



**RH D NEGATIVE BLOOD DONORS: STRATEGIES  
TO IMPROVE BLOOD DONATION**

**BY  
DR ANIS SALWA BT ABAS**

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## **DECLARATION**

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Masters of Medicine in Transfusion Medicine. It is also not to be sent to any other universities. With that, this research might be used for consultation and will be photocopied as reference.



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**Dr Anis Salwa Binti Abas**

**P-IPM0003/12**

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## **LIST OF ABBREVIATIONS**

|         |                                                                                                        |
|---------|--------------------------------------------------------------------------------------------------------|
| AABB    | American Association of Blood Banks                                                                    |
| AIDS    | Acquired Immunodeficiency Syndrome                                                                     |
| BBIS    | Blood Bank Information System                                                                          |
| BTS     | Blood Transfusion Service                                                                              |
| DOSM    | Department of Statistics Malaysia                                                                      |
| DOMAINE | Donor Management In Europe                                                                             |
| HDFN    | Haemolytic Disease of Foetal and Newborn                                                               |
| HTR     | Haemolytic Transfusion Reaction                                                                        |
| ICH     | International Council for Harmonisation of Technical Requirements for<br>Pharmaceuticals for Human Use |
| MAMPU   | Malaysian Administrative Modernisation and Management Planning<br>Unit                                 |
| MASCO   | Malaysian Standard Classification of Occupation                                                        |
| MSBOS   | Maximum Surgical Blood Ordering Schedule                                                               |
| NBCKL   | National Blood Centre, Kuala Lumpur                                                                    |
| NGO     | Non-Government Organisation                                                                            |
| PBM     | Patient Blood Management                                                                               |
| RBC     | Red Blood Cells                                                                                        |
| SMS     | Short Message Services                                                                                 |

## ABSTRAK

**Latar belakang:** Hanya 2.2% peratus rakyat Malaysia adalah penderma darah dan kurang dari 2.5% adalah penderma darah Rh D negatif. Kaedah yang berkesan untuk mengekalkan penderma darah Rh D negatif yang responsif adalah penting. Walaubagaimanapun, hanya 7% dari kalangan penderma darah baru di Pusat Darah Negara, Kuala Lumpur hadir apabila dijemput untuk menderma darah dengan menggunakan kaedah sedia ada. Kajian ini dijalankan untuk membandingkan keberkesanan kaedah jemputan menderma darah yang baru dengan kaedah sedia ada. Kajian ini juga bertujuan untuk mengenalpasti sebarang kaitan antara faktor sosio-demografik dan ciri-ciri pendermaan darah dengan kehadiran untuk menderma darah.

**Kaedah:** Satu kajian intervensi dengan kumpulan kawalan lalu telah dilaksanakan. Kumpulan intervensi telah dipilih daripada penderma darah yang telah menderma di antara 1 Januari 2016 sehingga 31 Disember 2016. Penderma darah dalam kumpulan intervensi telah dijemput untuk menderma darah melalui surat jemputan secara personal dan menerima risalah pendidikan mengenai kumpulan darah Rh D negatif diikuti dengan satu panggilan telefon. Manakala kumpulan kawalan adalah penderma darah Rh D negatif yang telah dijemput untuk menderma darah menggunakan kaedah sedia ada iaitu melalui khidmat pesanan ringkas (SMS) diikuti dengan satu panggilan telefon di antara 1 Julai 2013 sehingga 31 Disember 2014. Kehadiran penderma darah menggunakan dua kaedah jemputan ini diukur dalam tempoh 6 minggu pemerhatian. Faktor sosio-demografik dan ciri pendermaan darah telah dianalisis.

**Keputusan:** Didapati kaedah baru menghasilkan kehadiran yang lebih tinggi dan signifikan secara statistik di kalangan penderma baru Rh D negatif berbanding kaedah sedia ada. Sebanyak 24.7% penderma dari kumpulan intervensi telah hadir berbanding 5.6% penderma dari kumpulan kawalan. Kebarangkalian kumpulan intervensi hadir adalah sebanyak 5.6 kali ( $p<0.001$ ). Penderma darah Rh D negatif dengan selang masa antara pendermaan terdahulu yang lebih pendek iaitu di antara 3 ke 12 bulan didapati mempunyai 5.9 kali lebih kebarangkalian untuk hadir ( $p=0.009$ ). Tiada kaitan yang signifikan antara umur, jantina dan bangsa dikenalpasti. Tetapi penderma darah dari kalangan bukan profesional didapati mempunyai 78% kemungkinan untuk tidak hadir ( $p=0.045$ ).

**Kesimpulan:** Jemputan untuk menderma darah secara personal dan risalah pendidikan mengenai kumpulan darah Rh D negatif telah meningkatkan kehadiran di kalangan penderma darah Rh D negatif baru. Selang masa antara pendermaan terdahulu dan pekerjaan penderma darah didapati mempunyai kaitan dengan kehadiran untuk menderma darah.

**Kata kunci:** Rh D negatif, pengekalan penderma darah, penderma darah baru, Pusat Darah Negara, Kuala Lumpur (NBCKL)

## ABSTRACT

**Background:** Only 2.2% of Malaysians are blood donors and less than 2.5% of them are Rh D negative blood donors. An effective blood donor retention strategy to sustain the responsive and reliable Rh D negative blood donor pool is paramount. However at National Blood Centre, Kuala Lumpur (NBCKL) only 7% of early career blood donors responded to the standard blood donation invitation. This study compared a new blood donation invitation strategy against the standard method. This study also aims to identify any association between the blood donors socio-demographic and donation characteristics with responses towards the blood donation invitation.

**Methods:** An interventional with historical control study was conducted. The interventional group was selected from the blood donors who had donated within 1<sup>st</sup> January 2016 to 31<sup>st</sup> December 2016. The interventional group received a personalised blood donation invitation letter with an educational brochure followed by a phone call. The historical control group was the blood donors who previously invited through a general short message service (SMS) and a phone call within 1<sup>st</sup> July 2013 to 31<sup>st</sup> December 2014. The blood donors' response was measured within 6 weeks period after the invitations. The blood donors' socio-demographic and donation characteristics were analysed.

**Results:** The new blood donation invitation strategy had resulted in a significantly more attendance among the early career Rh D negative blood donors as compared to the standard blood donation invitation. About 24.7% of participants in the interventional group had responded compared to 5.6% of participants in the historical control group.

The odd for the interventional group to respond was 5.6 ( $p<0.001$ ). The Rh D negative blood donors who had a shorter interval of previous blood donation of 3 to 12 months had 5.9 times the odd to respond ( $p=0.009$ ). No significant association of blood donors' age, gender and race but the blood donors who were non-professional were 78% less likely to respond ( $p=0.045$ ).

**Conclusions:** A personalised blood donation invitation with an educational brochure on Rh D negative phenotype had resulted in more attendance among early career Rh D negative blood donors. The blood donors' previous blood donation interval and occupation were associated with responses towards blood donation invitation.

**Keywords:** Rh D negative, blood donor retention, early career blood donors, National Blood Centre, Kuala Lumpur (NBCKL)

## CHAPTER 1: INTRODUCTION

### 1.1 Overview

Rh blood group is the second most important blood group system after ABO blood group. It was discovered in 1939, when a woman who had delivered a stillborn baby, developed haemolytic transfusion reaction (HTR) when she was transfused with her husband's ABO compatible blood (Levine and Stetson, 1939). Since the discovery, Rh antigens have expanded in number. Now the Rh blood group comprises of 54 antigens (Daniels, 2013).

Among Rh antigens, D antigen is the most immunogenic. Up to 80% of Rh D negative healthy volunteers who were exposed to D antigen developed anti D (Gunson, 1970). Studies in various patient populations showed sensitisation rate of 20 to 30% (Frohn *et al.*, 2003; Yazer and Triulzi, 2007). It was noted that 30.4% of Rh D negative patients who were transfused with Rh D positive red blood cells (RBC) in abdominal, cardiothoracic surgery and trauma cases developed anti D (Frohn *et al.*, 2003). In non-oncology Rh D negative patients who were transfused with Rh D positive RBC, 22% developed anti D (Yazer and Triulzi, 2007).

Anti D is a clinically significant antibody. It can cause haemolytic transfusion reaction (HTR) and haemolytic disease of foetal and newborn (HDFN). An exposure to D antigen via blood transfusion or pregnancy initiates antibody production. In sensitised individual, re-exposure to D antigen will activate anamnestic immunological response. So transfusion of Rh D positive RBC to an individual with anti D will result in extravascular haemolysis. It may present clinically as a mild delayed haemolytic

anaemia, but a more severe form may lead to morbidity and mortality (Harmening, 2012).

It is extremely important to avoid sensitisation to D antigen in women of reproductive age to prevent HDFN. Alloimmunisation to D antigen occurred during the first pregnancy in Rh D negative women. An exposure to foetal Rh D positive cell of paternal origin will initiate anti D formation. Initially IgM antibodies are produced, before the transition to IgG form. As IgG antibodies are transferred by placenta, all subsequent pregnancies with D antigen positive foetus will be affected. The destruction of foetal RBC by maternal anti D will lead to fetal anaemia. HDFN due to anti D can manifest as mild, moderate or severe fetal anaemia complicated with hydrops foetalis or intra uterine death (Harmening, 2012).

Approximately 16% of D antigen negative pregnant women with D antigen positive babies will develop anti D (Urbaniak and Greiss, 2000). Before the introduction of prophylaxis anti D immunoglobulin, 95% of HDFN is due to alloimmunisation to D antigen (Harmening, 2012). In the 1960s to 1970s, studies in obstetrics patients showed that 48.3% to 65.3% had anti D (Queenan *et al.*, 1969; Geifman-Holtzman *et al.*, 1997). A reduction to 18.4% and 19.0% was observed in 1990s after the implementation of routine Rh D immunoglobulin prophylaxis (Filbey *et al.*, 1995; Geifman-Holtzman *et al.*, 1997).

Post-delivery anti D immunoglobulin administration had reduced the sensitisation rate to D antigen in the Rh D negative pregnant women to 1-2% (de Silva *et al.*, 2003; Qureshi *et al.*, 2014). The initiation of routine antenatal anti D

immunoglobulin administration had further lowered the sensitisation rate to 0.1% to 0.3% (Mayne *et al.*, 1997; MacKenzie *et al.*, 1999; de Silva *et al.*, 2003; Tiblad *et al.*, 2013; de Haas *et al.*, 2014). In spite of the compliance to the administration of Rh D immunoglobulin during antenatal, post-delivery and post potentially sensitising events, alloimmunisation to Rh D antigen still occurs in Rh D negative pregnant women (Keidan, 2017).

Transfusion of Rh D incompatible blood product is avoided in Rh D negative patients. In an ideal clinical situation, Rh D negative patients should receive blood from the Rh D negative donors. In fact, Rh D grouping is a mandatory pre transfusion testing after ABO blood grouping due to its clinical significance. The determination of ABO and Rh D group should be carried out and any unanticipated findings should be resolved prior to transfusion of blood products (National Blood Centre, 2016b).

The expression of Rh D positive and Rh D negative phenotypes varies in different population. It is estimated that 15% of Caucasians are Rh D negative (Daniels, 2013; Westhoff and Siegel, 2016). In Africans approximately 4% are Rh D negative. Studies in Kenya, Nigeria and Guinea on the percentage of their population with Rh D negative phenotype shows 3.9%, 5.0% and 4.1% are Rh D negative respectively (Mwangi, 1999; Jeremiah and Buseri, 2003; Loua *et al.*, 2007). Meanwhile in Hong Kong, there are only 0.3% Chinese blood donors who are Rh D negative (Mak *et al.*, 1993). In Malaysian blood donors, less than 2.5% are Rh D negative and more than 97.5% are Rh D positive (Musa *et al.*, 2012).

The low expression of Rh D negative phenotype in a population is a challenge for blood transfusion service to sustain enough Rh D negative blood. In order to be able to provide adequate and safe Rh D negative blood, each blood transfusion service has its own pre-determined safety level. This safety level is based on the daily usage, supply pattern and type of health provider that receive the blood supply from the blood transfusion service (National Blood Centre, 2016a). A shortage of Rh D negative phenotype blood may be faced at any point of time.

To ensure adequate and safe supply of Rh D negative blood to patients who specifically require them, the retention of reliable Rh D negative blood donor pools is important. Any prompt responses from these Rh D negative blood donors to blood donation pledge will assist in timed and secured supply of Rh D negative blood. As a result, there is no unmet clinical need due to unavailability of Rh D negative blood. Thus, any cancellation or postponement of elective surgical date can be avoided. A good collaboration between the blood transfusion service and the clinicians will reduce or eliminate this unnecessary delay of planned procedure (National Blood Centre, 2016d).

Various approaches are used by the blood transfusion service to overcome the shortage in blood supply. A well planned policy will facilitate the organisation to overcome the small short term shortage or a more widespread deficit (National Blood Authority, 2008). A surge in demand can arise at hospital level due to multiple trauma patients been admitted. A supply failure at national level can arise from a large scale disaster or public health threat like pandemic influenza which will result in shortage of all blood types (National Blood Authority, 2008). An established policy that outlined

mitigation steps is important and the method selected must be tailored to suit the targeted blood donor group.

Blood donation pledge via short message service (SMS), phone calls and emails to the registered donors are among the methods used (Veildhuizen *et al.*, 2010). The efficacy of these techniques had been proven by many researchers (Geyer, 2005; Chamla *et al.*, 2006; Agrawal and Tiwari, 2014). Short message service (SMS) and phone calls were found to be effective as a modality to invite blood donors. Agrawal & Tiwari (2014) found that 13% of total blood donations at their center were from blood donors contacted via short message service (SMS) and phone calls. Another study found that blood donation invitation by e-mail campaigns had resulted in 5% of blood donor who had agreed to donate and registered online (Geyer, 2005).

Besides, the positive responses to blood donation invitation depend on the promotional strategy used. Personalised informative invitation letters were proven to be a successful tool (Chamla *et al.*, 2006). The blood donors who were informed regarding their blood type and the low percentage of population with the same phenotype who donate blood are 43% more likely to give positive responses (Chamla *et al.*, 2006).

In addition, appeal on personal experiences is another successful promotional strategy. Price *et al.* (2006) stated that education given to African Americans regarding the importance of blood donation to children with sickle cell disease, has helped to increase the number of total African American blood donors. In this study, educational video was sent by mail to prospective blood donors. There was an increase of 75% in the total African American blood donors (Price *et al.*, 2006).

The other example of strategy used in order to increase the responses to blood donation is to enhance prospective blood donor confidence. France *et al.* (2010) found that the likelihood to volunteer for blood donation increased in the study subjects who were exposed to a brief educational brochure on how to cope with common adverse donor reaction (France *et al.*, 2010).

It is important for a blood transfusion service to have effective ways to ensure retention of these blood donors. In order to do so, application and manipulation of psychosocial determinants of blood donation is a must. Studies in the social and behavioral science of blood donation had enlightened the understanding and guided the intervention planning in blood donor recruitment and retention (Ferguson *et al.*, 2007). The integration of social and behavior science theory and model, for example theory of planned behavior, motivation, altruism and donor identity had been proven as a useful tool in blood donor recruitment and retention (Ferguson *et al.*, 2007).

It is also worth to note that, the blood donors should not be treated as a homogenous group because the factors that influence blood donation act vary throughout the blood donor career (Ferguson *et al.*, 2007; Veldhuizen, 2013). As an example, for a new blood donor, his or her personal moral norm is a predictor of the blood donation (Armitage and Conner, 2001; Lemmens *et al.*, 2005). The personal norm is how a blood donor felt that he or she is morally obligate to donate blood (Ferguson *et al.*, 2007). In comparison, for a regular blood donor, past blood donation experience is a better predictor of the subsequent blood donation (Ferguson and Bibby, 2002).

Other than that, the understanding on the blood donor socio-demographic profile is crucial as the age, gender and occupation are associated with active or lapsed blood donor status. Blood donors who are at younger age groups, females and unemployed are less likely to return for subsequent blood donations (Germain *et al.*, 2007; Schlumpf *et al.*, 2008; Veldhuizen *et al.*, 2009; Ringwald, 2010; Weidmann *et al.*, 2012).

Their previous blood donation number and the time interval between blood donations are the other characteristics that had proven association with blood donor return. The blood donors who had more number of blood donations within the first 12 months after their initial blood donation are more likely to become regular blood donors (Schreiber *et al.*, 2005; Kasraian and Tavassoli, 2012; Kheiri and Alibeigi, 2015). A similar finding is noted among the blood donors with a shorter time interval between the blood donations (Kheiri and Alibeigi, 2015). The distance to the blood donation sites is another factor that influenced the blood donor return. As the distance increases, the less likely the blood donor will return for a subsequent blood donation (Poon *et al.*, 2013; Hyun-Ji *et al.*, 2017).

The proportion of ABO and Rh D blood groups of the blood donors provide a general overview of the blood donor base. Furthermore, some studies had reported a higher blood donor return among the Rh D negative blood donors (Ownby *et al.*, 1999; Ou *et al.*, 2016). The O Rh D negative blood donors are more likely to return for subsequent blood donations than the non O Rh D negative blood donors (Veldhuizen *et al.*, 2009).

The information on the blood donor socio-demographic profile and blood donation characteristics can be utilised by the blood transfusion service to understand their blood donor base. Understanding on the characteristics of the specific blood donors group will provide valuable information in guiding the blood transfusion service in formulating the strategy to retain their blood donor pools as in this study contact, the Rh D negative blood donors.

## **1.2 Research Justification and Benefits**

The National Blood Centre, Kuala Lumpur (NBCKL) is the national reference center for blood transfusion service in Malaysia. It is involved in collecting, processing and distribution of blood and blood products to the patients in the government and private hospitals in Selangor, Wilayah Persekutuan Kuala Lumpur and Putrajaya. One of its visions is to provide adequate and safe blood products.

In terms of Rh D negative bloods, NBCKL low inventory stock is defined as having less than 5 units for each A, B and O Rh D negative red blood cells/whole bloods (National Blood Centre, 2015). Whenever the stock falls below this level or the number of request exceeds the number of available units, blood donation invitation via short message service (SMS) will be activated. A list of 100 to 200 registered Rh D negative blood donors based on the specific ABO grouping required will be generated from the NBCKL Blood Bank Information System (BBIS). The SMS will be distributed to all the blood donors in the list via mySMS 15888 system. The mySMS 15888 is a SMS system developed by the Malaysian Administrative Modernisation and Management Planning Unit (MAMPU) as a communication tool between Malaysian

Government Agencies and the public. The NBCKL Registration and Donor Record Unit will monitor the responses to the blood donation invitation. If the number of the Rh D negative blood donor who turned up on the day after SMS was send is not adequate, invitations via phone calls will be initiated. The workflow for blood donation invitation at NBCKL is illustrated in Figure 1.

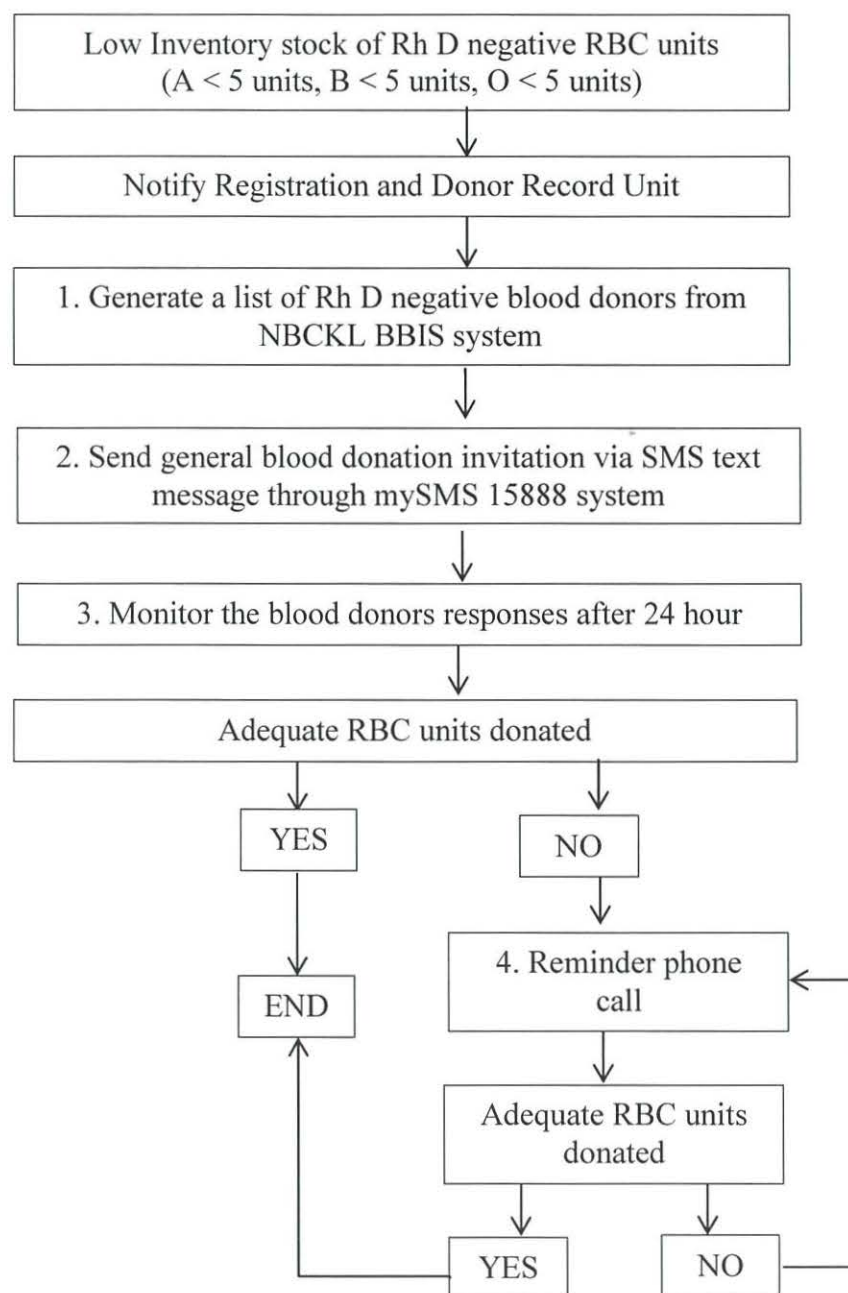


Figure 1: Blood Donation Invitation at NBCKL

Unfortunately, the positive responses by the Rh D negative blood donors to blood donation invitations sent by this method is low. From January to June 2013, there were four (4) episodes of the Rh D negative donor invitations via SMS done by the registration and donor record unit in response to the low inventory stock. A total number of 73 Rh D negative donors were invited through a phone call, but only 28 responded (PDN/IH/WI 11/01, 2012). Among the 28 Rh D negative blood donors who came for the blood donation, only two (2) or 7% of them were early career blood donors (blood donor who had donated one or two times previously).

Blood donation is a planned behavior. Knowledge is the foundation of psychosocial determinants of a behavior (Conner, 2010). Therefore it is postulated that an intervention that educates and manipulates the known social and behavior determinants of blood donation will boost the positive response towards blood donation invitation. Thus, a new educational brochure on Rh D negative will be developed and used in inviting these early career Rh D negative blood donors. Furthermore, there is no updated educational brochure on the Rh D negative phenotype is in use at the NBCKL. The previously used Rh D negative educational brochure was last printed in 2011. It is hoped that more Rh D negative blood donors will fulfil the blood donation invitations with the usage of this new educational brochure.

Currently, only 2.2% of the Malaysian population are the blood donors (Edward, 2015). The percentage is below the 5% target by Malaysia Ministry of Health (Niam, 2012). The proportion of the Rh D negative blood donors in Malaysia is less than 2.5% (Musa *et al.*, 2012). This reflected that, the NBCKL has to source the Rh D negative blood supply from a small percentage of the population with the Rh D

negative phenotype that opted to become the blood donors. The retention of a reliable and responsive Rh D negative blood donor pool will benefit the organisation.

An effective Rh D negative blood donor retention will help to ensure smooth blood inventory management and the prevention of Rh D mismatched transfusion. It will also reduce the operational cost indirectly, as less phone calls will be made and less time allocated by the staff involved in the blood donation invitation process. To the early career Rh D negative blood donors, it is aimed that the information gained from the educational brochure will increase their knowledge, improve their self-efficacy and motivate them to become dedicated regular blood donors.

The socio-demographic data and blood donation characteristics of the Rh D negative blood donors who responded and not responded will provide an insight on their characteristics and can be used in the planning of directed blood donor retention strategy in the future.

### **1.3 Research Objectives**

The general and specific objectives of the study are as the following:

#### **General Objective**

To investigate if a new blood donation invitation strategy to early career Rh D negative blood donors will increase the response to blood donation invitation.

#### **Specific Objectives**

1. To compare the response rate to blood donation invitation between the interventional group and historical control group among early career Rh D negative blood donors.  
  
(Interventional group received new invitation strategy: personalised invitation letter + educational brochure + phone call and historical control group received standard invitation: SMS message + phone call).
2. To determine early career Rh D negative blood donors' socio-demographic profile (age, gender, occupation) association with responses towards blood donation invitation.
3. To determine early career Rh D negative blood donors' donation characteristics (ABO blood group, previous blood donation interval and distance to donation sites) association with responses towards blood donation invitation.

#### **1.4 Research Hypothesis**

There is a significant difference in the response rate of the early career Rh D negative blood donors to blood donation invitation between the interventional group (blood donors who received the new blood donation invitation) and the historical control group (blood donor who were invited with the standard blood donation invitation).

#### **1.5 Null Hypothesis**

There is no significant difference in the response of the early career Rh D negative blood donor to blood donation invitation between the interventional group (blood donors who received the new blood donation invitation) and the historical control group (blood donor who were invited with the standard blood donation invitation).

#### **1.6 Operational Definitions**

Operational definitions used in this study are as tabulated in table 1.6.1

Table 1.6.1 Operational definitions

| No  | Term                             | Operational Definition                                                                                                                                                                                                                                                                              | Reference                                |
|-----|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| i   | Early career blood donors        | Blood donors who had donated one or two times previously AND                                                                                                                                                                                                                                        | Chamla <i>et al.</i> , 2006              |
|     |                                  | The last donation date was within 24 months                                                                                                                                                                                                                                                         | National Blood Centre, 2016e             |
| ii  | Historical Control Study         | A study intended to support a comparative conclusion regarding the treatment/intervention. The comparator to the treated/intervened is a separated control group and the outcome measured happens in two different times                                                                            | Walton, 2012                             |
| iii | Job Category<br>(a) Professional | A profession governed by professional bodies, adhere to ethical standard, meet the minimum requirement of specialised knowledge/skills with a lifelong commitment to practise in the best interest of others/public such as medical doctors, dentists, lawyers, engineers and accountants           | Beaton, 2010                             |
|     |                                  | Professionals increase the existing stock of knowledge, apply scientific or artistic concepts and theories, teach about the foregoing in a systematic manner, or engage in any combination of these three activities. Most occupations in this major group require skills at the fourth skill level | Ministry of Human Resources, 2008        |
|     | (b) Non-Professional             | Other occupations including semi-professionals, managerial, technical, skilled, partly skilled and unskilled workers.                                                                                                                                                                               | Rose & Pevalin, 2001<br>Kokemuller, 2016 |

|    |                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                              |
|----|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
|    | (c) Student               | All categories of students including secondary school, college, undergraduate and postgraduate students                                                                                                                                                                                                                                                                                                                                                        | National Blood Centre, 2016e |
|    | (d) Unemployed            | Someone who is not engaged in a gainful occupation including housewife                                                                                                                                                                                                                                                                                                                                                                                         | Merriam-Webster, 2017        |
| iv | Distance to donation site | Distance in kilometre from the blood donors' home addresses to the blood donation sites measured by Google Map                                                                                                                                                                                                                                                                                                                                                 | Poon <i>et al.</i> , 2013    |
| v  | Blood donors' responses   | <p>The blood donors responses towards blood donation invitations are categorised as:</p> <p>(a) Responded</p> <p>The blood donor had donated blood at any NBCKL's blood donation sites after received the invitation</p> <p>This include the blood donor who had attempted to donate blood but was temporarily deferred</p> <p>(b) Not Responded:</p> <p>The blood donor did not turn up at any NBCKL's blood donation sites after received the invitation</p> | Godin <i>et al.</i> , 2011   |

## 1.7 Conceptual Framework

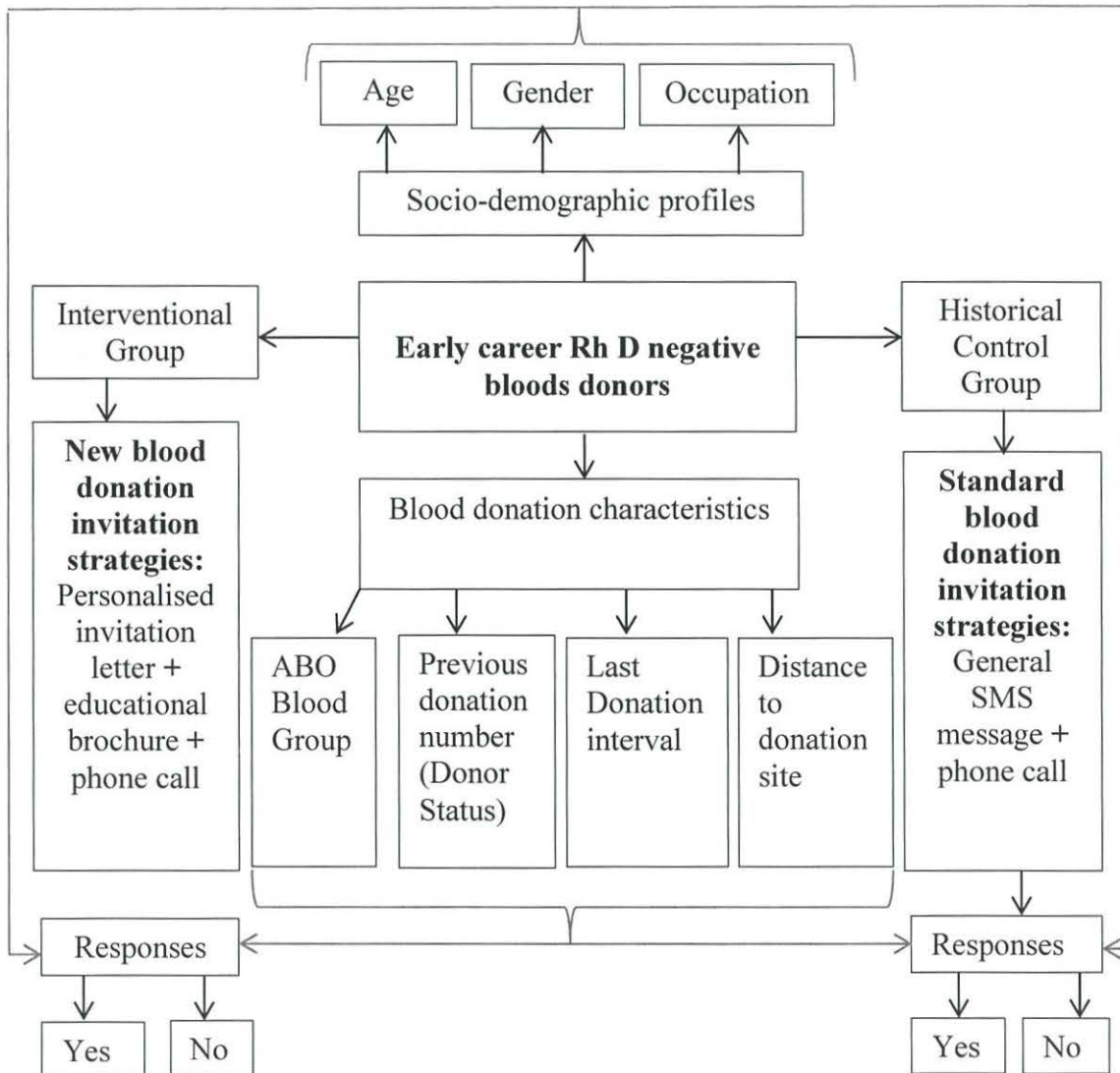


Figure 2: Conceptual Framework

## CHAPTER 2: LITERATURE REVIEW

### 2.1 The Rh D negative phenotype.

It is known that two (2) genes are responsible for the inheritance of the Rh Blood Group System (Colin *et al.*, 1991; Harmening, 2012; Daniels, 2013). The first gene is the RHD gene which determines the coding of the Rh D antigen. The second gene is the RHCE gene. The RHCE gene regulates the Rh C, Rh c, Rh E and Rh e antigens production. The expression of the Rh antigens on the red blood cell depends on the presence of the Rh Ag protein coded by a co-expressor gene named as the RHAG gene (Harmening, 2012; Daniels, 2013).

The Rh D negative phenotype is a result of mutation in the RHD gene. As RHD gene is codominant in nature, the Rh D negative individuals inherit mutated RHD genes from both paternal and maternal origin (Daniels, 2013; Harmening, 2012). Several types of mutation had been described. The Rh D negative phenotypes are most commonly due to the complete deletion of the RHD gene (Colin *et al.*, 1991; Avent *et al.*, 1997; Andrews *et al.*, 1998; Wagner and Flegel 2000). Two other types of RHD mutations commonly observed are due to inactive RHD pseudogene or RHD-CE-D hybrid gene (Singleton *et al.*, 2000; Shao *et al.*, 2002; Daniels, 2013; Harmening, 2012).

Most of the Rh D negative individuals have homozygous complete deletion of RHD genes resulting in no expression of the entire Rh D protein (Avent *et al.*, 1996). Any Rh D negative individual who is exposed to D antigens has a high probability to develop anti D. An exposure to a merely small amount of less than one (1) mL of the

Rh D positive blood is able to stimulate anti D production in the Rh D negative study subjects (Gunson *et al.*, 1970; Jakobowicz *et al.*, 1972; Gunson *et al.*, 1976). The sensitisation rate of 75% to 88% is observed when healthy Rh D negative volunteers were exposed to Rh D positive RBC (Gunson *et al.*, 1970; Jakobowicz *et al.*, 1972; Gunson *et al.*, 1976).

A much lower sensitisation rate to D antigen exposure is documented in studies involving patient populations. Sensitisation rate of 20% to 30% is observed (Frohn *et al.*, 2003; Yazer and Triulzi, 2007). The difference in the rate of sensitisation to D antigen is attributed to the state of immune suppression in these patients as compared to the normal immunocompetent subjects (Frohn *et al.*, 2003). A review on 445 units of Rh D positive RBC issued to the Rh D negative patients in the non-oncology wards, reported that 22% of the patients developed anti D (Yazer and Triulzi 2007). A study by Arora *et al.* (2017) found that 14% of all the Rh D negative oncology patients at their cancer centre who were transfused with the Rh D positive RBC developed anti D (Arora *et al.*, 2017). A study done on orthotopic liver transplantation recipients, showed that none of their Rh D negative patients who received the Rh D positive RBC during surgery and/or early post-operative period developed anti D (Casanueva *et al.*, 1994). A similar observation was noted in Acquired Immune Deficiency Syndrome (AIDS) Rh D negative patients transfused with Rh D positive RBC. None of them developed anti D (Boctor *et al.*, 2003).

Despite the variations observed in alloimmunisation rate towards Rh D antigen in different study populations, D antigen remain as the most immunogenic RBC antigen after ABO blood group antigens. The other RBC antigens are relatively less

immunogenic. For example, K antigen immunogenicity is recorded as 5%, Fya antigen as 0.2% and Jka antigen as 0.07% (Kaushansky, 2010). Due to the low immunogenicity, the requirement to type and match the RBC for the other RBC antigens is less critical (Westhoff and Siegel, 2016). After ABO blood group antigens, only D antigen is prophylactically matched before the transfusion for all patients (Norfolk, 2013; National Blood Centre, 2016b; Westhoff and Siegel, 2016).

## **2.2 Rh D negative transfusion policy**

The discovery of the Rh D antigen in the investigation of a woman who developed haemolytic transfusion reaction (HTR) and her still born baby affected by haemolytic disease of fetal and newborn (HDFN) reflected the clinical importance of anti D (Levine and Stetson, 1939). In order to prevent HTR and HDFN due to anti D, all Rh D negative patients should receive Rh D negative RBC (Norfolk, 2013; National Blood Centre, 2016b; Westhoff and Siegel, 2016).

However, in certain circumstances, mismatched Rh D RBC transfusion is not avoidable. One example is in the case of profusely bleeding patient, whereby the number of Rh D negative RBC units required is more than the available units at the blood bank. Unlike ABO mismatched RBC transfusion which will result in immediate intravascular haemolysis, Rh D mismatched transfusion of red blood cells in emergency situation to Rh D negative patient without anti D does not result in immediate acute sequelae. This is because, in average the immune system takes up to 120 days before anti D appear in circulation (Harmening, 2012). As most of the anti D subtype is immunoglobulin G (Ig G), the remaining donor RBC will be destructed via

extravascular haemolysis and manifest as delayed transfusion reaction. However in a secondary anamnestic immune response, it takes within two (2) to seven (7) days for the full blown action of anti D (Harmening, 2012).

This basic understanding of anti D characteristics lead to the policy of allowing Rh D mismatched RBCs transfusion in emergency situation with blood shortages especially to the males and non-reproductive females patients. But in the females of reproductive age and transfusion dependent patients Rh D mismatched transfusion is avoided. The concern of anti D development and the later sequelae of delayed HTR in subsequent RBC transfusion and HDFN risk serve as the basis of the policy to prioritise Rh D negative RBC units to the latter group of patients (National Health Service, 2012; Australian Red Cross Blood Service, 2014).

As a measure to prevent alloimmunisation to Rh D antigen, O Rh D negative RBC units are stocked in the emergency department. The patient who needs immediate RBC transfusion before the exact ABO and Rh D specific blood group is known will be transfused with this 'universal' O Rh D negative RBC units. Nonetheless, this practice has become a burden for a blood transfusion service to provide adequate number of O Rh D negative RBC. The demands exceed the number of O Rh D negative blood donors, resulting in increased donation frequency among this specific blood donor population. There is an extra urge of commitment to the O Rh D negative blood donors as they have to donate 20% more than average to oblige the demand (National Health Service, 2012). Data from United Kingdom and Australia showed that 10% to 12% of total RBC units donated must be O Rh D negative RBC units to accommodate the requirement for emergency RBC transfusion (National Health Service, 2012;

Australian Red Cross Blood Service, 2014). This is a strain even to a country with a 7% to 8% of population with O Rh D negative phenotype.

The challenge to supply O Rh D negative RBC units in emergency setting is greater and difficult to be met by a blood transfusion service in countries with a low expression of Rh D negative phenotype in their population. Since the probability of Rh D mismatched transfusion is also lesser, O Rh D positive RBC are stocked at emergency departments (National Blood Centre, 2016a). In countries like Malaysia and Singapore, the attending physician will justify the usage of O Rh D positive RBC, in emergency life threatening bleeding patients with unknown ABO and Rh D status requiring instant RBC transfusion (National Blood Centre, 2016d; Singapore Health Sciences Authority, 2011). However due to multiracial population, Singapore opted for the policy of using O Rh D positive in emergency RBC transfusion for the Chinese and Malay but O Rh D negative for emergency RBC transfusion for the Indian and other races especially for women of reproductive age. This approach is made because 6% of Indians in Singapore are Rh D negative compare to less than 1% of Chinese and Malay are Rh D negative (Singapore Health Sciences Authority, 2011).

A recent study by Selleng *et al.* (2017) supported the practice to use O Rh D positive RBC units to all patient requiring immediate RBC transfusion in emergency department. They found that the overall risk to develop anti D in all emergency patients who were transfused with Rh D positive RBCs were 4%. In contrast, 26% of known Rh D negative patients developed anti D after received Rh D positive RBC due to the shortages of Rh D negative units during the same study period. The use of O Rh D positive RBC in emergency department at their center resulted in 10% saving of overall

O Rh D negative demand (Selleng *et al.*, 2017). It is worth to note that, this study was done in Germany where 17% of the populations are Rh D negative and 83% are Rh D positive (Wagner *et al.*, 1995).

In the other health facility, a retrospective study was done by Meyer and Uhl (2015) to evaluate the usage of un-crossmatched O Rh D negative RBC units. They found that 88% of these O Rh D negative RBC units in the emergency department were transfused to a group of patients who are considered eligible for O Rh D positive RBC units. These patients are either Rh D positive patients who required immediate RBC transfusion before their exact Rh D phenotype is established or Rh D negative male patients and Rh D negative female patients aged more or equal to 50 years (Meyer and Uhl, 2015).

To conserve this limited resource of Rh D negative RBC units, transfusion indication is further refined. It is a mandatory to transfuse Rh D negative RBC units to the following three (3) groups of patient. First, to the patient who is Rh D negative with anti D. Second, to the Rh D negative female patients with childbearing potential. Third, to the Rh D negative children of both genders. The cut off age limit for female patient considered to bear child bearing potential and children's age definition is determine per institutional policy (National Health Service, 2012; Australian Red Cross Blood Service, 2014).

It is a recommended to transfuse Rh D negative RBC units to the Rh D negative patients who are transfusion dependent. Examples are patients with thalassaemia,

haemoglobinopathy, aplastic anaemia and myelodysplastic syndrome (National Health Service, 2012; Australian Red Cross Blood Service, 2014).

The transfusion of Rh D positive RBC to Rh D negative patients are considered as acceptable indication in a few clinical conditions. Namely, in massive blood losses whereby at least one blood volume need to be replaced. This is equivalent to eight (8) or more units of RBC transfusion in adults. This policy is applicable to Rh D negative adult males and females with no childbearing potential, whom without anti D (National Health Service, 2012; Australian Red Cross Blood Service, 2014).

A prospective study by Gonzalez *et al.* (2008) who adopted the above refine indications in their institution policy of RBC transfusion to Rh D negative patients found that they are able to save 25.6% of their Rh D negative RBC stock. In this study, the alloimmunisation rate to D antigen is comparable to the other studies at 21.4% (Gonzalez *et al.*, 2008).

To ensure good stewardship in managing Rh D negative blood product, each blood transfusion service has to define and implement the most suitable policy to their local setting.

### **2.3 Rh D negative blood inventory management**

Blood inventory management is a delicate and dynamic process. The balance between blood collection and supply is important to prevent both shortage and wastage. It is especially more challenging in managing the Rh D negative blood stock due to the

scarcity of the blood donors. The accurate prediction of the demand will help the blood transfusion service to operate efficiently. The historical usage patterns are usually used to guide the blood transfusion service to pre-determine its own safety level for the Rh D negative blood stock (National Blood Centre, 2016a).

This usage pattern depends on many factors. The type of the health provider and the services offered is a major determinant. A health facility with a trauma center or a reference center for major surgeries will have a different requirement as compared to the other health facilities not offering the services (National Blood Authority, 2013). A five-year review in a trauma center on the usage of un-crossmatch O RBC to a total of 802 patients, found that their yearly usage of O Rh D negative RBC were 140 units from an average 600 units of the total released of un-crossmatch O RBC (Murthi *et al.*, 2008).

The institutional policy on blood transfusion in the Rh D negative patients and the collaboration status between the blood transfusion service (BTS) and clinicians are the other factors that determine the average usage of the Rh D negative blood products. Most of the blood banks will stock the minimum number of the Rh D negative RBC units in their inventory based on the usual usage pattern (National Blood Centre, 2016a). The blood bank should be informed earlier for the arrangement of the Rh D negative RBC units prior to elective surgery date. Early notification is essential to provide adequate time for sourcing of the Rh D negative blood. For an instance, a clinician has to inform the National Blood Centre Kuala Lumpur, at least five (5) working days before the date of an elective procedure in Rh D negative patient (National Blood Centre, 2016d). Adherence to the local maximum surgical blood