. These will be discussed with regards to its importance to the blood donor and how it relates to future studies of donor health.
1.1 Blood donors, iron and iron supplementation

1.1.1 National Health Service Blood and Transplant (NHSBT) and blood donors

NHSBT is a Special Health Authority formed in 2005. It operates primarily within England and North Wales but has additional responsibilities for organ donation and transplantation across the United Kingdom. It comprises of the National Blood Service (NBS – concerned with blood supply) and Stem Cell, Tissue and Organ Donation and Transplantation (NHSBT, n.d.-d).

Through the provision of a safe and reliable supply of blood components, solid organs, stem cells, tissues and related services to both the NHS and other UK health services, its stated core purpose is to 'save and improve lives'.

In England, NHSBT is responsible for maintaining the supply of blood and blood products to approximately 350 hospitals within the NBS catchment area in England (NHSBT, n.d.-a). Blood is collected from volunteer donors and processed into constituent components (red blood cells - RBC, plasma and platelets) on an almost industrial scale. The collection process may be manual, producing multiple components from one whole blood (WB) donation, or by machine (apheresis) to produce a greater volume of a single component. RBCs are the most frequently transfused blood component, with NHSBT collecting over two million blood donations from 1.4 million donors in 2011-12, and supplying 1.7 million units of RBC for transfusion (NHSBT, n.d.-a). During that period NHSBT also supplied some 250,000 platelet donations, 87% of them being produced by 13,000 plateletpheresis donors (Gheveart, 2013).

Having adequate supplies to meet the needs of health services with respect to donor collection is becoming increasingly difficult. In part this is due to changes in attitude within society to the act of donation, especially in young people (“Chloe”, 2012) and, in part, because of over-reliance on more useful blood groups (O Rh D Negative donors comprise only 7% of the population but are used in 11% of transfusions, especially as a “Universal Donor” for emergency issue, and so are frequently in short supply (Better Blood Transfusion Team, 2012)).

Furthermore, it may be difficult to obtain compatible blood for multi-transfused patients developing multiple or widely reactive antibodies, for example patients with thalassaemia or myelodysplasia, or for patients with rare blood groups. These problems are compounded by the potentially devastating impact of emerging
infectious diseases transmissible by transfusion as shown by the clinical and economic impact of variant Creutzfeldt-Jakob disease (vCJD) on the supply of blood components in the UK in the past decade (Turner & Ludlam, 2009). This current trend of declining rates of blood donation, combined with an increase in the requirement for blood components, is likely to continue in coming years (Seifried et al., 2011).

In order to ensure the quality of the blood supply to the patient and the continued health of the donor, members of the population undergo rigorous health screening prior to donation, part of which is exceeding a minimum blood haemoglobin (Hb) level. Blood donors may fail this Hb test, which means they are unable to donate on that occasion and are “deferred” to a future donation date, or even permanently excluded. Studies have shown that those deferred may well become reluctant to try again (Custer, Chinn, Hirschler, Busch, & Murphy, 2007). Ensuring donors have a good experience is very important and identified as such in the NHSBT Annual Review for 2012-13 (NHSBT, n.d.-b). What factors lead to a blood donor failing the Hb test and whether the NHSBT can, by giving the donor access to iron supplementation, improve retention of donors and thereby improve blood supply, is poorly understood.

Iron deficiency remains a significant cause of morbidity in both the general population and blood donors (Baart, de Kort, Moons, & Vergouwe, 2011). Up to 5% of new donors (and a similar percentage of regular donors) cannot be accepted because of low Hb levels, leading to deferral. Little is understood as to why some individuals are unable to donate repeatedly, how measures of iron stores are affected by blood donation or why some donors are more susceptible to iron deficiency than others.

In England, each donation of whole blood (470 mL/unit plus 30 mL samples) contains approximately 250 mg of iron (Page, Coppock, & Harrison, 2010); with the maximum permissible frequency of donation being 3 - 4 times a year (Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC), 2013). A "double-dose" of red cells (two red cell units collected by machine in a process termed apheresis) may be collected every 26 weeks (Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC), 2013). Platelet donation by apheresis results in a lower loss of blood per donation (~100 mL) but the increased frequency of donation (up to 24 times per year) is equivalent to 4 - 5 whole blood donations (Page et al., 2010). If this iron is not replaced then donors may deplete their iron stores and become iron deficient or develop frank iron-deficiency anaemia (Simon, Hunt, & Garry, 1984). Blood services
have a duty of care, both for blood donors and patients. Not only do they need to ensure an adequate blood supply to service the needs of the patient, they also need to ensure the donor is fit to donate. For the donor there is a need to avoid both the harmful effects of donation and their deferral due to their Hb falling below the current UK Guideline level of 125 g/L for females or 135 g/L for males (Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC), 2013). Indeed, these minimum levels are themselves by no means universally adopted by the World’s Blood Transfusion Services and have only recently been increased by the NHSBT in response to EU legislation. After donation, Hb levels fall too far to permit repeat donation on schedule in up to 10% of donors each year (Baart et al., 2011).

Although donor management practices are aimed at donor safety, they can have an adverse effect on future donor behavior (Custer et al., 2007). Deferral is associated with non-return of donors, with up to 75% of deferred donors not attending in the following year (Bianco et al., 2002). Ever more restrictive donor selection criteria and demographic changes have reduced the numbers of first time donors and the recruitment and care of donors has become a vital issue for Transfusion Services. Therefore it is necessary not only to minimise deferral but also reduce the risk of provoking iron deficiency or anaemia to optimise the number of donors and donations.

It is well known that Hb levels and measures of iron stores fall in regular blood donors, particularly in pre-menopausal women (Alvarez-Ossorio, Kirchner, Kluter, & Schlenke, 2000; C. A. Finch, Cook, Labbe, & Culala, 1977; Milman, 1996; Skikne, Lynch, Borek, & Cook, 1984; Worwood & Darke, 1993). Other factors have been associated with increased rate of deferral. Hoekstra, Veldhuizen, van Noord, and de Kort (2007) reported a seasonal fluctuation in Hb levels leading to increased deferral during the summer months. Age and race/ethnicity have both been shown to have an effect on Hb in whole blood donors and plateletpheresis donors (Alvarez-Ossorio et al., 2000; Jeremiah & Koate, 2009; Shaz, James, Hillyer, Schreiber, & Hillyer, 2010; Tondon, Pandey, & Chaudhry, 2008). Additionally, Mast et al. (2010) found, in men, body weight to be inversely proportional to Hb level and attaining a higher education level decreased the risk of deferral due to low Hb.
1.1.2 Iron

The human body contains 3 - 4g of iron, mainly associated with oxygen-binding proteins such as haemoglobin (blood) and myoglobin (muscle), but also with transport or storage proteins. It acts as a co-enzyme in the transfer of electrons by cytochromes, peroxidases, ribonucleotide reductases and catalases. Iron is stored bound to protein in two forms within the body – an insoluble complex known as haemosiderin and a soluble form found in all cells, known as ferritin. Transport of iron is by the blood plasma glycoprotein, transferrin.

Iron balance (homeostasis) is regulated by intestinal absorption, but there is no mechanism for physiological excretion; losses result only from bleeding and exfoliation of skin and mucosal cells. Approximately 1 - 2 milligrams of iron are both gained daily in the diet and lost by excretion (see Figure 1.1). As with most metabolic processes, the level of iron is critical: too high a level (iron overload) can lead to cirrhosis, diabetes, cardiomyopathy, arthritis and testicular failure; too low a level (iron deficiency) to anaemia (IDA), irritability, weakness, pica and restless legs syndrome.

The amount of iron absorbed compared to the amount actually ingested is typically low and dependent on a number of factors. The efficiency with which iron is absorbed varies depending on the source. In general, the best absorbed forms of iron come from animal products. Iron from animal (heme) and some plant (non-heme) sources is absorbed more efficiently (15% to 35% of intake), whereas between 10% and 20% of iron in iron salt form (as found in most supplements) is absorbed.

Absorption of dietary iron varies according to the body's need for iron, typically iron is absorbed at only 1 - 2mg/day (equivalent to a dietary intake of ~15 mg/day). More absorption occurs in the iron-deficient individual. For example: an adolescent requires 2 – 3 mg/day, as does a fertile woman whereas a pregnant woman needs 3 – 4 mg/day. A maximum level of 4 mg iron a day is capable of being absorbed (Provan, 2009). However, the amount of iron absorbed decreases with increasing doses. For this reason, and to avoid the toxic effects of iron poisoning (plasma iron levels of greater than 350-500 μg/dL) it is recommended supplements are taken in smaller, equally spaced, doses (Office of Dietary Supplements, 2014).
Iron Gain
in food
~15 mg/day

Iron Loss
Desquamation
Sloughed mucosal cells
Menstruation (+other blood loss)
(~1-2 mg Fe/day)

Duodenal absorption
(~1-2 mg Fe/day)

Erythropoiesis in bone marrow
(300 mg)

Muscle myoglobin
(300 mg)

Liver parenchyma
(1000 mg)

Iron Gain
in food
~15 mg/day

Plasma transferrin
(3 mg)

Fe recycling by macrophages in liver and spleen (30 mg Fe/day)

Reticulo-Endothelial system
(600 mg)

Red blood cells
(1800 mg)

Figure 1-1: Iron distribution in the body.
Adapted from Andrews (1999) and Roberts (2012).
As a healthy gastro-intestinal tract (GIT) is important for efficient absorption then factors that affect the GIT (gastritis, gastric surgery, coeliac disease) may affect the body’s ability to assimilate iron. Rates of absorption can be affected by the diet. Orange juice (and vitamin C in general), pickles (vinegar-containing), soy sauce and alcohol are all known to enhance iron absorption whereas tea, coffee, oregano and milk are inhibitors. Foods with high levels of iron include pulses, clams, meat, liver, tofu and oatmeal. Vegetarians have higher levels of IDA compared with non-vegetarians as the body does not absorb the type of iron found in plants as well as it absorbs the iron from meat (International Nutritional Anemia Consultative Group (INACG), 1998).

As previously stated, donating a unit of red cells removes ~250 mg of iron from the body’s store and it has been suggested a regular blood donor needs to absorb 3 – 4 mg/day to replenish lost RBC iron stores (C. Finch, 1994; Page et al., 2010).

### 1.1.3 Iron deficiency

Iron deficiency has been described as occurring in three progressive phases:

1. Initially, stored iron in the bone marrow diminishes due to insufficient supply. Usually this stage is asymptomatic, has no apparent effect on erythropoiesis, and escapes detection i.e. the donor would pass an Hb screening test.

2. The second stage, of iron deficiency, is when continued depletion leads to substantially reduced storage levels and Hb production begins to be affected. The donor may, or may not, pass the screening test at this time.

3. Finally, full IDA develops at a point when iron stores are insufficient to maintain Hb production. This advanced stage is reflected in low Hb values and it is only at this time that the donor would fail the low Hb threshold (Lesperance, Wu, & Bernstein, 2002; Wu, Lesperance, & Bernstein, 2002).
1.1.3.1 Anaemia

The term "anaemia" derives from the Ancient Greek meaning "lack of blood". Although most commonly defined as having too few, or smaller, red blood cells, measurement of anaemia is most often in terms of reduced Hb levels. Less frequently, it refers to a decreased oxygen-binding capacity of Hb due to reduced number of molecules or deformity within those molecules. Therefore, an automated full blood count (FBC) would reveal the red cell count (RCC), the size of those red cells via the mean cell/corpuscular volume (MCV) and the level of Hb within those cells (Mean Cell/Corpuscular Haemoglobin Concentration – MCHC). Decreased oxygen-binding can only be revealed by additional tests (usually biochemical in nature) and the underlying reason for the abnormality might require genetic testing.

Anaemia diagnosis can be broadly split into two approaches – morphological and kinetic. The first differentiates on the basis red cell size (MCV) and colour (MCHC); cells being termed microcytic (MCV <80fL), normocytic (MCV = 80 – 100 fL) or macrocytic (MCV >100 fL); hypochromic (MHCH <315 g/L), normochromic (MHCH = 315 – 330 g/L), or hyperchromic (MHCH >330 g/L) - see Fig 1.2 below. The kinetic approach to diagnosis involves the enumeration of reticulocytes, showing the degree of new red cell production by the bone marrow. The latter approach is more common in the US (Munker, 2007; Silver, 2010).

1.1.3.1.1 Microcytic anaemia

This is primarily the result of the failure of, or inadequate, Hb synthesis. There can be defects in heme synthesis (e.g. IDA), globin synthesis (alpha- and beta-thalassaemia, HbE and HbC syndromes) or sideroblast production (hereditary or acquired sideroblastic anaemia). Populations with a high incidence of these disease states would be more likely to fail the low Hb thresholds set for those where no such predisposition exists.

IDA is the most common type of anaemia and results from insufficient dietary intake or absorption of iron to meet the needs of the individual (Hoffbrand, Moss, & Pettit, 2006). However, IDA has many causes and common in the developed world is through bleeding or blood loss, especially from the GIT, menstrual bleeding and frequent blood donation. World-wide the most frequent cause of IDA is parasitic infection. Not only is the anaemia in IDA microcytic, but it is also hypochromic (having reduced colour – MCHC - due to containing less Hb).
Macrocytic and normocytic anaemia

Megaloblastic anaemia, a deficiency in vitamin B12 and/or folate, is the most frequent cause of macrocytic anaemia resulting in decreased red cell production. Vitamin B12 deficiency is both macrocytic and normochromic. Hypothyroidism, alcoholism and certain drugs (methotrexate and zidovudine) cause anaemia described as non-megaloblastic anaemia.

Normocytic anaemia – where RBC are of normal size but the Hb level within that cell is decreased – occurs in cases of acute blood loss, chronic disease, aplastic anaemia and haemolytic anaemia.

Figure 1-2: Morphologic classification of anaemia, showing the common red cell form in iron-deficiency anaemia (circled) (The McGill Physiology Virtual Lab, n.d.).
Although the individual blood donor may suffer with one or more of these, neither macrocytic or normocytic anaemia results from donation (as far as we know). However, they may affect a population with poor nutrition (megaloblastic) or a higher level of alcoholism (non-megaloblastic) or of parasitism (microcytic) (Hoffbrand et al., 2006; Munker, 2007).

### 1.1.3.2 Physical symptoms of Anaemia

As mentioned earlier, there are a number of physical manifestations of anaemia. In addition to commonly understood complaints such as lethargy, tiredness, dyspnoea on activity and cognitive impairment these include:

- **Pica** – a tendency to eat non-nutritive, non-food, substances (such as soil, hair or sand) over an extended period of time (usually around four weeks). It is thought to be a “specific hunger” – a need to eat substances containing something missing from the normal diet – in this instance iron.

- **Restless Legs Syndrome (RLS)** is characterised by an urgent need to move the body to try and relieve a seemingly unrelenting and uncomfortable or odd sensation, most often in the legs. Activity helps relieve the condition and continued movement provides ongoing relief. Although the exact mechanism is unknown studies have shown differences in iron-related markers (ferritin levels, etc.) comparing groups of RLS sufferers with controls. The dopamine system within the brain has been postulated as being involved (Clemens, Rye, & Hochman, 2006).

### 1.1.4 Measures and measurement of iron, iron deficiency and anaemia

Table 1.1 gives a brief outline of a number of haematological and biochemical parameters used within the systematic reviews detailed in Chapters 2 and 3 to measure the effects of blood donation on iron homeostasis. It should also be made apparent that the measurement of these parameters is dependent on the blood donation setting. What methods are available to a “mobile” session (i.e. one where a blood donation team travels to a facility where they set up a temporary collection site) differ to those found at a “static” (fixed) site. Indeed, static sites themselves differ, in that they may be permanently situated in a hospital or blood transfusion centre or be in a blood collection unit on a remote site.
Table 1.1: Haematological and biochemical tests for iron status

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (±2SD) or Range</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (Hb)*</td>
<td>150 (±20)</td>
<td>9.31 (±1.24)</td>
<td>135 (±15)</td>
</tr>
<tr>
<td>Red Cell Count (RCC)*</td>
<td>5.0 (±0.5)</td>
<td>4.3 (±0.5)</td>
<td>x 10¹²/L</td>
</tr>
<tr>
<td>Haematocrit (Hct)*</td>
<td>0.45 (±0.05)</td>
<td>0.41 (±0.05)</td>
<td>L/L</td>
</tr>
<tr>
<td>Mean Corpuscular / Cell Volume (MCV)*</td>
<td>92 (±9)</td>
<td>92 (±9)</td>
<td>fL</td>
</tr>
<tr>
<td>Mean Cell Hb (MCH)*</td>
<td>29.5 (±2.5)</td>
<td>29.5 (±2.5)</td>
<td>pg</td>
</tr>
<tr>
<td>Mean Cell Hb Concentration (MCHC)*</td>
<td>330 (±15)</td>
<td>330 (±15)</td>
<td>g/L</td>
</tr>
<tr>
<td>Ferritin (Serum or Red Cell)</td>
<td>30 -300</td>
<td>10 -200</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Transferrins</td>
<td>240 -450</td>
<td>250 -370</td>
<td>45-66</td>
</tr>
<tr>
<td>(Soluble) Transferrin receptor (TfR)</td>
<td>9.6 – 29.6</td>
<td>9.6 – 29.6</td>
<td>nmol/L</td>
</tr>
</tbody>
</table>
## Test Mean (±2SD) or Range Units Description

<table>
<thead>
<tr>
<th>Test</th>
<th>Male</th>
<th>Female</th>
<th>%</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net Iron Absorption</td>
<td>60-170</td>
<td>60-170</td>
<td>%</td>
<td>Amount of iron ingested, less that recovered in faeces, given as a percentage. This would be increased in IDA.</td>
</tr>
<tr>
<td>Serum/plasma Iron</td>
<td>60-170</td>
<td>60-170</td>
<td>µg/dL</td>
<td>Measures how much iron is in the blood [bound to Transferrin]. Serum iron is decreased in IDA due to depletion of stores (Lesperance et al., 2002).</td>
</tr>
<tr>
<td>Total Iron Binding Capacity (TIBC)</td>
<td>250–370</td>
<td>250–370</td>
<td>µg/dL</td>
<td>A measure of how much transferrin (the iron-carrying protein) is present in the blood which indicates iron availability to tissues and is raised in IDA.</td>
</tr>
<tr>
<td>Transferrin Saturation Percentage</td>
<td>15 – 50</td>
<td>12 – 45</td>
<td>%</td>
<td>Abbreviated as TSAT and reported as a percentage. it is the ratio of serum iron and TIBC, multiplied by 100. Of the transferrin that is available to bind iron (transferrin has ~4500 iron binding sites per molecule) this value informs how much serum iron is actually bound, e.g. a value of 15% means that 15% of iron-binding sites of transferrin are being occupied by iron. It is a measure of iron in transport, not in stores. A combination of high TIBC and low amounts of iron in IDA typically gives a TSAT of &lt;5% (values of 5 -10% indicate possible, but not definitive, IDA). When used in combination with another variable (such as sTfR) it has improved sensitivity and specificity for response to iron therapy.</td>
</tr>
<tr>
<td>Free Erythrocyte Protoporphyrin (FEP)</td>
<td>160-360</td>
<td>160-360</td>
<td>µg/L red cells</td>
<td>FEP is a heme precursor, which reflects incorporation of iron into the Hb molecule. The test assesses whether there is too little iron in the blood by measuring the non-complexed, non-heme protoporphyrin concentration and the levels are seen to rise in IDA.</td>
</tr>
<tr>
<td>Zinc Protoporphyrin (ZPP)</td>
<td>≤40</td>
<td>≤40</td>
<td>µmol/mol heme</td>
<td>When an individual has anaemia, zinc is incorporated into protoporphyrin in place of iron. ZPP is a by-product of disordered heme synthesis, with higher ZPP levels indicating greater anaemia. It is not specific for IDA, being raised in conditions where iron is not deficient, such as lead poisoning and α- and β-thalassaemia traits. (Thomas et al., 2013). Current practice is to measure on washed red cells and report the molar ratio of ZPP to heme (µmol/mol).</td>
</tr>
</tbody>
</table>

* The results of serum iron, TIBC and TSAT are usually reported together.
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1.1.4.1 Measurement of IDA in blood donors

Copper sulphate (CuSO\(_4\)) screening

Within the UK the routine anaemia screening test for blood donors is the copper sulphate (Cu\(^{2+}\)SO\(_4\)) gravimetric method (M. H. Miller, 1947). A drop of blood taken by finger-prick is placed on the surface of a 30 mL tube of Cu\(^{2+}\)SO\(_4\) solution and has to sink to the bottom within a certain time (30 seconds). The Cu\(^{2+}\)SO\(_4\) solution is of a specific gravity (SG) set to allow only red cells above a minimum Hb level to sink; the SG being different for men and women. The Hb threshold for men is set at 135 g/L; for women it is 125 g/L (NHSBT, n.d.-c).

Point of Care Testing (POCT) by colorimetric determination

If a donor has too low an Hb for the cells to sink, they are retested using a portable Hb meter (HemoCue\textsuperscript{®}) which uses a cyanmethaemoglobin colorimetric determination system on a 10 \(\mu\)L blood sample from a fingerprick. These are reputedly as accurate as the automated haematology analyser mentioned below.

Automated haematology analyser

These are bench-based machines that rely on a variety of methodologies (usually colorimetric) and use a separate venous blood sample. They not only measure Hb but can determine a number of other useful parameters. Those concerned with the estimation of iron and iron-deficiency are shown as "*" in Table 1.1 (Lewis, 2006).

Other tests

At present, other than Hb and Hct, there appear to be no POCT devices that can be easily employed to screen donors prior to donation for any of the indices mentioned above. This means that a blood collection service is limited to only preventing donation from those donors with stage three ID, i.e. a drop in Hb levels to such an extent that the donor fails the anaemia screening tests. However, in the UK the low Hb threshold is set at such a level there is still a margin of 5 g/L before the donor becomes clinically anaemic according to the WHO definition (World Health Organization, 2011). It might be considered a duty of care to retrospectively test these donors who have passed the Hb screens after having given blood within a static testing laboratory for a marker of IDA such as ferritin. If there are indications of stage one or two ID, they may be temporarily deferred from donation until their iron stores have recovered (possibly after being offered a course of iron supplementation). These tests would attract a significant additional cost for the collection service which may not be offset by increased donor retention.
1.1.5 Iron Supplementation (IS)

Figure 1-3: Iron Jelloids (Ferrous sulphate/Vitamin B1, B2 & C preparation) from 1930s. Photograph taken at Bucks Railway Museum, Quainton.

Blaud’s pills were the first iron pills and were named after P. Blaud of Beaucaire, the French physician who introduced the use of these medications as a treatment for patients with anaemia (Robinson, 1939). Since that time, the number of Iron supplements (IS) has proliferated, with the number of preparations listed in the catalog.md website reaching over 600 (catalog.md, 2013).

1.1.5.1 Indications

IS are primarily used to treat iron-deficiency and iron-deficiency anaemia, although parenteral (intra-venous, intra-muscular) iron preparations can be used to treat malabsorption problems, such as inflammation of the gut. It is only after other causes of anaemia have been excluded (vitamin B12/folate deficiency, lead poisoning, drugs) that IS should be considered.

1.1.5.2 Administration

Iron stores are regulated through absorption of iron and so interventions either directly or indirectly increase iron available for absorption. This could be in the form of dietary advice to increase the amount of iron-rich food or in the form of oral iron supplementation, such as iron salts. Parenteral iron is unlikely to be a common intervention for blood donors as invasive procedures are costly in terms of money, time and risk of infection.
1.1.5.3 Oral route

The most common and cheapest iron salt is ferrous (II) sulphate but it is also available complexed to gluconate, dextran, carbonyl iron, and other salts. Ascorbic acid (Vitamin C) is sometimes added to the preparation (or taken as an accompanying medication) for better absorption.

When standard preparations, such as ferrous sulphate or ferrous fumarate, are not tolerated or readily absorbed then heme iron in the form of a polypeptide (HIP) can be used. A clinical study demonstrated that HIP increased serum iron levels 23 times greater than ferrous fumarate on a milligram-per-milligram basis (Seligman, Moore, & Schleicher, 2000).

Ferrous glycine sulphate is another alternative which has been shown not only to have a very high bio-availability (especially as a liquid) but also to result in fewer GIT side-effects than regular iron supplements, such as ferrous fumarate (Aronstam & Aston, 1982).

Ferrous (2+) salts are three times more bioavailable than ferric (3+) salts, as ferric salts have to be first reduced to the ferrous form by stomach acid before entry to the mucosal cells (Tom, 2008).

A further option would be to offer blood donors dietary advice, especially in those who would be averse to taking pills. Not only could they be directed towards high iron-containing foods, such as outlined in the introduction (Section 1.1.2), but there are commercial preparations of naturally-occurring spring water which have a high iron content.

Oral iron has a higher frequency of intolerance and, coupled with a slower rate of improvement, is often replaced by parenteral iron in an acute setting. This would not be a common intervention for blood donors.
1.1.5.4 Parenteral routes

Parenteral iron therapy (by intravenous or intramuscular injection) is usually given when oral therapy has failed (not tolerated by the recipient), oral absorption is seriously impaired (by illness, or by inability to swallow), benefit from oral therapy is unlikely or a rapid improvement is required (e.g. prior to an elective procedure). None of these conditions is likely to be found in the blood donor. Parenteral therapy is more expensive than oral iron preparations, requires an additional invasive procedure which requires more time and skilled staff to perform. As such, the number of studies of parenteral IS in blood donors is likely to be few.

1.1.5.5 Side effects

The most common side effects found with oral iron therapy are diarrhoea, constipation or epigastric (the area of central abdomen lying below the sternum and above the umbilicus) pain. Stools may become black. If iron supplements are given in liquid form teeth may become discoloured (although not irreversibly so) and the site of intramuscular injection can become sore and discoloured. Donors should be made aware of these symptoms so they may counteract their effect by taking stool softeners or adding fibre to their diet, or by discontinuing treatment. In the case of oral iron, symptoms are ameliorated if the supplement is taken after a meal. However, there is an increased risk of interaction with foodstuffs and alteration of pH that may decrease absorption.

Side effects are dose-dependent, so the dose may need to be adjusted for the donor. Starting with a lower dose than the daily recommended amount, then gradually increasing to the full dose, may help minimise side effects (Hayhoe, 1960).

Bivalent iron (Fe$^{2+}$) salts, such as ferrous sulphate have been associated with more adverse effects than trivalent (Fe$^{3+}$) salts (Santiago, 2012), especially if not in a prolonged-release formulation such as iron (Fe$^{2+}$) bis-glycinate chelate (Ashmead, 2001; Szarfarc, de Cassana, Fujimori, Guerra-Shinohara, & de Oliveira, 2001). However, although side effects tend to be reduced when trivalent iron (such as iron (III)-hydroxide polymaltose complex –IPC) is used, the treatments are absorbed more slowly and are more expensive (Geisser, 2007; Saha, Pandhi, Gopalan, Malhotra, & Saha, 2007; Toblli & Brignoli, 2007) when compared to treatments with iron (II) sulphate, although there is some evidence to the contrary (Tom, 2008).
1.1.5.6 Contraindications

Before commencing treatment for anaemia it is essential to determine the type of anaemia present, as inappropriate dosing with iron salts can result in iron overload in non-IDAs. Hypersensitivity has been documented to all formulations. Some can be used in ID, others require IDA to be present. Some (especially parenteral preparations) are also contraindicated in those with a history of allergy, such as asthma and eczema, infection and rheumatoid arthritis (Joint Formulary Committee, 2014).

1.1.5.7 Interactions

In addition to those with food, it is recommended an interval of 2 – 3 hours between the iron intake and that of other drugs is advisable. Donors would tend to be less likely to be on a course of medication (as many drugs would exclude them from donating) but any delay between having to take different drugs would make it less convenient and so may have an impact on compliance.

1.1.5.8 Precautions

Iron in too large a quantity acts on the mucosa and results in haematemesis (vomiting of blood) and diarrhoea with patients becoming hypovolaemic due to fluid and blood loss. It is recommended adults should not take any more than 45 mg of iron a day unless they are being treated with iron under close medical supervision (not a common situation for the blood donor). At an absorption rate of 10% this is close to the 3-4 mg suggested as being the recommended daily requirement needed to replenish lost RBC iron stores in a regular blood donor (C. Finch, 1994).

With iron ingestion of 20 - 40 mg/kg individuals can demonstrate signs of gastrointestinal toxicity resulting in systemic iron toxicity. Severe overdose causes impaired oxidative phosphorylation and mitochondrial dysfunction, which leads to cellular death. The liver is one of the organs most affected by iron toxicity, but other organs such as the heart, kidneys, lungs, and the haematologic systems also may be impaired.
Individuals with the hereditary disorder haemochromatosis can absorb up to 30% of the iron they ingest, much more than the 10 - 20% of normal individuals, and so have trouble regulating their iron absorption. As such, the iron in their body can more rapidly build up to the dangerous levels seen in iron overload, with the resultant iron deposits in organs leading to cirrhosis, heart failure and diabetes. For that reason, haemochromatosis sufferers have been excluded from this study as they should not take iron supplements.

1.1.6 Iron Supplementation (IS) in Blood Donors
To be able to donate, blood donors have to answer a number of questions regarding their lifestyle, health, risk of infection and travel prior to donation (donor health check - DHC), as well as exceed minimum physical requirements such as weight and Hb level. Donors with major illness, recent cold, fever, infection, gastrointestinal upset or generally feeling unwell are deferred from donating.

A number of markers of iron-deficiency have been studied in existing Cochrane reviews, both of iron stores (ferritin) and circulating iron and iron available for erythropoiesis (serum iron, Total Iron Binding Capacity [TIBC] and percentage of Hb saturated with oxygen [% saturation]). Haemoglobin levels and measures of iron deficiency fall in regular blood donors, particularly in pre-menopausal women (Alvarez-Ossorio et al., 2000; C. A. Finch et al., 1977; Milman, 1996; Skikne et al., 1984; Worwood & Darke, 1993).

A blood collection service such as the NHSBT has a duty of care to maintain the health of its donor base. Not only does this mean not over-bleeding its donors, but also they should not be seen to be putting their donors at a potential risk of iron-overdosing. Should they consider providing IS, then it would be a fine balance between providing sufficient iron to make a meaningful contribution to avoiding anaemia but not enough that a donor could inadvertently suffer from iron toxicity.
1.2 Evidence-based practice (EBP), the Cochrane Collaboration and the NHSBT Systematic Review Initiative (SRI)

1.2.1 Evidence-based practice
Although the belief in an evidence-base for medical intervention has been in existence for hundreds of years, momentum gathered pace in the UK during the early 1990s and was crystallised in the paper by Sackett, Rosenberg, Gray, Haynes, and Richardson (1996). Here it was explicitly stated that that the current best evidence was to be used in the making of decisions regarding the care of individual patients. The current best evidence is a bottom up approach amalgamating both external evidence with individual clinical expertise and the wishes of the patient. It is a fundamental belief behind the National Institute for Health Research (NIHR), founded in 2006 to improve the research environment by patient involvement, improved funding and reduced bureaucracy. The medical Royal Colleges informed Parliament on the 25th April 2013 that EBM was key to the success of modern healthcare (Academy of Medical Royal Colleges, 2013).

How this is brought about varies between institution, from the five stages of EBP outlined on the evidence-based nursing practice website (Evidence Based Nursing Practice, n.d.) to the seven steps of EBP described by Melnyk, Fineout-Overholt, Stillwell, and Williamson (2010). Whether they include the nurturing of a questioning environment, or the dissemination of the research as a separate step, they hold to a number of common processes:

1. Ask the (research) question
2. Find the evidence
3. Appraise that evidence
4. Act on it
5. Evaluate and reflect on those actions

1.2.2 The hierarchy of evidence
Not all evidence is created equal. It has been recognised for some years that research findings differ in their quality in terms of the risk of both error and bias. A number of different hierarchies exist (1979; Cook, Guyatt, Laupacis, & Sackett, 1992; Sackett, 1986; M. C. Wilson, Hayward, Tunis, Bass, & Guyatt, 1995; Woolf, Battista, Anderson, Logan, & Wang, 1990). Although they agree in broad terms (see Figure 1.4, below) they present their findings in a number of different ways.
In the absence of experimental evidence the best information on which to base practice is that of expert opinion. However, individuals, or even groups of like-minded individuals, are subject to a number of biases (Tidy, 2010).

Individual studies, such as case-controlled, cohort and randomised-controlled trials (RCT), produce unfiltered ("raw") evidence of increasing quality, with the highest level of evidence being provided by RCT.

1.2.2.1 Cohort studies
Cohort studies are more at risk of bias than randomised controlled trials but less so than case-controlled studies. The potential for bias in cohort studies (Kanchanaraksa, 2008) include:

Selection - where participants are selected into group A rather than group B on a characteristic that may affect outcome
Information - the quality and extent of information differs between the groups, or
- there is different loss to follow-up between the two cohorts

Misclassification - participants exposure is wrongly identified

With retrospective studies, confounding and bias are the principle causes of error (StatsDirect, 2000-2014), whereas loss to follow-up is the main cause of error for prospective studies (Euser, Zoccali, Jager, & Dekker, 2009).

1.2.2.2 Cross-sectional studies

Cross-sectional surveys examine the relationship between particular (health-related) characteristics and other variables as they are present in a defined population at a given point in time so that both exposure and outcomes are measured concurrently (Centre for Evidence-based Medicine, 2014). They are best for quantifying the prevalence of a disease or risk factor.

Advantages:
- cheap and simple
- ethically safe

Disadvantages:
- establishes association at most, not causality
- recall bias susceptibility
- confounders may be unequally distributed
- Neyman (selective survival) bias
- group sizes may be unequal

1.2.2.3 Randomised Controlled Trials

An experimental comparison study in which participants are allocated to an intervention or control or placebo group using a mechanism of randomisation. These are best for study of the effect of an intervention.

*Advantages:
- unbiased distribution of confounders
- blinding more likely
- randomisation facilitates statistical analysis
Disadvantages:
- expensive: time and money
- volunteer bias
- ethically problematic at times.” (Centre for Evidence-based Medicine, 2014)

CONSORT, the Consolidated Standards of Reporting Trials, provides an evidence-based set of minimum standards for transparent reporting of RCTs (Begg, Cho, Eastwood, & et al., 1996). The World Health Organization (WHO) is responsible for the reporting of such trials through the International Clinical Trials Registry Platform (ICTRP). The AllTrials campaign (www.alltrials.net) is a movement that urges all past, present and future trials should be registered, and their results reported publicly, in line with the Declaration of Helsinki (the World Medical Association’s assertion that all human clinical research should be officially recorded and reported). Perhaps the important point is not with whom the trial is registered, but that it is registered.

1.2.2.4 Meta-analyses and systematic reviews

It might be logical to extrapolate that if one were to critically look at the data from a number of studies the findings might give a more accurate determination of an effect or might minimise the bias from individual investigations. As such, it should be able to provide one of the highest levels of evidence possible.

Meta-analysis is a statistical method for combining the findings of two or more studies and is used most frequently to assess the effectiveness of clinical trials. It is often, but not exclusively, a component of systematic reviews and can be thought of as the quantitative component of a systematic review.

Systematic Reviews

What is a systematic review (SR)? The Cochrane Handbook defines it as an attempt “to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question. Researchers conducting systematic reviews use explicit methods aimed at minimizing bias in order to produce more reliable findings that can be used to inform decision making.” (The Cochrane Collaboration, 2014).

Although in the majority of instances a SR is regarded as the highest grade of evidence, the Centre for Evidence-Based Medicine (CEBM) suggest that the quality of the evidence is dependent of the context in which it is to be used (OCEBM Levels of Evidence Working Group, 2011) - Appendix 1.
Criticism has been levelled at SRs as being outdated at the time of publication. A recent study (Beller, Chen, Wang, & Glasziou, 2013) showed that although some (10%) SRs did not publish the time of their last search and those that did showed an average delay of eight months between search and publication. However, Shekelle, Motala, Johnsen, and Newberry (2014) reported a surveillance system to determine the degree by which the conclusions from SRs were out of date and to prioritise the need for updating. This was based on an limited search of top-rated medical journals and speciality journals from the field under study and had a predictive value (κ statistic) of 0.74 (0 = no agreement; 1 = complete agreement).

1.2.3 Quality of evidence and strength of recommendations

The Scottish Intercollegiate Guidelines Network (SIGN at www.sign.ac.uk), an organisation formed in 1993 to develop evidence-based guidelines, developed a alpha-numerical indication of the size and strength of the evidence base for guidelines. The methodology used for each study is assessed to ensure its validity. The result affects the level of evidence allocated to that study, which influences the grade of recommendation based on that research (Table 1.2a,b).

**LEVELS OF EVIDENCE**

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++ High quality systematic reviews of case control or cohort or studies

High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies, e.g. case reports, case series

4 Expert opinion

Table 1.1a: Scottish Intercollegiate Guidelines Network Levels of Evidence (Scottish Intercollegiate Guidelines Network (SIGN), 2011).
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**GRADES OF RECOMMENDATIONS**

A
At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B
A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C
A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D
Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

**Good practice points**

Recommended best practice based on the clinical experience of the guideline development group

Table 1.2b: SIGN Grades of Recommendation (Scottish Intercollegiate Guidelines Network (SIGN), 2011).

1.2.3.1 *The Cochrane Collaboration*

The Cochrane Collaboration (www.cochrane.org) is an international organisation which attempts to minimise the risks of bias and to quantify those that remain in a formalised structure that assists the reviewer and enables people to be as assured as possible of the evidence they are accessing in order to make well-informed decisions regarding healthcare. It aims to produce evidence that would be classified by SIGN 50 as 1++, but does so using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (http://www.gradeworkinggroup.org/index.htm).

The quality of evidence is graded as:

A - high quality randomised clinical trials which further research is unlikely to undermine the confidence in the findings

B - moderate quality evidence for which further research is likely to improve the confidence in the estimate of any effect and may even change that estimate
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C - low quality studies where additional research is very likely to affect both the confidence in the findings and the findings themselves

D - very low quality where there is a very uncertain estimate of effect

Strong Grade 1 recommendations are made when there is confidence that the benefits clearly outweigh the undesirable effects of treatment (harm, burden or cost) and can be applied uniformly to most patients.

Weak Grade 2 recommendations are made where the degree of benefit is less certain and those recommendations ("suggestions") require more careful application.

This grading system represents a continuous scale which, although displaying some degree of being derived arbitrarily, provides a simple and clear recommendation. Thus, evidence graded as 1A has a strong recommendation based on high quality evidence (Atkins et al., 2004; Guyatt et al., 2008).

This grading system has been used by the National Institute of Health and Care Excellence (National Institute of Health and Care Excellence (NICE), 2012) as well as the British Committee for Standards in Haematology since January 2010 (with the exception that level D evidence is not used in BCSH guidelines (British Committee for Standards in Haematology (BCSH), n.d.). BCSH is the body which produces the majority of Blood Transfusion guidelines for the UK Blood Transfusion Services (Pavord et al., 2012; Qureshi et al., 2014; Tinegate et al., 2012; Treleaven et al., 2011).

Heterogeneity

What is heterogeneity? A heterogeneous group is a diverse group. In an attempt to systematically review a cohort of studies it is highly likely they will differ in a number of key areas, areas which can be distinguished to aid to assessing their relative importance.

Clinical (design) heterogeneity

Clinical heterogeneity is found where the intervention effect is affected by factors that vary across studies - what might be termed PICO factors (Population, Intervention, Comparators and Outcomes). Their variation means the true intervention effect will be different in different studies, and meta-analysis should only be undertaken when a group of studies is sufficiently homogeneous (Deeks, Higgins, & Altman, 2011). It is infrequent for there to be a formal evaluation of design heterogeneity prior to meta-analysis, more common is for it to be used afterwards as an attempt to explain
statistical heterogeneity (Althuis, Weed, & Frankenfeld, 2014). Althuis et al. (2014) described, and illustrated using a worked example, an evidence-based mapping approach with which to assess clinical heterogeneity.

**Methodological heterogeneity (Risk of bias)**

Variation in the study design and risk of bias may be termed methodological heterogeneity. Bias is a systematic deviation from the truth which can result in an underestimate or exaggeration of the true effect of an intervention (J. P. T. Higgins & Altman, 2011). Examples of different biases which may be found within the study design are shown in Table 1.3. Differences in what intervention effects are seen may result from whether blinding or allocation concealment are employed.

**Statistical heterogeneity**

Statistical diversity is influenced by either, or both, clinical and methodological heterogeneity. It most often is apparent when the difference in observed intervention effects between studies is more than would be expected due to chance alone. The chi-squared ($X^2$) test is a statistical measure of heterogeneity which is a part of the forest plots found within Cochrane reviews. A low probability ($P$) value (or a large $X^2$ value relative to its degrees of freedom, df), provides evidence of heterogeneity. By combining the $X^2$ value with its df a useful statistic, $I^2$, is derived which allows a rough guide to interpretation of heterogeneity (J. P. Higgins, Thompson, Deeks, & Altman, 2003) (Table 1.4) using the following formula:

$$I^2 = \left( \frac{X^2 - df}{X^2} \right) \times 100\%$$

<table>
<thead>
<tr>
<th>$I^2$ (%) range</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>75</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 1.3: Interpretation of statistical heterogeneity (Deeks et al., 2011).
<table>
<thead>
<tr>
<th>Domain</th>
<th>Support for judgement</th>
<th>Review authors’ judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias</td>
<td>Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.</td>
<td>Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.</td>
</tr>
<tr>
<td>Random sequence generation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment.</td>
<td>Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.</td>
<td>Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.</td>
</tr>
<tr>
<td>Performance bias.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</td>
<td>Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.</td>
</tr>
<tr>
<td>Assessments should be made for each main outcome (or class of outcomes).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection bias.</td>
<td>Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</td>
<td>Detection bias due to knowledge of the allocated interventions by outcome assessors.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessments should be made for each main outcome (or class of outcomes).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attrition bias.</td>
<td>Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.</td>
<td>Attrition bias due to amount, nature or handling of incomplete outcome data.</td>
</tr>
<tr>
<td>Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reporting bias.</td>
<td>State how the possibility of selective outcome reporting was examined by the review authors, and what was found.</td>
<td>Reporting bias due to selective outcome reporting.</td>
</tr>
<tr>
<td>Selective reporting.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other bias.</td>
<td>State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review’s protocol, responses should be provided for each question/entry.</td>
<td>Bias due to problems not covered elsewhere in the table.</td>
</tr>
<tr>
<td>Other sources of bias.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.4: The Cochrane Collaboration’s tool for assessing risk of bias, Table 8.5.a. Reproduced from The Cochrane Handbook (J. P. T. Higgins & Altman, 2011).
1.2.3.2 PROSPERO

It should be noted that Cochrane is not the only register of SRs. PROSPERO, an international prospective register of SRs, was launched in 2011 and is funded by the NIHR in the UK. Its aim was similar to that of Cochrane, to produce high quality, unique reviews whilst simplifying the process of registration as compared to Cochrane (Booth et al., 2013). Reviews registered on PROSPERO do not appear in Cochrane, and vice versa.

1.2.4 NHSBT Systematic Review Initiative (SRI)

SRI is a clinical research group that was created to support the R&D activities, not only of the English NHSBT but also of the other three (Northern Ireland, Scottish and Welsh) UK Blood Services. Based in NHSBT – Oxford at the John Radcliffe Hospital, it was formed in 2001 and receives funding from all four UK Blood Services (SRI, 2014).

Blood Transfusion practice is, in general, not supported by reliable evidence and the primary function of the SRI is to help increase the evidence base for the practice of transfusion medicine through evaluation of the scientific rigour of the current literature and its implications for further R&D (Brunskill et al., 2009). It hopes to accomplish this aim by building effective relationships with and between clinicians and researchers throughout the world. An independent steering committee identifies and prioritises those areas for investigation by SRI. It comprises of clinical experts and representatives from relevant professional bodies within the UK and North America.

1.2.4.1 Handsearching

Handsearching of the more important transfusion medicine publications is another activity performed by the SRI. In one study, it found between 92% and 100% of the total number of reports of randomised trials found by all the methods compared. (Hopewell, Clarke, Lefebvre, & Scherer, 2007). This procedure involves page-by-page examination of journals, conference proceedings and other potential sources for relevant studies. Included in this is the checking of reference lists of journal articles and other documents retrieved from electronic searches in order to identify economic studies (ES), systematic reviews (SR) and randomised controlled trials (RCT) relevant to transfusion medicine. The process is both prospective and retrospective (SRI search from 1980 onwards) and is important because it finds items poorly indexed or not indexed at all. All the content in journal issues, supplements, special issues, or conference abstracts may not be indexed comprehensively, or not indexed
Chapter 1 – Introduction

at all, by some databases. These include abstracts from the following annual meetings or congresses: American Association of Blood Banks (AABB), American Society of Hematology (ASH), British Blood Transfusion Society (BBTS), British Society of Haematology (BSH), European Group for Blood & Bone Marrow Transplantation (EBMT), European Haematology Association (EHA), Haematology Society of Australia & New Zealand (HSANZ), International, Regional & Asia Society of Blood Transfusion (ISBT), International Society on Thrombosis & Haemostasis (ISTH) and the Network for the Advancement of Transfusion Alternatives (NATA).

Additionally, it allows researchers to scan content quickly for relevant studies from high-impact journals and ensures that relevant studies are not overlooked (University of Newcastle (Australia), 2014).

1.2.4.2 Electronic searching

SRI perform monthly electronic searches for SR of the major medical databases and appraised reviews from those searches are entered into the UKBTS SRI Transfusion Evidence Library. There is an annual submission of RCT to CENTRAL, the Cochrane Database of Controlled Trials (part of The Cochrane Library).

1.2.4.3 The Transfusion Evidence Library (TEL)

The UKBTS SRI Transfusion Evidence Library (TEL), launched in September 2009, contains SR, RCT, ES and handsearched references relevant to transfusion medicine which may be searched through various criteria (see Figure 1.2.2). It can be accessed through the link: http://www.transfusionevidencelibrary.com/

![Figure 1-5: Screenshot of UKBTS Transfusion Evidence Library search facility.](image-url)
TEL aims to be a key and current (it is updated monthly) resource for transfusion practitioners, policy makers and researchers anywhere in the world. When accessed (19 September, 2014 through link above) it contained 762 SR, 4272 RCT and 58 EE.

An in-house search strategy designed to be highly sensitive has been developed, although it has not been benchmarked with, or tested against, a 'gold standard' reference set of studies. It will identify papers relevant to all aspects of transfusion medicine and was designed and combined with the SIGN SR and ES search filters.

Exhaustive searches of The Cochrane Library, MEDLINE, EMBASE and from handsearching of the journals Blood Reviews and Transfusion Medicine Reviews identifies SR and ES suitable for inclusion. Only those that meet stringent criteria (based mainly on the quality of the SR’s search) are included in the TEL database. After an extensive critical appraisal by members of SRI (which are linked to the full references in the TEL) some reviews of special interest may be included.

For inclusion in TEL the authors of a SR have to have searched PubMed/MEDLINE and at least one other database. Those reviews that had only searched MEDLINE have been excluded. ES are only included if they are based on a SR. By searching the NHS Economic Evaluations Database (NHSEED) ES of other types can be found. This database is compiled through either the Centre for Reviews and Dissemination from:

http://www.crd.york.ac.uk/crdweb/

or, the Cochrane Library at:

http://www.thecochranelibrary.org/

Only where the participants have been randomly allocated (randomised) to the trial groups in a controlled clinical intervention are they included in TEL.
1.3 Research & Development (R&D) within the NHSBT

The aim of R&D within NHSBT is to ensure the strategic objectives and targets of its Operating Divisions (Blood Supply, Organ Donation and Transplantation, Tissues, Diagnostic Services, Stem Cell Services and Specialist Therapeutic Services) are supported by a targeted programme of R&D. This extensive research programme is funded from both external sources and from within NHSBT (NHSBT, 2013).

Supporting functions have been developed for all the R&D activities, such as the Clinical Biotechnology Centre (Bristol), which manufactures GMP-grade biologicals for Phase 1 clinical trials, the NHSBT/MRC Clinical Studies Unit (Oxford/ Cambridge/ London), which supports clinical studies and trials, the previously mentioned Systematic Review Initiative (Oxford), the Statistics and Clinical Audit team (Bristol) and the R&D office team, which provide support and guidance (NHSBT, 2014). When reviewed by external experts in 2010 NHSBT's R&D programme was assessed as outstanding and identified as making world-class contributions to Transfusion Medicine. It was also recognised as high-quality when benchmarked against National and International standards as well as against other blood services. However, a parallel review identified that connections between R&D and operational areas of the NHSBT could be improved.

1.3.1 NIHR R&D programmes

In 2009 it was proposed by the NIHR that NHSBT R&D rebid for a new five-year cycle of funding that would replace any existing funding. Four programmes were submitted to a total of £14M and would form the major proportion of NHSBT's laboratory research. One of these, Programme D - Erythropoiesis in Health and Disease was successful in obtaining £3.5M and the programme began on 1st October, 2010. It was at this stage I was invited to join Programme D to join the Systematic Review Initiative in providing evidence for proposed randomised controlled trials (RCTs).

1.3.1.1 Programme D - Erythropoiesis in Health and Disease

The central ideology behind this research programme is to improve the health of blood donors and of the quality of the blood supply by a systematic analysis of the published data, advancing the understanding of the basis of iron deficiency in blood donors and suggesting how this may be predicted and prevented.
Erythropoiesis - the process by which red blood cells (erythrocytes) are produced - is fundamental to all human health; not only to that of blood donors but also in many patients requiring blood products. A number of related projects (termed “AIMS”) comprise Programme D which intends to improve the supply of red blood cells by having a better understanding of ID in blood donors. It will suggest how it may be predicted and prevented (AIMS 1 & 2), develop \textit{ex vivo} sources for producing RBC (AIMS 3 & 4) and investigating the basis of abnormal and deficient red blood production in the largest single group of chronically transfused (Myelodysplastic) patients in the UK (AIM 4).

\textbf{AIM 1}

In general terms, this AIM intends to review the current evidence of the efficacy and safety of IS in blood donors and describe the extent, associations and consequences of ID and anaemia in blood donors in England. It is divided into six sections (Roberts, 2014):

1A Review the effectiveness of IS in blood donors in preventing a fall in Hb and reducing deferral from donation due to anaemia (Table 1.5).

1B Review the effectiveness of IS in reducing systemic, neurological or cognitive symptoms in ID but non-anaemic adults (Table 1.5).

1C Describe of the development of ID and IDA in blood donors (Table 1.5).

1D Define genetic traits associated with ID in blood donors.

1E Define sensitive and specific screening tests for ID in blood donors.

1F Develop algorithms to predict ID for repeat donors.
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Table 1.5: Relationship between the systematic reviews and the relevant sections of AIM 1.

<table>
<thead>
<tr>
<th>Review No.</th>
<th>Objective</th>
<th>AIM 1 Objective</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A longitudinal study systematic review (LR) to identify and explore what demographic, donation and haematological factors have been examined or suggested as possible causes of deferral due to low Hb in blood donors.</td>
<td>1C</td>
<td>Non-UK studies published. No Cochrane review.</td>
</tr>
<tr>
<td>2</td>
<td>The efficacy and safety of iron supplementation in blood donors.</td>
<td>1A, 1B</td>
<td>Non-UK studies published. No Cochrane review.</td>
</tr>
</tbody>
</table>

1.3.2 New research strategy

In response to the recommendations from the R&D quality reviews mentioned in section 1.1.2, a new four-year strategy was approved by the NHSBT Board. In this, research was organised into eight themes, each linked to areas of NHSBT business, with a strategy group increasingly developing the programme for each theme. The strategy group would comprise of research, development and operational staff.

The research themes approved in the 2011 strategy were:

1. Donor health and behaviour
2. Transfusion and transplantation virology and microbiology
3. Appropriate and safe use of blood components
4. Erythrocyte (red cell) biology and immunology
5. Platelet biology and genomics
6. Organ donation and transplantation
7. Stem cells and immunotherapies
8. Molecular and tissue engineering.

These themes covered work already in place, but two new themes were added. One (Donor Health and Behaviour) would now specifically cover the area of this project. Although the Systematic Reviews with which I was involved still remained within the old NIHR Programme D, the RCTs which they were designed to inform have now been absorbed into Theme 1.
1.3.2.1 **Theme 1: (Donor health and behaviour)**

Not only a new area of research for the NHSBT it has also been neglected by the wider international research community and so provides ample opportunity to build a strong research reputation. The theme has been awarded approximately seven per cent of an £18.2 million national research budget, provided by a tariff on the price of blood and from external sources.

The first project is a collaboration between NHSBT R&D and the University of Cambridge Department of Public Health and Primary care for a large strategic study (INTERVAL) which was commenced in June 2012. This aimed to provide evidence to determine policy on the optimal time between blood donations whilst minimising the risk of ID/IDA in donors and maximising the use of a diminishing donor pool. This study also has the potential to personalise the donor call up, by using genetic and other factors to predict tolerance to donation.

Future projects include:

1. Qualitative studies on the factors influencing the motivation of blood donors
2. Collection of DNA, plasma and serum together with information on lifestyle and health into a large biobank from many thousand donors to allow studies on the associations between genes and diseases
3. An RCT looking at the optimal use of IS in blood donors

1.3.3 **Governance**

NHSBT R&D is conducted within the DH Research Governance Framework for Health and Social Care (Department of Health, 2010). Intellectual Property (IP) support is provided by an external contract, which facilitates Freedom to Operate searches to be performed as well as the patenting and exploitation of new IP.

1.3.4 **Outputs and benchmarking**

Traditionally, successful academic research is measured by the numbers of both external grants awarded and/or high impact papers published (Fig 1-6).
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As all the Principal Investigators responsible for the various Themes are affiliated with academic institutions their outputs are assessed through the National Research Assessment Exercise, the last being performed in 2008 (http://www.rae.ac.uk/). Additionally, key measures for NHSBT would be making a significant impact on service activities and clinical practice. However, there may be a lag phase of up to 10 years for the translation of research findings into routine practice. Benchmarking R&D activity against other, international, blood services has been made possible by the formation of a new R&D group under the auspices of the Alliance of Blood Operators (Alliance of Blood Operators (ABO), n.d.).

1.4 Aims and objectives

The aims of this thesis are, via systematic review, to provide a better understanding of the factors that lead to ID in blood donors and examine the current evidence of the benefits and costs of IS to blood donors. This knowledge will be used to inform the design of subsequent randomised controlled trials into donation frequency, with and without IS, in the expectation that blood donors will donate according to what is optimal for their continued health and wellbeing.

My involvement has been, in collaboration with the Systematic Review Initiative, NHSBT-Oxford, in the provision of these reviews.
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

This chapter discusses the systematic review of literature describing the factors that have been identified as potentially having an effect on blood donors not meeting the low Hb thresholds of blood collection agencies from around the world.
2.1 Abstract

2.1.1 Background
Donors may be unable to donate blood due to a failure to meet low Hb thresholds set by the collecting organisation, leading to a temporary deferral from blood donation. A number of studies have identified factors, either singly or acting together, which influence the incidence of falling below these thresholds. However, there is no systematic review of the relative importance of those factors.

2.1.2 Objectives
To identify, define and quantify those factors which predispose a donor to temporary deferral from donation of whole blood (WB), red blood cells (RBCs) or platelets due to failure to meet Hb standards.

2.1.3 Search Methods
The following databases were searched for relevant studies:


2.1.4 Selection Criteria
All types of studies (retrospective, prospective, cross-sectional etc.) were included. The minimum study size for inclusion was 100 (red blood cell donors) or 50 (platelepheresis) participants. Publications before 1980, foreign language publications, haemochromatosis studies, autologous donations, plasma donations and studies with donors pre-selected by Hb level were excluded.
2.1.5 Data Collection and Analysis

Data were collected using customised data extraction forms using Microsoft Excel. Two co-authors independently extracted data which included demographic information, donor history, haematological and biological factors. The primary outcome was deferral due to failure to meet Hb thresholds for donation.

The analyses were both descriptive and quantitative. Odds ratios from individual studies were pooled using meta-analyses using the systematic review software RevMan 5.

2.1.6 Main Results

Of the 6706 records identified from electronic searches a total of 55 studies met the inclusion criteria. A higher rate of low Hb deferral (LHD) was consistently reported in females as compared to males, with meta-analysis showing a significantly higher risk of LHD in females compared with males in studies with universal Hb thresholds for males and females (OR 14.91, 95% CI 12.82 to 17.34) as well as in studies with sex-specific Hb thresholds (OR 8.19, 95% CI 4.88 to 13.74). LHD was also associated with ethnicity, increasing age, higher ambient temperature, low body weight, previous donation and inter-donation interval. Other factors gave less clear evidence for being a risk factor for low Hb deferral.

2.1.7 Authors' Conclusions

Female donors are strongly predisposed to falling below the minimum Hb thresholds set for their population. Increasing age is associated with a similar increase in deferral in males whereas a reduced body weight for both sexes results in Hb levels lower than acceptable for donation.
2.2. Plain Language Summary

Factors influencing the deferral of donors failing to meet low haemoglobin thresholds

Donors that fail to meet the lower Hb thresholds set by a blood collection organisation are deferred until a later date when it is hoped their Hb level will normalise. This phenomenon contributes a significant drain on that organisation in terms lost time and effort, and to the donor in demoralisation. Determination of exactly what factors might lead to low Hb deferral (LHD) would help an organisation target donors appropriately, enabling optimal donation schedules to be set. This review was performed to see if there was sufficiently robust and valid information upon which to base those schedules. Fifty seven studies looking at 55 independent trials were included, involving well over 40M subjects from 25 countries across six continents. Results from some of the studies showed conflicting evidence for certain of the factors (e.g. ethnicity and donation intensity in males). However, there was a clear difference in LHD between the genders, with women having an eleven-fold increased odds of LHD. Also, it was readily apparent that the older male donors become, the more likely they are to defer due to low Hb, especially after the age of 45-50. Black and Hispanic women are at an increased likelihood of LHD as compared to their White US counterparts. Donors of all persuasions are more prone to LHD in the warmer summer months than they are in winter. The study of donor body weight revealed the heavier a donor is the less chance they have of unsuccessful donation. Several other contributory factors were identified (first-time donation, education level, donating for friends and family) but with fewer studies looking at them the evidence was less convincing. Indeed, the fact that many of the studies looked at different types of donor (red cell and/or platelet), used dissimilar Hb thresholds and had diverse numbers of female participant showed that more studies are needed to see if donation strategies can be successfully tailored towards individual donors.
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

2.3 Background

A systematic review is required to answer the question of what factors lead to the deferral of blood donors due to a low Hb level.

Studies exist on the effect of different donation intervals but they have not been carried out on a UK population. Before such a study can be performed, an SR on the risk factors for deferral due to failure to meet Hb standards is required. A SR focuses on foreground knowledge (i.e. the difference between two options) using rigorous methods to improve the reliability of conclusions and can provide estimates of benefits and risks.

2.4 Objectives

This study will help inform a programme of research that will improve the health of blood donors and the blood supply by systematically analysing the published data, advancing our understanding of the basis of anaemia in blood donors and suggest how this may be predicted and prevented. This will be a longitudinal study SR to identify and explore what demographic, donation and haematological factors have been examined or suggested as possible causes of deferral due to low Hb in blood donors.
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

2.5 Methods
This review is written in the style of a Cochrane Review to provide continuity with Chapter 3, which is a Cochrane Review. However, the methodology used for this review was not exactly the same as would be used in a Cochrane review. The purpose of the investigation was to provide evidence on which to base a future RCT.

2.5.1 Criteria for considering studies for this review

2.5.1.1 Types of studies
The objectives for this review were to determine the risk factors for deferral so finding RCTs would be unlikely as they would prove both impractical and, possibly, unethical. The study design with the least risk of bias was expected to be cohort studies with retrospective or prospective data collection. The findings of any case-control studies retrieved were analysed separately due to the high risk of bias. It was agreed between the study team that the minimum number of participants had to be greater than 100 for donors of red blood cells (RBC) and greater than 50 for platelet donors (referred to as plateletpheresis). These cut-offs were chosen because:

a) Approximately 3% of donors are deferred due to low Hb (Baart et al., 2011). Studies with less than 100 participants would be difficult to investigate for the associations of multiple variables with low Hb deferral.

b) In England, approximately 1.7 million donations are collected annually (NHSBT, 2010). Larger studies are more representative of higher quality studies.

c) Smaller studies are unlikely to yield meaningful findings due to the low frequency of people expressing the risk factor under study. A lower threshold for studies of platelet donors was chosen as fewer platelet donations are collected annually than RBC donations (an order of magnitude lower than those for RBCs), and fewer still of those platelet donations are by plateletpheresis (NHSBT, 2010).
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

A systematic review of cohort studies with a high degree of homogeneity would suggest a level of evidence assessed as Level 2a according to the Oxford Centre for Evidence-based Medicine (OCEBM), 2009. Under their latest revision (OCEBM Levels of Evidence Working Group, 2011) systematic review of cohort studies are not specifically mentioned. However, it is unclear how this type of study would be graded as these evidence tables are for interventions, not risk factors. The closest is the prognostic question, i.e. what happens if we do not treat inception cohorts, which is not the case here.

2.5.1.2 Types of participants
Any population is eligible for inclusion within the study. The study populations were compared to an English donor population and any differences discussed. How generalisable the findings of a study are a measure of its external validity. Particular consideration will be made as to the country, ethnicity, economic development and collection setting (mobile donation unit, hospital or transfusion service) of the study populations.

2.5.1.3 Types of risk factors
Any factor that might pre-dispose a donor to fail to meet a low Hb threshold was considered, but in particular included:

- Age
- Gender
- Diet
- Ethnicity
- Education level/ socioeconomic class
- Hb level at previous donation
- Donation history (frequency, interval, total)
- Other factors, as may be revealed during searching

2.5.1.4 Types of outcome measures

Primary outcomes
Deferral of donors due to failure to meet Hb standards. The technical aspects of Hb measurement were not considered beyond noting the Hb screening method(s).
Secondary outcomes
Changes in any additional factors related to low Hb in donors.

In order to capture likely outcomes of importance a workshop was held in November 2010 with participants from all the UK Blood Services. In July 2011 a meeting took place between relevant research arms of the NHSBT to inform them of the current findings so they might take account when formulating the study protocol for their RCT on donation interval and donor health (Chapter 4, Table 4.2).

2.5.2 Search methods for identification of studies

2.5.2.1 Electronic searches
A comprehensive search strategy was developed in conjunction with the NHSBT Information Specialist (CD) from NHSBT covering the main bibliographic databases (MEDLINE, EMBASE and the Cochrane Library - searches shown in Appendix 2.1).

2.5.2.2 Searching other resources

Handsearching of reference lists
The references of all identified studies, relevant review articles, and current treatment guidelines were checked for further literature and limited those searches to the 'first generation' reference lists.

Personal contacts
Authors, study groups and worldwide experts of any relevant studies were contacted for any additional published or unpublished work of which they were aware.

Ongoing trials
The U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH at clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) were searched for ongoing or unpublished trials.
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

2.5.3 Data collection and analysis

2.5.3.1 Selection of studies
One author (CD) screened all search hits at the title stage for relevance against the eligibility criteria and discarded all those that were clearly irrelevant. Thereafter, two authors (GAS and SF) independently screened the abstracts of all the remaining hits for relevance against the full eligibility criteria. Full text papers were retrieved for all those references for which a decision of eligibility could not be made from title and abstract alone. Differences of opinion were resolved through discussion and consensus, and, where necessary, with reference to a third reviewer (DR).

2.5.3.2 Data extraction and management
Two reviewers (GAS and SF), independently extracted data onto a standardised Excel form developed in collaboration. These forms were piloted on two included studies and changes made to the data extraction form where appropriate and agreed. Again, throughout the data extraction process any disagreements were resolved by consensus. In this instance there was no need to resort to a third reviewer to resolve differences. There was no blinding to names of authors, institutions, journals or the outcomes of the trials during this process. The information collected was categorised thus:

General information
Review author's name, date of data extraction, study ID, first author of study, citation of paper, objectives of the trial.

Study details
Study design, location, setting, sample size, power calculation, methods of treatment allocation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow up, stratification, stopping rules described, statistical analysis, results and conclusion.

Characteristics of participants
Age, gender, ethnicity, total number recruited, total number analysed, losses to follow-up, drop outs with reasons, protocol violations, donation history, whether donors were paid.
Comparators/interventions
Type of comparator (age, gender, ethnicity socioeconomic status, education, etc.), additional comparators, any differences between interventions.

Outcomes
Deferral due to low Hb, modelling of deferral due to low Hb.

2.5.3.3 Dealing with missing data
Authors of relevant studies were contacted for clarification, supply of missing data or to request any unpublished material they might possess. (Appendix 2.2. Example of contact letter/e-mail).

2.5.3.4 Data analysis
Where possible, data were combined and meta-analysis performed as described in the Cochrane Handbook of Systematic Reviews of Interventions (Reeves, Deeks, Higgins, & Wells, 2011). Practically, this was only possible for one comparator, that of sex, as there was too much variation in the trials. The validity of the data was critically assessed in relation to the characteristics of the included study and noted in the Characteristics of Included Studies (Table 2.1).
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

2.6 Results

2.6.1 Study selection
A PRISMA flow diagram of study selection is given in Figure 2.1. Electronic database searches identified 6706 records, which were reduced to 1456 after initial screening for relevance and de-duplication. Further, separate, screening of these 1456 records by GAS and another reviewer (SF) resulted in 151 potentially eligible studies for inclusion (95 full papers and 56 conference abstracts). Of these, 93 records (55 full papers and 39 abstracts) were subsequently excluded as they failed to meet the inclusion criteria (Figure 2-1) 34 abstracts and 35 papers due to insufficient data, a further 11 papers because of pre-selection by Hb level, four were unobtainable, one study revealed on closer inspection to have too few participants (after translation) and four papers and five abstracts appeared to overlap with another included study.

Figure 2-1: PRISMA flow diagram of study selection
2.6.2 Description of studies

The inclusion criteria were met by 40 full papers and 17 conference abstracts which described 55 independent studies (Summary of Characteristics of Included Studies - Table 2.1 and referenced in Appendix 2.3). Four studies involved both RBC and platelet donation, 27 studies included RBC/whole blood donation only and two studies included platelet donors only. The remaining studies did not explicitly state the donation type. Studies were undertaken in 25 countries across six continents.

Hb thresholds for blood donation were reported in 38 studies; a further three used haematocrit (Hct) levels to determine donation eligibility and the remaining 14 reports did not report either (Table 2.1). Of the 21 studies using the same threshold for both males and females, 18 used an Hb of 125 g/L (including eight studies from the USA, seven from India and one each from, Nigeria, Iran and Papua-New Guinea). The lowest universal threshold was 110 g/L in a study from the Ivory Coast (Kouao et al., 2012); the highest universal threshold was a Hct of 40% (approximately equivalent to an Hb of 135 g/L) in a Turkish study (Gulen et al., 2006). Of the 20 studies which employed gender-specific thresholds, 18 reported Hb and two reported Hct thresholds. Thirteen of these studies used an Hb of 135 g/L for males and 125 g/L for females (including all but one European study as well as studies from Trinidad and Tobago, India, Mexico and Malaysia).

Those studies that reported methods of Hb determination used a variety of techniques: copper sulphate, microhaematocrit, portable photometric device and automated cell analyser - using both capillary and venous blood (Table 2.1).

Most studies (43/55) reported deferrals due to other reasons as well as low Hb. However, eight studies excluded deferrals due to other reasons prior to the study and in a further four studies, the number of deferrals due to other reasons was not explicitly reported, or it was unclear whether deferrals due to other reasons were excluded from the study. Therefore, in order to provide a comparative measure of deferral across the maximum possible number of studies, the LHD rate was defined as the number of deferrals due to low Hb divided by the total number of potential donations, excluding all deferrals due to reasons other than low Hb. This estimate gives a slightly higher measure of the rate of low Hb deferral than that obtained for a population where other causes of deferral are included.
2.6.2.1 Discussion of bias

The studies were a mixture of descriptive cross-sectional surveys and observational analytic cohort studies.

With cohort studies, sample sizes for rarer factors may not have been sufficiently large and there may have been unknown confounders. Within some studies, the number of donors within certain sub-groups into which a factor had been stratified varied greatly (by a factor of 150, in the case of weight sub-groups in the study of Mast et al. (2010).

Within the cross-sectional surveys these confounders may have been unequally distributed, especially with some of unequal group sizes seen. Neyman and recall bias should not have been a problem with these studies.

Specific discussion of bias is given within each comparison.
Table 2.1: Summary of characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of Study</th>
<th>Donation Type</th>
<th>Hb screen</th>
<th>Hb Threshold (M/F)</th>
<th>Donation Attempts</th>
<th>% Male</th>
<th>Hb Deferrals (%)</th>
<th>Description of Study Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agnihotri 2010</td>
<td>India</td>
<td>RBC</td>
<td>C + H</td>
<td>125</td>
<td>6032 [6357]</td>
<td>90.0</td>
<td>6.8</td>
<td>Voluntary and replacement donors recruited over one and half years.</td>
</tr>
<tr>
<td>Arslan 2007</td>
<td>Turkey</td>
<td>RBC</td>
<td>H</td>
<td>135/125</td>
<td>83899 [94919]</td>
<td>89.5</td>
<td>3.4</td>
<td>Hospital blood bank donors aged 18-65 collected over 5 years 2001-2005.</td>
</tr>
<tr>
<td>Baart 2012</td>
<td>The Netherlands</td>
<td>RBC</td>
<td>H^cap</td>
<td>135/125</td>
<td>220946 [220946]</td>
<td>50.9</td>
<td>5.8</td>
<td>Previous donors who visited a blood collection centre during 2007-2009; previous two donations were whole blood donations.</td>
</tr>
<tr>
<td>Bahadur 2011</td>
<td>India</td>
<td>RBC</td>
<td>C + H</td>
<td>125</td>
<td>6152 [6817]</td>
<td>98.3</td>
<td>2.0</td>
<td>Tertiary care centre donors during 2009. Donations were replacement (99.5%) and voluntary (0.5%).</td>
</tr>
<tr>
<td>Bischke 2011</td>
<td>Denmark</td>
<td>n/r</td>
<td>n/r</td>
<td>135/125</td>
<td>219 [219]</td>
<td>65.3</td>
<td>16.4^8</td>
<td>Donors failing previous Hb test would have been offered iron tablets.</td>
</tr>
<tr>
<td>Bryant 2009</td>
<td>USA</td>
<td>RBC</td>
<td>C</td>
<td>125</td>
<td>3549 [3730]</td>
<td>53.0</td>
<td>9.2</td>
<td>Consented donors &gt;18yrs old attending a blood donor centre between 27/10/08 - 10/04/09.</td>
</tr>
<tr>
<td>Charles 2010</td>
<td>Trinidad/Tobago</td>
<td>RBC</td>
<td>C</td>
<td>135/125</td>
<td>8199 [11346]</td>
<td>66.6</td>
<td>10.9</td>
<td>Donor presentations during 2005. Replacement (93.7%) and voluntary (6.2%) donors.</td>
</tr>
<tr>
<td>Chaudhary 1995</td>
<td>India</td>
<td>RBC</td>
<td>C</td>
<td>135/125</td>
<td>12363 [14269]</td>
<td>91.3</td>
<td>3.5</td>
<td>Prospective donors over 15 months (Oct 1992 – Dec 1993). All donor were unpaid voluntary relatives aged 18-60. Paid or professional donors were excluded.</td>
</tr>
<tr>
<td>Custer 2004</td>
<td>USA</td>
<td>RBC</td>
<td>C</td>
<td>125</td>
<td>4987704 [5607922]</td>
<td>50.2</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>
## A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of Study</th>
<th>Donation Type</th>
<th>Hb screen</th>
<th>Hb Threshold (M/F)</th>
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<th>% Male</th>
<th>Hb Deferrals (%)</th>
<th>Description of Study Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortes 2005</td>
<td>Colombia</td>
<td>RBC</td>
<td>H$_{cap}$</td>
<td>135/130</td>
<td>210 [210]</td>
<td>59.5</td>
<td>7.6</td>
<td>0 18.8</td>
</tr>
<tr>
<td>Dartote 2010</td>
<td>Mexico</td>
<td>n/r</td>
<td>n/r</td>
<td>135/125</td>
<td>52178 [82171]</td>
<td>71.0</td>
<td>9.8</td>
<td>n/r n/r</td>
</tr>
<tr>
<td>Di Lorenzo 2009/2011</td>
<td>Brazil</td>
<td>n/r</td>
<td>Hct$_c$</td>
<td>[40%/38%]</td>
<td>265173 [335109]</td>
<td>66.0</td>
<td>2.8</td>
<td>0.6 5.5</td>
</tr>
<tr>
<td>Donovan 2011</td>
<td>USA</td>
<td>n/r</td>
<td>n/r$_{cap}$</td>
<td>n/r</td>
<td>3466 [3668]</td>
<td>n/r</td>
<td>5.0</td>
<td>n/r n/r</td>
</tr>
<tr>
<td>Eder 2010</td>
<td>USA</td>
<td>n/r</td>
<td>Mixed</td>
<td>125</td>
<td>7546213 [7871268]</td>
<td>49.3</td>
<td>7.7</td>
<td>1.4 13.9</td>
</tr>
<tr>
<td>Gandhi 2012</td>
<td>USA</td>
<td>RBC</td>
<td>n/r</td>
<td>125</td>
<td>35053 [35053]</td>
<td>46.7</td>
<td>12.4</td>
<td>3.8 20.1</td>
</tr>
<tr>
<td>Girish 2012</td>
<td>India</td>
<td>RBC</td>
<td>n/r</td>
<td>125</td>
<td>8732 [9113]</td>
<td>97.3</td>
<td>1.1</td>
<td>0.7 16.6</td>
</tr>
<tr>
<td>Gonzalez 2013</td>
<td>Brazil</td>
<td>RBC</td>
<td>Hb, Hct</td>
<td>130/125</td>
<td>787228 [963519]</td>
<td>65.9</td>
<td>5.2</td>
<td>0.9 13.5</td>
</tr>
<tr>
<td>Guerreiro 2011</td>
<td>Portugal</td>
<td>RBC/A</td>
<td>Hb</td>
<td>n/r</td>
<td>4117 [4175]</td>
<td>n/r</td>
<td>0.9</td>
<td>n/r n/r</td>
</tr>
<tr>
<td>Gulen 2006</td>
<td>Turkey</td>
<td>RBC/P</td>
<td>Hct$_c$</td>
<td>[40%]</td>
<td>1683 [2207]</td>
<td>n/r</td>
<td>5.1</td>
<td>n/r n/r</td>
</tr>
<tr>
<td>Gupta 2011</td>
<td>India</td>
<td>RBC</td>
<td>n/r</td>
<td>n/r</td>
<td>5605 [5989]</td>
<td>n/r</td>
<td>1.5</td>
<td>n/r n/r</td>
</tr>
<tr>
<td>Hillgrove 2011</td>
<td>Australia</td>
<td>RBC</td>
<td>H$_{cap}$</td>
<td>128/118</td>
<td>69686 [69686]</td>
<td>47.1</td>
<td>1.5</td>
<td>0.5 2.3</td>
</tr>
<tr>
<td>Hoekstra 2007</td>
<td>Netherlands</td>
<td>RBC</td>
<td>A, H$_c$</td>
<td>135/125</td>
<td>520236 [520236]</td>
<td>59.6</td>
<td>4.7</td>
<td>2.5 8.0</td>
</tr>
</tbody>
</table>

300 donors presenting to a blood centre between April – June 2004, differentiated by altitude of city of residence.

Prospective donor study attending in 2009.

Donor data collected in 2006 from 18 centres. Ethnic composition of participants was 41.7% white; 57.1% non-white; 1.2% not declared.

Selected individual collection operations from Jan 2008 – Dec 2010 that had a minimum of 600 donors attending.

American Red Cross donors during 2008.

WB donors recruited over a 12-month period from two hospital blood donation sites and one fixed site collection unit.

Whole blood donors recruited Jan 2009 – Dec 2010 from one fixed site collection unit.


Retrospective records of donors attending during 2010.

Prospective blood donors recruited at a blood centre at a children’s hospital over a 6-month period (Jul–Dec 2002).

Whole blood donors recruited Mar – Aug 2011 from three fixed site collection units.

Australian Red Cross Blood Service (ARCBS) - all donors attending in two states (New South Wales and South Australia).

Participants had to have donated twice during the study period (Jan 2002 – Dec 2004).
### Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

<table>
<thead>
<tr>
<th>Study</th>
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<th>Donation Attempts</th>
<th>% Male</th>
<th>Hb Deferrals (%)</th>
<th>Description of Study Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islam 2004</td>
<td>Bangladesh</td>
<td>n/r</td>
<td>n/r</td>
<td>n/r</td>
<td>1942 [2196]</td>
<td>85.8</td>
<td>1.9</td>
<td>All non-remunerated and some directed donations included.</td>
</tr>
<tr>
<td>Kagu 2010</td>
<td>Nigeria</td>
<td>n/r</td>
<td>H^cap</td>
<td>125</td>
<td>3724 [4032]</td>
<td>n/r</td>
<td>10.9</td>
<td>Voluntary non-remunerated donors over 2 years. 4.4% were previous donors; number of previous donations ranged from 1 - 6. Low Hb deferral donors were routinely given dietary advice with haematinic supplements.</td>
</tr>
<tr>
<td>Kouao 2012</td>
<td>Ivory Coast</td>
<td>RBC</td>
<td>Hct, H^cap</td>
<td>110</td>
<td>22516 [24363]</td>
<td>75.0</td>
<td>3.4</td>
<td>Volunteer and non-remunerated donors presenting at a hospital blood bank 01/01/06 – 31/12/08.</td>
</tr>
<tr>
<td>Kuhnel 2011</td>
<td>Germany</td>
<td>RBC</td>
<td>n/r</td>
<td>n/r</td>
<td>2658273 [2897377]</td>
<td>n/r</td>
<td>2.3</td>
<td>Retrospective 10 year period mainly on mobile blood donation sites.</td>
</tr>
<tr>
<td>Lim 1993</td>
<td>Singapore</td>
<td>n/r</td>
<td>n/r</td>
<td>125/120</td>
<td>242167 [278401]</td>
<td>n/r</td>
<td>1.6</td>
<td>Prospective donors attending Singapore Blood Transfusion Service over four years 1988-1991.</td>
</tr>
<tr>
<td>Majumdar 1999</td>
<td>India</td>
<td>RBC</td>
<td>Col</td>
<td>125</td>
<td>1033 [1044]</td>
<td>92.1</td>
<td>10.2</td>
<td>Voluntary blood donors collected over 4 years (excluding 9 month period of blood bank closure).</td>
</tr>
<tr>
<td>Mirrezaie 2011</td>
<td>Iran</td>
<td>n/r</td>
<td>H</td>
<td>125</td>
<td>2000 [2000]^15</td>
<td>70.0</td>
<td>16.3</td>
<td>Unselected, prospective blood donors had Hb measurement by haematology analyser and finger stick methods.</td>
</tr>
<tr>
<td>Misso 2011</td>
<td>Italy</td>
<td>n/r</td>
<td>n/r</td>
<td>1220 [1266]</td>
<td>n/r</td>
<td>1.6</td>
<td>n/r</td>
<td>Study of donors attending during 2010.</td>
</tr>
<tr>
<td>Moog 2004</td>
<td>Germany</td>
<td>RBC/P</td>
<td>n/r</td>
<td>135/125</td>
<td>437 [594]</td>
<td>73.3</td>
<td>7.6</td>
<td>Retrospective records of donors attending during 2002. Minimum interdonation time of 3 months; minimum body weight of &gt;60 kg.</td>
</tr>
<tr>
<td>Study</td>
<td>Country of Study</td>
<td>Donation Type</td>
<td>Hb screen</td>
<td>Hb Threshold (M/F)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Munasinghe 2011</td>
<td>Sri Lanka</td>
<td>RBC</td>
<td>n/r</td>
<td>6964 [7609]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadarajan 2010</td>
<td>Malaysia</td>
<td>n/r</td>
<td>C + H/A</td>
<td>84989 [93807]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikolic 2011</td>
<td>Serbia</td>
<td>n/r</td>
<td>n/r</td>
<td>21417 [22352]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Meara 2011</td>
<td>Switzerland</td>
<td>RBC</td>
<td>A</td>
<td>160612 [160612]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pandey 2012</td>
<td>India</td>
<td>P</td>
<td>n/r</td>
<td>2312 [2558]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pierelli 2011</td>
<td>Italy</td>
<td>n/r</td>
<td>New method?</td>
<td>13196 [13347]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabeya 2008</td>
<td>Malaysia</td>
<td>RBC</td>
<td>n/r</td>
<td>4001 [4138]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raka 2010</td>
<td>Macedonia</td>
<td>RBC</td>
<td>n/r</td>
<td>21331 [21915]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosochova 2011</td>
<td>Switzerland</td>
<td>RBC</td>
<td>H^cap</td>
<td>19296 [19296]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sebok 2007</td>
<td>USA</td>
<td>n/r</td>
<td>C + Hct</td>
<td>23.1M [24.3M]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaz 2010</td>
<td>USA</td>
<td>n/r</td>
<td>C + Hct</td>
<td>547261 [576317]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sundar 2010</td>
<td>India</td>
<td>RBC</td>
<td>C, Col</td>
<td>16132 [16706]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talonu 1983</td>
<td>Papua New Guinea</td>
<td>n/r</td>
<td>C</td>
<td>5068 [5279]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
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<th>Donation Type</th>
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<th>Hb Threshold (M/F)</th>
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<td>6964 [7609]</td>
</tr>
<tr>
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<td>Malaysia</td>
<td>n/r</td>
<td>C + H/A</td>
<td>84989 [93807]</td>
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<tr>
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<td>Serbia</td>
<td>n/r</td>
<td>n/r</td>
<td>21417 [22352]</td>
</tr>
<tr>
<td>O’Meara 2011</td>
<td>Switzerland</td>
<td>RBC</td>
<td>A</td>
<td>160612 [160612]</td>
</tr>
<tr>
<td>Pandey 2012</td>
<td>India</td>
<td>P</td>
<td>n/r</td>
<td>2312 [2558]</td>
</tr>
<tr>
<td>Pierelli 2011</td>
<td>Italy</td>
<td>n/r</td>
<td>New method?</td>
<td>13196 [13347]</td>
</tr>
<tr>
<td>Rabeya 2008</td>
<td>Malaysia</td>
<td>RBC</td>
<td>n/r</td>
<td>4001 [4138]</td>
</tr>
<tr>
<td>Raka 2010</td>
<td>Macedonia</td>
<td>RBC</td>
<td>n/r</td>
<td>21331 [21915]</td>
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<td>Rosochova 2011</td>
<td>Switzerland</td>
<td>RBC</td>
<td>H^cap</td>
<td>19296 [19296]</td>
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<tr>
<td>Sebok 2007</td>
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<td>n/r</td>
<td>C + Hct</td>
<td>23.1M [24.3M]</td>
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<tr>
<td>Shaz 2010</td>
<td>USA</td>
<td>n/r</td>
<td>C + Hct</td>
<td>547261 [576317]</td>
</tr>
<tr>
<td>Sundar 2010</td>
<td>India</td>
<td>RBC</td>
<td>C, Col</td>
<td>16132 [16706]</td>
</tr>
<tr>
<td>Talonu 1983</td>
<td>Papua New Guinea</td>
<td>n/r</td>
<td>C</td>
<td>5068 [5279]</td>
</tr>
</tbody>
</table>

Donors attending a base hospital during 2008 - 2010.
Retrospective records of donors attending during 2010.
Includes first time and repeat donors. Median number of donations per volunteer over the 14 year study period (1996 – 2009) was 2 (range 1 - 56). Optional iron supplementation offered from 2004 onwards.
Attendees of tertiary healthcare centre between Jan 2010 – Mar 2011.
Donors attending a transfusion medicine unit between Jan 2006 – Dec 2006.
Donors attending a transfusion centre for 12 months.
Voluntary and replacement (approx 10% replacement) donors aged ≤60 years. Retrospective donors attending various locations during 2005 – 2007.
Volunteer donors attending a blood bank or mobile teams during 14.09.79 – 02.10.80.
# Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of Study</th>
<th>Donation Type</th>
<th>Hb screen</th>
<th>Hb Threshold (M/F)</th>
<th>Donation Attempts</th>
<th>% Male</th>
<th>Hb Deferrals (%)</th>
<th>Description of Study Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tondon 2008</td>
<td>India</td>
<td>P</td>
<td>A</td>
<td>125</td>
<td>n/r</td>
<td>5.0</td>
<td>n/r</td>
<td>Volunteer donors attending a blood bank or mobile teams during 14.09.79 – 02.10.80.</td>
</tr>
<tr>
<td>Unnikrishnan 2011</td>
<td>India</td>
<td>n/r</td>
<td>n/r</td>
<td>125</td>
<td>1165 [1515]</td>
<td>95.2</td>
<td>0.7</td>
<td>Donors, mostly under 25 and predominantly educated males attending a tertiary care hospital in 2008.</td>
</tr>
<tr>
<td>Wilkinson 1982</td>
<td>Ireland</td>
<td>n/r</td>
<td>C</td>
<td>1225</td>
<td>1763903 [1763903]</td>
<td>65.7</td>
<td>5.7</td>
<td>Volunteer donors aged 18 - 65.</td>
</tr>
<tr>
<td>Wijesiri 2011</td>
<td>Sri Lanka</td>
<td>RBC</td>
<td>n/r</td>
<td>24016 [25948]</td>
<td>n/r</td>
<td>0.4</td>
<td>n/r</td>
<td>Volunteer donors attending four mobile teams during April – Sept 2010.</td>
</tr>
<tr>
<td>Ziemann 2006</td>
<td>Germany</td>
<td>RBC</td>
<td>A</td>
<td>81913 [81913]</td>
<td>n/r</td>
<td>57.5</td>
<td>6.4</td>
<td>Consecutive whole blood donors between May 2003 – Nov 2005 analyzed on diversion samples taken from sample pouch.</td>
</tr>
</tbody>
</table>

n/r = not reported;  
1. RBC = red blood cells; P = platelets, A = apheresis;  
2. A = Analyser; C = CuSO4; H\textsuperscript{cap or v} = Portable photometric device (capillary or venous blood); Hct\textsuperscript{U or c} = Haematocrit by ultrasound or centrifuge; Col = Colorimetric; Mixed;  
3. number of donation attempts excluding deferrals due to reasons other than low Hb [total number of donation attempts];  
4. where possible, the low Hb deferral rate is calculated as a percentage of the combined total number of Hb deferrals and accepted donations, i.e. deferrals due to other reasons were excluded in the calculation of the low Hb deferral rate;  
5. deferrals due to reasons other than low Hb were excluded from the study;  
6. the total number of donation attempts excluding deferrals due to other reasons was not reported for males and females; the deferral rate is calculated as a proportion of the total number of donation attempts reported;  
7. studies in which data discrepancies deferrals were observed within the study report and in which the best estimate of deferral rate was made;  
8. the combined low Hb deferral rate has been calculated from the estimated number of deferrals based on reported percentages in males and females;  
9. this study included three cohorts with Hb thresholds defined according to altitude. Only the largest cohort from the Manizales area meet the inclusion criteria and are included here;  
10. Di Lorenzo-Oliveira 2009/2011: where discrepancies are observed between the two reports, the most recently published data has been extracted;  
11. although not explicitly reported, 125g/L is assumed as the current Indian thresholds.;  
12. Hb and Hct thresholds were defined differently for different sites;  
13. the number of deferrals due to reasons other than low Hb could not be determined; the deferral rate is therefore given as a percentage of all donation attempts, including those deferred due to other reasons;  
14. Mathur 2012: only deferrals from the initial CuSO4 test are included here;  
15. unclear whether deferrals due to other reasons were included in the total number of donation attempts or excluded from the study. The Hb deferral rate is calculated as a proportion of the total number of donation attempts reported.
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

2.6.3 Factors associated with deferral through failure to meet Hb threshold

2.6.3.1 Sex

The overall percentage of donation attempts which were deferrals due to failure to meet Hb standards ranged from 0.4% to 16.4% (Table 2.1). The ratio of male to female participants varied greatly across studies with a range of 46.2% to 98.3% for male participants. The highest proportion of male participants was found in studies based in India (median 91.3%, range 74.4% to 98.3%) compared with an approximately equal male: female ratio in US studies (median 50.2%, range 46.7% to 53.0%). Deferral rates were reported separately for men and women in 25 studies. Hb deferral was higher in females than males in all 25 studies, ranging from 2.3% to 47.2% in females compared with 0% to 10.0% in males. Although most (22) of these studies used a threshold of 125 g/L for females, with LHD rates varying from 5.6% to 47.2%, it is of interest to note the lowest percentage LHD for females (2.3%) was associated with the lowest Hb threshold (Hillgrove, Moore, Doherty, & Ryan, 2011). Meta-analysis showed a significantly higher risk of deferral due to low Hb in females compared with males in studies where the LHD level is set the same ("universal") for both male and female (OR 14.91, 95% CI 12.82 to 17.34) as well as in studies with sex-specific Hb thresholds (OR 8.19, 95% CI 4.88 to 13.74) (Figure 2.2). However, considerable heterogeneity was observed across studies for all subgroups ($I^2 = 100\%$).
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

Figure 2-2: Meta-analysis of risk of deferral due to failing low Hb thresholds in males and females stratified by universal and sex-specific Hb threshold.

N.B. Gonzalez 2012 listed here is the e-publication of Gonzalez 2013

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Female</th>
<th>Male</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>Male; Female</td>
</tr>
<tr>
<td>1.9.1 Universal Hb thresholds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agnihotri 2010</td>
<td>284</td>
<td>559</td>
<td>147</td>
<td>5473</td>
</tr>
<tr>
<td>Bhattacharya 2011</td>
<td>46</td>
<td>117</td>
<td>92</td>
<td>6700</td>
</tr>
<tr>
<td>Cusster 2012(Mast 2010)</td>
<td>39689</td>
<td>256789</td>
<td>20747</td>
<td>248169</td>
</tr>
<tr>
<td>Ester 2010</td>
<td>532689</td>
<td>361141</td>
<td>51727</td>
<td>3733186</td>
</tr>
<tr>
<td>Gandhi 2012</td>
<td>3752</td>
<td>18985</td>
<td>623</td>
<td>18988</td>
</tr>
<tr>
<td>Ghish 2012</td>
<td>34</td>
<td>205</td>
<td>58</td>
<td>8527</td>
</tr>
<tr>
<td>Kames 2011</td>
<td>23075</td>
<td>82335</td>
<td>3229</td>
<td>52936</td>
</tr>
<tr>
<td>Minimale 2011</td>
<td>186</td>
<td>500</td>
<td>149</td>
<td>14400</td>
</tr>
<tr>
<td>Shaz 2010</td>
<td>4373</td>
<td>275260</td>
<td>2867</td>
<td>247338</td>
</tr>
<tr>
<td>Sundar 2010</td>
<td>176</td>
<td>1747</td>
<td>45</td>
<td>41385</td>
</tr>
<tr>
<td>Wilkinson 1982</td>
<td>88336</td>
<td>804158</td>
<td>11715</td>
<td>1159745</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>754367</td>
<td>8192980</td>
<td>47.8%</td>
<td>14.91 (14.87, 14.94)</td>
</tr>
<tr>
<td>Total events</td>
<td>1099156</td>
<td>97509</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.66; ^{2} P = 0.426; ^{2} I^2 = 100%$
Test for overall effect: $Z = 13.13 (P < 0.00001)$

<table>
<thead>
<tr>
<th>1.9.2 Sex-specific Hb thresholds</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aysial 2007</td>
<td>1327</td>
<td>8726</td>
<td>1553</td>
<td>75174</td>
</tr>
<tr>
<td>Blaft 2012</td>
<td>837</td>
<td>103405</td>
<td>4608</td>
<td>112491</td>
</tr>
<tr>
<td>Bhattacharya 2011</td>
<td>27</td>
<td>99</td>
<td>8</td>
<td>130</td>
</tr>
<tr>
<td>Chandra 2010</td>
<td>716</td>
<td>2901</td>
<td>109</td>
<td>5396</td>
</tr>
<tr>
<td>Chauhan 1995</td>
<td>286</td>
<td>1124</td>
<td>149</td>
<td>11890</td>
</tr>
<tr>
<td>Corleto 2005</td>
<td>14</td>
<td>68</td>
<td>0</td>
<td>125</td>
</tr>
<tr>
<td>di Lorenzo Oliveira 2011</td>
<td>624</td>
<td>11380</td>
<td>1209</td>
<td>221816</td>
</tr>
<tr>
<td>Gonzalez 2012</td>
<td>23798</td>
<td>265340</td>
<td>4777</td>
<td>521887</td>
</tr>
<tr>
<td>Hargrove 2011</td>
<td>195</td>
<td>30668</td>
<td>108</td>
<td>32840</td>
</tr>
<tr>
<td>Houndhun 2007</td>
<td>16832</td>
<td>201418</td>
<td>7745</td>
<td>363618</td>
</tr>
<tr>
<td>Kames 2011</td>
<td>39457</td>
<td>523355</td>
<td>3329</td>
<td>528385</td>
</tr>
<tr>
<td>Rabaya 2012</td>
<td>96</td>
<td>1241</td>
<td>25</td>
<td>2907</td>
</tr>
<tr>
<td>Zaretta 1999</td>
<td>62</td>
<td>5390</td>
<td>110</td>
<td>9371</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>127777</td>
<td>183129</td>
<td>52.2%</td>
<td>0.19 (4.60, 18.74)</td>
</tr>
</tbody>
</table>

Total events: 109502 | 23675
Heterogeneity: $\chi^2 = 0.84; ^{2} P = 11.3895; ^{2} I^2 = 100%$
Test for overall effect: $Z = 7.56 (P < 0.00001)$

Total events: 109429 | 121375
Heterogeneity: $\chi^2 = 0.93; ^{2} P = 22.6534; ^{2} I^2 = 100%$
Test for overall effect: $Z = 20.45 (P < 0.00001)$

2.6.3.2 Ethnicity

Three studies (Mast et al., 2010; Oliveira et al., 2011; Shaz et al., 2010) reported the relationship between LHD and ethnicity. One study, J. C. Lim, Tien, and Ong (1993), did not provide sufficient figures to determine Hb deferral rates either for the population presenting for donation or for those able to donate after surmounting other causes of deferral. The remainder showed what percentage of deferrals were due to low Hb levels (Table 2.2). The two US-based studies (Mast et al., 2010; Shaz et al., 2010) both reported a significantly increased risk of LHD in Black or African-American compared with white females (adjusted OR 2.11, 95% CI 2.06 to 2.16 (Mast et al., 2010); OR 1.49, 95% CI 1.45 to 1.53 (Shaz et al., 2010)).
A significant increased risk of LHD was also reported for Hispanic compared with white females in both US studies (adjusted OR 1.29, 95% CI 1.25 to 1.34 ((Mast et al., 2010); OR 1.17, 95% CI 1.10 to 1.25 (Shaz et al., 2010)). The first of these studies also reported a significant increased risk of LHD associated with Black or Hispanic ethnicity in males compared with white males (Black: adjusted OR 2.42, 95% CI 2.21 to 2.65; adjusted Hispanic: OR 2.11, 95% CI 2.06 to 2.16). However, the second US study (Shaz et al., 2010) reported a significantly reduced risk of LHD in males in these two populations (Black: OR 0.89, 95% CI 0.79 to 0.99; Hispanic: 0.53, 95% CI 0.38 to 0.73) compared to their white counterparts. No significant differences in LHD risk were observed between Asian and white males or females (Mast et al., 2010). The third study (Oliveira et al., 2011) reported a slight increase in the risk of LHD in non-white donors compared with white donors (OR 1.06, 95% CI 1.01 to 1.11); however, this study did not report LHD by ethnicity separately for males and females.

### Table 2.2: Deferral due to low Hb by ethnic origin.

<table>
<thead>
<tr>
<th>Study</th>
<th>Donation group by Ethnicity</th>
<th>Hb Deferral % (M/F)*</th>
<th>Odds Ratio (95% CI) (M/F)**</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Lorenzo Oliveira 2011</td>
<td>White*</td>
<td>2.2</td>
<td>1</td>
<td>Sex-specific odds ratios, or sufficient data to allow calculation of sex-specific odds ratios, were not reported.</td>
</tr>
<tr>
<td></td>
<td>Non-white</td>
<td>2.3</td>
<td>1.06 (1.01 - 1.11)</td>
<td></td>
</tr>
<tr>
<td>Mast 2010</td>
<td>White*</td>
<td>1.6 / 16.6</td>
<td>1 / 1</td>
<td>Sex-specific odds ratios (male/female) are reported in original study as adjusted but by which other factors is unclear.</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1.1 / 20.5</td>
<td>1.10 (0.94 - 1.28) / 1.05 (1.00 - 1.10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>2.4 / 29.2</td>
<td>2.42 (2.21 - 2.65) / 2.11 (2.06 - 2.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>1.1 / 22.6</td>
<td>1.06 (0.92-1.23) / 1.29 (1.25 -1.34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1.2 / 21.5</td>
<td>1.15 (0.95 - 1.40) / 1.27 (1.21 -1.33)</td>
<td></td>
</tr>
<tr>
<td>Shaz 2010</td>
<td>African American</td>
<td>1.1 / 19.0</td>
<td>0.89 (0.79 - 0.99) / 1.49 (1.45 -1.53)</td>
<td>Unadjusted odds ratios are calculated from original data provided by authors. Unclear whether Asians included in &quot;other&quot; – need to confirm with authors who supplied data.</td>
</tr>
<tr>
<td></td>
<td>White*</td>
<td>1.2 / 13.6</td>
<td>1 / 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>0.6 / 15.6</td>
<td>0.53 (0.38 - 0.73) / 1.17 (1.10 -1.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2.5 / 34.5</td>
<td>2.11 (1.87 - 2.39) / 3.35 (3.23 -3.47)</td>
<td></td>
</tr>
</tbody>
</table>

* Where results were given for males and females, both sets of data are shown separated by a "/".
Where only one figure is shown the results are for a mixed sex population.

** Odds ratios were calculated for the various ethnic groups as compared to the white population.
Given these reports of differences in LHD associated with ethnicity, particularly in females, the studies were stratified according to their geographical location (Figure 2.3). Of particular interest is the significantly increased risk of LHD for females as compared to males in four Indian studies (OR 34.04, 95% CI 28.92 to 40.07) when compared with four US studies (OR 10.55, 95% CI 8.80 to 12.64) (P value < 0.00001) despite identical Hb thresholds for these two groups of studies. A significant difference in the risk of LHD in females as compared to males was also observed between five European studies (OR 4.85, 95% CI 2.94 to 8.00) and three Southern American studies (OR 13.59, 95% CI 8.17 to 22.61) (P value = 0.005), all of which implement sex-specific thresholds of 135 g/L and 125 g/L for males and females, respectively.

Table 2.3 shows the risk for female LHD increases according to the nationality of the study population, which may consist of different ethnic groups. Again, considerable heterogeneity was observed across studies for three of the subgroups ($I^2= 99 - 100\%$) but not for those studies from India ($I^2= 0\%$).
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

Figure 2-3: Meta-analysis of risk of deferral due to failing low Hb thresholds in males and females, stratified by study setting.

N.B. Gonzalez 2012 listed here is the e-publication of Gonzalez 2013

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Female</th>
<th>Male</th>
<th>Odd Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8.1 USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edel 2010</td>
<td>512869</td>
<td>261141</td>
<td>51772</td>
<td>37231 85</td>
<td>6.8%</td>
</tr>
<tr>
<td>Gandi 2012</td>
<td>3752</td>
<td>19685</td>
<td>623</td>
<td>16369 6.6%</td>
<td>6.35 (5.92, 6.83)</td>
</tr>
<tr>
<td>Kamel 2011</td>
<td>34057</td>
<td>534255</td>
<td>3329</td>
<td>528365 6.6%</td>
<td>10.96 (10.59, 11.30)</td>
</tr>
<tr>
<td>Shaz 2010</td>
<td>40332</td>
<td>275260</td>
<td>2987</td>
<td>247538 6.6%</td>
<td>14.71 (14.10, 15.38)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4429441</td>
<td>451257</td>
<td>27.2%</td>
<td>16.67 (8.06, 12.67)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>811230</td>
<td>56868</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Tau^2 = 0.03, Chi^2 = 340.20, df = 3 (P &lt; 0.00001), P = 99%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 27.02 (P < 0.00001)

1.8.2 Southern American

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Female</th>
<th>Male</th>
<th>Odd Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contes 2006</td>
<td>18</td>
<td>85</td>
<td>0</td>
<td>125</td>
<td>1.4%</td>
</tr>
<tr>
<td>Di Lorenzo 2009</td>
<td>6245</td>
<td>11380</td>
<td>1280</td>
<td>21098 6.8%</td>
<td>9.67 (9.38, 10.99)</td>
</tr>
<tr>
<td>Gonzalez 2012</td>
<td>35788</td>
<td>285340</td>
<td>4777</td>
<td>521687 6.6%</td>
<td>18.96 (18.37, 17.41)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>379225</td>
<td>743828</td>
<td>15.0%</td>
<td>13.59 (8.17, 22.61)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>42059</td>
<td>6857</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Tau^2 = 0.14, Chi^2 = 229.92, df = 2 (P &lt; 0.00001), P = 99%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 10.05 (P < 0.00001)

1.8.3 Indian

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Female</th>
<th>Male</th>
<th>Odd Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal 2010</td>
<td>264</td>
<td>566</td>
<td>147</td>
<td>5473 6.6%</td>
<td>32.42 (25.60, 40.94)</td>
</tr>
<tr>
<td>Bahadur 2011</td>
<td>40</td>
<td>117</td>
<td>82</td>
<td>6700 6.2%</td>
<td>41.93 (27.01, 66.00)</td>
</tr>
<tr>
<td>Oommen 2012</td>
<td>34</td>
<td>205</td>
<td>59</td>
<td>8527 6.2%</td>
<td>29.93 (25.32, 36.51)</td>
</tr>
<tr>
<td>Sundar 2010</td>
<td>178</td>
<td>1747</td>
<td>45</td>
<td>14355 6.5%</td>
<td>35.38 (26.13, 50.50)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2628</td>
<td>35688</td>
<td>25.5%</td>
<td>34.84 (29.08, 40.07)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>617</td>
<td>332</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Tau^2 = 0.00, Chi^2 = 1.67, df = 3 (P = 0.64), P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 42.41 (P < 0.00001)

1.8.4 European

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Female</th>
<th>Male</th>
<th>Odd Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arslan 2007</td>
<td>1327</td>
<td>9725</td>
<td>1553</td>
<td>75174 6.8%</td>
<td>6.60 (7.07, 6.19)</td>
</tr>
<tr>
<td>Baart 2011</td>
<td>8237</td>
<td>10865</td>
<td>4588</td>
<td>112491 6.8%</td>
<td>1.66 (1.86, 2.03)</td>
</tr>
<tr>
<td>Bischof 2011</td>
<td>27</td>
<td>86</td>
<td>9</td>
<td>130   5.1%</td>
<td>5.88 (3.59, 13.22)</td>
</tr>
<tr>
<td>Hoekstra 2007</td>
<td>10633</td>
<td>20418</td>
<td>7745</td>
<td>209619 6.6%</td>
<td>3.35 (3.30, 3.40)</td>
</tr>
<tr>
<td>Zanetti 1995</td>
<td>520</td>
<td>5370</td>
<td>110</td>
<td>9271 6.7%</td>
<td>0.65 (7.25, 11.00)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>339057</td>
<td>506884</td>
<td>32.2%</td>
<td>4.85 (2.94, 8.00)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>27004</td>
<td>13865</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Tau^2 = 0.30, Chi^2 = 1390.10, df = 4 (P &lt; 0.00001), P = 100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 6.16 (P < 0.00001)

Total (95% CI) | 5141351 | 5899251 | 100.0% | 11.75 (8.12, 17.02) |

Test for overall effect: Z = 13.05 (P < 0.00001)

Test for subgroup differences: Chi^2 = 121.83, df = 3 (P = 0.00001), P = 97.5%

Table 2.3: Increasing risk of low Hb deferral in women (as compared to men) by nationality.

<table>
<thead>
<tr>
<th>Country</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>4.85</td>
<td>2.94 - 8.00</td>
</tr>
<tr>
<td>American</td>
<td>10.67</td>
<td>8.98 - 12.67</td>
</tr>
<tr>
<td>South American</td>
<td>13.59</td>
<td>8.17 - 22.61</td>
</tr>
<tr>
<td>Indian</td>
<td>34.04</td>
<td>28.92 - 40.07</td>
</tr>
</tbody>
</table>
2.6.3.3 Age

Sixteen studies reported LHD by age; eight of these (Arslan, 2007; Gandhi, Duffy, Benike, Jenkins, & Stubbs, 2012; Hillgrove et al., 2011; Hoekstra et al., 2007; Mast et al., 2010; Sebok, Notari, Chambers, Benjamin, & Eder, 2007; Shaz et al., 2010; Zanella et al., 1989) reported LHD rates for males and females separately, whilst the remaining eight studies either reported LHD rates by age for males and females combined (Agnihotri, 2010; Baart, de Kort, Atsma, Moons, & Vergouwe, 2012; Di Lorenzo Oliveira, Loureiro, de Bastos, Proietti, & Carneiro-Proietti, 2009; Girish, Chandrashekhar, Ramesh, & Kantikar, 2012; Goncalez et al., 2013; Tondon et al., 2008), or did not report sufficient data to calculate LHD rates for both males and females (Custer et al., 2004; Sundar, Sangeetha, Seema, Marimuthu, & Shivanna, 2010). When LHD by age was assessed across all 16 studies, no relationship between age and deferral was apparent (data not shown). However, in those eight studies which reported LHD separately for males and females, all studies showed an increase in LHD with increasing age in males (Figure 2.4A). In particular, these studies suggested a low and stable deferral rate for males under 40 years old of typically less than 3%, whereas the deferral rate for men over 45 - 50 increased with age in the majority of studies. The change in Hb deferral with age in females was less clear; some studies reported the highest rates of LHD for the youngest age group (Gandhi et al., 2012; Hillgrove et al., 2011; Hoekstra et al., 2007; Mast et al., 2010), e.g. 3.1% for females less than 18 compared to 1.9% for those greater than 65 (Hillgrove et al., 2011) while others reported the maximum LHD rate for older age groups (Sebok et al., 2007; Zanella et al., 1989) e.g. 7.6% for females aged 18 - 30 compared to 18.6% for those greater than 50 (Zanella et al., 1989) (Figure 2.4B).
Figure 2-4: Low Hb deferral by age. The percentage of deferrals is shown for the midpoint of each age group as described in individual studies for (A) men and (B) women. Data from each included study is plotted as indicated.
2.6.3.4 Seasonal temperature

Four studies reported LHD deferral rates by season/temperature (Baart et al., 2012; Hoekstra et al., 2007; Lau, Hansen, & Sererat, 1988; Sebok et al., 2007), although one study did not provide sample sizes by season to enable calculation of ORs (Sebok et al., 2007). All four studies showed a higher LHD rate during summer months or at high mean maximum monthly temperatures compared with winter months or low mean maximum monthly temperatures. In one study, the risk of LHD (adjusted for body weight) increased consistently with each 5°C rise in temperature (from less than 5°C to greater than 25°C) with the highest temperature range conferring a 96% increased risk of deferral in males (OR 1.96, 95% CI 1.76 to 2.18) and an 80% increased odds of LHD in females (OR 1.80, 95% CI 1.68 to 1.94) (Hoekstra et al., 2007). The OR for LHD also rose consistently with mean maximum monthly temperature in one study (Lau et al., 1988) with a 1.7-fold increased odds ratio associated with the highest temperature range (18 to 24°C) compared with the lowest (less than -4°C) (OR 1.68, 95% CI 1.53 to 1.86). In the second study (Baart et al., 2012) which calculated the OR for each season, a significant increased OR was associated with donation during Spring (OR 1.44, 95% CI 1.31 to 1.57 in males; OR 1.20, 95% CI 1.13 to 1.29 in females) and Summer months (OR 1.44, 95% CI 1.31 to 1.57 in males; OR 1.20, 95% CI 1.13 to 1.29 in females) compared with Winter months. In this study, the OR for LHD was reduced during the Autumn season, although this only reached statistical significance in females (OR 0.89, 95% CI 0.83 to 0.96).
Table 2.4: Low Hb deferral by seasonal temperature.

<table>
<thead>
<tr>
<th>Study</th>
<th>Donation Group by Seasonal Temperature</th>
<th>Hb Deferral (%) (M/F)*</th>
<th>Odds Ratio (95% CI) (M/F)*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baart 2012</td>
<td>Winter (Dec - Feb)</td>
<td>3.4 / 7.1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spring (Mar – May)</td>
<td>4.8 / 8.4</td>
<td>1.44 (1.31 - 1.57) / 1.20 (1.13 - 1.29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Summer (Jun - Aug)</td>
<td>4.7 / 8.5</td>
<td>1.41 (1.29 - 1.54) / 1.21 (1.14 - 1.30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autumn (Sep – Nov)</td>
<td>3.1 / 6.4</td>
<td>0.92 (0.83 - 1.01) / 0.89 (0.83 - 0.96)</td>
<td></td>
</tr>
<tr>
<td>Hoekstra 2007</td>
<td>Mean of max. monthly temperature at donation:</td>
<td></td>
<td></td>
<td>Hb deferral rate and odds ratios given separately for males and females. Odds ratios are unadjusted.</td>
</tr>
<tr>
<td></td>
<td>&lt;5°C</td>
<td>1.8 / 6.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-10°C</td>
<td>2.0 / 7.1</td>
<td>1.13 (1.02 - 1.24) / 1.09 (1.02 - 1.16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-15°C</td>
<td>2.2 / 7.3</td>
<td>1.19 (1.08 - 1.31) / 1.12 (1.05 - 1.20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-20°C</td>
<td>2.5 / 7.9</td>
<td>1.42 (1.29 - 1.56) / 1.21 (1.14 - 1.29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-25°C</td>
<td>3.2 / 9.1</td>
<td>1.78 (1.62 - 1.96) / 1.40 (1.32 - 1.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;25°C</td>
<td>3.6 / 11.1</td>
<td>1.96 (1.76 - 2.18) / 1.80 (1.68 - 1.94)</td>
<td></td>
</tr>
<tr>
<td>Lau 1988</td>
<td>Mean of max. monthly temperature at donation:</td>
<td></td>
<td></td>
<td>Hb deferral rate and odds ratios given separately for males and females. Odds ratios and confidence intervals are calculated from reported numbers of non-deferrals and Hb deferrals in each group, excluding deferrals for other reasons.</td>
</tr>
<tr>
<td></td>
<td>25.1-35°F([-4] – 2°C)</td>
<td>3.5</td>
<td>0.93 (0.83 - 1.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35.1-45°F(2 – 7°C)</td>
<td>3.7</td>
<td>1.00 (0.89 - 1.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45.1-55°F(7 – 13°C)</td>
<td>4.8</td>
<td>1.32 (1.18 - 1.46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55.1-65°F(13 – 18°C)</td>
<td>4.8</td>
<td>1.30 (1.16 - 1.45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65.1-75°F(18 – 24°C)</td>
<td>6.1</td>
<td>1.68 (1.53 - 1.86)</td>
<td></td>
</tr>
<tr>
<td>Seebok 2007</td>
<td>Winter (Dec - Feb)</td>
<td>0.8 / 12.9</td>
<td>n/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spring (Mar – May)</td>
<td>1.0 / 13.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Summer (Jun - Aug)</td>
<td>1.3 / 14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autumn (Sep – Nov)</td>
<td>1.0 / 13.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Where results were given for males and females, both sets of data are shown separated by a "/". Where only one figure is shown the results are for a mixed sex population.
2.6.3.5 **Body weight**

LHD by weight was reported in two studies (Figure 2-5) (Hoekstra et al., 2007; Mast et al., 2010). In both studies, the OR for LHD decreased consistently with increasing body weight in both males and females. In the Dutch study, the age-adjusted risk of LHD in a male donor weighing more than 100 kg was just 22% of the risk in males weighing less than 60 kg (OR 0.22, 95% CI 0.178 to 0.27) (Hoekstra et al., 2007). In the US study, the OR in males in the highest body weight group of greater than 200 lb (approximately 91 kg) was 50% lower than those in the lowest body weight category (less than 109 lb (approximately 50 kg) (OR 0.50, 95% CI 0.32 to 0.79) (Mast et al., 2010). In females, the OR for donors in the highest body weight group was reduced by 43% (OR 0.57, 95% CI 0.50 to 0.66) compared with the lowest weight group in the Dutch study (Hoekstra et al., 2007). A consistent reduction in LHD OR associated with increasing body weight was also observed in the US study (Mast et al., 2010). Compared with the lowest body weight group, the reduced risk of LHD was statistically significant in females of between 150 lb and 200 lb (approximately 68 – 90 kg), although the reduced risk in the highest weight category (>200 lb) did not reach statistical significance (OR 0.85, 95% CI 0.71 to 1.01) (Mast et al., 2010).
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

Figure 2-5: Low Hb deferral by body weight
Odds ratios are shown for each weight group relative to the reference group of lowest body weight, separately for males and females. Error bars indicate 95% confidence intervals. Figures shown within the bars indicate the LHD rate for each weight group.
2.6.3.6 Donation characteristics

Donation intensity

Four studies reported LHD by donation intensity in RBC donors (Table 2.5), which was defined as the inter-donation interval (Ziemann et al., 2006), number of donations in the past 12 months (Mast et al., 2010; Zanella et al., 1989), or number of donations in the past two years as a continuous variable (Baart et al., 2012). One study described LHD stratified by the number of platelet donations in the past 12 months (Mast et al., 2010).

Baart et al. (2012) showed significantly increased risk of LHD was seen to be associated with the number of donations during the previous two years in males, but a significantly decreased comparative risk in females. A second study (Mast et al., 2010) also reported for females a reduced risk of LHD associated with five or more donations in the previous 12 months (for example, a 50% reduction in LHD risk for ≥6 donations). Conversely, this study found a significantly reduced risk of LHD in males only donating one or two times in the previous year. This study also showed a protective effect against LHD from a higher platelet donation intensity (four or more in the previous 12 months) and an increased LHD with a lower frequency (one to three donations per year). However, the results were not separated by gender.

In a third study (Zanella et al., 1989) the deferral rate of male and female donors was reported graphically, stratified into three groups giving low, medium and high annual rates of donation. By the time of the eighth donation, the trend was for LHD rates in males of all three groups to fall to similar levels irrespective of donation intensity, and continue to fall with each subsequent donation. Similarly for women in the medium and high frequency donation groups, by donation eight it appeared they were less likely to fail Hb thresholds, whereas females giving less frequently showed an increasing likelihood of LHD with each successive donation.

In the final study (Ziemann et al., 2006) reported a significantly reduced risk of LHD in donors who had donated within the past year (for those having donated less than six months, and those having donated in the past 6-11 months, prior to the present visit having OR 0.70, 95% CI 0.56 to 0.87, and OR 0.68, 95% CI 0.54 to 0.86, respectively) when compared to donors who had not donated within the previous two years. This study did not report results separately for males and females.
## Table 2.5: Low Hb deferral by donation characteristics: Donation intensity

<table>
<thead>
<tr>
<th>Study</th>
<th>Donation Group</th>
<th>Hb Deferral Rate (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baart 2012</td>
<td>Number of whole blood donations in past two years</td>
<td>Continuous</td>
<td>n/r</td>
</tr>
<tr>
<td>Custer 2012</td>
<td>Number of whole blood donations during previous 12 months</td>
<td>0</td>
<td>1.3 / 18.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1.1 / 17.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>1.5 / 18.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>2.1 / 18.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>2.3 / 16.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>2.6 / 13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥6</td>
<td>2.8 / 8.8</td>
</tr>
<tr>
<td>Mast 2010</td>
<td>Number of platelet donations during previous 12 months</td>
<td>0 (RBC donors)</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4+</td>
<td>5.6</td>
</tr>
<tr>
<td>Zanella 1989#</td>
<td>Annual rate of donation:</td>
<td>M: &lt;2/year</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: &lt;1.5/year</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: 2-3/year</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: 1.5-2.5/year</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: &gt;3/year</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: &gt;2.5/year</td>
<td></td>
</tr>
<tr>
<td>Ziemann 2006</td>
<td>Interdonation interval:</td>
<td>&lt;6 mths</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 to 11 mths</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 to 23 mths</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥24 mths</td>
<td>8.8</td>
</tr>
</tbody>
</table>

* values reported separately for males and females where available.
# Incidence of Hb deferrals is reported graphically as a function of number of donations in repeat donors according to sex and annual rate of donations.
New versus repeat donors

LHD rates for new versus repeat donors were reported in five studies (Custer et al., 2004; Custer et al., 2012; Goncalez et al., 2013; Kouao et al., 2012; Wilkinson, 1982) (Table 2.6). In four studies a significantly lower risk of LHD was found in repeat donors as compared to those who had not donated previously (Custer et al., 2004; Custer et al., 2012; Goncalez et al., 2013; Wilkinson, 1982); this effect was apparent in both male and female donors (Custer et al., 2004; Wilkinson, 1982). Only one study (Kouao et al., 2012) showed a significantly increased risk in repeat donors.

Table 2.6: Low Hb deferral by donation characteristics: New/repeat donors.

<table>
<thead>
<tr>
<th>Study</th>
<th>Donation Group</th>
<th>Hb Deferral Rate (%) (M/F)*</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goncalez 2013</td>
<td>New</td>
<td>7.9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Repeat</td>
<td>3.9</td>
<td>0.47 (0.47 - 0.48)</td>
</tr>
<tr>
<td>Kouao 2012</td>
<td>New</td>
<td>2.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Repeat</td>
<td>4.0</td>
<td>1.61 (1.23 - 2.11)</td>
</tr>
<tr>
<td>Custer 2012</td>
<td>New</td>
<td>8.8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Repeat</td>
<td>8.1</td>
<td>0.87 (0.86 - 0.88)</td>
</tr>
<tr>
<td>Custer 2004^</td>
<td>New</td>
<td>0.7 / 12.6</td>
<td>1 / 1</td>
</tr>
<tr>
<td></td>
<td>Repeat</td>
<td>0.5 / 10.3</td>
<td>0.69 (0.47 - 1.03) / 0.80 (0.76 - 0.85)</td>
</tr>
<tr>
<td>Wilkinson 1982</td>
<td>New</td>
<td>1.2 / 17.6</td>
<td>1 / 1</td>
</tr>
<tr>
<td></td>
<td>Repeat</td>
<td>1.0 / 13.2</td>
<td>0.78 (0.75 - 0.81) / 0.71 (0.70 - 0.72)</td>
</tr>
</tbody>
</table>

* Where results were given for males and females, both sets of data are shown separated by a “/”. Where only one figure is shown the results are for a mixed sex population.

^ Males restricted to those aged ≥ 40.
Reason for deferral at previous visit

Two studies (Baart et al., 2012; Hillgrove et al., 2011) reported LHD according to the reason for deferral at the previous visit (Baart et al., 2012) or during the previous 12 months (Hillgrove et al., 2011); both studies showed a significantly increased risk of LHD in donors who had been previously deferred for LHD. This increased risk was six-fold in the Australian study (OR 6.22, 95% CI 3.72 to 10.4) (Hillgrove et al., 2011), with a similar risk in males (OR 6.16, 95% CI 5.64 to 6.73) and a slightly lower risk in females (OR 4.82, 95% CI 4.54 to 5.12) in the Dutch study (Baart et al., 2012).

Table 2.7: Low Hb deferral by donation characteristics: Previous deferral reason.

<table>
<thead>
<tr>
<th>Study</th>
<th>Donation group</th>
<th>Hb Deferral (%) (M/F)*</th>
<th>Odds Ratio (95% CI) (M/F)*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baart 2012</td>
<td>Due to low Hb</td>
<td>18.9 / 25.3</td>
<td>6.16 (5.64 - 6.73) / 4.82 (4.54 - 5.12)</td>
<td>Sex-specific odds ratios (male/female) are reported in original study as adjusted but by which other factors is unclear.</td>
</tr>
<tr>
<td></td>
<td>Due to other reasons</td>
<td>1.4 / 3.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hillgrove 2011</td>
<td>Due to low Hb</td>
<td>8.2</td>
<td>6.23 (3.72 - 10.4)</td>
<td>Sex-specific odds ratios, or sufficient data to allow calculation of sex-specific odds ratios, were not reported.</td>
</tr>
<tr>
<td></td>
<td>Due to other reasons</td>
<td>2.0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Where results were given for males and females, both sets of data are shown separated by a "/". Where only one figure is shown the results are for a mixed sex population.

Donation at a static versus mobile donation session

A small but significant increased risk of LHD associated with donation at static blood centres compared to mobile donation units was reported in two studies (OR 1.11, 95% CI 1.06 to 1.17 (Lau et al., 1988); OR 1.18 (1.17 to 1.18) (Custer et al., 2012)).

Table 2.8: Low Hb deferral by donation characteristics: Donation site.

<table>
<thead>
<tr>
<th>Study</th>
<th>Donation group</th>
<th>Hb Deferral (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau 1988</td>
<td>Blood Centre</td>
<td>5.1</td>
<td>1.11 (1.06 - 1.17)</td>
</tr>
<tr>
<td></td>
<td>Blood Mobile</td>
<td>4.6</td>
<td>1</td>
</tr>
<tr>
<td>Custer 2012</td>
<td>Fixed</td>
<td>9.5</td>
<td>1.18 (1.17 - 1.18)</td>
</tr>
<tr>
<td></td>
<td>Mobile</td>
<td>8.2</td>
<td>1</td>
</tr>
</tbody>
</table>
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Directed versus voluntary donors
Two studies (Agnihotri, 2010; Charles, Hughes, Gadd, Bodkyn, & Rodriguez, 2010) compared LHD in directed (i.e. family and friends) donors with normal volunteer donors. Both showed decreased LHD in the directed groups (3.4% v 9.0%; 7.8% v 9.1%), but the difference reached significance only in the Indian study (OR 0.34, CI 0.30 – 0.52).

Table 2.9: Low Hb deferral by donation characteristics: Donor type

<table>
<thead>
<tr>
<th>Study</th>
<th>Donation group</th>
<th>Hb Deferral (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agnihotri 2010</td>
<td>Related</td>
<td>3.4</td>
<td>0.34 (0.30 – 0.52)</td>
</tr>
<tr>
<td></td>
<td>Voluntary</td>
<td>9.0</td>
<td>1</td>
</tr>
<tr>
<td>Charles 2010</td>
<td>Directed</td>
<td>7.8</td>
<td>0.85 (0.66 - 1.11)</td>
</tr>
<tr>
<td></td>
<td>Voluntary</td>
<td>9.1</td>
<td>1</td>
</tr>
</tbody>
</table>

Education
One study showed a slight decreased risk (OR = 0.84; 95% CI = 0.84 – 0.85) in LHD in those who were older than 21 and had completed education to at least first degree level as compared to those who had not progressed further than a high school education (Data not shown - Custer et al. (2012)).
2.7 Discussion

The dominant factor in the differences in rates of LHD is clearly gender. A wide range of other factors, including age, ethnicity, weight, seasonal temperature and donation characteristics, appear to be associated with differences in rates of LHD but these differences are likely to be confounded by the ratio of females included in the studies and so should be stratified by that characteristic. However, the high levels of variability (shown by the majority of $I^2$ statistics which would be classified as "considerable" by the Cochrane Collaboration (Deeks et al., 2011)), the lack of consistency in data classification and reporting across studies prohibits formal comparison of results and accurate risk estimates.

All studies showed increased LHD in women compared to men, but high levels of heterogeneity were observed. Meta-analysis of gender effect has shown that women are 11 times (ORs ranging from 1.96 – 59.6) more likely than men to be deferred due to having an Hb level deemed too low for donation; this effect is present irrespective of whether universal or sex-specific Hb thresholds are used. Both physiological and social causes have been suggested for this phenomenon. Pre-menopausal women are known to have reduced iron stores resulting from the effects of menstruation and pregnancy (C. A. Finch et al., 1977) whereas men have increased testosterone levels which are linked to higher Hb levels (Bhasin et al., 2001). Additionally, smoking is associated with an increase in Hct (Mast et al., 2008) and in general men display a higher incidence of cigarette smoking (Action on Smoking and Health (ASH), 2007). Indeed, it has been suggested that Hb thresholds may not be set at appropriate levels for women (Beutler & Waalen, 2006). In the US, where blood donation eligibility guidelines set by the US Food and Drug Administration state a universal minimum Hb threshold of 125 g/L, sex-specific thresholds are being considered by the United States Food and Drug Administration (2008).

Studies showing gender effects can be seen to have high heterogeneity (Figures 2-2 and 2-3), even when sub-group analyses are performed. A likely cause for such high values of statistical heterogeneity, $I^2$ (99-100%), could be the result of high variance in the ethnic mix within the study populations (clinical heterogeneity). This may explain why subgroup analysis of the studies from India, where the population is likely to be ethnically homogenous, has a low $I^2$ value (0%). Interestingly, although the overall $I^2$ statistic was high, all studies agree on the direction of the effect. Had a more formal evidence-based mapping of design (clinical) heterogeneity been performed then perhaps the $I^2$ statistic could be reduced (Althuis et al., 2014).
Ethnicity has also been shown as a contributory factor in determining whether a prospective donor meets the specified Hb threshold for donation (Mast et al., 2010; Oliveira et al., 2011; Shaz et al., 2010). In particular, Black or African-American women have a higher rate of LHD, although the picture in men is less clear (Mast et al., 2010; Shaz et al., 2010). The study by Mast et al. (2010) states that leiomyoma and heavier menstrual bleeding are known to be more common in African American women. Additionally, as stated in Chapter 1, there are different inherited genotypes that are associated with lower Hb levels. High frequencies, of 80% or more in some populations, may be carriers for the condition α-thalassaemia, which may result in a mild microcytic anaemia (Harteveld & Higgs, 2010). The study of J. C. Lim et al. (1993) from Singapore has shown a greater proportion of Indian donors deferred due to lower Hb than either Chinese, Malay or “other” ethnic groups, although this finding was not reflected in a US study (Mast et al., 2010). Shaz et al. (2010) described an “other” ethnic group which did have a higher rate of LHD which may have included the Asian donors. Nutritional differences may account for some ethnic variation. For example, a recent survey (Yadav & Kumar, 2006) suggests that 31% of the Indian population may be vegetarian with certain religious groups having an even higher percentage. Vastly different proportions of vegetarians have been reported in different countries (European Vegetarian Society). One study, after controlling for individual factors and socioeconomic characteristics, showed a daily diet of meat, fish, and eggs was associated with lower odds of being moderately or severely anaemic (Rammohan, Awofeso, & Robitaille, 2012). A recent study (Rigas et al., 2014) has shown a diet rich in meat is protective of iron-deficiency for men and pre-menopausal women. Beutler and Waalen (2006) have proposed different low Hb thresholds for males and females according to their ethnic origin.

Overall, the deferral patterns for different populations within the 55 studies under review, albeit at different time points with varying Hb cut-offs and other inclusion criteria, show wide variation in LHD rates – ranging from 0.7% in an Indian study (Unnikrishnan et al., 2011) to 16.4% in a Danish population (Bischke & Michelsen, 2011) (Table 2.1). The absolute rate of deferral must reflect at least in part the Hb threshold and the proportion of female donors and so these rates are not in themselves comparable. However, the risk of LHD in women compared with men varies according to the country of study with identical thresholds used in studies within each setting, a further indication of ethnic differences in the ability to meet specified Hb thresholds.
All studies reporting LHD with increasing age show an increase in LHD with increasing age in males. This is likely to be associated with a slow decline in testosterone levels and the average Hb in males falls with age (Bhasin et al., 2001; Guralnik, Eisenstaedt, Ferrucci, Klein, & Woodman, 2004; Guralnik, Ershler, Schrier, & Piccotti, 2005; Nilsson-Ehle, Jagenburg, Landahl, Svanborg, & Westin, 1988). The effect of age on deferral and Hb is less clear in females, probably due to the combined effect of menstruation and pregnancy in younger women and the effect of menopause in older women. In older donors, falling Hb is associated caused by a number of factors, including nutritional changes and underlying medical conditions, such as arthritis, kidney disease and “anaemia of aging” (Mast et al., 2008). An increased incidence of these conditions with age may account for increased LHD with age but the contribution of individual factors is impossible to quantify without more detailed information on the medical condition of donors.

Increasing rates of LHD are associated with rising temperatures (Baart et al., 2012; Hoekstra et al., 2007; Lau et al., 1988; Sebok et al., 2007). In the Hoekstra study, which reported temperature effects separately for males and females, there was an increase in LHD over the temperatures studied of 1.8% to 3.6% for men and 6.5% to 11.1% for women. Although the effect seems more profound in females the increase in ORs is more marked in males, suggesting that increased temperature has more of an effect on males. It was proposed the effect might be due to transient haemodilution as an element of the heat balance mechanism (Watanabe, 1958), although alternative indirect factors of influence on Hb level such as nutrition, physical activity and virus infections have been proposed (Hoekstra et al., 2007). However, seasonal effects on the techniques used for measurement of Hb levels might also be an explanation, especially in the case of gravimetric CuSO₄ determination (Lau et al., 1988).

A reduction in the risk of LHD is also associated with increasing body weight (Hoekstra et al., 2007; Mast et al., 2010). Heavier individuals might be expected to have a greater blood volume and so would donate proportionally less than a smaller person and so better withstand the loss of iron (Mast et al., 2010). Less clear results for females in one study (Mast et al., 2010) may result in a similar effect being masked by differences in menstrual bleeding independent of the donor’s weight. Obesity may cause a female to have no (amenorrhea); infrequent (oligomenorrhea) or heavy or long periods (menorrhagia) or no ovulation (anovulation). Likewise,
underweight female donors may stop menstruation (in the UK the general lower limit for donation is 50 kgs - 7st 12lb). A low BMI may result from excess physical training, lack of calorie intake or genetics (Wonderly, 2014).

Donation characteristics associated with LHD include donation intensity (Baart et al., 2012; Mast et al., 2010; Zanella et al., 1989; Ziemann et al., 2006), previous donation (Custer et al., 2004; Custer et al., 2012; Goncalez et al., 2013; Kouao et al., 2012; Wilkinson, 1982) and previous deferral due to Hb (Baart et al., 2012; Hillgrove et al., 2011). Results suggest a reduced risk of LHD associated with a high frequency of donations in females, but the corresponding risk in males is less clear. One study showed that in women who were experienced donors (i.e. who had donated on more than six occasions) donating at a higher intensity were less likely to defer due to low Hb (Zanella et al., 1989). This is likely to be in part due to women with a predisposition to a lower Hb having been selected out at earlier visits but does not explain why the same effect was not seen in males. Some high intensity donors may be preferentially selected due to self-medication with iron supplements (Mast et al., 2008). As males have larger iron stores than female, typically two to four times greater (C. A. Finch et al., 1977) which are better suited to produce new blood cells after repeated donation, it would be expected that males are better suited to high intensity donation than women. Donating at a frequency of four or more times per year may be close to the limit of dietary iron absorption for replacement, but high donation frequency may be advantageous for blood collection from female donors.

A higher risk of LHD has also been observed in new donors (Custer et al., 2004; Custer et al., 2012; Goncalez et al., 2013; Wilkinson, 1982) where those with low or borderline Hb and/or iron stores will be first revealed. Donors who have previously been deferred for LHD also have a higher rate of LHD (Baart et al., 2012; Hillgrove et al., 2011), which must reflect a slow restoration of iron.

Two studies showed that individuals that donate in response to the needs of a friend or family member (“directed” donations) show a reduced likelihood of being unable to give blood due to failing the lower Hb threshold (although this difference only reached significance in one study (Agnihotri, 2010). Agnihotri postulated that these “directed” donors have a tendency to self-deferral rather than compromise the integrity of the donation to a patient known to them.
Both studies that looked at LHD at fixed static sites as compared to mobile donating sessions found a lower rate of deferral at the latter. Lau et al. (1988) suggested the recruitment characteristics for donors attending static blood centres would differ from those donating in mobile donation units (often these donors give more specialised products and so may experience less stringent donor health checks). Although Custer et al. (2012) offered no explanation for the phenomenon, Donovan (2011) suggested that the more “mobile” donors are, the less likely they are to fail the Hb test, as likely at mobile sites.

One study in the US looking at the effect of education on LHD suggested that socioeconomic factors may have a slight effect on LHD (Custer et al., 2012). It may well be those who have successfully progressed through further education have better opportunity to gain well paid jobs and so are more likely to eat more healthily than those who have limited options available.

This study has a number of limitations. Firstly, a number of important sources of heterogeneity exist across studies, including type of donation (RBCs, platelets or both), Hb donation thresholds (sex-specific versus universal as well as study-specific), ethnic mix within the study population and the ratio of male to female donors in the study. Hb levels were determined using a variety of techniques applied to both capillary and venous blood; this has an effect on the degree of accuracy of Hb measurement leading to variability across studies. Secondly, some studies included a single donation attempt per donor whereas others included multiple donation attempts which would introduce a potential confounding effect in the comparison of study results. Thirdly, most studies reported only one reason for deferral for each prospective donor, i.e. the first that prohibited the donor from further consideration for donation. Therefore, dependent on the donor screening protocol, low Hb levels may be over- or under-represented. The likelihood is the latter, as most protocols would visit non-invasive deferral criteria before taking blood for Hb. Furthermore, reasons for deferral other than low Hb have not always been reported, or have been reported to a different extent across studies. Finally, many studies presented results for male and female donors combined and therefore, despite the clear differences in LHD between males and females, sex-specific risk estimates could not be obtained.
2.8 Author's conclusions

2.8.1 Implications for practice
Donating at a frequency of four or more times per year may be close to the limit of dietary iron absorption for replacement, but high donation frequency may be advantageous for blood collection from female donors.

Deferrals have a cost implication for blood collection organisations and a negative effect on donor motivation. If organisations can reduce the level of deferral, especially LHD which is a major cause of deferral, they may maximise donor return and reduce costs. This systematic review has highlighted the effects of sex, ethnicity, age, ambient temperature, body weight and donation history on LHD. By tailoring donation characteristics (frequency, season, etc.) to the individual donor may donor retention and blood supply may be improved.

2.8.2 Implications for research
A number of important sources of potential heterogeneity exist across the studies including the type of donation, country of study, Hb donation threshold. These parameters and their effect on risk estimates and conclusions should be investigated.

Beutler and Waalen (2006) proposed different lower thresholds for males and females according to their ethnic origin. Given the vastly higher incidence of LHD, separate analyses for males and females is clearly warranted in any future study. Identification of the causal relationship between these factors and LHD remains a challenge.

Any study of LHD may do well to note sociological factors such as smoking habit, education and diet.

Further larger prospective studies with statistical modelling are required in order to establish the combined effect of these multiple factors on deferral of blood donors due to failure to meet Hb standards.
Chapter 2 – A systematic review of factors influencing the deferral of donors failing to meet low haemoglobin thresholds

2.9 Acknowledgements

SRI was supported by NHSBT and the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme (SF, CD) and the NIHR under its Programme Grant Scheme (NIHR-RP-PG-0310-1004, SF).

2.10 Contribution of authors

Graham Smith (GAS) is a content expert for this review (stem cells) and contributed to the search strategies, carried out the screening and selection of trials, data extraction, analysis of results and preparation of the final report.

Sheila Fisher (SF) is a methodological expert for this review, and carried out the screening and selection of trials, data extraction, analysis of results and preparation of the final report.

Carolyn Dorée (CD) is an information specialist, who developed and implemented the search strategies and contributed to the preparation of the final report.

David Roberts (DR) is a content expert for this review (red blood cells and transfusion medicine), and assisted with eligibility screening and contributed to the preparation of the final report.

2.11 Declarations of interest

The authors have no competing interests

2.12 Sources of support

This work was supported by NHSBT, National Institute of Health Research (NIHR) Biomedical Research Centre and a NIHR Programme Grant NIHR-RP-PG-0310-1004-AN. GAS was self-funded, with the exception of being granted study leave.
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

This chapter discusses the systematic review (SR) of literature describing studies of the provision of iron supplements, either through oral or non-oral (e.g. intra-muscular or intra-venous) routes, to blood donors with the aim of improving their health and ability to meet the low Hb thresholds of blood collection agencies from around the world (hereinafter termed the "Iron Supplementation SR"). The intention was to submit the review to The Cochrane Collaboration (http://www.cochrane.org/) and so this Chapter is written in the style of a Cochrane Review. In doing so, it will provide continuity with Chapter 2. The purpose of the investigation was to provide evidence on which to base a proposed future RCT.
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

3.1 Abstract

3.1.1 Background
Donors may be unable to donate blood due to a failure to meet low Hb thresholds set by the collecting organisation, leading to a temporary deferral from blood donation. More importantly, collecting organisations have a duty of care to maintain the health of their donor base. A number of studies have investigated the provision of iron supplements as a means to increase the iron levels in donors, so improving health and reducing the incidence of falling below low Hb thresholds. However, there is no Cochrane systematic review of the relative efficacy and safety of those studies.

3.1.2 Objectives
To assess the efficacy and safety of iron supplementation to reduce iron deficiency and/or anaemia in blood donors of whole blood (WB), red blood cells (RBCs) or platelets when compared with placebo or other treatments.

3.1.3 Search Methods
The Cochrane Injuries Group Specialised Register, CENTRAL, PubMed, MEDLINE (OvidSP), EMBASE (OvidSP), CINAHL (EBSCO Host) and six other databases were searched for relevant trials up to 18 November 2013. Clinical trials registers and screened guidelines reference lists were also searched.

3.1.4 Selection Criteria
Randomised controlled trials (RCTs) comparing iron supplementation versus placebo or control, oral versus parenteral iron supplementation, iron supplementation versus iron-rich food supplements, and different doses, treatment durations and preparations of iron supplementation in healthy blood donors. Autologous blood donors were excluded.

3.1.5 Data Collection and Analysis
Two authors independently extracted data using customised data extraction forms using Microsoft Excel. Data were combined using random effects meta analyses. Heterogeneity was evaluated using the $I^2$ statistic and considerable heterogeneity ($I^2 > 75\%$) was explored using subgroup analyses. The impact of trial quality on the findings was assessed using sensitivity analyses.
3.1.6 Main Results

Thirty RCTs including a total of 4,704 participants met the eligibility criteria, including 19 comparisons of iron supplementation and placebo or control, one comparison of oral and parenteral iron supplementation; four comparisons of different doses of iron supplementation; one comparison of different treatment durations of iron supplementation and 12 comparisons of different iron supplementation preparations.

The methodological quality of the studies was low or uncertain for many studies resulting in an unclear or high risk of bias. For many outcomes the quality of evidence was assessed as moderate. There was a significantly reduced risk of deferral due to low Hb in donors who received iron supplementation compared with donors who received no iron supplementation, both at the first donation visit after commencement of iron supplementation (risk ratio [RR] 0.34; 95% confidence interval [CI] 0.21 to 0.55: four studies; 1194 participants; P value <0.0001) and at subsequent donations (RR 0.25; 95% CI 0.15 to 0.41; three studies; 793 participants; P value <0.00001). Meta-analyses also showed that iron supplementation resulted in significantly higher levels of Hb (mean difference [MD] 2.36 g/L; 95% CI 0.06 to 4.66; eight studies: 847 participants: P value = 0.04), and iron stores, including serum ferritin (MD 13.98 ng/mL; 95% CI 8.92 to 19.03; five studies; 640 participants; P value <0.00001) and transferrin saturation (MD 3.91%; 95% CI 2.02 to 5.80; four studies; 344 participants; P value <0.0001) prior to further donation, and that these significant differences were maintained after subsequent donation(s). Results were robust to sensitivity analyses; no significant differences in the effects of iron supplementation between male and female donors were found.

Adverse effects were widely reported and were more frequent in donors who received iron supplementation than those who did not (RR 1.60; 95% CI 1.23 to 2.07: 4 studies: 1748 participants: P=0.0005), with a significantly increased risk of constipation, diarrhoea, nausea/vomiting and taste disturbances. Some participants stopped treatment due to side effects.
3.1.7 Author’s Conclusions

Iron deficiency is a significant cause of deferral for people wishing to donate blood. Blood donation intervals are set to minimise iron deficiency in repeat blood donors, and all donors are screened at each repeat visit for low Hb levels. However, donors who are deferred through failure to pass the Hb threshold have a high risk of not returning to donate in the future. Minimising iron deficiency in repeat blood donors is therefore essential not only to reduce morbidity from iron deficiency or anaemia, but also to reduce the inconvenience and costs associated with deferral. Iron supplementation for blood donors has been considered and in some jurisdictions has been implemented for some groups of donors. Rigorous evidence for the cost and benefits of iron supplementation is essential to guide policy.

There is moderate evidence to suggest that rates of donor deferral due to low Hb are considerably less in those taking iron supplements compared with those without iron supplementation, both at the first donation visit and at subsequent donation. Iron supplemented donors also show elevated Hb and iron stores. These beneficial effects are balanced by more frequent adverse events in donors who received iron supplementation than in those who did not which is likely to limit acceptability and compliance.

The long term effects of iron supplementation without measurement of iron stores are unknown. These considerations are likely to preclude widespread use of iron supplementation by tablets. Blood services may consider targeted use of supplementation at groups or individuals at greater risk of iron deficiency, personalised donation intervals and provision of effective dietary advice.
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

3.2 Plain Language Summary

The effects of iron supplementation on iron deficiency and deferral in blood donors

Iron deficiency (ID), even without anaemia, can cause symptoms of tiredness, impaired wound healing, lack of attention and RLS so the interval between blood donations is set by independent regulators to minimise ID in donors. Potential blood donors are screened each time they visit to give blood to see if they are anaemic. Donors who do not pass this screening test and so cannot give blood are deferred from giving blood, but many of these donors do not return. If blood donors take iron tablets then the risk of becoming ID may be reduced. However, the balance between the benefits of giving iron and the possible side effects are not clear. All the randomised trials testing the benefits of giving blood donors iron have been reviewed. The evidence is current up to 18 November 2013.

There were 30 randomised trials of iron supplementation (IS) in blood donors with a total of 4704 participants. Some of the studies did not report details of their design very well and people in some of the studies left the study early and did not contribute data. By combining the results from four studies, it was shown that around 3% of donors who were given IS were unable to give blood when they next came to donate because the levels of iron in their blood were too low, compared with 10% of donors who did not take iron. More than this, 4% of IS donors were unable to give blood at any future donation due to low iron levels, compared with around 20% of donors not given IS.

However, 29% of donors who took iron tablets experienced side effects compared with 17% of donors who were given dummy tablets. Combined data from two studies showed that the iron-supplemented donors had nearly five times more stomach upsets and changes in their taste compared to donors who did not take these tablets.

Due to the issues around how reliable the studies were, the quality of evidence is moderate and these results could change with more research.

Donors can benefit from iron tablets but the rate of side effects is high, which means in practice giving all donors iron tablets is unlikely to be acceptable; it is not known whether giving iron causes extra problems over a long period of time. Blood services may target IS at groups or individuals who are at risk of ID, may try to reduce deferral by adjusting donation intervals to suit the donor’s ability to give blood without becoming ID or may give donors specific dietary advice.
Table 3.1: Summary of findings for the main comparison.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Low Hb deferral - at first donation visit after commencement of treatment</td>
<td>105 per 1000</td>
<td>36 per 1000 (22 to 58)</td>
<td>RR 0.34 (0.21 to 0.55)</td>
<td>1194 (4 studies)</td>
</tr>
<tr>
<td>Low¹</td>
<td>28 per 1000</td>
<td>10 per 1000 (6 to 15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High¹</td>
<td>237 per 1000</td>
<td>81 per 1000 (50 to 130)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Hb deferral - after multiple donation visits</td>
<td>Study population¹</td>
<td>199 per 1000</td>
<td>50 per 1000 (30 to 81)</td>
<td>RR 0.25 (0.15 to 0.41)</td>
<td>793 (3 studies)</td>
</tr>
</tbody>
</table>
Table 3.1: Summary of findings for the main comparison (continued).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb (g/L) - before further donation</strong></td>
<td>The mean Hb (g/L) - before further donation in the control groups was 135.2 g/L</td>
<td></td>
<td>847 (8 studies)</td>
<td>⊕⊕⊕⊝ moderate^4</td>
<td></td>
</tr>
<tr>
<td>Scale from: 123 to 152.</td>
<td>The mean Hb (g/L) - before further donation in the intervention groups was 2.36 higher (0.06 to 4.66 higher)^3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hb (g/L) - after subsequent donation(s)</strong></td>
<td>The mean Hb (g/L) - after subsequent donation(s) in the control groups was 127.8 g/L</td>
<td></td>
<td>406 (3 studies)</td>
<td>⊕⊕⊕⊝ moderate^5</td>
<td></td>
</tr>
<tr>
<td>Scale from: 127.3 to 129.</td>
<td>The mean Hb (g/L) - after subsequent donation(s) in the intervention groups was 6.37 higher (2.36 to 10.39 higher)^3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serum ferritin (ng/mL) - before further donation</strong></td>
<td>The mean serum ferritin (ng/mL) - before further donation in the control groups was 21.1 ng/mL</td>
<td></td>
<td>640 (5 studies)</td>
<td>⊕⊕⊕⊝ moderate^6</td>
<td></td>
</tr>
<tr>
<td>Scale from: 12.9 to 57.8.</td>
<td>The mean serum ferritin (ng/mL) - before further donation in the intervention groups was 13.98 higher (8.92 to 19.03 higher)^3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serum ferritin (ng/mL) - after subsequent donation(s)</strong></td>
<td>The mean serum ferritin (ng/mL) - after subsequent donation(s) in the control groups was 18.6 ng/mL</td>
<td></td>
<td>619 (3 studies)</td>
<td>⊕⊕⊕⊝ moderate^7</td>
<td></td>
</tr>
<tr>
<td>Scale from: 18 to 19.</td>
<td>The mean serum ferritin (ng/mL) - after subsequent donation(s) in the intervention groups was 9.01 higher (5.76 to 12.25 higher)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse effects (any)</strong></td>
<td>171 per 1000</td>
<td>RR 1.6 (1.23 to 2.07)</td>
<td>1748 (4 studies)</td>
<td>⊕⊕⊕⊝ moderate^8</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.1: Summary of findings for the main comparison (continued).

<table>
<thead>
<tr>
<th>Footnotes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Control risks will depend on study-specific low haemoglobin deferral thresholds. Low and high control risks correspond to the minimum and maximum control risks in the included studies.</td>
<td></td>
</tr>
<tr>
<td>2 Most of the information is from studies with an unclear risk of bias. All but one study had a high risk of attrition bias and two studies were partially commercially funded. Potential limitations are likely to lower confidence in the estimate of the effect.</td>
<td></td>
</tr>
<tr>
<td>3 The range of scores is based on the lowest and highest estimate of the scores in the control groups in individual trials.</td>
<td></td>
</tr>
<tr>
<td>4 Most of the information is from studies with an unclear risk of bias. Four studies had a high risk of attrition bias, one study received assistance with data analysis from suppliers of the iron supplementation, and one study did not blind participants. Potential limitations are likely to lower confidence in the estimate of the effect.</td>
<td></td>
</tr>
<tr>
<td>5 Most of the information is from studies with an unclear risk of bias. All studies had a high risk of attrition bias. Potential limitations are likely to lower confidence in the estimate of the effect.</td>
<td></td>
</tr>
<tr>
<td>6 Most of the information is from studies with an unclear risk of bias. Two studies had a high risk of attrition bias and one study was partially commercially funded. Potential limitations are likely to lower confidence in the estimate of the effect.</td>
<td></td>
</tr>
<tr>
<td>7 Most of the information is from studies with an unclear risk of bias. All studies had a high risk of attrition bias and one study was partially commercially funded. Potential limitations are likely to lower confidence in the estimate of the effect.</td>
<td></td>
</tr>
<tr>
<td>8 Most of the information is from studies with an unclear risk of bias. Two studies had a high risk of attrition bias. Potential limitations are likely to lower confidence in the estimate of the effect.</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

3.3 Background

3.3.1 Description of the Condition
Currently, IS for blood donors is not a standard of care in NHSBT although it was once employed by individual Blood Transfusion Centres prior to Nationalisation (personal observation). There are a limited number of completed or planned randomised controlled trials (RCTs) of IS in regular blood donors (Cable, Morse, Keltonic, Kakaiya, & Kiraly, 1988; Garry, Koehler, & Simon, 1995; Gordeuk, Brittenham, Bravo, Hughes, & Keating, 1990; Mackintosh & Jacobs, 1988; Maghsudlu et al., 2008; Magnussen, Bork, & Asmussen, 2008; Pedrazzini et al., 2009; Radtke, Mayer, Röcker, Salama, & Kiesewetter, 2004; Radtke, Tegtmeier, Röcker, Salama, & Kiesewetter, 2004). Those studies that do exist have not been carried out on a UK population. Interestingly, there is some evidence from RCTs of improvement of exercise tolerance, mood disturbance and restless legs syndrome after treatment of iron-deficient but non-anaemic adults (Earley et al., 2009; Grote, Leissner, Hedner, & Ulfberg, 2009). However, there are at present no formal systematic reviews of the benefits of such IS interventions in terms of improved Hb, iron status, subjective symptoms of fatigue or mood disturbance or cognitive function in blood donors or, of crucial interest to the blood services, of their deferral for low Hb at the next attendance at donor clinics, nor of the side effects and costs of these supplementation strategies.

In spite of medical, logistic and even ethical problems that may be faced in implementing a programme of IS for blood donors, a pragmatic review of the benefits and costs for the donor and the blood service is essential to inform policy. A systematic review has been undertaken to answer the specific questions of the efficacy and safety of IS in blood donors in preventing a fall in Hb, improving iron stores and reducing systemic, neurological or cognitive symptoms in donors.

3.3.2 Description of the Intervention
A detailed description of iron supplementation is given in Chapter 1 (1.1.5)

3.3.3 How the Intervention Might Work
Iron supplementation interventions aim to increase iron stores in blood donors by making available more iron for them to absorb.
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

3.3.4 Why it is Important To Do This Review
This review is important since maintaining the supply and health of blood donors is imperative for health services. The role of IS in maintaining the health of donors and their ability to donate is poorly understood and the available evidence has not been synthesised. A systematic review of the current evidence of the efficacy and safety of IS in blood donors in crucial to inform future trials and policy of IS in donors.

3.4 Objectives
To define the efficacy and benefits of IS to reduce deferral, iron deficiency and/or anaemia in blood donors.

3.5 Methods
3.5.1 Criteria for considering studies for this review

3.5.1.1 Types of studies
The Cochrane Review process is primarily concerned with the systematic review of randomised controlled trials (RCT) – only in a few fields (such as Occupational Health) are non-randomised observational studies considered (Scholten, Clarke, & Hetherington, 2005).

3.5.1.2 Types of participants
Healthy, prospective, first-time or repeat blood donors of whole blood (standard one unit collections), double-dose red blood cell (RBC) donors by apheresis or platelets by apheresis (referred to as plateletpheresis) from any population. Autologous blood donors (donors who donate for their own subsequent use) were excluded.

3.5.1.3 Types of interventions
Therapy with any preparation, dose or regimen of oral or parenteral iron-containing compounds, with particular reference to:

- Iron supplementation versus placebo or control.
- Oral versus parenteral iron supplementation.
- Iron supplementation versus iron rich food supplements (fortified foods with a quantifiable amount of iron).
- Iron supplement: dose A, versus dose B.
- Iron supplementation: treatment duration A, versus treatment duration B.
- Iron supplement: preparation A, versus iron supplement, preparation B.
3.5.1.4 Types of outcome measures

Primary outcomes
The primary outcome in this review was the risk ratio of deferral of blood donors (number of prospective blood donors who are at least temporarily rejected from blood donation) due to low Hb.

The low Hb deferral threshold differs across studies according to the population and sex of the donor studied (see Summary of Characteristics of included studies Table 3.2).

Secondary outcomes
Secondary outcomes included any changes in any additional factors related to donors or donor health, including the following:

- Mean levels of Haemoglobin (Hb), mean cell volume (MCV), other blood indices and iron stores before further donations.
- Mean levels of Hb, MCV, other blood indices and iron stores after subsequent donations.
- Health-related Quality of Life (QoL), especially changes in cognitive function, 'mood' disturbances, aerobic power, fatigue score, physical activity.
- Adverse effects from interventions received.
- Compliance.

Analysis of blood indices were restricted to Hb, MCV, serum ferritin, serum or plasma iron, total iron binding capacity (TIBC) and transferrin saturation. Other reported blood indices were noted and are described in the Characteristics of included studies tables.

3.5.2 Search methods for identification of studies
The NHSBT Information Specialist (Carolyn Doree - CD) and the Cochrane Injuries Group developed a comprehensive search strategy covering the main bibliographic databases. In order to reduce publication and retrieval bias the search was not restricted by language, date or publication status.
3.5.2.1 Electronic searches

The following databases were searched for RCT and systematic reviews (Appendix 3.8):

- Cochrane Injuries Group Specialised Register (December 2013)
- CENTRAL (Cochrane Central Register of Controlled Trials, *The Cochrane Library*, 2013, Issue 10)
- PubMed (epublications only)
- MEDLINE (OvidSP) (1948 to 18 November 2013)
- EMBASE (OvidSP) (1974 to 18 November 2013)
- CINAHL (EBSCO Host) (1982 to 18 November 2013)
- British Nursing Index and Archive (1985 to 18 November 2013)
- SRI Transfusion Evidence Library (1980 to 18 November 2013)
- LILACS (1982 to 18 November 2013)
- IndMed (1985 to 18 November 2013)
- KoreaMed (1997 to 18 November 2013)
- PakMediNet (1995 to 18 November 2013)
- Web of Science Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 18 November 2013)

The following clinical trials registers were searched:

- ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) (18 November 2013)
- ISRCTN Register (18 November 2013)
- WHO International Clinical Trials Registry Platform ([http://apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)) (18 November 2013)
- Hong Kong Clinical Trials Registry ([http://www.hkclinicaltrials.com/](http://www.hkclinicaltrials.com/)) (18 November 2013)

Search strategies used to search the registers are listed in Appendix 3.8.13.
In MEDLINE, the search strategy was combined with the Cochrane highly sensitive filter for identifying RCT, as described in Chapter 6.4.11 of the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre, Manheimer, & Glanville, 2011). In EMBASE and CINAHL, the search strategies were combined with adaptations of the relevant SIGN RCT filters (http://www.sign.ac.uk/methodology/filters.html). No language restrictions were applied.

Two of the ongoing trial databases listed in the protocol (the Chinese Clinical Trials Registry and the Sri Lanka Clinical Trials Registry) are now included within the WHO ICTRP database.

3.5.2.2 Searching other resources

Handsearching of reference lists

References of all identified studies, relevant review articles and current treatment guidelines were checked for further literature with searches limited to the "first generation" reference lists.

3.5.3 Data collection and analysis

3.5.3.1 Selection of studies

The NHSBT Information Specialist, CD, initially screened all search hits for relevance against the eligibility criteria and discarded all those that were clearly irrelevant. Thereafter, two authors (Graham Smith - GAS - and Sheila Fisher - SF) independently screened the abstracts of all the remaining references (titles, abstracts and full text) for relevance against the full eligibility criteria. Full text papers were retrieved for all those references for which a decision of eligibility could not be made from title and abstract alone. Where possible, further information was sought from the authors where articles contained insufficient data to make a decision about eligibility. Differences of opinion were resolved through discussion and consensus; any remaining unresolved were referred to a third reviewer (David Roberts - DR). Studies which did not meet the eligibility criteria are detailed in the 'Characteristics of excluded studies' table (Appendix 3.2).
3.5.3.2 **Data extraction and management**

GAS, and a second reviewer (SF), independently extracted data onto a standardised Excel form developed in collaboration. These forms were piloted on two included RCT studies and changes made to the data extraction form where appropriate and agreed by both reviewers. Again, throughout the data extraction process any disagreements were resolved by consensus and we referred to a third reviewer (DR) to resolve any remaining differences. There was no blinding to names of authors, institutions, journals or the outcomes of the trials during this process.

**Categorisation of extracted information**

The information extracted was categorised thus:

**General information**

Review author’s name, date of data extraction, study ID, first author of study, citation of paper, objectives of the trial.

**Trial details**

Trial design, location, setting, sample size, power calculation, methods of treatment allocation, randomisation and blinding, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow up, stratification, stopping rules described, statistical analysis, results, conclusion, funding and possible conflicts of interest.

**Characteristics of participants**

Age, gender, ethnicity, total number recruited, total number randomised, total number analysed, losses to follow-up, drop outs (percentage in each arm) with reasons, protocol violations, donation history, whether donors were paid.

**Comparators/Interventions**

Experimental and control interventions, type of IS given, type of comparator given, timing of intervention, dosage of intervention and comparator given, compliance to interventions, additional comparators or interventions given, any differences between interventions.
Outcomes

- Reduction in deferral rates of blood donors due to low Hb.
- Number of blood donors with increased iron stores.
- Total number of successful donations (per donor and per intervention).
- Number of donors with increased Hb levels, mean cell volume (MCV) and other blood indices before donations.
- Rate of increase in Hb levels, mean cell volume (MCV) and other blood indices between donations.
- Health related QoL, especially changes in cognitive function, ‘mood’ disturbances, aerobic power, fatigue score, physical activity.
- Side effects from interventions received.
- Compliance.

Adverse events from interventions received are often overlooked. Examination of such effects are warranted when the difference between benefits of treatment and its adverse events are small; where the treatments, although effective, have different degrees of safety and when those side effects deter a patient from continuing the treatment (Loke, Price, & Herxheimer, 2011).

Dealing with graphical data

Three studies (Devasthali et al., 1991; Gordeuk et al., 1990; Simon et al., 1984) presented relevant data graphically and the graphs were of sufficient quality to extract data. In order to obtain this information we obtained enlarged photocopies of the graphs from the papers. These were duplicated and an independent estimate made of the data presented by two reviewers (GAS, SF). The two estimates were assessed for comparability and, where they differed markedly, a consensus sought. When estimates agreed an average value across both estimates was used.

Combining data

Where possible, data were combined and meta-analysis performed as described in the Cochrane Handbook of Systematic Reviews of Interventions (Reeves et al., 2011). Practically, this was only possible for one comparator, that of gender, as there was too much variation in the trials. Several studies reported outcomes separately for males and females. In these studies, data for males and females were combined to enable comparisons with other studies.
Obtaining standard deviations from standard errors and confidence intervals for group means

Standard Deviations were obtained according to the Cochrane-recommended formula for meta-analyses (J. P. T. Higgins & Deeks, 2011).

3.5.3.3 Assessment of risk of bias in included studies

Two review authors (GAS and SF) independently assessed all included studies for possible risk of bias and made explicit judgements about whether studies were at risk of bias according to the criteria given in the Cochrane Handbook of Systematic Reviews of Interventions (J. P. T. Higgins & Altman, 2011). The design, conduct and analysis of the trial was assessed using a three-point scale: yes (low risk of bias), no (high risk of bias), or unclear. To assess risk of bias, the authors included the following questions in the "Risk of bias" table for each included study:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented (i.e. blinded) throughout the study?
- Was knowledge of the outcome assessment adequately prevented (i.e. blinded)?
- Were incomplete outcome data adequately addressed for every outcome?
- Were reports of the study free of selective outcome reporting?
- Was the study apparently free of any other problems that could put it at risk of bias?

The impact of the level of bias was explored by undertaking sensitivity analyses (see Sensitivity analysis).

In many of the included studies, reporting of randomisation and blinding methods used was poor. Several studies reported only that the trial was "double-blind". We interpreted "double-blind" in the context of IS trials as an indication that the participants (but not necessarily the outcome assessors) were blinded, and have classified such studies as having a low risk of performance bias. Use of a placebo was not considered sufficient alone to indicate blinding of participants.
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3.5.3.4 Measurement of treatment effect
Dichotomous outcomes are presented as risk ratios (RR) with 95% confidence intervals (CI). For continuous outcomes, the mean and standard deviation was recorded. For continuous outcomes measured using the same scale, the effect measure is the mean difference (MD) with 95% CI.

3.5.3.5 Unit of analysis issues
Within each comparison of interventions of this review, for studies with more than two treatment arms, multiple pairwise comparisons of treatment groups were avoided by pooling treatment groups as appropriate. For dichotomous variables, count data were summed across groups and for continuous variables, the mean and standard deviation of the combined group was calculated from the mean and standard deviations of each subgroup.

Thus, for the comparison of IS versus placebo, multiple IS trial arms were combined for an overall comparison with the control or placebo arm. Similarly, in the comparison of different iron preparations, different doses of an identical preparation were combined for comparison with an alternative iron preparation.

For studies in which results were reported separately for males and females, these data were combined for the main analyses. Standard errors, P values and confidence intervals were converted to standard deviations where necessary. Studies in which continuous variables were reported as medians or geometric means without a measure of variation were excluded from the analysis.

Conversion of units of total iron from µmol/L to µg/dL was undertaken using 1 µg/dL = 0.179 µmol/L where necessary to allow meta-analysis across studies reporting outcome values using different units.

3.5.3.6 Dealing with missing data
In view of the time that had elapsed since publication of the majority of studies, no attempt was made to contact individual study authors or institutions regarding missing data. The number of patients lost to follow-up for each trial was recorded as unexplained or undocumented differences between the number of patients randomised and the number of patients analysed, and incorporated into the assessment of risk of bias. The preferred analysis was intention-to-treat (ITT), but where insufficient data were presented in the included studies, per-protocol analysis was used. Studies which performed ITT analyses are shown in the Characteristics of included studies tables (Appendix 3.1).
3.5.3.7 Assessment of heterogeneity
Statistical heterogeneity of treatment effects between trials was assessed using a Chi² test with a significant level at $P < 0.1$. The $I^2$ statistic was used to quantify the amount of possible heterogeneity, ($I^2 > 30\%$ moderate heterogeneity and $I^2 > 75\%$ as considerable heterogeneity). Uncertainty in $I^2$ values was assessed with 95% confidence intervals calculated using the test based method (J. P. Higgins & Thompson, 2002). Potential causes of heterogeneity were explored by sensitivity and subgroup analyses.

Clinical heterogeneity was assessed based on individual study characteristics (e.g. by examining differences in study quality, in the donation history and donor characteristics, and in the definition or measurement of outcomes of each study).

3.5.3.8 Assessment of reporting biases
Every effort was made to identify unpublished studies through searching of conference abstracts and ongoing trial databases as described in the Search methods for identification of studies (section 3.5.2). It was intended to assess publication bias using funnel plots but the number of included studies was lower than the minimum suggested for evaluation of funnel plot asymmetry for all outcomes (J. P. T. Higgins & Altman, 2011) therefore formal assessment of publication bias was not possible.

3.5.3.9 Data synthesis
Meta-analysis was performed using the Review Manager software ("Review Manager (RevMan)," 2014). It was intended to carry out meta-analyses using fixed effect models initially. However, in view of the differences in study participants (first time donors, repeat donors, deferred donors) in the included studies and the likely heterogeneity between these groups, random-effects models were used for all meta-analyses.

The dichotomous outcome of rate of low Hb deferral at the first post-treatment donation visit as well as after multiple post-donation visits (i.e. the final visit over study period) and cumulatively over all donation visits during the study period was assessed.
Few studies reported continuous outcomes as mean change from baseline values and therefore endpoint (follow-up) values for all comparisons were compared, with the exception of one study (Borch-Iohnsen, Halvorsen, Stenberg, Flesland, & Mowinckel, 1993) in which no endpoint values were reported. Data from this study were reported graphically with no measures of variation and therefore were not analysed. Continuous outcomes were assessed at the first post-donation visit prior to donation, and after post-treatment donation or donations. One study in which measurements were taken at the first post-treatment visit was excluded as it was unclear whether the measurement was taken prior to, or after, donation (Blot et al., 1980).

A Summary of Findings table was created using the GRADE profiler, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann et al.).

3.5.3.10 Subgroup analysis and investigation of heterogeneity
Heterogeneity was investigated by visual inspection of forest plots and by formal subgroup analyses by sex for the comparison of IS versus placebo by comparing outcomes between male- and female-specific studies as well as sex-specific results reported within individual studies. One study of predominantly (98.8%) male participants was included as a male-specific study in subgroup analyses of sex (Radtke, Tegtmeier, et al., 2004). The number of studies for all other comparisons precluded subgroup analysis.

3.5.3.11 Sensitivity analysis
How robust the findings were for the primary outcome, risk ratio of low Hb deferral and for Hb and serum ferritin levels was assessed using sensitivity analyses, including only those trials at low risk of performance bias and including only those trials in which 25%, or less, of randomised participants were lost to follow up.
3.6 Results

3.6.1 Description of studies

3.6.1.1 Results of the search

Searches of electronic databases carried out in April 2011 and updated in May 2013 and November 2013 identified a total of 1951 references. Removal of duplicates resulted in 1032 references which were screened independently by two reviewers (GAS, SF). Discrepancies were resolved through discussion with a third reviewer (DR). Initial screening of these 1032 references for eligibility against the inclusion criteria excluded a further 964 references. Of the remaining 68 references, 21 were excluded after closer inspection of the full text showed that they did not fully meet the eligibility criteria (as described in the Characteristics of excluded studies - Appendix 3.2, referenced in Appendix 3.6.2). Eight additional references describing seven independent trials met the inclusion criteria but did not report sufficient data for inclusion; details are given in Studies awaiting classification - Appendix 3.3, referenced in Appendix 3.6.3). One other reference described a trial protocol (see Characteristics of ongoing studies - Appendix 3.4, referenced in Appendix 3.6.4). Searches of ongoing trial databases resulted in 33 ongoing trials for screening, six of which were unpublished trials relevant to this review and are included as ongoing studies. Study classification is summarised by a PRISMA flow diagram (Figure 3.1).
3.6.1.2 Included studies

A total of 38 references (31 full papers and seven conference abstracts) describing 30 independent trials met the inclusion criteria (detailed in Appendix 3.1, referenced in Appendix 3.6.1). In one study, participants were stratified into two subgroups according to serum ferritin levels and each of the two treatments was randomised within both subgroups. For the purposes of this review, these two independent participant subgroups were treated as two separate trials (Mackintosh 1988_HSF; Mackintosh 1988_LSF). Throughout this review they will be referenced only once as Mackintosh and Jacobs (1988) but will, at all times, refer to both trials (Mackintosh 1988_HSF and Mackintosh 1988_LSF) unless explicitly stated otherwise.
Studies were carried out worldwide, including seven studies from the United States (Brittenham et al., 1996; Cable et al., 1988; Devasthali et al., 1991; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, Keating, & Opplt, 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987; Simon et al., 1984), six from Sweden (Birgegård, Schneider, & Ulfberg, 2010; Ehn, Lieden, & Oldfelt, 1968; Frykman, Bystrom, Jansson, Edberg, & Hansen, 1994; Lieden, 1975; Lindholm, Creutzer, & Skinhoj, 1981; Rybo & Sölvell, 1971) four from South Africa (Jacobs, Fransman, & Coghlan, 1993; Jacobs, Wood, & Bird, 2000; Mackintosh & Jacobs, 1988) (Mackintosh 1988_HSF; Mackintosh 1988_LSF), three from Germany (Busch & Gohrbandt, 1972; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004), three from Switzerland (Bucher, Baumann, & Keller, 1973; Buzi & Siegenthaler, 1980; Waldvogel et al., 2012), two from Iran (Maghsudlu et al., 2008; Mirrezaie, Parsi, Torabghahromi, & Askarian, 2008); two from Norway (Borch-Iohnsen et al., 1993; Røsvik, Hervig, Wentzel-Larsen, & Ulvik, 2010) and one each from France (Blot et al., 1980), Italy (Landucci & Frontespezi, 1987), and Thailand (Linpisarn et al., 1986).

Seven references describing six independent studies required translation into English language (Blot et al., 1980; Bucher et al., 1973; Busch & Gohrbant, 1972; Buzi & Siegenthaler, 1980; Ehn et al., 1968; Lindholm et al., 1981).

Participants
Six studies were of male donors only (Ehn et al., 1968; Lieden, Hoglund, & Ehn, 1975; Lindholm et al., 1981; Linpisarn et al., 1986; Mackintosh & Jacobs, 1988) and in a further study (Radtke, Tegtmeier, et al., 2004), 98.8% of participants were male. Eleven studies included only females (Borch-Iohnsen et al., 1993; Brittenham et al., 1996; Cable et al., 1988; Devasthali et al., 1991; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987; Maghsudlu et al., 2008; Mirrezaie et al., 2008; Simon et al., 1984; Waldvogel et al., 2012); eight of these were studies of women who were menstruating or of child-bearing age (Borch-Iohnsen et al., 1993; Devasthali et al., 1991; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987; Maghsudlu et al., 2008; Mirrezaie et al., 2008; Waldvogel et al., 2012). Of the remaining 12 studies, five reported results separately for males and female donors (Birgegård et al., 2010; Frykman et al., 1994; Radtke, Mayer, et al., 2004; Røsvik et al., 2010; Rybo & Sölvell, 1971), and six studies reported results pooled across male and female donors (Blot et al., 1980; Bucher et al., 1973; Busch &
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Gohrbandt, 1972; Buzzi & Siegenthaler, 1980; Jacobs et al., 1993; Landucci & Frontespezi, 1987; one study did not specify the sex of the participants (Jacobs et al., 2000). In studies of male and female donors, the percentage of male participants ranged from 3.1% to 71.2%.

With the exception of those studies of women of child-bearing age, only two studies reported an age restriction on participants which was from 18 to 56 years (Landucci & Frontespezi, 1987) and from 18 to 25 years (Lieden, 1975). Participants in a third study were exclusively military service recruits (Ehn et al., 1968).

Studies included both regular/repeat and first-time donors. Thirteen studies recruited regular donors, defined as having donated at least five donations in the previous two years (Birgegård et al., 2010), at least four donations (Mackintosh & Jacobs, 1988) or two donations (Mirrezaie et al., 2008) in the past year, or with an undefined donation history (Blot et al., 1980; Borch-Iohnsen et al., 1993; Brittenham et al., 1996; Frykman et al., 1994; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004; Rybo & Sölvell, 1971; Simon et al., 1984). Donors in six studies had made at least one previous donation (Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Landucci & Frontespezi, 1987; Lindholm et al., 1981; Linpisarn et al., 1986; Røsvik et al., 2010) or included a majority (89%) of repeat donors (Waldvogel et al., 2012). Only two studies recruited participants with no previous history of donation (Ehn et al., 1968; Lieden et al., 1975); the donation history was unknown in two studies (Bucher et al., 1973; Busch & Gohrbandt, 1972). Five studies were of deferred donors with Hb <130 g/L (Buzzi & Siegenthaler, 1980), haematocrit <35% (Devasthali et al., 1991), low haematocrit (Gordeuk, Brittenham, Hughes, Keating, et al., 1987) or failing a copper sulphate test at enrolment (Jacobs et al., 1993; Jacobs et al., 2000), or donors deferred at their previous visit (Cable et al., 1988).

Interventions

Nineteen studies included two trial arms; which included comparisons of IS versus placebo (Cable et al., 1988; Gordeuk et al., 1990; Linpisarn et al., 1986; Maghsudlu et al., 2008; Mirrezaie et al., 2008; Radtke, Tegtmeier, et al., 2004; Waldvogel et al., 2012) or no IS (Blot et al., 1980; Brittenham et al., 1996; Røsvik et al., 2010), oral versus parenteral IS (Birgegård et al., 2010), different doses of the same iron preparation (Lieden et al., 1975) and different preparations of IS (Borch-Iohnsen et al., 1993; Buzzi & Siegenthaler, 1980; Devasthali et al., 1991; Frykman et al., 1994; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Landucci & Frontespezi, 1987; Lindholm et al., 1981).
In one report, participants were stratified according to serum ferritin levels and two independent trials were carried out, comparing IS with placebo (Mackintosh & Jacobs, 1988).

Seven studies involved three trial arms, of two different iron preparations versus a placebo (Busch & Gohrbandt, 1972; Gordeuk, Brittenham, Hughes, & Keating, 1987; Rybo & Sölvell, 1971), two different doses of IS versus placebo (Ehn et al., 1968; Radtke, Mayer, et al., 2004), IS and/or vitamin C (Simon et al., 1984), and IS versus two doses of an alternative iron preparation (Jacobs et al., 1993).

One four-arm study compared different durations of IS or placebo, administered in vials, with IS administered in sachets at the full dose or replaced with placebo for the latter part of the trial (Bucher et al., 1973); a second four-arm study compared IS with two different levels of glycerophosphate and with an alternative iron preparation (Jacobs et al., 2000).

From these studies, 19 comparisons of IS and placebo or control, one comparison of oral and parenteral IS, four comparisons of different doses of IS, one comparison of different durations of IS and 12 comparisons of different iron preparations were included.

Iron preparations included carbonyl or elemental iron, ferrous compounds (ferrous sulphate, ferrous carbonate, ferrous gluconate, ferrous glycine, ferrous fumarate, ferrous sulphate heptahydrate), and ferric compounds (ferric polymaltose, ferric protein succinylate, ferric sucrose, ferric glycerophosphate). The dose and duration of IS varied greatly across studies; from 50 mg ferrous sulphate three times daily for seven days, to 100 mg ferrous carbonate daily for one year (Lieden et al., 1975). Four studies described iron preparations which included Vitamin C (Blot et al., 1980; Borch-Johnsen et al., 1993; Busch & Gohrbandt, 1972; Simon et al., 1984).

Full details of the interventions in each trial are given in Table 3.2.
Table 3.2: Summary of included study characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention [elemental iron dose]</th>
<th>Reported outcomes</th>
<th>Follow-up timepoints</th>
<th>Description of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birgegard 2010</td>
<td>$\text{Fe}^{2+}\text{SO}_4$ (Duraferon) [20 mg daily for 20 days]</td>
<td>Hb, SeFe, RLS, AE</td>
<td>Week 4 and week 8 (non-donation); Donation 2-4 ($♀$) or 2-5 ($♂$); last donation is $≥$ 1yr post-1$^{st}$ donation.</td>
<td>Experienced donors having given at least five donations in last 1 - 2 years.</td>
</tr>
<tr>
<td></td>
<td>$\text{Fe}^{2+}$ sucrose (Venofer) [1 x 200 mg given intravenously]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blot 1980*</td>
<td>$\text{Fe}^{2+}\text{SO}_4 + \text{Vit C}$ (Ferro-Grad Abbott) [105 mg (+ 500 mg Vit C) daily for &quot;following months&quot;]</td>
<td>Hb, MCV, SeFe, TIBC, AE, SI, Sat</td>
<td>At second donation.</td>
<td>Regular donors.</td>
</tr>
<tr>
<td></td>
<td>Control (no placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borch-Iohnsen 1993</td>
<td>$\text{Fe}^{2+}$ fumarate + Vit C (Collett Iron) [20 mg (+ 120 mg Vit C) daily, treatment duration unclear]</td>
<td>Hb, SeFe, transferrin</td>
<td>Five months after baseline measures.</td>
<td>Female blood donors with depleted iron stores (serum ferritin $&lt;$ 20 μg/L and Hb $&gt;$ 120 g/L).</td>
</tr>
<tr>
<td>Brittenham 1996</td>
<td>Carbonyl iron [100 mg daily for 56 days] with scheduled visits</td>
<td>Mean no. donations per year</td>
<td>After 30 months.</td>
<td>Females pledged to donate four times each year.</td>
</tr>
<tr>
<td></td>
<td>Control (scheduled visits only)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention [elemental iron dose]</th>
<th>Reported outcomes</th>
<th>Follow-up timepoints</th>
<th>Description of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bucher 1973*</td>
<td>Fe$^{2+}$SO$_4$ (Resoferon) [37 mg three times daily for 28 days (one vial)]</td>
<td>Low Hb deferral, Hb, Hct, MCHC, transferrin, AE, PI</td>
<td>Day 14 and day 28 post-donation.</td>
<td>Healthy blood donors blood group B; Hb 125 - 135 g/L.</td>
</tr>
<tr>
<td></td>
<td>Fe$^{2+}$SO$_4$ (Resoferon) [37 mg three times daily for 28 days (28 sachets)]</td>
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<tr>
<td></td>
<td>Fe$^{2+}$SO$_4$ (Resoferon) [37 mg three times daily for 4 days (4 sachets) followed by placebo for 24 days (24 sachets)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo [three times daily for 28 days (one vial)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busch 1972*</td>
<td>Fe$^{2+}$SO$_4$ (Eryfer) [50 mg (+ 222 mg Vit C + 84 mg NaHCO$_3$) twice daily for 30 days]</td>
<td>AE</td>
<td>After 30 days of treatment.</td>
<td>Blood donors.</td>
</tr>
<tr>
<td></td>
<td>Fe$^{2+}$SO$_4$ (alternative) [50 mg (+ 222 mg Vit C) twice daily for 30 days]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo [273.8 mg maize starch + 1.2 mg aerosil twice daily for 30 days]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buzi 1980*</td>
<td>Fe$^{2+}$SO$_4$ (Tardyferon) [80 mg (+ 80 mg muco-protein) daily for 30 days]</td>
<td>Hb, Hct, TIBC, AE, SI</td>
<td>Day 2 after end of treatment.</td>
<td>Deferred donors with an Hb &lt; 130 g/L [Hct &lt;37%] and no history of medical pathology for anaemia.</td>
</tr>
<tr>
<td></td>
<td>Fe$^{2+}$ fumarate [66 mg twice daily for 18 days]</td>
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</tbody>
</table>
### Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention [elemental iron dose]</th>
<th>Reported outcomes</th>
<th>Follow-up timepoints</th>
<th>Description of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cable 1988</td>
<td>Fe²⁺ gluconate (Fergon) [37.5 mg twice daily for trial duration]</td>
<td>Low Hb deferral, Hb, SeFe, transferrin, ZP</td>
<td>≥8 weeks since previous donation or 4 weeks since deferral, for 5 visits including initial visit.</td>
<td>Female donors failing previous Hb screen (some were eligible to donate at start of study)</td>
</tr>
<tr>
<td></td>
<td>Placebo [calcium phosphate twice daily for trial duration]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devasthali 1991</td>
<td>Carbonyl iron [100 mg daily for 84 days]</td>
<td>Hb, MCV, SeFe, transferrin, TIBC, AE, SI</td>
<td>Weeks 0, 1, 3, 6, 12, 16 (none were donation visits).</td>
<td>Menstruating, non-pregnant women 18 - 40 yrs old recently deferred from donation (Ht &lt;35%) with an absence of known medical disorders and no iron supplementation since deferral from blood donation and a MCV &lt;85fL and ferritin &lt;12 μg/L.</td>
</tr>
<tr>
<td></td>
<td>Fe²⁺SO₄ [100 mg daily for 84 days]</td>
<td></td>
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</tr>
<tr>
<td>Ehn 1968* (Adolfsson 1968*; Lieden 1975)</td>
<td>Fe²⁺ succinate (Ferromyn S) [74 mg (+220 mg succinic acid) twice daily for two weeks]</td>
<td>Hb, Hct, TIBC, PA, SI</td>
<td>2 months after 6 subsequent donations (inter-donation interval 2 months).</td>
<td>Young healthy male conscripts with no past history of haematological, gastrointestinal or renal disorder. None had previous haemorrhage or had served as blood donors.</td>
</tr>
<tr>
<td></td>
<td>Fe²⁺ succinate (Ferromyn S) [34 mg (+110 mg succinic acid) twice daily for two weeks]</td>
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</tr>
<tr>
<td></td>
<td>Placebo (twice daily for two weeks)</td>
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<tr>
<td>Frykman 1994</td>
<td>Fe²⁺ fumarate (Hemofer) [8 mg (+1.2 mg heme iron from porcine blood) twice daily for first month then 2nd or 3rd mth]</td>
<td>Hb, SeFe, AE</td>
<td>After 3 months.</td>
<td>Regular blood donors.</td>
</tr>
<tr>
<td></td>
<td>Fe²⁺ fumarate (Ercofer) [60 mg daily for first month then second or third month]</td>
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</tbody>
</table>
## Study of Iron Supplementation for Blood Donors

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention* [elemental iron dose]</th>
<th>Reported outcomes</th>
<th>Follow-up timepoints</th>
<th>Description of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordeuk 1987a</td>
<td>Carbonyl iron [600 mg three times daily for 7 days]</td>
<td>Hb, MCV, SeFe, TIBC, AE, SI, Sat, FEP</td>
<td>Day 56 after successful donation.</td>
<td>Previous (at least once) female donors of child-bearing age who were not pregnant and came to donate blood.</td>
</tr>
<tr>
<td></td>
<td>Fe^{2+}SO₄ [60 mg three times daily for 7 days]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo [three times daily for 7 days]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordeuk, 1987b</td>
<td>Carbonyl iron [600 mg three times daily for 21 days]</td>
<td>Hb, MCV, SeFe, TIBC, AE, SI, Sat, FEP</td>
<td>Weeks 1, 3, 6, 12, 16.</td>
<td>Female blood donors of child-bearing age who were not pregnant recently deferred from repeat donation due to low Hct.</td>
</tr>
<tr>
<td></td>
<td>Fe^{2+}SO₄ [60 mg three times daily for 21 days]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gordeuk 1990</td>
<td>Carbonyl iron [100 mg daily for 56 days]</td>
<td>Low Hb deferral, Hb, MCV, SeFe, transferrin, TIBC, AE, SI</td>
<td>Day 56 after successful donation.</td>
<td>Repeat female donors of child-bearing age who were not pregnant and came to donate blood.</td>
</tr>
<tr>
<td></td>
<td>Placebo [daily for 56 days]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobs 1993</td>
<td>Fe^{2+}SO₄ [60 mg twice daily for 84 days]</td>
<td>Low Hb deferral, Hb, SeFe, NIA, AE, SI, Sat</td>
<td>Weeks 1, 2, 4, 8, 12. Not donation visits.</td>
<td>Donors failing CuSO₄ Hb screening test, i.e. deferred donors.</td>
</tr>
<tr>
<td></td>
<td>Fe^{3+} polymaltose [100 mg daily for 84 days]</td>
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<tr>
<td></td>
<td>Fe^{3+} polymaltose [100 mg twice daily for 84 days]</td>
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</table>
### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention [elemental iron dose]</th>
<th>Reported outcomes</th>
<th>Follow-up timepoints</th>
<th>Description of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs 2000</td>
<td>Fe\textsuperscript{3+} polymaltose [100 mg (+3.6 mMol/L GlyP) twice daily for 84 days]</td>
<td>Hb, SeFe, transferrin, AE, SI, RCF</td>
<td>Weeks 4, 8 and 12. Not donation visits.</td>
<td>Regular donors failing CuSO\textsubscript{4} Hb screening test.</td>
</tr>
<tr>
<td></td>
<td>Fe\textsuperscript{2+} polymaltose [100 mg (+1.9 mMol/L GlyP) twice daily for 84 days]</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Fe\textsuperscript{2+} polymaltose [100 mg twice daily for 84 days]</td>
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<tr>
<td></td>
<td>Fe\textsuperscript{2+}SO\textsubscript{4} [&quot;equivalent dose&quot; twice daily for 84 days]</td>
<td></td>
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</tr>
<tr>
<td>Landucci 1987</td>
<td>Fe\textsuperscript{3+} protein succinate (Legofer) [80 mg daily for 30 days]</td>
<td>Hb, Hct, MCV, MCH, MCHC, SeFe, transferrin, AE, SI</td>
<td>End of trial: mean 30 +/- 2.2 days (range 23-33)</td>
<td>Blood donors aged 18 - 56 with low levels of stored iron (serum ferritin &lt;30 ng/100mL).</td>
</tr>
<tr>
<td></td>
<td>Fe\textsuperscript{2+}SO\textsubscript{4} [105 mg daily for 30 days]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lieden 1975</td>
<td>Fe\textsuperscript{3+} carbonate [100 mg daily for one year]</td>
<td>Low Hb deferral, TIBC, NIA, AE, SI, PCV</td>
<td>After 4th and 6th donations.</td>
<td>Young male first-time donor conscripts with no history of bleeding.</td>
</tr>
<tr>
<td></td>
<td>Fe\textsuperscript{2+} carbonate [20 mg daily for one year]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindholm 1981*</td>
<td>Fe\textsuperscript{2+}SO\textsubscript{4} (ACO) [100 mg daily for 30 days]</td>
<td>Low Hb deferral, Hb, TIBC, AE, SI</td>
<td>After 1st, 2nd and 3rd donations.</td>
<td>Previous donors (all except 14/500) without iron deficiency anaemia during the most recent years, could tolerate different iron preparations and intended to continue to give blood.</td>
</tr>
<tr>
<td></td>
<td>Fe\textsuperscript{2+} fumarate (Erco-Fer) [60 mg daily for 30 days]</td>
<td></td>
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</tr>
<tr>
<td>Study</td>
<td>Intervention [elemental iron dose]</td>
<td>Reported outcomes</td>
<td>Follow-up timepoints</td>
<td>Description of study participants</td>
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</tr>
<tr>
<td>Linpisarn 1986</td>
<td>“Elemental” iron [56 mg daily for 90 days]</td>
<td>Hb, Hct, SeFe, transferrin</td>
<td>After ~3 months (assumed no donations)</td>
<td>Male volunteer and paid blood donors who had previously donated.</td>
</tr>
<tr>
<td>Mackintosh 1988_LSF</td>
<td>Fe³⁺ polymaltose (Ferrimed DS) [100 mg twice daily for 56 days]</td>
<td>Hb, SeFe, AE</td>
<td>After 56 days of treatment (not donation visit)</td>
<td>Regular donors (at least four donations in previous year) passing the Hb test and with low serum ferritin (less than 20 μg/L).</td>
</tr>
<tr>
<td>Mackintosh 1988_HSF</td>
<td>Fe²⁺ polymaltose (Ferrimed DS) [100 mg twice daily for 56 days]</td>
<td>Hb, SeFe, AE</td>
<td>After 56 days of treatment (not donation visit)</td>
<td>Regular donors (at least four donations in previous year) passing the Hb test and with high serum ferritin (between 50 and 150 μg/L).</td>
</tr>
<tr>
<td>Maghsudlu 2008</td>
<td>Fe²⁺SO₄ [150 mg three times daily for 7 days]</td>
<td>Low Hb deferral, Hb, Hct, SeFe, TIBC, AE, SI, Sat</td>
<td>Visits 1 (4 months), 2 (8 months) and 3 (12 months).</td>
<td>Female successful blood donors aged &lt;45 years who were not pregnant.</td>
</tr>
<tr>
<td>Mirrezaie 2008</td>
<td>Fe²⁺SO₄ [50 mg daily for 56 days]</td>
<td>SeFe, AE</td>
<td>Day 7, 28 and 56. Not donation visits.</td>
<td>Regular (at least two donations in past year) healthy female donors of childbearing age. 72% had previously been taking iron supplements.</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention [elemental iron dose]</td>
<td>Reported outcomes</td>
<td>Follow-up timepoints</td>
<td>Description of study participants</td>
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</tr>
<tr>
<td>Radtke, 2004a</td>
<td>Fe$^{2+}$ gluconate [20 mg (+ 400 mg Vit C) twice daily for 6 months] Fe$^{2+}$ gluconate (+ 400 mg Vit C) [10 mg twice daily for 6 months] Placebo (+400 mg Vit C) [twice daily for six months]</td>
<td>Low Hb deferral, SeFe, transferrin, AE</td>
<td>♂ = 2/4/6 months; ♀ = 3/6 months. All were donation visits.</td>
<td>Regular healthy donors.</td>
</tr>
<tr>
<td>Radtke, 2004b</td>
<td>Fe$^{2+}$ Glycine SO$_4$ (ferro sanol duodenal) [100 mg daily for 8 - 10 weeks] Placebo [daily for 8 - 10 weeks]</td>
<td>Low Hb deferral Before donation visits 1, 2, 3 Inter-donation interval 8-10 weeks.</td>
<td></td>
<td>Regular healthy donors with a minimum body wt. of 68 kg and an Hb of 145 g/L giving two-unit RBC by apheresis.</td>
</tr>
<tr>
<td>Rosvik 2010</td>
<td>Fe$^{2+}$ Glycine SO$_4$ (Niferex©) [100 mg daily for 8 days] Control (no placebo)</td>
<td>Hb, SeFe, transferrin</td>
<td>Day 8 (+/- 2) after initial donation.</td>
<td>Donors with at least one prior donation.</td>
</tr>
<tr>
<td>Rybo 1971</td>
<td>Fe$^{2+}$SO$_4$ [100 mg twice daily for 14 days] Fe$^{2+}$SO$_4$ heptahydrate [100 mg twice daily for 14 days] Placebo [twice daily for 14 days]</td>
<td>AE</td>
<td>Day 14 post-donation.</td>
<td>Regular blood donors.</td>
</tr>
</tbody>
</table>
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

<table>
<thead>
<tr>
<th>Study a</th>
<th>Intervention b [elemental iron dose]</th>
<th>Reported outcomes c</th>
<th>Follow-up timepoints d</th>
<th>Description of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon 1984</td>
<td>Fe²⁺SO₄ [37 mg daily for 56 days]</td>
<td>Hb, SeFe, TIBC</td>
<td>Donation visits 2,3,4,5 etc. (inter-donation interval 8 - 12 weeks, mean 9.5 weeks) with at least 4 donation visits</td>
<td>Regular female blood donors committing to donate blood every 8 weeks for one year.</td>
</tr>
<tr>
<td></td>
<td>Fe²⁺SO₄ [37 mg (+75 mg VitC) daily for 56 days]</td>
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<td></td>
<td>[100 mg Vit C daily for 56 days]</td>
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</tr>
<tr>
<td>Waldvogel 2012</td>
<td>Fe²⁺SO₄ (Tardyferon) [80 mg daily for 28 days]</td>
<td>Hb, SeFe, Cog, PA, AE</td>
<td>1 week after donation (randomisation) &amp; 4 weeks post- randomisation.</td>
<td>Successful female blood donors (non-anaemic but iron-deficient after donation).</td>
</tr>
<tr>
<td></td>
<td>Placebo [daily for 28 days]</td>
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</tbody>
</table>

a = translated  
b = Fe²⁺SO₄ = Iron (II) sulphate; Fe³⁺sucrose = Iron (III) sucrose; Fe²⁺ = ferrous (II) salt; Fe³⁺ = ferric (III) salt; Vit C = Vitamin C; GlyP⁻ = glycerophosphate; All treatments were administered orally with the exception of ferric sucrose given intravenously in Birgegard 2010.  
c = Hb = haemoglobin, Hct = haematocrit; MCV = Mean Cell Volume; MCH = Mean Cell Hb; MCHC = MCH concentration; SeFe = serum ferritin; TIBC = Total Iron Binding Capacity, NIA = Net Iron Absorption; Cog = cognitive function; PA = physical activity; RLS = restless legs syndrome; SI = serum iron; Sat = percentage saturation; PI = plasma iron; FEP = free erythrocyte protoporphyrin; ZP = zinc protoporphyrin; AE = adverse effects  
d = ♂ = males, ♀ = female
Outcomes

The duration of follow-up varied greatly between studies. Ten studies reported outcomes after up to five donations subsequent to the administration of IS (Birgegård et al., 2010; Brittenham et al., 1996; Cable et al., 1988; Ehn et al., 1968; Lieden et al., 1975; Lindholm et al., 1981; Maghsudlu et al., 2008; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004; Simon et al., 1984). In two studies it was unclear whether any donations following treatment had taken place at the time of follow-up (Blot et al., 1980; Frykman et al., 1994). The remaining 18 studies measured outcomes before further donation. Timepoints ranged from a mean of 8 days (Røsvik et al., 2010) to 16 weeks (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987) with a median follow-up time before further donation of 56 days.

The primary outcome of this review, risk ratio of low Hb deferral, was reported in only eight studies (Bucher et al., 1973; Cable et al., 1988; Gordeuk et al., 1990; Lieden, 1975; Lindholm et al., 1981; Maghsudlu et al., 2008; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004). Haemoglobin and serum ferritin levels were widely reported; other reported blood indices included mean cell/corpuscular volume (MCV), serum or plasma iron, total iron binding capacity (TIBC) and transferrin saturation. Health related QoL measures were poorly reported; only two studies included measures of physical activity and fatigue (Ehn et al., 1968; Waldvogel et al., 2012), and no studies reported measures of mood disturbance or cognitive function. The majority of studies described adverse effects. Reported outcomes (including those not considered in this review) and endpoints in individual studies are shown in Table 3.2.

3.6.1.3 Excluded studies

Twenty studies described in 21 references were excluded from the review following full-text assessment against the eligibility criteria (see Characteristics of excluded studies Appendix 3.2). In summary, three studies included a single treatment arm, two studies allocated treatment without randomisation, in two studies randomisation of treatment could not be confirmed, three studies were of short-term iron absorption levels, one study randomised vitamin C dose with all participants receiving identical iron supplementation, two observational studies included no IS, two studies were of non-donors, one study was of plasmapheresis donors, one study reported results for both blood donors and non-donors combined, one study was a commentary of iron deficiency in blood donors, one study administered erythropoietin to autologous blood donors, one study was no longer available in print.
3.6.2 Risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (J. P. T. Higgins & Altman, 2011). Disagreements were restricted to where one reviewer deemed risk of bias as unclear rather than high or low and were mainly concerned with the interpretation of "double-blind" (see assessment of "Risk of bias" in Characteristics of included studies, Appendix 3.1). All disagreements were resolved by discussion and with further reference to the Cochrane Handbook for Systematic Reviews of Interventions (J. P. T. Higgins & Altman, 2011).

Overall, the risk of bias varied from low to high, with the majority of studies being unclear as to their quality (see Characteristics of included studies, Appendix 3.1). This was mainly due to the age of the studies, with more recent studies using more rigorous methodologies. A summary of the risk of bias is shown in Figure 3.2.
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

| Figure 3-2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. |
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

3.6.2.1 Allocation (selection bias)

Of the 30 included studies only seven were assessed as having a low likelihood of selection bias (Birgegård et al., 2010; Blot et al., 1980; Jacobs et al., 1993; Mirrezaie et al., 2008; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004; Simon et al., 1984; Waldvogel et al., 2012). In these studies, treatment allocation was randomised using web-based systems, computer-generated charts (n=2), random block design (n=3) and participant choice of randomised cards in envelopes. The risk of selection bias in the remaining studies was unclear as none reported their method of randomisation.

No method for concealment of allocation was reported in 23 studies. Of the seven remaining studies, two did not conceal allocation (Jacobs et al., 2000; Røsvik et al., 2010) and one used computer-generated charts (Jacobs et al., 1993); these were assessed as having a high risk of selection bias. The remaining four studies were assessed as being of low risk due to the use of code-marked prescriptions (Lindholm et al., 1981; Rybo & Sölvell, 1971; Simon et al., 1984; Waldvogel et al., 2012).

3.6.2.2 Blinding (performance bias and detection bias)

There was no blinding of participants in six of the studies so these were considered to have a high risk of performance bias (Birgegård et al., 2010; Blot et al., 1980; Borch-Johnsen et al., 1993; Jacobs et al., 1993; Jacobs et al., 2000; Røsvik et al., 2010).

Eleven studies gave no indication of participant blinding so were recorded as having an unclear risk. Of the 13 studies assessed as low risk, nine stated the studies as being double-blind, either with the use of a placebo (Busch & Gohrbandt, 1972; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987; Mirrezaie et al., 2008) or assumed to include participant blinding without explicitly stating so (Devasthali et al., 1991; Frykman et al., 1994; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004). Four used coded bottles for the prescriptions (Lindholm et al., 1981; Rybo & Sölvell, 1971; Simon et al., 1984; Waldvogel et al., 2012).

Only three of the 30 studies described any blinding of the outcome assessment and were rated as “low risk” (Lindholm et al., 1981; Simon et al., 1984; Waldvogel et al., 2012); the remainder were classified as “unclear risk”.
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3.6.2.3 **Incomplete outcome data (attrition bias)**

Completeness of data was investigated and the reasons for attrition or exclusion where reported for each included study and whether missing data were balanced across groups have been described. Ten studies were rated as being low risk (Birgegård et al., 2010; Borch-Iohnsen et al., 1993; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Landucci & Frontespezi, 1987; Lindholm et al., 1981; Mackintosh & Jacobs, 1988; Radtke, Tegtmeier, et al., 2004; Rybo & Sölvell, 1971; Waldvogel et al., 2012), two were of unclear risk (Brittenham et al., 1996; Ehn et al., 1968) and the remainder had high risk of attrition bias, with a difference in missing data of greater than 5% between treatment arms, a high rate of loss to follow-up, or in one case because the number of participants randomised to each arm was not reported (Bucher et al., 1973).

3.6.2.4 **Selective reporting (reporting bias)**

All of the pre-specified outcomes published in the protocol for the study of Waldvogel et al. (2012) were reported and this study was deemed to have a low risk of bias. A high risk of bias was associated with one study in which the authors failed to report three pre-specified outcomes of interest (Lindholm et al., 1981). In all 29 remaining studies, where all outcomes listed in the manuscript were reported but no study protocol was available to determine the full list of pre-specified outcomes, the risk of reporting bias was unclear. No unpublished data was received, so there is currently no additional evidence of reporting bias.

3.6.2.5 **Other potential sources of bias**

Each included study was assessed for other factors that might contribute to additional risk of bias. We have noted any concerns we had about other possible sources of bias and rated them thus:

- high risk of further bias - where the manufacturer has provided support in terms of a grant (Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004) and additional help (Bucher et al., 1973; Ehn et al., 1968; Lieden et al., 1975) or where the manufacturer supplied some co-authors (Lindholm et al., 1981).
- unclear - where the risk of further bias is uncertain, most commonly where a study has been supplied with iron supplements and/or placebo by a particular manufacturer (Borch-Iohnsen et al., 1993; Jacobs et al., 1993; Jacobs et al., 2000) or there was limited data available from a conference abstract (Brittenham et al., 1996).
low risk of further bias - where there was explicit declaration of independence from study sponsors (Birgégård et al., 2010; Waldvogel et al., 2012) or where no other sources of bias could be identified (18 studies).

3.6.3 Effects of interventions
See: Table 3.1 Summary of findings for the main comparison. Iron supplementation for iron deficiency and/or anaemia in blood donors.

3.6.3.1 Iron supplementation versus placebo/control
Nineteen studies compared IS with placebo or control (see Table 3.2). Hb, serum ferritin and TIBC were reported graphically in one study (Simon et al., 1984); data for this study were estimated from the graphs as described in the Methods section.

Risk ratio of low Hb deferral (primary outcome)
Four studies reported LHD rates (Gordeuk et al., 1990; Maghsudlu et al., 2008; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004). One other study reported the mean number of donations per donor per year (Brittenham et al., 1996). At the first donation visit after commencement of treatment, all four studies reported a lower rate of LHD in donors who received IS than those who had not, with three studies reporting a significant difference between treatment arms (Gordeuk et al., 1990; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004). Combined evidence from all four studies showed a significantly reduced risk of LHD at the first donation visit after treatment in donors who received IS (risk ratio [RR] 0.34; 95% confidence interval [CI] 0.21 to 0.55; four studies; 1194 participants; P value <0.0001) (Appendix 3.5.1 - Analysis 1.1) (Figure 3.3). There was no evidence of heterogeneity between studies ($I^2 = 0\%$; 95% CI 0\% to 79.3\%). This LHD risk reduction was maintained after multiple donation visits reported in three studies (RR 0.25; 95% CI 0.15 to 0.41: three studies: 793 participants: P value <0.00001) (Maghsudlu et al., 2008; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004) and over cumulative donation visits (RR 0.31; 95% CI 0.18 to 0.52; four studies; 2740 participants; P value <0.00001) (Appendix 3.5.1 - Analysis 1.1) (Figure 3.3).
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

Subgroup analyses revealed no significant differences between male and female donors in LHD rates at first donation (P value = 0.90) (Appendix 3.5.10.1 - Analysis 10.1), after multiple donation visits (P value = 0.81) (Appendix 3.5.10.2 - Analysis 10.2) or over cumulative donation visits (P value = 0.85) (Appendix 3.5.10.3 - Analysis 10.3). Results were robust to performance bias (Appendix 3.5.11.1 - Analysis 11.1) and attrition bias (Appendix 3.5.12.1 - Analysis 12.1).
Hb levels, mean cell volume (MCV), other blood indices and iron stores

*Haemoglobin (Hb)*

Mean Hb levels were reported in 12 studies (Bucher et al., 1973; Cable et al., 1988; Ehn et al., 1968; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Linpisarn et al., 1986; Mackintosh & Jacobs, 1988; Maghsudlu et al., 2008; Røsvik et al., 2010; Simon et al., 1984; Waldvogel et al., 2012) although in one study, results were reported graphically and data extraction could not be undertaken (Ehn et al., 1968); this study reported no significant differences between treatment groups.

In eight studies which reported Hb levels at follow-up prior to further donation (Bucher et al., 1973; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Linpisarn et al., 1986; Mackintosh & Jacobs, 1988; Røsvik et al., 2010; Waldvogel et al., 2012), meta-analysis showed that IS resulted in significantly higher levels of Hb at follow-up (mean difference [MD] 2.36 g/L; 95% CI 0.06 to 4.46; eight studies; 847 participants; P value = 0.04). A moderate level of heterogeneity was observed between studies ($I^2 = 69\%$; 95% CI 34.3% to 85.1%) (Appendix 3.5.1.2 - Analysis 1.2) (Figure 3.4).

Sensitivity analyses showed that the effect of IS on Hb levels before further donation remained significant when five studies with a high or unclear risk of performance bias were excluded (MD 4.76 g/L; 95% CI 1.07 to 8.45; three studies: 270 participants: P value = 0.01) (Appendix 3.5.11.2 - Analysis 11.2), and when studies with less than 75% of randomised participants included in the analysis were excluded (MD 2.90 g/L; 95% CI 0.23 to 5.57; six studies: 698 participants: P value = 0.03) (Appendix 3.5.12.2 - Analysis 12.2).
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

### Figure 3-4

**Forest plot of comparison 1: Iron supplementation vs. placebo/control, outcome: 1.2 Hb (g/L).**

#### Study or subgroup

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iron supplementation</th>
<th>Control</th>
<th>Mean Difference IV,Random,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Before further donation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bucher 1973</td>
<td>81</td>
<td>38</td>
<td>15.7 %</td>
<td>15.7 %</td>
<td>3.00 [0.19, 5.81]</td>
</tr>
<tr>
<td>Gordeuk 1987a</td>
<td>32</td>
<td>19</td>
<td>8.1 %</td>
<td>8.1 %</td>
<td>-1.00 [-7.31, 5.31]</td>
</tr>
<tr>
<td>Gordeuk 1990</td>
<td>40</td>
<td>36</td>
<td>13.1 %</td>
<td>13.1 %</td>
<td>8.00 [4.15, 11.85]</td>
</tr>
<tr>
<td>Linpisarn 1986</td>
<td>47</td>
<td>51</td>
<td>11.0 %</td>
<td>11.0 %</td>
<td>0.70 [-4.02, 5.42]</td>
</tr>
<tr>
<td>Mackintosh 1988_HSF</td>
<td>11</td>
<td>12</td>
<td>8.8 %</td>
<td>8.8 %</td>
<td>-1.80 [-7.65, 4.05]</td>
</tr>
<tr>
<td>Mackintosh 1988_LSF</td>
<td>11</td>
<td>12</td>
<td>8.5 %</td>
<td>8.5 %</td>
<td>1.50 [-4.55, 7.55]</td>
</tr>
<tr>
<td>Rosvik 2010</td>
<td>153</td>
<td>161</td>
<td>16.9 %</td>
<td>16.9 %</td>
<td>-0.10 [-2.46, 2.26]</td>
</tr>
<tr>
<td>Waldvogel 2012</td>
<td>74</td>
<td>69</td>
<td>17.9 %</td>
<td>17.9 %</td>
<td>5.00 [3.03, 6.97]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

<table>
<thead>
<tr>
<th>N</th>
<th>Mean(SD)</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Mean Difference IV,Random,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>449</td>
<td>398</td>
<td></td>
<td>100.0 %</td>
<td></td>
<td>2.36 [0.06, 4.66]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 6.71$; $\chi^2 = 22.33$, df = 7 (P = 0.002); $I^2 = 69$

Test for overall effect: $Z = 2.01$ (P = 0.045)

#### After subsequent donation(s)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iron supplementation</th>
<th>Control</th>
<th>Mean Difference IV,Random,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cable 1988</td>
<td>46</td>
<td>45</td>
<td>33.2 %</td>
<td>33.2 %</td>
<td>5.00 [2.12, 7.88]</td>
</tr>
<tr>
<td>Maghsudlu 2008</td>
<td>132</td>
<td>120</td>
<td>35.7 %</td>
<td>35.7 %</td>
<td>3.70 [1.48, 5.92]</td>
</tr>
<tr>
<td>Simon 1984</td>
<td>44</td>
<td>19</td>
<td>31.1 %</td>
<td>31.1 %</td>
<td>10.90 [7.50, 14.30]</td>
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</tbody>
</table>

**Subtotal (95% CI)**

<table>
<thead>
<tr>
<th>N</th>
<th>Mean(SD)</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Mean Difference IV,Random,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Random,95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>222</td>
<td>184</td>
<td></td>
<td>100.0 %</td>
<td></td>
<td>6.37 [2.36, 10.39]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 10.49$; $\chi^2 = 12.31$, df = 2 (P = 0.002); $I^2 = 84$

Test for overall effect: $Z = 3.11$ (P = 0.0019)
Subgroup analysis by sex revealed that the difference in Hb level between treatment arms was found in female donors (MD 3.56 g/L; 95% CI 0.21 to 6.92; four studies: 431 participants: P value = 0.04) but not male donors (MD 0.08 g/L; 95% CI -1.90 to 2.05; four studies: 297 participants: P value = 0.94). A test for subgroup differences was not significant (P value = 0.08) (Appendix 3.5.10.4 - Analysis 10.4) although the number of studies provided low power to detect a difference between subgroups. No heterogeneity was observed across four studies reporting Hb levels in males ($I^2 = 0$%; 95% CI 0% to 32.8%); however, four studies reporting Hb levels in females showed high heterogeneity ($I^2 = 80$%; 95% CI 48.3% to 92.6%) with no obvious clinical differences apparent between these studies.

Hb after subsequent donation(s) was reported in three studies (Cable et al., 1988; Maghsudlu et al., 2008; Simon et al., 1984). A significant difference in Hb levels was found between treatment arms in favour of IS after donation (MD 6.37 g/L; 95% CI 2.36 to 10.39; three studies: 406 participants: P value = 0.002) (Appendix 3.5.1.2 - Analysis 1.2) (Figure 3.4) with high heterogeneity across studies ($I^2 = 84$%; 95% CI 50.9% to 94.6%). Visual inspection of the forest plot showed a particularly strong effect from one study of menstruating female blood donors with an interdonation interval of between eight and 12 weeks (Simon et al., 1984). There was no residual evidence for heterogeneity when this study was excluded ($I^2 = 0$%).

**Mean corpuscular volume (MCV)**

Two studies reported MCV before further donation; both studies reported higher mean MCV levels in donors who received IS compared with those who did not (Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987). However, meta-analyses of these two studies did not provide evidence for a difference in MCV between treatment arms (MD 1.37 fL; 95% CI -0.17 to 2.92; two studies: 127 participants: P value = 0.08) (Appendix 3.5.1.3 - Analysis 1.3).
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

**Serum ferritin**

Serum ferritin (ng/mL) before further donation was reported as an outcome in nine studies (Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Linpisarn et al., 1986; Mackintosh & Jacobs, 1988; Mirrezaie et al., 2008; Radtke, Mayer, et al., 2004; Røsvik et al., 2010; Waldvogel et al., 2012). However, three studies reported serum ferritin as geometric mean (Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Røsvik et al., 2010) and a fourth study reported median serum ferritin values, with no suitable measure of variation for inclusion of the data from these studies in a quantitative synthesis (Linpisarn et al., 1986). In these four studies, one reported a significant difference in serum ferritin between treatment arms in favour of IS (Røsvik et al., 2010); two reported significant increases in serum ferritin from baseline in the IS group but not the placebo/control group (Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987) and one reported no difference in serum ferritin between treatment groups (Gordeuk, Brittenham, Hughes, & Keating, 1987).

In five studies, significantly higher mean serum ferritin levels at follow-up were found in donors who received IS compared with those who did not in all but one study (Mackintosh 1988_HSF), in which donors were pre-selected for high serum ferritin (between 50 and 150 ng/mL). Meta-analysis of all five studies showed that IS resulted in significantly higher levels of serum ferritin (MD 13.98 ng/mL; 95% CI 8.92 to 19.03; five studies; 640 participants; \( P \) value < 0.00001). A moderate level of heterogeneity (\( I^2 = 68\% \); 95% CI 16.0% to 87.5%) was found between studies (Appendix 3.5.1.4 - Analysis 1.4) (Figure 3.5). The effect remained significant when the study with high baseline serum ferritin levels was excluded (MD -13.67 ng/mL; 95% CI 8.39 to 18.95; four studies; 617 participants; \( P \) value < 0.00001).

Subgroup analysis showed the significant improvement in serum ferritin associated with IS was found in both male and female donors (males: MD 10.94 ng/mL; 95% CI -1.00 to 20.88; three studies; 265 participants; \( P \) value =0.03; females: MD 14.39 ng/mL; 95% CI -9.90 to 18.88; three studies; 375 participants; \( P \) value < 0.00001; test for subgroup differences: \( P \) value = 0.53) (Appendix 3.5.10.5 - Analysis 10.5).
Sensitivity analyses showed that the increase in serum ferritin levels associated with IS before further donation remained significant when two studies with an unclear risk of performance bias were excluded in a sensitivity analysis (MD 13.31 ng/mL; 95% CI 7.22 to 19.40; three studies; 594 participants; P value < 0.0001) (Appendix 3.5.11 - Analysis 11.3) and when studies with less than 75% of randomised participants included in the analysis were excluded (MD 15.24 ng/mL; 95% CI 12.37 to 18.11; three studies; 189 participants; P value < 0.00001) (Appendix 3.5.12.3 - Analysis 12.3).

Mean serum ferritin levels after subsequent donation(s) were reported in three trials (Cable et al., 1988; Maghsudlu et al., 2008; Radtke, Mayer, et al., 2004). One other study reported serum ferritin levels graphically as geometric mean values (Simon et al., 1984). Meta-analysis of the three trials reporting mean values showed that the significant difference in mean serum ferritin in favour of IS was maintained after subsequent donation(s) (MD 9.01 ng/mL, 95% CI 5.76 to 12.25; three studies; 619 participants; P value <0.0001), with no evidence for heterogeneity across studies (I²=0%; 95% CI 0% to 86.7%) (Appendix 3.5.1.4 - Analysis 1.4) (Figure 3.5).

Figure 3.5: Forest plot of comparison: 1 Iron supplementation vs. placebo/control, outcome: 1.4 Serum ferritin (ng/mL).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Iron supplementation</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Mackintosh 1988 HS</td>
<td>61.0</td>
<td>22.6</td>
<td>11.75</td>
<td>36.94</td>
</tr>
<tr>
<td>Mackintosh 1988 LSF</td>
<td>43.18</td>
<td>17.84</td>
<td>11.27</td>
<td>25.6</td>
</tr>
<tr>
<td>Minera 2000</td>
<td>51.7</td>
<td>13.4</td>
<td>39</td>
<td>13.6</td>
</tr>
<tr>
<td>Radtke 2004a</td>
<td>29.6</td>
<td>25.9</td>
<td>271</td>
<td>23.83</td>
</tr>
<tr>
<td>Váralogó 2012</td>
<td>28</td>
<td>9.8</td>
<td>74</td>
<td>12.9</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>406</td>
<td>234</td>
<td>100.0%</td>
<td>13.06 [8.92, 19.03]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 13.30; Chi² = 12.35; df = 4 (P = 0.01); p = 68%
Test for overall effect: Z = 5.42 (P = 0.00001)

1.4.2 After subsequent donation(s)

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cable 1988b</td>
<td>30</td>
<td>20.3</td>
<td>49</td>
<td>18.134</td>
<td>45</td>
<td>21.1%</td>
<td>12.06 [4.95, 19.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maghsudlu 2000</td>
<td>20</td>
<td>18.07</td>
<td>132</td>
<td>19.02</td>
<td>16.28</td>
<td>120</td>
<td>48.4%</td>
<td>7.10 [2.04, 11.63]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>384</td>
<td>235</td>
<td>100.0%</td>
<td>9.04 [5.76, 12.26]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.56; df = 2 (P = 0.48); p = 5%
Test for overall effect: Z = 5.44 (P = 0.00001)
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

Serum or plasma iron
Serum or plasma iron concentration was reported in five studies (Bucher et al., 1973; Ehn et al., 1968; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Maghsudlu et al., 2008) although in one study, results were reported graphically and data extraction could not be undertaken (Ehn et al., 1968); no significant differences between treatment groups were reported in this study. In three studies which reported serum or plasma iron concentration before further donation (Bucher et al., 1973; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987), meta-analysis showed no evidence for a difference between treatment arms (MD 11.76 μg/dL, 95% CI -1.67 to 25.20; three studies; 246 participants; P value = 0.09), with moderate heterogeneity across studies ($I^2$=59%; 95% CI 0% to 88.4%). Only one study (Maghsudlu et al., 2008) reported serum or plasma iron concentration after post-treatment donation(s); this study found significantly higher levels of serum iron in donors receiving IS (MD 7.89 μg/dL; 95% CI 1.12 to 14.66; 252 participants; P value = 0.02) (Appendix 3.5.1.5 - Analysis 1.5).

Total iron binding capacity (TIBC)
TIBC was reported in five studies (Ehn et al., 1968; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Maghsudlu et al., 2008; Simon et al., 1984) although in one study results were reported graphically and data extraction could not be undertaken (Ehn et al., 1968); this study reported no significant differences between treatment groups. Two studies reported TIBC before further donation (Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987) and two studies reported values after subsequent donation(s) (Maghsudlu et al., 2008; Simon et al., 1984). Iron supplementation resulted in significantly lower levels of TIBC consistent with a beneficial effect for IS both before further donation (MD 32.05 μg/dL; 95% CI 2.65 to 61.45; two studies; 127 participants; P value = 0.03) and after subsequent donations (MD 42.64 μg/dL; 95% CI 28.28 to 56.99; two studies; 315 participants; P value < 0.00001) with low to moderate heterogeneity across studies ($I^2$=43%; $I^2$=29% respectively) (Appendix 3.5.1.6 - Analysis 1.6).
Transferrin saturation (%)

Transferrin saturation (also described as saturation of TIBC) was reported in four studies (Bucher et al., 1973; Cable et al., 1988; Gordeuk et al., 1990; Linpisarn et al., 1986). Meta-analysis of these four studies showed a significant difference in mean transferrin saturation levels in favour of IS (MD 3.91%; 95% CI 2.02 to 5.80; four studies; 344 participants; P value < 0.0001) with no evidence for heterogeneity across studies ($I^2=0$%; 95% CI 0% to 60.9%) (Appendix 3.5.1 - Analysis 1.7). Evidence from two studies showed that an increase in transferrin saturation in iron supplemented donors compared with placebo was maintained after subsequent donations (MD 4.84%; 95% CI 2.78 to 6.90; 2 studies; 343 participants; P value < 0.00001) (Cable et al., 1988; Maghsudlu et al., 2008) (Appendix 3.5.1.7 - Analysis 1.7).

Health related quality of life and physical activity

One study reported health-related quality of life as an outcome which was assessed by fatigue (level of fatigue on a visual analogue scale and a subjective fatigue severity scale), quality of life (SF-12V2 self-questionnaire: vitality, physical and mental condition) and aerobic capacity (Chester step test) (Waldvogel et al., 2012). In this study, there were no differences in health-related quality of life measures after four weeks of treatment in any of the measures used, with the exception of physical condition (MD 2.40; 95% CI 0.93 to 3.87; one study; 133 participants; ; P value = 0.001) (Appendix 3.5.1.8 - Analysis 1.8).

In one other study which reported physical capacity using a bicycle test, no standard deviations were provided and therefore a formal assessment of the results from this study was not possible (Ehn et al., 1968). No significant differences between treatment groups were reported.
Adverse effects
Fourteen studies reported adverse effects as an outcome although two studies (Blot et al., 1980; Rosvik et al., 2010) reported adverse effects in the treatment group only and five studies did not report adverse effects separately for each treatment arm (Bucher et al., 1973; Mackintosh & Jacobs, 1988; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004). Reported adverse effects included constipation, diarrhoea, nausea, vomiting, gastric discomfort, abdominal cramps, headache, dizziness and taste disturbances. Four studies reported the occurrence of cumulative adverse events (Gordeuk, Brittenham, Hughes, & Keating, 1987; Maghsudlu et al., 2008; Rybo & Sölvell, 1971; Waldvogel et al., 2012). Meta-analysis of these four studies showed a significant increased risk of adverse effects associated with IS (RR 1.60; 95% CI 1.23 to 2.07; four studies; 1748 participants; P value = 0.0005) (Appendix 3.5.1.9 - Analysis 1.9) (Figure 3.6).

Meta analysis of studies reporting specific adverse effects showed that IS was associated with an increased risk of constipation (RR 1.63; 95% CI 1.16 to 2.31; five studies; 1849 participants; P value = 0.005), diarrhoea (RR 2.17; 95% CI 1.38 to 3.42; five studies; 1555 participants; P value = 0.0008), nausea/vomiting (RR 1.75, 95% CI 1.20 to 2.56; six studies; 1922 participants; P value = 0.004) and taste disturbances (RR 5.78, 95% CI 2.10 to 15.95; two studies; 171 participants; P value = 0.0007), whilst there was insufficient evidence for an increased risk of abdominal pain and/or cramps (RR 2.21, 95% CI 0.95 to 5.16; four studies; 683 participants; P value = 0.07), gastric/epigastric pain (RR 1.26, 95% CI 0.73 to 2.19; two studies; 1242 participants; P value = 0.41), or headache (RR 0.91, 95% CI 0.53 to 1.56; five studies; 681 participants; P value = 0.72) (Appendix 3.5.1.9 - Analysis 1.9) (Figure 3.6).

Compliance
Three studies reported compliance as continuation of treatment (IS or placebo) (Busch & Gohrbandt, 1972; Gordeuk, Brittenham, Hughes, & Keating, 1987; Rybo & Sölvell, 1971). Meta-analysis showed a high risk of discontinuation of treatment in participants who received IS compared with those who received placebo although this difference failed to meet statistical significance (RR 0.83; 95% CI 0.99 to 1.47; three studies; 1336 participants; P value = 0.06) (Appendix 3.5.1.10 - Analysis 1.10).
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

Figure 3-6: Forest plot of comparison: 1 Iron supplementation vs. placebo/control, outcome: 1.9 Adverse effects.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Iron supplement</th>
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<th>Risk Ratio</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
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<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>3 Cumulative adverse effects</td>
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<td></td>
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<td>4 Iron deficiency</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5 Abdominal pain and cramps</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Gastrointestinal pain</td>
<td></td>
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</table>

Figure 3-7: Forest plot of comparison: 1 Iron supplementation vs. placebo/control, outcome: 1.9 Adverse effects.

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<th>Study or subgroup</th>
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<th>Risk Ratio</th>
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<td>6 Gastrointestinal pain</td>
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Figure 3-8: Forest plot of comparison: 1 Iron supplementation vs. placebo/control, outcome: 1.9 Adverse effects.

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Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

Five studies reported the number of individuals who achieved a high compliance rate, defined as 100% compliance (Gordeuk et al., 1990; Røsvik et al., 2010) or over 90% compliance (Mirrezaie et al., 2008; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004); however only two trials reported compliance rates separately for both treatment groups (Gordeuk et al., 1990; Mirrezaie et al., 2008). Meta-analysis of these two trials showed no evidence for a difference in compliance rates between treatment groups (RR 0.76; 95% CI 0.51 to 1.15; two studies; 146 participants; P value = 0.19) (Appendix 3.5.1.10 - Analysis 1.10). Compliance (ingestion of over 90% of tablets) was poor in one third of men and one quarter of women in one study (Radtke, Mayer, et al., 2004); a second study by the same group (Radtke, Tegtmeier, et al., 2004) reported that compliance was "largely similar in both groups". One study (Røsvik et al., 2010) reported that full compliance was achieved in 92.8% of participants who received iron supplementation. In the study of Blot et al. (1980), IS was "well adhered to" in 81.8% of patients although no definition of compliance was given.

One study reported the number of days over a total treatment period of 28 days on which tablets were taken (Bucher et al., 1973); tablets were taken for between 87.7% and 93.4% of total treatment days in participants who received IS compared with 88.2% in the placebo group. One study reported a mean of 1.6 (standard deviation [SD ] = 0.4) tablets per day were taken in the IS group compared with 1.5 (SD 0.7) in the placebo group (Cable et al., 1988). A compliance rate of 96% was reported in the study of Waldvogel et al. (2012) with similar adherence in both groups. In the Ehn et al. (1968) study, no more than 10 tablets were not consumed by any participant over the entire study period.

Seven studies identified reasons for non-compliance or discontinuation of treatment associated with adverse effects (Blot et al., 1980; Busch & Gohrbandt, 1972; Cable et al., 1988; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Rybo & Sölvell, 1971; Waldvogel et al., 2012).

3.6.3.2 Iron supplementation: oral versus parenteral

Only one study (Birgegård et al., 2010) compared oral and parenteral iron supplementation.
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**Risk ratio of low Hb deferral (primary outcome)**
Low Hb deferral was not reported in this study.

**Hb levels, MCV, other blood indices and iron stores**

*Haemoglobin (Hb)*
Hb was reported as an outcome in this study, although results were given descriptively, whereby "no significant differences in Hb between the treatment groups were seen".

*Mean corpuscular volume (MCV)*
MCV was not reported in this study.

*Serum ferritin*
Mean serum ferritin was reported both before further donation and after four (women) or five (men) subsequent donations. There was no difference in post-treatment serum ferritin levels at follow-up prior to further donation between treatment arms (MD 2.10 ng/mL; 95% CI -5.91 to 10.11; 120 participants; P value = 0.61) (Appendix 3.5.2.1 - Analysis 2.1). However, after further multiple donations, the mean serum ferritin level was significantly higher in donors who received IS intravenously in a single dose after each donation, compared with those who were administered oral iron supplements (MD 7.65 ng/mL; 95% CI 0.36 to 14.94; 120 participants; P value = 0.04) (Appendix 3.5.2.1 - Analysis 2.1).

*Serum or plasma iron*
Serum or plasma iron levels were not reported in this study.

*Total iron binding capacity (TIBC)*
TIBC was not reported in this study.

*Transferrin saturation (%)*
Transferrin saturation was not reported in this study.

**Health related quality of life and physical activity**
No measures of health-related quality of life or physical activity were measured in this study.
Adverse effects
No serious adverse effects occurred during the trial. In donors who received oral iron supplementation, two cases of constipation and two cases of diarrhoea were reported. In addition, six donors who received oral IS reported gastric discomfort. A non-severe headache in one donor was the only adverse event reported in the intravenous iron group.

This study also compared the frequencies of restless leg syndrome, measured by the International Restless Legs Syndrome Study Group Severity Scale (IRLS) in each treatment group. A significant difference in IRLS score between treatment groups in favour of intravenous administration of iron was reported; however, no standard deviations were reported to enable an estimation of the effect size.

Compliance
Treatment compliance (defined as 100% of medication taken) between visit four and seven ranged from 88% to 91.7% for oral IS compared with 88% to 100% for iron administered intravenously.

3.6.3.3 Iron supplementation versus iron rich food supplements
No studies comparing IS versus iron rich food supplements were identified.

3.6.3.4 Iron supplementation: dose A versus dose B
Four studies (Ehn et al., 1968; Jacobs et al., 1993; Lieden et al., 1975; Radtke, Mayer, et al., 2004) compared different doses of iron supplementation. Details of the doses and duration of treatment in individual studies are given in Table 3.2.

Risk ratio of low Hb deferral (primary outcome)
Two studies reported LHD at donation although in the first of these, discrepancies in the paper prevented reliable extraction of the data (Jacobs et al., 1993; Radtke, Mayer, et al., 2004). In the second study there was no evidence for a difference in the rate of LHD between treatment groups, either at the first donation visit after commencement of IS (RR 0.66; 95% CI 0.11 to 3.92; 351 participants; P value = 0.65), after subsequent donation visits (RR 1.87; 95% CI 0.17 to 20.33; 236 participants; P value = 0.61), or over cumulative donation visits (RR 0.98; 95% CI 0.25 to 3.90; 742 participants; P value = 0.98) (Radtke, Mayer, et al., 2004) (Appendix 3.5.3.1 - Analysis 3.1).
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Hb levels, MCV, other blood indices and iron stores

Haemoglobin (Hb)

Hb levels before further donation were reported in one study (Jacobs et al., 1993), in which there was no evidence for a difference in Hb levels at follow-up between treatment dosage groups (MD 5.00 g/L; 95% CI -0.47 to 10.47; 85 participants; P value = 0.07) (Appendix 3.5.3.2 - Analysis 3.2). One study reported Hb levels after subsequent donation(s) (Ehn et al., 1968) but results were reported graphically and data extraction could not be undertaken; no significant differences between groups were reported in this study.

Mean corpuscular volume (MCV)

No studies reported MCV as an outcome.

Serum ferritin

Two studies reported serum ferritin levels at follow-up before further donation (Jacobs et al., 1993; Radtke, Mayer, et al., 2004). Meta-analysis of these two studies showed no evidence for a difference in serum ferritin between dosage groups (MD 2.89 ng/mL; 95% CI -1.83 to 7.60; 2 studies; 356 participants; P value = 0.23). However, in one study which reported serum ferritin level after two (female) or three (male) subsequent donations, there was a significant difference in serum ferritin in favour of a higher dose (20 mg twice daily compared with 10 mg twice daily) of IS (MD 7.96 ng/mL; 95% CI 1.68 to 14.24; 206 participants; P value = 0.01) (Radtke, Mayer, et al., 2004) (Appendix 3.5.3.3 - Analysis 3.3).

Serum or plasma iron

One study reported serum iron levels after subsequent donations (Lieden et al., 1975). There was no evidence for a difference in serum iron levels between treatment groups in this study (MD 21.00 μg/dL; 95% CI -7.70 to 49.70; 17 participants; P value = 0.15) (Appendix 3.5.3.4 - Analysis 3.4). A further study reported results graphically and data extraction could not be undertaken; no significant differences between groups were reported (Ehn et al., 1968).
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Total iron binding capacity (TIBC)
Two studies reported TIBC after subsequent donations (Ehn et al., 1968; Lieden et al., 1975), although in the first of these, results were reported graphically and no data extraction could be undertaken; this study reported no significant differences between treatment groups. In the second study, there was no evidence for a difference in TIBC between treatment groups (MD -27.00 μg/dL; 95% CI -78.22 to 24.22; 17 participants; P value = 0.30) (Appendix 3.5.3.5 - Analysis 3.5).

Transferrin saturation (%)
Transferrin saturation before further donation was reported in one study (Jacobs et al., 1993); there was no evidence for a difference in transferrin saturation (MD 5.10%, 95% CI -0.46 to 10.66; 85 participants; P value = 0.07) (Appendix 3.5.3.6 - Analysis 3.6). No studies reported transferrin saturation after subsequent donation(s).

Health related quality of life and physical activity
Physical capacity using a bicycle test was reported in one study (Ehn et al., 1968); however, no standard deviations were provided and therefore a formal assessment of these results was not possible. No significant differences between treatment groups were reported.

Adverse effects
Adverse effects were reported descriptively in two studies in which no significant differences in the frequency of adverse effects between treatment groups were found (Jacobs et al., 1993; Radtke, Mayer, et al., 2004). Specific adverse effects were not reported.

Compliance
Compliance was measured in all four studies although it was not reported in one study (Jacobs et al., 1993) and no study reported compliance separately per treatment group. Two studies reported compliance as no more than 10 tablets not consumed during the whole period (Ehn et al., 1968; Lieden et al., 1975), which occurred in all, and 75% of participants, respectively. In the third study compliance, defined as the ingestion of at least 90% of prescribed capsules, was poor in one third of male and one quarter of female participants (Radtke, Mayer, et al., 2004).
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3.6.3.5  Iron supplementation: treatment duration A versus treatment duration B

One study compared different durations of IS between groups (3108 mg over 28 days versus 444 mg over four days) (Bucher et al., 1973).

Risk ratio of low Hb deferral (primary outcome)
Low Hb deferral was not reported in this study.

Hb levels, MCV, other blood indices and iron stores

Haemoglobin (Hb)
Post-treatment Hb levels before further donation visits were reported in this study; there was no evidence of a difference in Hb levels between treatment arms (MD 1.00 g/L; 95% CI -0.93 to 2.93; 123 participants; P value = 0.31) (Appendix 3.5.4.1 - Analysis 4.1).

Mean corpuscular volume (MCV)
MCV was not reported in this study.

Serum ferritin
Serum ferritin was not reported in this study.

Serum or plasma iron
Significantly higher plasma iron levels before further donation visits were found in donors who received IS for the longer treatment duration of 28 days (MD 24.12 μg/dL; 95% CI 9.36 to 38.88; 123 participants; P value = 0.001) (Appendix 3.5.4.2 - Analysis 4.2).

Total iron binding capacity (TIBC)
TIBC was not reported in this study.

Transferrin saturation (%)
A significant difference in transferrin saturation before further donation visits between treatment arms was found, in favour of a longer treatment duration of IS (MD 4.81%; 95% CI 1.93 to 7.69; 123 participants; P value = 0.001) (Appendix 3.5.4.3 - Analysis 4.3).

Health related quality of life and physical activity
No measures of health-related QoL or physical activity were measured in this study.
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Adverse effects
Mainly minor side effects were reported in 19 - 29% of donors; this study did not provide results separately for each treatment group.

Compliance
This study reported treatment compliance only in participants who received treatment for the longer period of 28 days; in these participants, tablets were taken on between 87.7% and 93.4% of total treatment days.

3.6.3.6 Iron supplementation: preparation A versus preparation B
Twelve studies compared different preparations of IS, which included a comparison of ferrous sulphate versus ferrous fumarate (Buzi & Siegenthaler, 1980; Lindholm et al., 1981), ferrous sulphate versus carbonyl iron (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987), ferrous sulphate versus two or three different doses of ferric polymaltose (Jacobs et al., 1993; Jacobs et al., 2000), ferrous sulphate versus ferric protein succinylate (Landucci & Frontespezi, 1987), two different preparations of ferrous sulphate (Busch & Gohrbann, 1972; Rybo & Sölvell, 1971), and two different preparations of ferrous fumarate, heme iron versus non-heme iron (Frykman et al., 1994) or non-heme iron versus a lower dose of non-heme iron but supplemented with heme iron (Borch-lohnsen et al., 1993).

Three studies reported Hb levels and other blood indices graphically (Borch-lohnsen et al., 1993; Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987). In the first study, data were estimated from the graphs as described in the Methods section (Devasthali et al., 1991). However, in the remaining two studies, graphs were of insufficient quality to allow reliable data extraction (Borch-lohnsen et al., 1993; Gordeuk, Brittenham, Hughes, Keating, et al., 1987), and in one case (Borch-lohnsen et al., 1993), did not include standard deviations.

Risk ratio of low Hb deferral (primary outcome)
One study comparing ferrous sulphate with ferric polymaltose reported low Hb deferral rates; however these data were not able to be extracted due to data discrepancies in the study report (Jacobs et al., 1993).
In the comparison of ferrous sulphate with ferrous fumarate, there was no evidence from one study of a difference in the rate of LHD after multiple donation visits (RR 0.51, 95% CI 0.05 to 5.60; 419 participants; P value = 0.58) (Lindholm et al., 1981) (Appendix 3.5.5.1 - Analysis 5.1).

Hb levels, MCV, other blood indices and iron stores

Haemoglobin (Hb)

Two studies comparing ferrous sulphate and ferrous fumarate reported Hb levels (Buzi & Siegenthaler, 1980; Lindholm et al., 1981); there was no evidence for a difference in Hb levels between iron preparations either before further donation (MD 2.00; 95% CI -2.85 to 6.85; one study; 61 participants; P value = 0.42) (Buzi & Siegenthaler, 1980) or after two subsequent donations (MD 1.00 g/L; 95% CI -0.79 to 2.79; one study; 346 participants; P value = 0.27) (Lindholm et al., 1981) (Appendix 3.5.5.2 - Analysis 5.2).

In the comparison of ferrous sulphate with carbonyl iron, three studies reported Hb levels before further donation (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987), although in one study, data was reported graphically and could not be extracted (Gordeuk, Brittenham, Hughes, Keating, et al., 1987). Combined evidence from the remaining two trials showed no evidence for a difference in Hb levels between treatment arms (MD 0.76 g/L; 95% CI -2.98 to 4.49; two studies; 79 participants; P value = 0.69) (Appendix 3.5.6.1 - Analysis 6.1).

Similarly, there was no evidence for a difference in Hb levels before further donation from three trials (Jacobs et al., 1993; Jacobs et al., 2000; Landucci & Frontespezi, 1987) which compared ferrous sulphate with ferric compounds as iron preparations (MD 2.36 g/L; 95% CI -0.63 to 5.34; three studies; 261 participants; P value = 0.12) (Appendix 3.5.7.1 - Analysis 7.1).

In the comparison of two preparations of ferrous fumarate (20 mg compared with 16 mg plus 2 mg heme iron from porcine blood), there was no evidence for a difference in mean change from baseline Hb levels (MD -20.0 g/L; 95% CI -80.59 to 40.59; one study; 34 participants; P value = 0.52) (Appendix 3.5.9.1 - Analysis 9.1). In another study which compared two different preparations of iron fumarate, Hb levels were reported as median values and therefore no formal assessment of the effect size could be undertaken (Frykman et al., 1994).
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**Mean corpuscular volume (MCV)**

Three studies which compared ferrous sulphate with carbonyl iron reported MCV before further donation (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987), although graphical data reporting in one study precluded data extraction (Gordeuk, Brittenham, Hughes, Keating, et al., 1987). Combined evidence from the remaining two studies showed no difference in MCV after treatment (MD 0.62 fL; 95% CI - 1.49 to 2.74; two studies; 79 participants; P value = 0.56) (Appendix 3.5.6.2 - Analysis 6.2).

There was also no difference in MCV before further donation in a study of ferrous sulphate compared with ferric protein succinylate (MD 1.00 fL; 95% CI -1.09 to 3.09; 40 participants; P value = 0.35) (Landucci & Frontespezi, 1987) (Appendix 3.5.7.2 - Analysis 7.2).

**Serum ferritin**

Serum ferritin levels before further donation were reported in three studies (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987) which compared ferrous sulphate with carbonyl iron, although data from one two studies could not be extracted (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987), and one study reported geometric mean values (Gordeuk, Brittenham, Hughes, & Keating, 1987).

There was also no evidence for a difference in serum ferritin levels before further donation from three studies (Jacobs et al., 1993; Jacobs et al., 2000; Landucci & Frontespezi, 1987) which compared ferrous sulphate with ferrous compounds (MD 8.07 ng/mL; 95% CI -1.50 to 17.63; three studies; 261 participants; P value = 0.10) (Appendix 3.5.7.3 - Analysis 7.3).

In the comparison of two preparations of ferrous fumarate (with and without heme iron), there was no evidence for a difference in mean change from baseline serum ferritin levels (MD -4.00 ng/mL; 95% CI -12.44 to 4.44; one study; 34 participants; P value = 0.35) (Appendix 3.5.9.2 - Analysis 9.2). Another study which compared different preparations of iron fumarate (Frykman et al., 1994) reported serum ferritin as median levels and therefore no formal assessment of the effect size could be undertaken (Frykman et al., 1994).
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*Serum or plasma iron*

In two studies which compared serum iron levels between ferrous sulphate and ferrous fumarate preparations, there was no evidence for a difference in serum iron levels between treatment arms either before further donation (MD 7.00 μg/dL; 95% CI -7.14 to 21.14; one study; 61 participants; P value = 0.33) (Buzi & Siegenthaler, 1980), or after subsequent donations (MD 0.00 μg/dL; 95% CI -7.06 to 7.06; one study; 346 participants; P value = 1.00) (Lindholm et al., 1981) (Appendix 3.5.5.3 - Analysis 5.3).

Combined evidence from two studies (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, & Keating, 1987) which compared ferrous sulphate and carbonyl iron, also showed no difference in serum iron levels before further donation (MD -1.76 μg/dL; 95% CI -26.49 to 22.97; two studies; 79 participants; P value = 0.89) (Appendix 3.5.6.3 - Analysis 6.3). In a third study, graphical data were of insufficient quality to allow extraction (Gordeuk, Brittenham, Hughes, Keating, et al., 1987).

Similarly, there was no evidence for a difference in serum iron levels between ferrous sulphate and ferric compound iron preparations before further donations (Jacobs et al., 2000; Landucci & Frontespezi, 1987) (MD 0.88; 95% CI -3.25 to 5.00; two studies; 131 participants; P value = 0.68) (Appendix 3.5.7.4 - Analysis 7.4).

*Total iron binding capacity (TIBC)*

There was no evidence for a difference in TIBC either before further donation (MD 0.00 μg/dL; 95% CI -3.76 to 3.76; one study; 61 participants; P value = 1.00) (Buzi & Siegenthaler, 1980), or after subsequent donations (MD 5.59 μg/dL; 95% CI -2.65 to 13.83; one study; 346 participants; P value = 0.18) (Lindholm et al., 1981) (Appendix 3.5.5.4 - Analysis 5.4), in studies which compared ferrous sulphate with ferrous fumarate.

There was also no evidence from two studies of a difference in TIBC before further donation between ferrous sulphate and carbonyl iron (MD -9.75 μg/dL; 95% CI -52.65 to 33.16; two studies; 79 participants; P value = 0.66) (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, & Keating, 1987) (Appendix 3.5.6.4 - Analysis 6.4).
In the comparison of two preparations of ferrous fumarate (with and without heme iron), there was no evidence for a difference in mean change from baseline TIBC levels (MD 0.60 μg/dL; 95% CI -2.77 to 3.97; one study; 34 participants; P value = 0.73) (Appendix 3.5.9.3 - Analysis 9.3).

Transferrin saturation (%)
Three studies which compared ferrous sulphate with carbonyl iron reported transferrin saturation (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987), although two of these reported data graphically and the quality of the graphs in the latter study precluded data extraction (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, Keating, et al., 1987). Meta-analysis of the remaining two studies showed no evidence for a difference in transferrin saturation between treatment arms (MD 2.45%; 95% CI -3.37 to 8.26; two studies; 79 studies; P value = 0.41) (Appendix 3.5.6.5 - Analysis 6.5).

However, combined evidence from two studies, which compared ferrous sulphate with ferric polymaltose, showed significantly higher levels of transferrin saturation before further donation in favour of ferrous sulphate (MD 5.33%; 95% CI 1.61 to 9.05; two studies; 221 participants; P value = 0.005), demonstrating a beneficial effect of ferrous sulphate over ferric polymaltose (Jacobs et al., 1993; Jacobs et al., 2000) (Appendix 3.5.7.5 - Analysis 7.5).

Health related quality of life and physical activity
No measures of health-related quality of life or physical activity were measured in studies which compared different iron preparations.

Adverse effects
In the comparison of ferrous sulphate with ferrous fumarate, one study showed a significant increase in overall adverse effects associated with ferrous sulphate (RR 1.40; 95% CI 1.04 to 1.88; 131 participants; P value = 0.03) (Lindholm et al., 1981) (Appendix 3.5.5.5 - Analysis 5.5). However, there were no significant differences observed in individual studies (Buzi & Siegenthaler, 1980; Lindholm et al., 1981), or from meta-analysis in the frequencies of specific adverse effects, which included constipation, diarrhoea, nausea/vomiting and abdominal pain and/or cramps.
There was no evidence for a difference in the overall frequency of adverse effects between ferrous sulphate and carbonyl iron from a meta-analysis of two studies (Devasthali et al., 1991; Gordeuk, Brittenham, Hughes, & Keating, 1987) (RR 0.89; 95% CI 0.75 to 1.06; two studies; 96 participants; P value = 0.18) (Appendix 3.5.6.6 - Analysis 6.6), or in the frequency of specific adverse effects which included constipation, diarrhoea, nausea/vomiting, abdominal pain and/or cramps, gastric/epigastric pain and headache. However, carbonyl iron was associated with an increased risk of taste disturbances compared with ferrous sulphate (RR 0.43; 95% CI 0.25 to 0.74; two studies; 96 participants; P value = 0.002) (Appendix 3.5.6.6 - Analysis 6.6).

Adverse effects were not reported in any of the studies which compared ferrous sulphate with ferric compound iron preparations.

In the comparison of heme iron with non-heme iron, one study reported a higher frequency of cumulative adverse effects for non-heme iron than heme iron (25% versus 14%) (Frykman et al., 1994), although the absence of actual numbers of participants prevented a statistical evaluation of this difference. In this study, participants who received non-heme iron also experienced a higher rate of gastric pain (19% versus 6%), obstipation (35% vs. 14%) and diarrhoea (37% vs. 26%).

In one study which compared Eryfer® with an alternative ferrous sulphate preparation (Busch & Gohrbandt, 1972), a lower frequency of cumulative adverse effects was observed in participants who received Eryfer® than those who received the alternative preparation in both the morning (11.2% versus 4.7%) and the evening (10.0% versus 2.9%), although actual numbers were not reported and therefore no formal statistical assessment of these differences could be undertaken. In this study, adverse effects were predominantly gastrointestinal complaints which included loss of appetite, indigestion and diarrhoea. In a second study which compared ferrous sulphate with an alternative sustained release iron preparation (Rybo & Sölvell, 1971), there were no significant differences in the frequency of cumulative adverse effects (RR 1.14; 95% CI 0.91 to 1.43; 781 participants; P value = 0.26) or specific adverse effects including constipation, diarrhoea, nausea/vomiting and epigastric pain (Appendix 3.5.8.1 - Analysis 8.1).
Compliance

In the comparison of ferrous sulphate with ferrous fumarate, there was no difference in the number of participants who were 100% compliant over the treatment period (77.5% vs. 82.5% respectively) (Lindholm et al., 1981).

In a meta-analysis of two studies comparing ferrous sulphate with carbonyl iron (Gordeuk, Brittenham, Hughes, Keating, et al., 1987; Gordeuk, Brittenham, Hughes, & Keating, 1987), there was no difference in compliance between treatment arms (RR 0.95; 95% CI 0.84 to 1.09; two studies; 95 participants; P value = 0.48) (Appendix 3.5.6.7 - Analysis 6.7). A third study reported full compliance in both treatment arms (Devasthal et al., 1991).

Compliance was reported descriptively in two studies (Jacobs et al., 1993; Jacobs et al., 2000) which compared ferrous sulphate with ferric compound iron preparations; the first of these reported only that some patients stopped treatment due to adverse effects (Jacobs et al., 1993). In the second study, tolerance was reported to be "much better with the complex exceeding 80% but this was only 60% with the ferrous sulphate" (Jacobs et al., 2000).

The number of study participants who discontinued treatment was similar for ferrous sulphate and an alternative sustained release iron preparation (85.1% versus 86.6% respectively) (Rybo & Sölvell, 1971). However, in the study of Eryfer® compared with an alternative ferrous sulphate preparation (Busch & Gohrbandt, 1972), compliance was significantly higher in participants who received Eryfer® than in those who received the alternative preparation (RR 1.80; 95% CI 1.24 to 2.61; one study; 89 participants; P value = 0.002) (Appendix 3.5.8.2 - Analysis 8.2). Meta-analysis was not carried out due to the differences in alternative iron preparation between the two studies.
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

3.7 Discussion

Iron deficiency is a significant cause of deferral in people wishing to donate blood. Donation intervals are set to minimise iron deficiency in repeat blood donors and all donors are screened pre-donation at each repeat visit for Hb levels. Deferral of donation for a period of six months through failure to pass the Hb threshold is associated with failure of donors to return to give blood. Avoiding iron deficiency is therefore essential not only to minimise symptoms and morbidity in donors and hence increase retention of donors in the long term, but also to maintain the efficiency of a donor session where deferral is costly and disruptive. IS for blood donors has been considered, and in some settings, has been implemented for certain groups of “at risk” donors. Rigorous evidence for the cost and benefits of IS is essential to guide policy.

3.7.1 Summary of main results

3.7.1.1 The relative and absolute benefits of iron supplementation

Thirty RCTs met the eligibility criteria, including comparisons of IS with placebo as well as different methods of administration, doses, duration and preparations of iron supplementation. Meta-analysis of four studies showed a significantly reduced risk of deferral due to low Hb in donors who received IS compared with donors who received no IS, both at the first donation visit (RR 0.34; 95% CI 0.21 to 0.55; four studies; 1194 participants; P value < 0.0001) and at subsequent donations (RR 0.25; 95% CI 0.15 to 0.41; three studies; 793 participants; P value < 0.00001). There is also a clear benefit of IS on markers of iron stores but the effect of iron on Hb level, although significant, is low. Detailed comparison of the effect of IS on iron stores is hampered by different assay methods and lack of standardisation.

Based on the data from the four studies, the absolute risk of LHD at the first donation visit after receiving IS is 3.6% in iron-supplemented donors compared with 10.5% in controls. The corresponding absolute risks of deferral after multiple donation visits are 5.0% and 19.9% respectively, based on the data from three studies.

Evidence from a single study of parenteral versus oral iron suggests that parenteral iron is significantly more effective than oral iron in increasing serum ferritin levels. There may also be fewer minor side-effects in donors given parenteral compared with oral iron, but widespread use of parenteral iron would not be practical in this
Chapter 3 – Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors

population. However, this review has identified four ongoing randomised trials and one study awaiting classification which include iron administered intravenously to blood donors. Nevertheless, it seems unlikely that parenteral iron would be accepted on a mass scale, particularly given recent evidence from a systematic review that use of parenteral iron is associated with an increased risk of infection (Litton, Xiao, & Ho, 2013).

3.7.1.2 Side effects of iron supplementation
The benefits of IS with tablets are substantial but the rate of significant side effects is high which is likely to limit acceptability and compliance. Adverse effects were widespread and were more frequent in donors who received IS than those who did not (RR 1.60; 95% CI 1.23 to 2.07; four studies; 1748 participants; P value = 0.0005), with a significantly increased risk of gastrointestinal upset and taste disturbances.

Due to the adverse effects associated with IS, treatment compliance is an issue. The absolute risk of adverse effects is 29% in iron supplemented donors compared with an absolute risk of 17% in controls. The impact of these side effects on compliance is uncertain. Although seven studies identified reasons for non-compliance or discontinuation of treatment associated with adverse effects (Blot et al., 1980; Busch & Gohrbandt, 1972; Cable et al., 1988; Gordeuk et al., 1990; Gordeuk, Brittenham, Hughes, & Keating, 1987; Rybo & Sölvell, 1971; Waldvogel et al., 2012), only two trials reported compliance rates separately for both treatment groups (Gordeuk et al., 1990; Mirrezaie et al., 2008) and taken together, showed no evidence for a difference in compliance rates between treatment groups (RR 0.76; 95% CI 0.51 to 1.15; two studies; 146 participants; P value = 0.19). Compliance (as measured by ingestion of over 90% of tablets) was poorly documented in many of the studies but variable when reported (Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004). There are unlikely to be significant cost issues associated with iron supplements but compliance may be a more important issue if IS is targeted at large numbers of donors in routine operational practice.

The long term effects of IS without measurement of iron stores are unknown and in other contexts, iron given indiscriminately has had deleterious consequences in some populations (Oppenheimer, 2001; Sazawal et al., 2006). These considerations are likely to preclude widespread use of IS by tablets.
3.7.2 Overall completeness and applicability of evidence

There are very few studies of the effects of IS on physical capacity and quality of life in blood donors.

Differences between studies in terms of type of participants, the preparation, dose and duration of treatment and the time at which outcomes were measured as well as inter-donation interval inevitably limited investigation of the effect of IS on physical capacity and quality of life. There is very limited evidence in non-blood donors that IS of iron deficient non-anaemic adults improves some aspects of cognitive function (Falkingham et al., 2010). Further evidence of the effect of iron stores on cognitive function and physical activity or capacity in donors from adequately powered RCTs would be crucial to inform future policies.

It is possible that effects of IS on physical function may take place quickly and be found in trials of short term IS. However, immediately after donation these effects are confounded by fluctuations in Hb. Furthermore, a reduction in physical or mental function may only be seen in those who are iron deficient over a longer period of time. While power calculations are difficult without more preliminary data, studies may indeed need larger sample sizes and longer follow up periods to see the effects of IS on wider measures of physical and mental function.

One potentially very important question for further study is whether low and/or intermittent IS may have a similar effect in reducing anaemia and low Hb deferral to a higher dose or continuous IS but with reduced side effects. Only one study directly addressed different durations of IS in donors and compared IS of 3108 mg over 28 days versus 444 mg over four days (Bucher et al., 1973). Unfortunately, deferral due to low Hb was not reported and adverse events were not discussed by study group. Our review can therefore only search for differences in outcomes among different trials of IS where iron was given for different durations.

The combined evidence from all four studies where deferral rates were reported showed a significantly reduced risk of LHD at the first donation visit after treatment in donors who received IS (RR 0.34; 95% CI 0.21 to 0.55; four studies; 1194 participants; P value < 0.0001) and this LHD risk reduction was maintained after multiple and/or cumulative donation visits with no evidence of heterogeneity between studies ($I^2 = 0%$; 95% CI 0% to 79.3%) (Gordeuk et al., 1990; Maghsudlu et al., 2008; Radtke, Mayer, et al., 2004; Radtke, Tegtmeier, et al., 2004). Furthermore, there were
no significant differences between male and female donors in LHD rates at first donation, after multiple donation visits or over cumulative donation visits (Analysis 10.1; Analysis 10.2; Analysis 10.3). Looking at the effect of different iron dosing schedules on iron stores, meta-analysis of two studies which reported serum ferritin levels at follow-up before further donation showed no evidence for a difference in serum ferritin between dosage groups (Jacobs et al., 1993; Radtke, Mayer, et al., 2004). However, in one study which reported serum ferritin levels after two (female) or three (male) subsequent donations, there was a significant difference in serum ferritin in favour of a higher dose (20 mg twice daily compared with 10 mg twice daily) of IS (Radtke, Mayer, et al., 2004)(Analysis 3.3). These differences did not translate into significant difference in deferral rates.

The question of the effect of duration or intensity of IS and outcome has been addressed in RCTs of IS in pregnancy and a recent Cochrane systematic review of intermittent versus daily IS concluded that there was a reduced incidence of mild to moderate anaemia in women taking daily, compared to intermittent, iron supplements but no differences in the incidence of adverse outcomes of the pregnancy or in the neonate could be ascertained. Nevertheless, there was a significantly reduced incidence of side effects in those women receiving intermittent compared to daily IS (RR 0.57, 95% CI 0.34 – 0.87) (Peña-Rosas, De-Regil, Dowswell, & Viteri, 2012).

One physiological explanation for the broadly similar effects of lower versus higher doses of iron is that absorption of iron is greater when iron stores are low and the proportion of iron absorbed is reduced as iron stores rise, reducing the benefit and possibly increasing the side effects as the dose and duration of IS is increased. Examining the benefits and adverse events of lower versus higher dose regimes of IS would quite clearly be a priority for further work.

No trials were reported from lower-middle-income or low-income countries. In many parts of the world recruitment of donors and blood safety has been the main focus of concern and research while low deferral rates in repeat donors have been less of a priority. Nevertheless, in many parts of the world iron deficiency is very common (S. S. Lim et al., 2012; J. L. Miller, 2013) and high deferral rates in first time donors who fail to meet the Hb threshold are certainly observed. Iron replacement in areas where malaria and other protozoa or community acquired bacterial infections are prevalent may predispose to infection (Drakesmith & Prentice, 2012) and it is likely that the question of iron replacement in donors will become an important topic of research in
middle-income and low-income countries as the donor base increases and a higher proportion of donors are repeat donors. The safety of IS with regard to infection will require careful scrutiny in well-designed trials, although it may be more straightforward to predict the likelihood of deferral to stratify donation intervals to reduce deferral in groups of donors at greater risk of iron deficiency.

This review highlights the limited amount of data available for IS in the context of blood donation. The number of studies is limited for each comparison and they usually involve a small number of participants. Small study effects (bias) should be considered when interpreting the results. The majority of the data are from studies comparing IS versus placebo, but even here, numbers are small. For example, only a few events are recorded in each study when looking at the effect of IS on LHD.

### 3.7.3 Quality of the evidence

Thirty RCTs including a total of 4704 participants met the eligibility criteria, including 19 comparisons of IS and placebo or control, one comparison of oral and parenteral IS, four comparisons of different doses of iron supplementation, one comparison of different treatment durations of IS, and 12 comparisons of different IS preparations. However, the number of studies included in meta-analyses was limited by differences in methods of outcome reporting, treatment duration and length of follow-up between studies. The reduction in LHD shows a large effect, but due to the risk of bias in the included studies the quality of evidence has been downgraded to moderate (see Summary of findings of the main characteristics - Table 3.1).

Heterogeneity confidence intervals for $I^2$ were generally wide due to the low number of studies included in each analysis. Visual inspection of forest plots revealed no obvious heterogeneity due to date of publication or study size.

### 3.7.4 Potential biases in the review process

The risk of bias was high or unclear in many studies, probably due to poor methods of reporting in studies published before 1990 including five that were published before 1980. Precise definition of the quality of studies is difficult as judgement is based on limited evidence but there is no definitive evidence of substantial bias nor of systematic error through poor quality studies.
3.7.5 Agreements and disagreements with other studies or reviews
The authors are unaware of any reviews in this area for comparison with the findings from other analyses.

3.8 Author's conclusions

3.8.1 Implications for practice
Overall, IS has a substantial effect on reducing the LHD risk but a significant proportion of donors taking iron suffer side effects. Blood services seeking a reduction in the levels of LHD would wish to consider any reasonable methods to prevent iron deficiency, weighing cost against benefits and feasibility. With this in mind, possible courses for future action by blood services would be the targeted use of supplementation at groups or individuals at greater risk of iron deficiency, stratified or personalised donation intervals and/or more effective dietary advice.

3.8.2 Implications for research
The effect of dose and preparation of iron on both efficacy and the frequency of side effects is unclear from the existing studies. Crucially, the studies do not allow any definition of the relationship between dose and duration of IS and benefits or side-effects. These questions would have to be explored, in large-scale RCTs or pilot studies, before widespread use of IS in donors could be considered. Potential differences in methods used to assess biomarkers could be important when interpreting the absolute change in biomarker values (such as ferritin). There is very limited evidence that dietary advice to improve iron store is efficacious and there are no trials of dietary advice in donors. Further work in this area should include RCTs of a range of interventions to determine efficacy precisely. Finally, there are few existing randomised trials of the effects of IS on the physical capacity and quality of life of blood donors; future studies should include an assessment of these measures in iron supplemented donors.

3.9 Acknowledgements
This research was supported by NHSBT and the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme (SF, CD) and the NIHR under its Programme Grant Scheme (NIHR-RP-PG-0310-1004, SF). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.
3.10 Contribution of authors

Graham Smith (GAS) is a content expert for this review (stem cells) and carried out the screening and selection of trials, data extraction and assessment of risk of bias, analysis of results and preparation of the protocol and final report.

Sheila Fisher (SF) is a methodological expert for this review, and carried out the screening and selection of trials, data extraction and assessment of risk of bias, analysis of results and preparation of the final report.

Carolyn Dorée (CD) is an information specialist, who developed and implemented the search strategies and contributed to the preparation of the protocol and final report.

Emanuele Di Angelantonio (EDA) is a content expert for this review (blood donors and iron) and contributed to the preparation of the final report.

David Roberts (DR) is a content expert for this review (red blood cells and transfusion medicine), and assisted with eligibility screening and contributed to the preparation of the protocol and final report.

3.11 Declarations of interest

Graham Smith, Sheila Fisher, Carolyn Dorée, David Roberts - none known.

Emanuele Di Angelantonio: reported as serving as a honorary consultant for NHSBT; receiving royalties from Elsevier (France) and that he has received grants from NHSBT, British Heart Foundation and the Medical Research Council.

3.12 Sources of support

3.12.1 Internal sources
Research and Development, NHSBT, UK.

3.12.2 External sources
No sources of support supplied.
3.13 Differences between protocol and review

The comparison of Iron Supplementation: schedule A versus schedule B has been redefined as a comparison of treatment duration A versus treatment duration B for clarity and to avoid any ambiguity in definition. In addition, the comparison of IS manufacturer A versus manufacturer B has been renamed as preparation A versus iron preparation B to more accurately describe different iron compounds.

There are some differences in outcomes between the protocol and the review.

In the protocol for this review, the outcomes "Number of blood donors with a change in iron stores" and "Number of donors with a change in Hb levels, mean cell volume (MCV) and other blood indices before donations" are vague, since it is unclear how "a change" in these measures should be defined. Any level of change in these measures may be of clinical interest. Hence, these outcomes have been replaced with a new single outcome which now includes iron stores as well as all other measures before donation as follows:

"Mean levels of Hb, MCV, other blood indices and iron stores before further donations".

Also, the outcome "Rate of change in Hb levels, MCV, other blood indices and iron stores between donations" included in the protocol for this review does not take into account the likely scenario of different numbers of donations at different timepoints between studies, and between demographic groups within studies (e.g. males versus females). Therefore this outcome has been redefined as measured after subsequent donations as follows:

"Mean levels of Hb, MCV, other blood indices and iron stores after subsequent donations".

The outcome "Total number of successful donations (per donor and per intervention)" defined in the protocol has been removed, since this measure is directly correlated with the primary outcome "Deferral rates of blood donors (number of prospective blood donors who are at least temporarily rejected from blood donation) due to low Hb" and is therefore deemed uninformative.
Finally, treatment compliance is an important issue in oral IS and this has been added as a new outcome.

It had been intended to analyse continuous outcomes as mean change from baseline; however, few studies reported continuous outcomes as mean change from baseline values and therefore endpoint (follow-up) values have been compared for all comparisons.

Additionally, it was intended to contact study authors in order to obtain information that was missing or unclear in the published report; however, this was not done due to the time that had elapsed since publication of the majority of studies.

Sensitivity analyses based on allocation concealment were not performed due to the high number of studies deemed to have a high risk of bias associated with allocation concealment. It was also the intention to carry out subgroup analyses by donation history, menopausal status, Hb threshold for donation and trial setting, but this was not possible due to a paucity of studies reporting these factors. These will be addressed in future updates of this review if sufficient data become available.
Chapter 4 – Dissemination and impact analysis

Chapters 2 and 3 described the two related systematic reviews regarding factors leading to blood donors falling below low Hb thresholds and how blood collection organisations around the world have attempted to improve donor health and the numbers of successful donation attempts by providing iron supplements.

This chapter describes the dissemination strategy and impact assessment.
4.1 Introduction to assessment of dissemination and impact

4.1.1 Dissemination

Dissemination (from Latin *disseminare* “scattering seeds”) is a key step in the transition from research to practice (knowledge translation) (P. Wilson, Petticrew, Calnan, & Nazareth, 2010a). If the primary purpose of research is to build a knowledge base, confirm or refute theories, test the effectiveness of practical approaches, and ultimately benefit patients, then the dissemination of findings is an integral component of the research process. In research, we need to be concerned with conveying our findings to other researchers, to practitioners, policymakers, and to the public. Knowledge in isolation is futile, especially in respect to evidence-based practice.

In a recent survey of principal investigators (P. Wilson, Petticrew, Calnan, & Nazareth, 2010b) it was found that, although researchers recognised the importance of dissemination (93% rating it as important or very important), only 9% actively planned their strategy for dissemination (although three quarters said they would wish to).

The Becker model (Sarli, Dubinsky, & Holmes, 2010) offers a number of strategies for improving the impact of one’s research, and that of Pardoe (2012) offers a guide for dissemination. Practically, it may well be most prudent to devise the dissemination strategy with respect to the criteria against which it will be evaluated, such as that of the Research Councils UK (Research Councils UK, n.d.)

However, dissemination is not without its pitfalls. Song et al (2010) concluded that the process is likely to be biased, even for systematic reviews such as these (Song et al., 2010). Studies that report positive effects were more likely to be published and so more likely to be included in a systematic review. These biases can be minimised by systematically searching for, and including, difficult to obtain studies such as grey literature (informally published material) for which traditional search methods prove ineffective) and foreign language articles, or performing statistical sensitivity analyses. Indeed, one of the reviewers of the Iron Supplementation Cochrane review specifically asked whether foreign language papers had been included. Of the included studies, seven papers from six separate studies first required translation. Additionally, several papers were not included after a translation had been reviewed.
4.1.1.1 Models for Knowledge Translation

There are a number of frameworks for transferring knowledge, such as the Becker Model previously mentioned and that of Grimshaw, Eccles, Lavis, Hill, and Squires (2012). The latter suggest five questions:

1. "What should be transferred?"

Current systematic reviews of good quality are needed to provide evidence to decision-makers so they produce clinical guidelines, policy briefs, patient decision aids and effective summaries. They should include not only what works and for whom, but why and at what cost.

2. "To whom should research knowledge be transferred?"

It should reach as many different target audiences to whom that knowledge may be relevant.

3. "By whom should research knowledge be transferred?"

Different messengers may be needed dependent on the nature of the message and the target audience.

4. "How should research knowledge be transferred?"

Grimshaw et al. (2012) state that little evidence exists as to the efficacy of different dissemination strategies. It is suggested that the message is more likely to be effectively transferred if there is an assessment made of the possible problems and promoters for any particular route.

5. "With what effect should research knowledge be transferred?"

How to measure the efficacy of a dissemination strategy remains subject to considerable debate. The outcome should determined by the intended audience. It should be read, find its way into policy documents and guidelines and so change practise. Knowledge is of little benefit even if published in an esteemed journal with a high impact factor if the policy makers for which it is intended do not read it and utilise its information.

This last question is concerned with the impact of the research and is discussed in the next section.
Chapter 4 – Dissemination and impact analysis

4.1.2 Impact assessment of output

Impact is defined by the Research Councils UK (RCUK) as “the demonstrable contribution that excellent research makes to society and the economy” (Research Councils UK, n.d.). This is not a simple task; the impacts from research can take many forms, become apparent at different times within, and even after, the research cycle and be promoted through different means. RCUK asks the central questions of who will benefit from the research, and how.

4.1.2.1 Research Output

With the ever growing body of scientific information the amount of information is so large that its physical storage is no longer possible. Additionally, financial constraints limit the amount resource that can be dedicated to the purchase of journals. Individuals and Institutions look to measures such as the Impact Factor (IF) to help decide which journals have sufficient merit to warrant purchase (Dong, Loh, & Mondry, 2005). The effects of a study - its impact - can be immediate and short-term as well broader and longer-term, either positive or negative, expected or unforeseen. What is important when assessing impact is the value to the recipients of the information contained. There are formal methods to define impact (see below), but less formal feedback can be gained from the stakeholders.

Citation Index

Citation indices, such as the Web of Science, Scopus and Google Scholar, are useful to see who is citing your work and in what way. They depend on the links between similar research items leading to matching or related scientific literature. In this way, an article's importance can be determined by cross-reference to all the articles citing it. Originally citation indices were used to retrieve related articles but increasingly they are employed in bibliometrics - a method to quantitate academic literature for research evaluation.

Journal Impact Factor (JIF)

As previously mentioned, it is difficult to objectively measure the quality of a journal and the accessibility of the JIF has contributed to its popularity. However, it must be borne in mind the JIF is prone to bias from a number of directions. These include the language of both the database and the articles it contains, how the citations are collected, the algorithm used to calculate the JIF, on-line availability of the articles, publication delay from acceptance, etc. (Royle, Kandala, Barnard, & Waugh, 2013).
4.1.3.2 Other indicators of impact

There are other performance indicators of the quality of research outputs beyond publication metrics. Some of these (adapted from the Becker Model) are listed below:

- **Clinical Implementation** - when research findings are adopted into clinical practice within the community, possibly through the implementation of guidelines (see below).
- **Community benefit** - where an improvement in the health or well-being of the community results from the research.
- **Legislation and policy** - when the research output forms the basis for new laws, guidelines, standards or policy.
- **Economic benefit** - cost improvements are derived from the research.
4.2 Planning the dissemination strategy and impact evaluation

One needs to consider the intended impact of the research when adopting a dissemination strategy so that the evidence can be used by the stakeholders to effect change. For the Iron and Blood donors review programme there were a number of different stakeholders. In the first instance, there were the policy makers in the Donor Services Directorate of NHSBT, whose interest was the factors that might predispose donors to defer and whether treating them with iron supplements would be a safe and effective means to prevent deferral. Researchers who will, or are likely to, design and implement RCTs investigating different donation rates in blood donors will know of what contributing factors to be aware when analysing their findings, or which formulation of iron and what dosing regimen might be most beneficial when providing IS to blood donors to prevent low LHD.

Additionally, the information generated would be of use to Blood Services of other countries who may be looking at similar issues. The findings could also improve the treatment of the chronically anaemic patient.

Finally, and more importantly, the blood donors themselves should be able to access the information that contributes to their health and wellbeing. By providing them with the data in an accessible format they can make informed decisions as to what they might do to improve their chance of donation (e.g. dietary changes), what personal factors may have contributed to a failed donation attempt and why they have been offered assistance to remedy their health should they have failed to meet the lower Hb thresholds.

However, remaining with the five questions from the Grimshaw Model:

1. "What should be transferred?"

The principal intention for the systematic reviews was to provide good quality evidence to inform the design of large-scale RCTs. However, progress reports need to be supplied to the commissioners of the research (National Institute for Health Research) and fellow researchers. Generalisable findings should be passed on to the public.
2. "To whom should research knowledge be transferred?"

Not only should it reach those researchers involved in the RCTs but also the NIHR. Colleagues in other Blood Services should be made aware of the findings, not only to help inform their decision-making but to avoid unnecessary duplication of effort. It should also go to the public in general and the donors in particular so they may understand the reasoning behind the trials in which they are being asked to participate and why the results of those trials may alter the way in which they are being asked to donate.

3. "By whom should research knowledge be transferred?"

Researcher to researcher. Principal Investigators have the duty to pass on the information to the commissioners, but they are reliant on the findings being handed to them by their researchers. It may be that someone of a higher academic standing can provide the necessary gravitas to approach policy makers to enable change in policy.

4. "How should research knowledge be transferred?"

A problem inherent with all forms of knowledge translation is 'will the information reach the target audience - will they attend, read, listen to the messages you are trying to convey'?

5. "With what effect should research knowledge be transferred?", i.e. assessing the impact

Were the reviews published?

Did they reach their target audience?

Were they in an appropriate format and of sufficient clarity for the target audience?

Were they well received?

Will they change practice for the better?

These will be presented in the next section and discussed.
<table>
<thead>
<tr>
<th>Method</th>
<th>Target audience</th>
<th>Why?</th>
<th>Possible problems</th>
<th>Promoters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion</td>
<td>Policy makers</td>
<td>Ensure correct information and requirements before start of project.</td>
<td>Is the information relevant and recorded.</td>
<td>Attendees from appropriate disciplines. Extensive minutes.</td>
</tr>
<tr>
<td></td>
<td>Fellow experts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reports</td>
<td>Commissioners</td>
<td>As above, and ensure the political will to convert into guidance.</td>
<td>Has sufficient progress been made.</td>
<td>Extensive experience in progress reports.</td>
</tr>
<tr>
<td>Posters</td>
<td>Researchers</td>
<td>Inform researchers gap in evidence Inform researchers about possible subgroups</td>
<td>Can sufficient detail be imparted.</td>
<td>Pre-presentation abstracts.</td>
</tr>
<tr>
<td>Presentation</td>
<td>Policy makers</td>
<td>As above.</td>
<td>Inexperience with public speaking.</td>
<td>Pre-presentation abstracts Presentation skills training.</td>
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<td></td>
<td>Researchers</td>
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<tr>
<td>Conferences</td>
<td>Policy makers</td>
<td>As above.</td>
<td>Attendance by presenter/ international audience.</td>
<td>Pre-presentation abstracts.</td>
</tr>
<tr>
<td></td>
<td>Researchers</td>
<td></td>
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</tr>
<tr>
<td>Papers</td>
<td>Researchers</td>
<td>Inform researchers of the quality of available evidence.</td>
<td>Will the research be published. Is the journal too specialised.</td>
<td>Work with experts in SR. Target publication to audience.</td>
</tr>
<tr>
<td>Web-based</td>
<td>Blood donors</td>
<td>Improve awareness by public Encourage new donors.</td>
<td>Public may not have access to internet. Lack of web-based media experience.</td>
<td>Work with Web experts to maximise uptake.</td>
</tr>
<tr>
<td></td>
<td>General public</td>
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</tbody>
</table>
### 4.3 Evaluation of dissemination and impact

Table 4.2: Timeline of dissemination.

<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
<th>Scope</th>
<th>Location</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 October 2008</td>
<td>Donor Iron Project</td>
<td><strong>Discussion.</strong> Support donor health in general and problems of anaemia and iron deficiency in particular.</td>
<td>Filton, Bristol</td>
<td>NHSBT Blood Donor Management</td>
</tr>
<tr>
<td>8 October 2010</td>
<td>First meeting of Systematic Review (SR) team</td>
<td><strong>Discussion.</strong> Define the scope of the SR and propose project plan. Discuss search strategies.</td>
<td>NHSBT, Oxford</td>
<td>Graham Smith, Dave Roberts, Sheila Fisher, Susan Brunskill, Carolyn Doree</td>
</tr>
<tr>
<td>27 July 2011</td>
<td>Iron and Blood Donors Workshop</td>
<td><strong>Presentation.</strong> Feed initial findings into proposed RCT and influence its design (INTERVAL study).</td>
<td>NHSBT, Oxford</td>
<td>Graham Smith, Dave Roberts, Sheila Fisher</td>
</tr>
<tr>
<td>19-20 September 2011</td>
<td>NHSBT Annual R&amp;D conference</td>
<td><strong>Poster.</strong> Sharing progress of different NHSBT R&amp;D strands. Presented poster on low Hb SR.</td>
<td>Robinson College, Cambridge</td>
<td>Graham Smith, Dave Roberts, NHSBT R&amp;D</td>
</tr>
<tr>
<td>12 April 2012</td>
<td>Programme D Review Meeting</td>
<td><strong>Presentation.</strong> Presented oral update of low Hb SR.</td>
<td>Lady Margaret Hall, Oxford</td>
<td>Graham Smith, Dave Roberts, Sheila Fisher, NHSBT R&amp;D</td>
</tr>
<tr>
<td>21 December 2012</td>
<td>Transfusion</td>
<td><strong>Paper.</strong> Rejection of low Hb SR due to fact that it presented no new work.</td>
<td></td>
<td>Graham Smith, Dave Roberts, Sheila Fisher, Carolyn Doree</td>
</tr>
<tr>
<td>Date</td>
<td>Title</td>
<td>Scope</td>
<td>Location</td>
<td>Participants</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------------</td>
<td>------------------------------------------------</td>
<td>----------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>10 January 2013</td>
<td>Programme D Review Meeting</td>
<td><strong>Presentation.</strong> Presented oral update of low Hb SR and progress with iron supplementation SR.</td>
<td>St Catherine’s College, Oxford</td>
<td>Graham Smith, Dave Roberts, Sheila Fisher NHSBT R&amp;D</td>
</tr>
<tr>
<td>2 July 2013</td>
<td>Programme D Review Meeting</td>
<td><strong>Presentation.</strong> Presented oral update of iron supplementation SR.</td>
<td>SS Great Britain, Bristol</td>
<td>Graham Smith, Dave Roberts, Sheila Fisher NHSBT R&amp;D</td>
</tr>
<tr>
<td>5 July 2013</td>
<td>Transfusion Medicine</td>
<td><strong>Paper.</strong> Low Hb SR accepted on 23 April 2013.</td>
<td>e-Published Vol. 23 (5) pp 309 – 320</td>
<td>Graham Smith, Dave Roberts, Sheila Fisher, Carolyn Doree</td>
</tr>
<tr>
<td>28 January 2014</td>
<td>Cochrane Collaboration</td>
<td><strong>Web-based.</strong> Volunteered to collaborate with Cochrane Wikipaedian in Residence.</td>
<td></td>
<td>Graham Smith</td>
</tr>
<tr>
<td>24-26 September 2014</td>
<td>British Blood Transfusion Society</td>
<td><strong>Conference.</strong> 24.09.14 All day meeting on iron therapy.</td>
<td>Harrogate, Yorkshire</td>
<td>Graham Smith, Dave Roberts</td>
</tr>
</tbody>
</table>

**Table 4.2: Timeline of dissemination (continued)**
4.3.1 Posters - See Appendix 4.1

4.3.1.1 NHSBT Annual R&D conference

4.3.2 Presentations - See Appendix 4.2

4.3.2.1 Programme D Review Meeting
12 April 2012. Lady Margaret Hall, Oxford - Appendix 4.2.1

4.3.2 Programme D Review Meeting
2 July 2013. SS Great Britain, Bristol - Appendix 4.2.2

4.3.3 Conferences
Presented poster on low Hb SR.

24-26 September 2014, British Blood Transfusion Society Annual Conference, Harrogate
International Conference Centre. Iron Therapy Symposium.

4.3.4 Papers
Two publications were produced during this study:


4.3.4.1 Impact Factors
ISI Web of Knowledge provides an index of impact factors (as well as other journal metrics) for the journals who rejected or accepted my papers (Table 4.3).

Table 4.3: Impact Factors for journals, as at 31 July 2014.

<table>
<thead>
<tr>
<th>Journal</th>
<th>Current Impact Factor (IF)</th>
<th>Five year average IF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion</td>
<td>3.526</td>
<td>3.180</td>
</tr>
<tr>
<td>Transfusion Medicine</td>
<td>1.259</td>
<td>1.599</td>
</tr>
<tr>
<td>Cochrane Review</td>
<td>5.785</td>
<td>Not available</td>
</tr>
</tbody>
</table>

4.3.4.2 Citations
Google Scholar Citations is a relatively simple way for me to keep track of citations to my two publications. By adding the references to this citation database I can follow who is citing my work. Indeed I can even map the number of citations with time. I made my profile public so it appears in Google Scholar results should people search on my name, but is available at http://scholar.google.com/citations?user=QOknVnlAAAAJ

Likewise, ResearchGate, an on-line research networking forum, provides a means to track those publications which have cited the papers you have added to your profile. It can be accessed at https://www.researchgate.net/home

Web of Science provides another way of monitoring citations of your work, at http://apps.webofknowledge.com/UA_GeneralSearch_input.do?SID=Y1dIfJtXX9QHxBppjvM&product=UA&search_mode=GeneralSearch&errorQid=1

Table 4.4: Google scholar/ResearchGate citations as at 15 September, 2014

<table>
<thead>
<tr>
<th>Paper</th>
<th>Google scholar</th>
<th>Research Gate</th>
<th>Web of Science</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Smith, Fisher, Dorée, &amp; Roberts, 2013)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>(Smith, Fisher, Doree, Di Angelantonio, &amp; Roberts, 2014)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

4.3.5 Web-based
At the time of submission, no specific web-based material had been disseminated.

Additionally, the possibility of recording a four minute podcast was discussed with the Cochrane Collaboration but was discounted for the reasons in 4.3.6, below.
4.3.6  Press Release

The Cochrane Press Office were very keen to have a release at the same time as the intended time of publication (mid-June, 2014). It was thought, within NHSBT Corporate Communications, not to be a good idea because they did not want the review to clash with World Blood Donor day (June 14) and deflect from the message that was being promoted. Also, as blood donation was likely to be high in the public awareness, there were concerns of a possible backlash from donors (phone calls to the donor centres/helplines asking "why am I not on iron", "am I going to get ill if I donate too much", etc.). The outcome was an agreement to delay the publication of the review for two weeks and to have a press release in waiting but only to issue if necessary in response to any queries.

4.3.7  The Becker List of Impact Indicators

See Appendix 4.3.
4.4 Discussion

It is difficult to assess the efficacy of the work I have carried out and of the routes I have employed to disseminate the information. Although the dissemination model of Grimshaw et al. (2012) was employed I cannot lay claim to have adopted a theoretically-informed approach to my dissemination strategy, such as advocated by Wilson et al (P. Wilson et al., 2010a). What I have tried to do is, first and foremost, get the findings to those I would consider my "Commissioners" - NHSBT - who might be supposed to have the greatest use for them. Secondly, I have tried to employ a multimodal communication approach, to use as many routes as possible (as laid out in Appendices 4.1 - 4.5). Finally, the journals in which these systematic reviews were published may not, as measured by numerical citation indices or impact factors, have had the greatest impact but would be seen by those who would employ the results to good effect.

Unsurprisingly, Table 4.4 shows very few citations (as of 15 September 2014) and, not unexpectedly, those solely of the paper published first (unless there was an extremely rapid publication, two and a half months between publication and its citation is unlikely). The various citation indices returned different citation rates; ResearchGate found none (but only returns those citations stored within its database by its network members) whereas Google Scholar and Web of Science each returned two citations. Interestingly, they described three different publications, highlighting the possibility that no one measure would accurately describe publication success.

Most non-published routes of dissemination were targeted towards researchers designing trials so that they may influence the design of those trials. This was done ahead of publication as a series of "update" sessions in order for those trials to proceed as rapidly as possible. Those trials have appeared, or will appear, in International Registries of Trials so would be available for researchers in other countries to use as a guide for their own research.

The first study, that of the risk factors for low Hb in blood donors, was published in a journal which, although not of the highest JIF, does have a history of publishing such articles and so would be read by an international audience with an interest in that particular area of study. It has been successful insofar as it has been acknowledged by NHSBT researchers for the design of the "Interval Study" (see 4.5.1- Future/Ongoing Work, below).
The Iron Supplementation SR was a study into an intervention that will lead to an evaluation as a potential treatment for reduction of iron-deficient anaemia in blood donors in England. It was released through the Cochrane Collaboration, an organisation with an international reputation for high quality systematic reviews, a greater than average JIF and a valued resource for researchers interested in a systematic review under their guidelines. Cochrane Reviews are also "Open Access" (OA), at least in the UK, the aim of which is to make the results of academic research freely and easily accessible to all. OA is not without its critics. In a recent on-line debate (chaired by Claire Shaw for Guardian Professional on 25th October 2013, 12.00-14.00 BST) OA was accused of promoting poor quality research by allowing less rigorous peer-review. Interestingly, one participant ("Curtrice") mooted the possibility of a Wikipedia model for scientific publication (http://curtrice.com/2012/06/07/wikipedia-as-a-model-for-scientific-publishing/). Something akin to this is being investigated by Cochrane in partnership with Wikipedia via the Wiki Project Med Foundation. I have volunteered to collaborate with the Wikipaedian-in-Residence, a new position created by the Cochrane Collaboration in February 2014 to promote the use of independent, high-quality evidence in Wikipedia articles (Appendix 4.5). The aim is for Cochrane to utilise Wikipedia's global resources to reach new audiences.

4.5 Future/ongoing work

4.5.1 Interval Study (Appendix 4.6)

INTERVAL Study: To Determine Whether the Interval Between Blood Donations in England Can be Safely and Acceptably Decreased

(ClinicalTrials.gov Identifier:NCT01610635).

This study began in 2012 after the initial findings of the systematic review were presented at a joint meeting with the trials organisers on 27th July 2011. The contribution of the Low Hb SR was acknowledged in the update briefings presented at the Program Review meetings (Appendix 4.6). As of June, 2014, over 50,000 blood donors had been recruited to the trial (I being one of them from January 2013) and recruitment was halted due to the recruitment target being reached. The donors will be followed for two years, the last enrolees until June 2016.
4.5.2 Iron Supplementation RCT

The next phase of the NHSBT’s plans to improve donor health is to use the 50,000 donors recruited for the Interval study as basis for investigating the effects of iron supplementation in an RCT (recruiting more, if required). The findings of the Iron Supplementation SR will determine whether the trial looks at type, duration and/or dose of Iron Supplementation, which haematological indices will best determine its efficacy and what adverse effects (AE) need to be observed. Indeed, these AE have been incorporated into quality of life questionnaires sent to participants in the Interval Study (4.5.1, above).

4.6 Impact for donors and donation

I have discussed the impact of the work from a scientific viewpoint. But what of other measures of impact (section 4.1.3.2), especially for the stakeholders, i.e. the donors and NHSBT? How have these studies helped with the original aims of the research programme described in Chapter One, that of determining the factors that contribute to donors failing the low Hb threshold required for a successful donation and describing the effects of iron supplementation in donors when used to prevent iron deficiency?

The Interval Study described in 4.5.1, although primarily designed to investigate the effect of inter-donation duration, will take into account the risk factors highlighted from the low Hb SR. Indeed, the study itself will provide new estimates of the relative risk factors which can be incorporated into new guidelines, such as the algorithms in preventative medicine developed during the Framingham Heart Study (D’Agostino et al., 2008). Studies have already assessed multiple risk factors to give a likelihood of failing pre-donation screening (Baart et al., 2014; Baart et al., 2012; Baart et al., 2011; Hillgrove et al., 2011; Rigas et al., 2014). By using those risk factors the donor can be assigned to a donation frequency tailored to their own particular risk characteristics and in order to minimise the likelihood of a failed donation attempt, with its associated effect on donor morale and its cost to NHSBT. For example, a hypothetical table of the cumulative relative risks could be created (Table 4.5a) and donation intervals set according to a donor’s characteristics (Table 4.5b). Although neither the Low Hb deferral SR, nor the Cochrane review, found studies regarding dietary effects in blood donors, there is a body of evidence that diet can effect anaemia rates in the general population (International Nutritional Anemia Consultative Group (INACG), 1998).
A young, white, omnivorous, male donor of higher BMI (cumulative risk - CR - of 5.0) would be assigned to the most frequent donation group (e.g. every eight weeks), whereas a much older, smaller, Asian vegetarian (CR = 8.1), would donate every 12 weeks (as would a white, omnivorous, woman - CR = 8.1 - whose BMI was greater than 30). A slight, black, vegetarian female (CR = 10.4) could be assigned to the lowest frequency donor group.

This would necessitate a donor database being created that would incorporate these algorithms using the risk factors data, and this information being applied so as to invite donors according to their ideal donation interval. In this way the management of the donor can be customised to their individual characteristics (Spencer, 2014). Ideally the database would be incorporate an artificial neural network, capable of machine learning and pattern recognition, so that it might improve its ability to optimise donation rates and donor health without the need for constant human re-evaluation of its algorithms.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>1.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1.6</td>
<td>&lt;30</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1.0</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-45</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>46-55</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>56-75</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vegetarian</td>
<td>1.0</td>
<td>Non-vegetarian</td>
</tr>
<tr>
<td>Vegetarian</td>
<td>1.5</td>
<td>Vegetarian</td>
</tr>
</tbody>
</table>

Table 4.5a: Theoretical donor risk factors for low Hb deferral.

<table>
<thead>
<tr>
<th>Cumulative Risk</th>
<th>Donation frequency (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>8</td>
</tr>
<tr>
<td>6.1 - 8.0</td>
<td>10</td>
</tr>
<tr>
<td>8.1 - 9.0</td>
<td>12</td>
</tr>
<tr>
<td>9.1 -10.0</td>
<td>14</td>
</tr>
<tr>
<td>&gt;10</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 4.5b: Donation frequency determined by cumulative risk for low Hb deferral.
The possibility exists that blood services would use this information to target potential donors according to those characteristics. Would concerted recruitment drives be aimed towards those individuals most likely to successfully donate? Would the ideal prospective donor be a young, white, omnivorous male graduate who, although exhibits the "bad" traits of being overweight and a smoker (wherein lies a contradiction; donors are traditionally chosen on the basis of good health), would donate regular (preferably at a mobile donation site) after appealing to their nepotistic tendencies.

Donors are already targeted; male donors are chosen in preference to females, and not because of their likelihood to donate successfully (NBC News, 2007). Blood products that contain a large proportion of plasma (FFP, platelets) are sourced from male donors to decrease the risk of Transfusion-related Acute Lung Injury (TRALI) as women are more likely to form the causative antibodies (Eder & Benjamin, 2009; Toy et al., 2012). This directed donation strategy is taken further when obtaining FFP for neonates, as it is only taken from non-UK sourced (from countries with low vCJD prevalence) male donors to lessen the risk of vCJD as well as reduce the risk of TRALI (British Committee for Standards in Haematology et al., 2004). It may be only a small step further to choose to concentrate resources on recruiting those potential donors who give a high return on investment. Taken to an extreme, potential donors who score above a theoretical threshold for cumulative risk might even be considered too cost-ineffective to attempt to bleed.

Beutler and Waalen (2006) suggested setting low Hb thresholds according to gender and ethnicity. Should thresholds be set according to other risk factors? Practically, this would be hard to achieve using the CuSO₄ screening method currently used within the UK Blood Services. Already there are two different vials containing CuSO₄ of different specific gravity (SG) for screening males and females, each used a limited number of times before being replaced. There would be considerable difficulty in expanding that to having a range of vials of different SG, recording how many times each had been used and then which one should be used for each donor, taking into account their gender, weight, age, ethnicity, etc. Clearly, a change to the screening procedure is required. The HemaCue® colorimetric POCT machines are already interfaced with Laboratory Information Management Systems (LIMS) within hospitals so should be able to be interfaced with donor databases to manage the appropriate threshold for a particular donor. Already laptops containing donor information are taken to mobile donor sessions within England. Ideally the screening method itself should be non-invasive, but those methods available at present are not sufficiently accurate.
A question is raised as to what level should those thresholds be set? Even when different, lower, thresholds are used every study observed in the low Hb SR recorded greater LHD for women. Should those thresholds be set to defer the same percentage of donors within that category? What should that percentage be - one, two, five, ten per cent? The WHO defines anaemia as Hb being below 130 g/L for males and 120 g/L for females, based on two standard deviations below the mean (Vitamin and Mineral Nutrition Information System, 2011). At these levels it would be expected that 2.5% of donors would fail. Some studies are showing as high as 47% LHD (Agnihotri, 2010) for women at a threshold level (120 g/L) only marginally higher than that defined as clinically anaemic by WHO (Agnihotri, 2010). I would suggest that normal ranges need to be set for the population they serve, and then related to the clinical effects of those ranges.

Currently, with respect to their iron status, donors are only prevented from giving blood when their iron levels have fallen sufficiently to reduce Hb to a level where they fail the CuSO₄ screening test. It would be far better to detect falling iron levels before the donor develops frank anaemia, so avoiding rejection and potential failure to return, and the administrative costs associated with that. There is no POCT screening test that provides a real-time evaluation of iron deficiency immediately prior to donation so we are left with retrospective testing, post-donation.

Those with iron-deficiency could be notified and given dietary advice and, possibly, informed of the risks of iron supplementation, should the donor wish to pursue that route. In this way a blood service might avoid the difficulties in having to prescribe IS, except in the most extreme of cases. In these instances it should only offer IS with the lowest incidence of side effects (despite the likelihood of them being more expensive). Of course, there would need to be a support structure to offer advice to donors (NHSBT already has its Donor Helpline - 0300 123 23 23 - but this would need to be reconfigured to deal with any increase in enquiries).

The findings of the IS systematic review show that serum ferritin levels are significantly associated with response to IS and that treatment of donors with iron is effective in preventing donors failing the Hb screening test by raising their serum ferritin levels, and thus the Hb level, although at a cost of a 60% increase in associated adverse effects. The proposed iron supplementation RCT will determine what is to be the best dosing regimen and the extent of the adverse events.
A cost-benefit analysis would need to be performed to see if the decreased administrative costs and increase in donor retention off-sets the cost of serum ferritin testing and cost of the iron supplementation itself. With respect to the side effects of the intervention (both negative and positive) it is also important to evaluate the quality of life indicators for the donor themselves.

By judicious tailoring of donation intervals according to the epidemiological profile of the donor and use of iron supplementation for those donors who fail, or are in danger of failing, the Hb test an holistic approach to improving donor health should be achieved. In this way, other impact indicators, such as improvements to clinical practice and donor health, new guidelines for donor testing and decreased costs from improved donor retention, will be evidenced.

My concern is that, with adverse publicity, this could be considered a form of blood farming.

NHSBT produces a magazine for donors ("The Donor") in which it highlights areas it believes to be of interest to the donor population, whether it be articles of human interest from patients whom have received blood products, biopics of various NHSBT departments involved in the production of blood products or testing of donors and items related to the health of donors. Future articles would publicise the research findings from the two RCT and so encourage those donors with lower risk ratings to donate, perhaps to alter their diet to help prevent deferral and explain why additional post-donation testing has been introduced for the supply of iron supplementation to improve donor health and well-being. My collaboration with the Wikipaedian-in-Residence should further help the health promotion aspects of this work by reaching a wider public audience allowing them to be more aware of blood donation and the importance of donor health.
Chapter 5 – Personal and professional development

The previous Chapters have introduced the context behind the systematic reviews, how I carried out those reviews and by what means I have tried to pass on their information to achieve an effective dissemination. This chapter discusses how I came to the professional doctorate, how it affected me as an individual, both on a personal and a professional level.
5.1 The journey begins?

“Sometimes it’s the journey that teaches you a lot about your destination”.- Drake (born Aubrey Drake Graham).

Looking back, I believe I first began on the path to the Professional Doctorate course in 1981, when I graduated from a four-year sandwich degree course. I realised at that time I wanted to progress further on the academic route; in hindsight I was more concerned with what Maslow described as fulfilling "lower" esteem needs, the need for the respect of others (i.e. the need for status) (Maslow, 1943).

![Figure 5-1 Maslow's Hierarchy of Needs. Reproduced from http://hansengeorge.blogspot.co.uk/2011/09/maslows-hierarchy-of-needs.html](http://hansengeorge.blogspot.co.uk/2011/09/maslows-hierarchy-of-needs.html)

My degree specialisation was general Animal Physiology, (Medical) Entomology in particular, and my sandwich placements had all been in the area of field trials work. I applied for a number of MSc courses (Entomology, Parasitology) but funding was difficult to obtain for anyone holding less than a 2:1 Honours degree (mine was a 2:2). The employment situation was not dissimilar to that currently (2014), with few opportunities available.
Chapter 5 – Personal and professional development

5.2 From there to here

“Our deeds still travel with us from afar, and what we have been makes us what we are.” - George Eliot.

I entered BioMedical Science (BMSc) after three months unemployment (a seemingly long period to a 22 year old) when I accepted a position as a Junior "B" Medical Laboratory Scientific Officer (MLSO) which would now be a Trainee BioMedical Scientist (BMS) within a hospital Haematology Laboratory. Although not my preferred career path (laboratory-based, rather than field work. Fewer insects!) it was related through its medical content.

Graduate entry into BMSc was rare in the early 1980s, and non-existent within this particular Laboratory. There was no formalised academic course for “State” Registration with the Council for Professions Supplementary to Medicine (now Registration with the Health and Care Professions Council) for a graduate; completion of twelve month’s work experience had to be followed by successful passing of an oral exam. Existing trainees had completed the two-year HNC course in Haematology and Blood Transfusion Science and some believed I was being preferentially fast-tracked to State Registration. On my part, there was an underlying belief that I was deserving of something better than a routine laboratory job, something more suited to an enquiring mind. A certain degree of friction resulted and I sought an alternative position although I was now convinced I wanted to remain in a clinically-based career.

Having successfully completed my training and obtained my registration as an MLSO in Haematology and Blood Transfusion I started a position in the Research and Development (R&D) Department of Southampton Blood Transfusion Centre as a Scientific Officer (later termed Clinical Scientist [CS]). Here I felt I might have more scope to develop any talents I might have gained from University in a clinical science (CSc) research environment as a CS than the more routine diagnostic setting of the BMS (as well as receiving more pay and annual leave!). Circumstance has since shown I did not have, nor still have in some areas, many of the skills needed for a successful BMS or CS.
I include this brief CV to highlight the confused nature of my career. I came to BMSc as a graduate, a route more typical for a CS, but Registered as a BMS before practising as a CS. In 2003 the HCPC made the titles of BMS and CS legally protected, so I had to decide which I wanted. I made a case for, and was successful in, "grandparenting", i.e. switching from registration with the BMS board of the HCPC to the CS board without having to meet the usual entry requirements. This is not without its problems, as there is no Transfusion Science modality within CSc. The confusion is further compounded as I have undertaken this Profession Doctorate (PD) which, originally was to lead to a Doctorate in BMSc (if successful) rather than CSc. Furthermore, since April 2010, I have held two Blood Transfusion service manager positions for which an essential person specification requirement was to be a BMS. In July 2014 I applied to transfer to the Professional Doctorate in Health Science, as it is a more flexible title more in keeping with my role.

Whilst working within R&D in Southampton I passed the Blood Group Serology and Transfusion Science course leading towards Fellowship of the Institute of Biomedical Sciences at what is now the University of Portsmouth (UoP). This was (and the MSc which replaced it) the highest discipline-specific qualification achievable. After supporting my line manager in the completion of his PhD it was time to progress my own aspirations. I registered with UoP for a MPhil/PhD in 1996; unfortunately the same year as NHSBT underwent extensive re-organisation of their R&D. This resulted in a change of job to a more service-orientated laboratory, albeit one with extensive ties to R&D and a promise to study for a PhD after 2 - 3 years, “when I had the lab running smoothly”.

Seven years later I had still not begun my PhD. Why? In part, there was never a period where I, or the laboratory, was not subject to some external change and partly because I found none of the potential PhD projects particularly stimulating. During an appraisal my line manager suggested that perhaps I lacked sufficient motivation to complete a PhD. I was stung into action, not least because I began to question whether he was correct.
I had to decide the direction of my career development. Although my role at the time was essentially managerial I still felt myself to be a scientist. Furthermore, study towards an MBA would not have been supported by my, then, line manager who was a Principal Investigator for NHSBT. Wanting to achieve the highest level of Maslow's Hierarchy of Needs, that of self-actualisation (being the best you can be) then within my chosen field this meant trying for Consultant level of expertise. Within the NHS Agenda for Change career framework a doctorate is seen as a required academic qualification for Advanced Practitioner or Consultant grade posts (University of Portsmouth). In the field of Pathology, outside of Medicine, not only is a doctorate required but also successful completion of the Membership of the Royal College of Pathology Part 1 and 2 examinations in a specific Pathology discipline. Obtaining a Consultant grade in Blood Transfusion is not, currently, available through examination; only through scientific publication (requiring at least 30 papers; 10 as first author (Royal College of Pathologists, n.d.))

So why did I choose the PD course, rather than the more culturally acceptable (within NHSBT, at least) PhD route? The recommendation of an existing PD student and having the approval of a new line manager meant I investigated the PD course. I had existing ties to Portsmouth University through study for the FIBMS, lecturing and research collaborations. The course itself appealed, as it appeared more relevant to my role as the head of a clinical laboratory whereas the PhD is more research oriented. Additionally, the taught element meant I, and the organisation, had to make a commitment – once the fees had been paid there was less chance organisational influence would prevent me from at least completing that element.
5.3 Where we are now

“Always do your best. What you plant now, you will harvest later”. - Og Mandino.

I feel that I benefitted enormously from my fellow students on the PD course. After an absence of over 20 years I found it difficult to begin formal study. When faced with the assignments I experienced panic and inertia, but found it of great help to find that my colleagues felt the same and together we would discuss ways to proceed, forming what de Haan would call a peer consultation group (de Haan, 2005). Although my primary peer group consisted of BMS from disciplines outside Haematology or Blood Transfusion, the unique insights gained from working with other healthcare professionals was invaluable, both during the PD course and, subsequently, in my professional life when dealing with diverse staff groups. Likewise, of the taught element of the PD I particularly enjoyed the qualitative research module, something I had not encountered previously and, although achieved only poor results from the assignment, am more receptive to their use and value in healthcare research.

The course as a whole, and the Research Resource assignment in particular, proved useful when mentoring others, not only for second degrees such as the MSc (three students) but also for those beginning their formal qualifications in BMSc with the Foundation Degree (one student).

A major challenge lay ahead in the choice of the project. My line manager and would-be supervisor's main interest at the time was the molecular biology behind platelet immunology. Although I had an interest in the field it failed to stimulate me sufficiently to want to make it my PD project. My supervisor was concerned that I would have to delay commencement until I had completed the taught element of the PD so passed the reins to others (although I did eventually work on, and help publish, the research (Jennings et al., 2007; Stafford et al., 2008).
Chapter 5 – Personal and professional development

In 2006, having successfully applied for an Accredited Prior Experiential Learning exemption from the Publication and Dissemination module, I was ready to begin a project that was of much greater interest to me. I was to investigate the molecular and serological nature of a rare platelet disorder, with a view to setting up a national reference service and external quality assessment scheme. I began the necessary paperwork for ethical approval, designed consent forms and information leaflets and, more importantly, gained a new line manager who was much more supportive of the research (due to a re-organisation within NHSBT). Unfortunately their strategy was to close my laboratory, which resulted in the gradual loss of staff necessary to back-fill me for the project and my eventual redundancy in 2007.

All the proposed PD projects had been lab-based. With no job the possibility of such research was minimal, and no better when I was finally employed as a locum in 2008 for two years managing a stem cell laboratory (for NHSBT). This period emphasised to me the lack of development opportunities available to locums, which has led me to offer as much support as possible to any in my employ.

In 2010 there was discussion within the PD course as to whether those who could not complete the project element but had been successful for the taught element should be awarded a Masters in Research. Having deferred for nearly five years, and with no apparent possibility of my even beginning any project, I thought this would be the only way in which I could gain a further qualification. However, Dr Sally Kilburn, my current supervisor, suggested I might consider the possibility of systematic review to form the project. She explained that the academic endeavour, and intellectual activities involved in carrying out systematic reviews, especially if involving different approaches would be more than sufficient for a professional doctorate. Sally believed the University might be prepared to accept two such reviews, properly researched and prepared, as being of sufficient academic merit to pass the project element of the PD.

I eagerly adopted the idea of being able to take control of the next phase of the PD without being reliant on others (or so I thought at the time) or the need for laboratory equipment and consumables (and associated costs as I was, in effect, self-funded). Fortunately, I was working nearby to the NHSBT Systematic Review (SR) team who were receptive to the collaboration. I contacted numerous NHSBT Principle Investigators (PI) for a "sponsor", who would have a research question which they thought would benefit from SR.
Initially, a number of reviews in the general area of my past platelet experience were discussed but finally the PI whom had previously agreed to be my work-based supervisor offered the present topics that would feed into his NIHR research programme on donor health. In July 2011 my project proposal was accepted by the University Examination Board.

The SRs themselves I approached with a degree of trepidation. I had no formal training in the area of SR and no expertise in the field of donor deferral and iron supplementation. However, the Advanced Research Techniques unit of the PD contained sections on systematic searching and critical appraisal, which would prove invaluable in this endeavour. To an extent, I thought it was hardly research at all, just regurgitation of the work of others (a sentiment echoed by some clinical scientists who do not understand the difference between a systematic review and a review article). What I found was the process was much harder than I had thought and in my opinion requiring a different, but no less expert, skill set than that required for laboratory-based research. I think I can honestly say I have not put in the same degree of work into my other papers and would alert anyone whom might be contemplating a similar route that it is not an easy option. Were it not for the support of the SRI team I am not sure I would have completed the SRs and I am sure they would not have been of the same high standard. However, I found the experience particularly rewarding and would hope this project might help or even inspire other health professionals who cannot do workplace-based projects to consider other less obvious avenues for their doctorate projects.

The work has already resulted in a change in other’s (and my own) perception of my area of expertise. I have been a reviewer for the journal Transfusion Medicine for a number of years, solely regarding articles within the field of platelet immunology, where I have 25 years of experience. Indeed, six years after leaving that field I was still being asked to review such papers. However, whilst I was writing up this thesis I was asked to review a paper on a study of low Hb deferral in German donors. Not only had this body of work left me much better equipped to review such an article effectively and to offer (hopefully) useful advice to the authors on how to re-write it in a manner that would enable it to be published, but it provided a welcome change in emphasis. It may also indicate that this project has enabled me to gain a small level of expertise beyond that which I had when I began the PD course.
Since 2010, I have been working with routine blood transfusion laboratories where involvement with R&D has been minimal. That does not mean that it has to be non-existent. Thinking "outside the box", as Sally did for this project, means I, too, have looked for potentially useful information for publication and dissemination in areas other than traditional research projects. I realise we in the NHS sit upon a wealth of information which we either do not realise its true value or lack the time to evaluate. I have written two papers in 2013/14 (other than those comprising this thesis). The first examined the reasoning behind the existing practise for neonatal transfusion within two hospitals in one Trust and offering evidence-based alternatives to reduce neonatal blood wastage and increase clinical safety. A second looked at a number of ways to reduce blood wastage in adults, and evaluated their efficacy.

Additionally, when I took over as Lead for the blood transfusion laboratories of three Trusts within a Pathology Network, I was able to use the analytical techniques I had gained from the PD course to benchmark staffing levels, workloads etcetera; not only between the three Trusts currently within my remit, but also to those two hospitals for which I was previously responsible. This benchmarking exercise has been distributed to the blood transfusion laboratories of London and the South East, so they might adopt it when negotiating safe staffing levels for their workload. I believe this, and the two previous exercises, benefited from the skills I gained from the PD course.
5.4 The future

"The only thing we know about the future is that it will be different." - Peter Drucker.

I hope to reach the level of Consultant Transfusion Scientist through publication. If the two papers above are accepted then I will have 36 publications in the field of Blood Transfusion, nine as first author. Although this does not strictly meet the current requirements of the Royal College of Pathology (they require a total of 30 publications, 10 as first author) I will make a preliminary application to see if they might accept the greater than minimum publications as an alternative. If successful, I would be only the second, to my knowledge, outside the NHSBT to gain Consultant status as a Transfusion Scientist.

In order to apply my knowledge and experience within the field of Blood Transfusion I have applied for Membership as the Blood Service Manager representative of the Advisory Committee on the Safety on Blood, Tissues and Organs (SaBTO). This committee gives impartial expert scientific advice to the Government on the risks associated with the supply and use of blood and blood products for transfusion purposes (similarly for those tissues, organs, etc. used in transplantation). I feel my background in R&D, my experience in both routine primary, secondary and tertiary referral laboratories in a variety of clinical specialisations and the knowledge and skills acquired from the PD, would prove useful in this setting. Unfortunately the closing date is not until September 2014 so the outcome may not be known by the time of submission.
5.5 Epilogue

"What we call the beginning is often the end. And to make an end is to make a beginning. The end is where we start from." - T. S. Eliot.

As I come towards what I hope will be the completion of the PD, I believe my reasons for needing to be successful have moved from the "lower" to the "higher" version of Maslow's esteem needs. If I am fortunate enough to obtain my doctorate it would not immediately help me in my current position (although I am certain it would help me with any future career aspirations). However, it will help me in terms of self-respect. I already feel more self-confident through achieving a degree of mastery, and were I to achieve the doctorate I would also gain professional independence and freedom. I do not know whether I will have reached the top-most level that of self-actualisation, being the best that I could be. I think I may have achieved the best I could be under the circumstances that I encountered. During the 10 years from commencement of the PD to submission I have had four jobs (being made redundant from three), the latter three being very different from the field in which I had spent 25 years. I have had four research projects, two of which I disliked, one which I would dearly have wished to complete, and the one I did which I started viewing only as a means to an end. My personal circumstances have changed dramatically too, with all three of my children being born during the active phase of this project. I believe, at least in my own mind, that I have laid to rest any doubts that I might have had regarding my commitment to obtaining a doctorate.
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