PRECONCEPTION ASSESSMENT OF REPRODUCTIVE GENETIC RISK IN PRIMARY CARE

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ABSTRACT

Optimizing maternal health and improving reproductive outcomes are widely acknowledged as major challenges in the health care system. Care during the antenatal period has been the focus of improving maternal health and reproductive outcomes. Yet, evidences have shown that antenatal care alone is not enough. Initiating care before conception or preconception care could be potentially effective to further improve maternal health and reproductive outcomes.

Preconception care encompasses a range of health promotion, risk assessment, preventative and curative interventions for women of reproductive age to reduce risks that potentially affect reproductive outcomes. It aims to provide prospective parents information and support with regards to preconception interventions that are beneficial for the parents and future children. Primary care providers are often being urged to provide preconception care as part of primary care services.

In support of preconception interventions, there has been increasing evidences for such interventions. However, existing reviews or studies of preconception interventions have been limited by being risk specific, for example; focussing on folate supplementation or women with diabetes. Adding to this, interventions were reported mainly carried out in the secondary care settings. There is still paucity of evidence that comprehensively evaluate the impact of providing preconception care as a systematic approach involving multifactorial risk factors and, in particular, in primary care.

Preconception care involved a range of risk assessment; assessment of genetic risk is no exception. The aim of preconception care for genetic risks is to allow women or prospective parents the opportunity to have informed reproductive decisions of future pregnancies. However,

experience of offering preconception care in addressing genetic risks is yet less explored.

This thesis specifically sought to evaluate the potential impact of preconception care involving assessment of reproductive genetic risk. Further, this thesis also aims to provide evidence for effectiveness of preconception interventions on multifactorial risk factors in the primary care settings.

As primary care providers especially GPs are increasingly being recognised to provide such care, it was thus important to explore their views. For this, this thesis aimed to explore the opinions and attitudes of GPs in the United Kingdom towards providing preconception care that involved assessment of reproductive genetic risk in current general practice. This study took place within the Primary Care Trusts of Nottinghamshire and Derbyshire.

The findings from this thesis are expected to help inform a strategy for the implementation of preconception assessment of reproductive genetic risk in the general practice in the United Kingdom.

The aim of this thesis was achieved by carrying out three components of work. These components of work involve three domains that could assist in the implementation; the interventions; the settings; and exploring attitudes and opinions.

1. The first component involved carrying out a systematic review of literatures on the effectiveness of preconception care interventions in the primary care settings.
2. The second component involved carrying out a systematic review of literatures on the effectiveness of preconception assessment of reproductive genetic risk.
3. The third component involved a postal questionnaire survey of GPs practicing in the Nottinghamshire, Nottingham City, Derbyshire and Derby City Primary Care Trusts, exploring

their attitudes and opinions. A new questionnaire was developed as the study instrument for this study.

The first component of work has synthesized the evidence of the effectiveness of preconception interventions in the areas of maternal knowledge of pregnancy-related risks; self-efficacy and health locus of control; risk behaviour modification (for example, folate and alcohol consumption); adverse pregnancy outcomes (for example, congenital anomalies and preterm birth); and psychological consequences. The review has identified that both risk specific interventions or interventions involved multifactorial risks, both demonstrated significant improvement in maternal knowledge, self-efficacy and health locus of control. There was positive evidence for risk specific interventions in the areas involving risk behaviour modification. However, the effects for adverse pregnancy outcomes and psychological outcomes remained unclear.

The second component of work sought to find evidence the effects of preconception assessment of reproductive genetic risk. The scope of literature search included family history and ancestry assessment, pre-carrier test education or consultation and carrier testing or screening. It was not possible to draw clear conclusion regarding its effectiveness as only two studies involving assessment of cystic fibrosis and haemoglobinopathies were identified. Nevertheless, the studies have provided information on potential benefits of preconception assessment of reproductive genetic risks on reproductive decisions, knowledge and understanding of carrier risk as well as psychological benefits.

The third component of work involved self-administered postal questionnaire survey. The impact of this survey is restricted due to low response rates. Nevertheless, the results of this survey indicated that a substantial proportion of GPs were already offering or providing preconception assessment on reproductive genetic risk opportunistically, in particular, with women planning pregnancy and women with known family history of genetic conditions. Even if they are

not offering of providing preconception assessment on reproductive genetic risk at present, majority of them indicated that they are prepared to offer and provide the service, especially when consulting women planning a pregnancy or women at-risk. Their primary concern was how to reach these women as not many would come to consult GPs for preconception advice. This study has demonstrated that family planning clinic was the most preferred primary care setting to offer preconception assessment on reproductive genetic risk. In the United Kingdom, family planning clinics serve a large proportion of women of reproductive age group, thus, this setting may provide opportunities to introduce preconception care and reproductive risk assessment including genetics.

While there is paucity of evidence from the systematic reviews in my thesis that could impact on the direction or implementation of offering preconception care addressing genetic risks, many factors other than scientific evidence can influence the implementation process. Observational studies have demonstrated potential benefits of preconception care specifically preconception assessment of genetic risk interventions such as early antenatal diagnosis to informed reproductive decisions. Broad interests from the international organization such as in the United States and Netherlands have a role in the implementation. Similarly, interest from the stakeholders in particular individuals of reproductive age groups and the primary care providers also may influence the development of the interventions. In this context, the GPs that participated in the survey have provided important information on opportunities and barriers, and potential ways to facilitate its development. Nevertheless, analysis of the data has identified some areas that were not fully addressed in this thesis and this is discussed in the final chapter.

Published paper from this thesis

Intervention protocol (2013)

Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease.

Hussein N, Qureshi N, Weng SF, Kleijnen J, Kai J. Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease. *Cochrane Database of Systematic Reviews* 2013, Issue 12. Art. No.: CD010849. DOI:10.1002/14651858.CD010849.

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Abbreviations

CDC	Centres for Disease Control and Prevention
CLAHRC-NDL-ABC	Collaboration for Leadership in Applied Health Research and Care – Nottinghamshire, Derbyshire and Lincolnshire – Action Before Conception
FG	Focus group
GMS	General Medical Service
GP	General Practitioner
NHS	National Health Service
PCT	Primary Care Trust
PEGASUS	Professional Education for Genetic Assessment and Screening
QOF	Quality and Outcomes Framework
UK	United Kingdom
WHO	World Health Organisation

Glossary

For reasons of consistency within this thesis, some terms have been standardised throughout the text.

Primary Care Provider

Primary care provider refers to general practitioners (GPs), practice nurses, midwives and in some centres, health visitors, nurse specialists or physician assistants who deliver health care in primary care setting.

Health Care Provider

Health care provider refers to any providers of medical and health services. This includes providers from primary, secondary and tertiary care.

Primary Care

A clinical speciality of health care that emphasizes the point at which the patient first seeks assistance from the medical care system. Primary care is comprehensive which includes health promotion, illness prevention, treatment and care of the sick, community development and rehabilitation.

General Practice

A primary care setting in which a medical practitioner provides comprehensive, coordinated and continuing medical care to individuals, families and communities. In this thesis, the term refers mainly to the setting in the United Kingdom.

General Practitioner

A registered medical practitioner for general practice.

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CHAPTER 1
INTRODUCTION

1.1 Introduction

Optimizing maternal health and improving pregnancy outcomes are widely acknowledged as major challenges in the health care system. Care during the antenatal period has been the focus of improving maternal health and its pregnancy consequences. Yet, evidences have shown that antenatal care alone is not enough. There are risks that affect pregnancy outcomes which can be modified or prevented before women planning to conceive.

The aim of this thesis is to examine the effectiveness of preconception interventions in primary care focussing specifically on preconception assessment of reproductive genetic risk. This thesis also aims to explore the attitudes and opinions of general practitioners (GPs) as primary care providers on preconception assessment of reproductive genetic risk. In this introductory chapter, an overview of the potentials of preconception care in general and specifically addressing reproductive genetic risk will be discussed. This chapter will further describe the direction of this thesis and place the studies undertaken in appropriate context.

1.2 Background

Improving maternal health is pivotal to reduce rates of poor health outcomes in mother and child. Traditionally, this has involved antenatal care which comprised of an organised and comprehensive health care received by the women throughout the course of a pregnancy (Tambor et al., 1994). Merkatz (1990) reported that organised antenatal care services was first introduced in the United States by nurses in the early 1900s leading to improved pregnancy outcomes particularly in

maternal and infant mortality (Durfy et al., 1994). Further, report by the Centre for Disease Control and Prevention (CDC) demonstrated a decline in maternal and infant mortality rate throughout 1915 to 1997. Maternal mortality rate declined almost 99%; from every 1000 live births, six to nine women in the United States died of pregnancy-related complications in the early 1900, to less than 0.1 reported death per 1000 live births reported in 1997. The infant mortality rate declined greater than 90%; approximately 100 infants died before the age of one year before 1915 to 7.2 per 1000 live births in 1997 (Delatycki, 2008, Levenkron et al., 1997).

However, this progress has slowed down during the last two decades and in some cases, pregnancy outcomes deteriorated. Hoyert (2006) reported, in the United States, despite more women received early antenatal care, the infant mortality rate was 7.0 per 1000 live births in 2002 compared with 6.8 per 1000 live births in 2001. Rates of preterm birth rose significantly to 12.5 percent in 2004 from 10.6 percent in 1990 as well as low birth weight births also increased to 8.1 percent in 2004 from 6.7 percent in 1984 (Levenkron et al., 1997). Although the proportion of women receiving antenatal care has increased, most organogenesis or development of foetal organs is already underway at the time of first antenatal visit (Cefalo et al., 1995). The World Health Organization (WHO) compilation reports on coverage of maternity care, also documented that majority of women receiving antenatal care particularly in the developing countries, they either present after the first trimester or late in pregnancy (Henneman et al., 2001a, Myer and Harrison, 2003, Honnor et al., 2000). Thus, the initiation of intervention during antenatal period is perhaps too late to affect pregnancy outcomes. This may be implied that antenatal care alone is not sufficient to improve maternal health and pregnancy outcomes. Realising this has led to national organizations such as the House of Commons Health Committee (1992), the March of Dimes (2002), and the American College of Obstetricians and Gynaecologists (ACOG) (2002) to recommend preconception care (House of Commons 1992,

March of Dimes 2002, American College of Obstetricians and Gynaecologists (ACOG) 2002), where interventions are delivered before the women conceive and identified as one of a 'key area' in maternal health care. The United States Public Health Service (1991) recommended that preconception care be offered to women by primary care providers (United States Public Health Service 1991). In 2006, the Centre for Disease Control and Prevention has recommended national guidelines for improving preconception health and to incorporate into practice in the United States (Rowley et al., 1997).

The main goal of preconception care is to provide health promotion, risk assessment and interventions for women of reproductive age to reduce risk factors that might affect future pregnancy outcomes (Cefalo et al., 1995). According to the Centre for Disease Control and Prevention (2006), the Select Panel of Preconception Care (SPPC) defined preconception care as "a series of interventions that aim to identify and modify biomedical, behavioural and social risks to women of reproductive age group prior to conception to improve the outcome of future pregnancies and the health of women, infants and families" (Rowley et al., 1997).

Health risks such as infections, anaemia, existing medical conditions; for example, hypertension and diabetes, and risk behaviours such as smoking and folate deficiency, which can affect pregnancy outcomes and foetal development are best modified or prevented before the women conceive (Atrash et al., 2006). Several documented preventative measures of these modifiable risk factors before pregnancy have shown to improve adverse events in mothers and foetal development. The introduction of routine rubella vaccination implemented in adolescents and young women has significantly reduced the incidence of congenital rubella syndrome from 20-70 annual cases in the 1970s to only two cases in 1985 (Garrard, 2006). Initiation of folate supplementation taken before conception has also shown to reduce the incidence of neural tube defects such as spina

bifida and anencephaly (Wald, 1991, Czeizel, 1993). In addition, a recent systematic review also confirmed that folate taken before and during early pregnancy can reduce the incidence of neural tube defects (Dixon et al., 2011). Previous studies on women with diabetes have also reported that proper management of diabetes before women conceive has improved glucose control during pregnancy and reduced incidence of congenital malformations in their offspring (Dunne et al., 1999). Maternal infections, folate supplementation and medical conditions as described above are modifiable reproductive risk factors. The studies had demonstrated benefits of improving the modifiable risks before women conceive.

There are also non-modifiable reproductive risks which include maternal age, carriers of genetic conditions or family history of genetic conditions. The effects of identifying reproductive risk factors, in particular, carriers of genetic conditions or family history of genetic conditions, before conception are less documented. The following section gives an overview of the importance of identifying carriers of genetic conditions or family history of genetic conditions as one of the components of preconception assessment. The term ‘preconception assessment of reproductive genetic risk’ will be used throughout this thesis to indicate this.

1.3 An overview of preconception assessment of reproductive genetic risk

Genetic medicine is rapidly expanding into almost every aspect of health care. Reproductive genetic risk assessment is an example. The importance of reproductive genetic risk assessment as an integral part of preconception care is gaining recognition and has constitute one of the main preconception care evaluation (Rowley et al., 1997).

Genetic conditions affect millions of families. According to the population statistics, globally, about five per cent of all pregnancies result in the birth of a child with congenital or genetic disorders (Buhi and Goodson, 2007). A couple has a baseline risk of two to three per cent of having a child with congenital or genetic disorder (Watson et al., 1992b). The probability of affected child further increases when there is a familial risk (Shapira et al., 2006, Watson et al., 1992b). Assessing genetic risk allows affected individuals or couples to be aware about their genetic predisposition, and, to be informed of the possibility of their future children having genetic conditions. This gives them the opportunity to make more informed reproductive decisions of future pregnancies (Borry et al., 2011).

Worldwide experiences of assessment of reproductive genetic risk before women conceive, were mainly documented on autosomal recessive conditions such as haemoglobinopathies (Modell et al., 1980a, Angastiniotis and Modell, 1998, Samavat and Modell, 2004, Alswaidi and O'Brien, 2009); cystic fibrosis (Christie et al., 2009, Massie et al., 2009) and Tay Sachs disease (Mitchell et al., 1996, Zeesman et al., 1984). The discussion of genetic conditions in this thesis will be confined to autosomal recessive namely, haemoglobinopathies such as thalassaemia and sickle cell disease, cystic fibrosis and Tay-Sachs disease. In these conditions carrier detection is feasible (Buhi and Goodson, 2007). Autosomal recessive conditions have implications on women or prospective parents with regards to future reproduction

decisions. Carrier couples or prospective parents are usually asymptomatic; however, their future offspring will be affected if he or she inherits both affected genes from their prospective parents. All carrier couples have a 25 per cent chance of having an affected child. These genetic conditions have a high morbidity risk, potentially life-threatening and have significant psychological impact on the affected child, as well as on the families or carers. These diseases are also more prevalent in individuals of particular ethnic or ancestry backgrounds (Buhi and Goodson, 2007).

Thalassaemia

In Haemoglobin disorders, it is estimated that between two to five per cent of the world's population are carriers and this is more prevalent in the Mediterranean and Southern Asian ancestry (Modell et al., 2001). According to the WHO, every year, 300,000 infants are born with major haemoglobin disorders, the most common being thalassaemia and sickle cell disease (Buhi and Goodson, 2007). It is characterised by defects or absence of synthesis of one of the two globin chains (α or β) that forms the normal adult human haemoglobin molecule and this leads to haemolytic anaemia (Peters et al., 2012). Thalassaemia can be diagnosed by measuring fractions of haemoglobin A and haemoglobin F with high performance liquid chromatography (HPLC) or electrophoresis. In addition, DNA analysis is required to detect α or β globin chain mutation. Morbidity is related to severe anaemia and an affected child will require life-long blood transfusion. Multiple blood transfusions may eventually result in iron overload and potentially causes heart failure, infection, hypogonadism and infertility, diabetes mellitus, and hypothyroidism. Unless given optimal medical management, affected individuals can die prematurely. In individuals with thalassaemia and their families or carers, psychosocial problems have also been reported, for example stigmatisation, isolation, family adjustment, coping with school and education, and social interaction (Ratip and Modell, 1996, Telfer et al., 2005, Gharaibeh et al., 2009).

Sickle cell disease

Sickle cell disease affects mainly individuals of African origin, but this is also recognised in Indian and some Mediterranean populations. The reported prevalence of carrier frequency ranges from 1 to 40 per cent, depending on the population group. The WHO estimates that sickle cell disease affects 275,000 conceptions each year globally (Modell and Darlison, 2008, Yusuf et al., 2011). The condition is caused by a mutation in the haemoglobin gene (βS) which individuals inherit from both parents. Diagnosis is confirmed using high performance liquid chromatography (HPLC) or electrophoresis with detection of haemoglobin S and C fraction. This condition causes the red blood cells to have a sickle shape, which results in premature haemolysis, hence, can lead to life-threatening acute and chronic vaso-occlusion; including renal and cardiovascular complications. Individuals with this condition are also susceptible to serious septicaemia. Like thalassaemia, individuals and families are also confronted with psychosocial challenges which include disruption of school and work, social isolation and loneliness, stigmatisation, teasing, and rejection by peers (Barbarin et al., 1999).

Cystic fibrosis

Cystic fibrosis is most common among people of European ancestry; having the carrier frequency of one in 25 (Murray et al., 1999). It is caused by mutation in the gene cystic fibrosis transmembrane conductance regulator (CFTR); more than 1500 CFTR mutations have been identified. Diagnosis is indicated by phenotypic features (chronic sino-pulmonary disease, gastrointestinal and nutritional abnormalities, obstructive azoospermia and salt-loss syndromes), family history of cystic fibrosis, or a positive newborn screening test, together with laboratory evidence of a CFTR abnormality as documented by elevated sweat chloride concentrations (sweat test), identification of two CFTR mutations associated with CF, or in vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium. Carriers are confirmed by identification of CFTR mutation from the blood or saliva

(Grosse et al., 2004). This condition commonly associated with recurrent pulmonary infections, which potentially leads to bronchiectasis and atelectasis and also pancreatic exocrine insufficiency. There is currently no cure for the disease, with treatment mainly aimed at improving quality of life. Major psychosocial consequences of concern mainly related to emotional and social adjustment, adherence to treatment and quality of life (Glasscoe and Quittner, 2008).

Tay Sachs disease

Tay Sachs disease is most prevalent in the Ashkenazi Jewish population with carrier frequency of around one in 30 (Petersen et al., 1983). It is caused by genetic mutation in the α chains of the hexosaminidase A (Hex A) isozyme in the gangliosides in nerve cells of the brain (Bach et al., 2001) which leads to progressive deterioration of mental and physical disabilities. It is diagnosed by measuring the activity of hexosaminidase A and further identification of genetic mutation in Hex A (2005). Death usually results before five years of age. At present, there is no cure or treatment available.

1.4 Potential benefits of preconception assessment of reproductive genetic risk

Generally, these autosomal recessive conditions have significant physically, socially and emotionally impact on the affected individuals and families or carers. The need for medical care as well as psychological intervention for behavioural and emotional support also imposes a potentially high economic and public health burden. Realising the magnitude of these conditions and their implications, there have been considerable efforts to identify reproductive genetic risk for the four specified conditions and offer support for prospective parents before the birth of an affected child.

To date, practical experience of assessing reproductive genetic risk focuses mainly on the antenatal period (Qureshi et al., 2004). In the United Kingdom, the NHS guidelines stated that the antenatal genetic screening should be completed before the end of the first trimester; ideally before 10 weeks' of gestation, and that prenatal diagnosis or any subsequent action should take place before the end of 12 weeks' gestation (NHS Sickle Cell and Thalassaemia Screening Programme Centre). Similarly in the United States and Canada as well as other developing countries such as Malaysia, India and Pakistan, genetic assessment and screening in pregnant women are offered within the first trimester of pregnancy (Tambor et al., 1994, Witt et al., 1996). If either couples or prospective parents are found to be carriers of a particular genetic condition, prenatal diagnosis is then offered. If the child is found to be affected, options are termination of pregnancy (if permissible in the countries) or decision to continue with the pregnancy. However, many women were reported delayed in seeking antenatal care; only after the first trimester when prenatal diagnosis is already relatively late (Lemke et al., 1998, Hoyert et al., 2006,). An observational study in the United Kingdom reported that the mean gestational age at uptake of screening was around 16 weeks, despite systematic guidelines to perform antenatal genetic screening; of about

74% of women consulted before 10 weeks' gestation, only 4.4% were screened before the target time of 10 weeks (Dormandy et al., 2008). The United Kingdom National Confidential Enquiry into Counselling of Genetic Disorders has also reported that from 1990 to 1994, only 67 percent of couples at risk of thalassaemia pregnancies were informed and offered prenatal diagnosis during their antenatal visits ((Modell et al., 2000).

Reproductive genetic screening requires a significant amount of time for counselling before as well as after the test results. Counselling involves explanation of the purpose of screening, explanation about the conditions being tested such as the clinical manifestation and management of the conditions, and offering options to couples or prospective parents if they are at risk of having an affected child (Solomon et al., 2008). This process is important before the couples are able to decide on subsequent actions. Screening during antenatal or at the time of pregnancy may only offers prenatal diagnosis to determine at risk pregnancy and subsequent termination of pregnancy. In countries were termination of pregnancy are not allowed or due to religious non-permissibility, the only choice is to continue with the pregnancy and caring for the affected child. Timing is important for the couples or prospective parents to prepare themselves clinically and emotionally before the birth of an affected child or choose to terminate the pregnancy. Screening at the time or during the pregnancy certainly adds a significant stress because of the specific time limits and restricted options (Modell et al., 1980b).

Realising the issues of antenatal genetic screening, assessment of reproductive genetic risk before pregnancy may confer additional benefits. Potentially, it allows the couples or prospective parents greater time to be counselled before deciding on future pregnancy. The primary aim of preconception assessment of reproductive genetic risk is to enhance informed reproductive decisions (Denayer et al., 1992). Preconception assessment offers the opportunity of a wider range of

reproductive options besides early prenatal diagnosis and termination of pregnancy (Morgan et al., 2004). These include avoiding pregnancy, adoption of another child, use of healthy donor gametes, and pre-implantation genetic diagnosis and in-vitro fertilization (Jones and Fallon, 2002, Wille et al., 2004).

Preconception assessment of reproductive genetic risk involves taking family and ancestry history, and carrying out genetic carrier testing or screening and genetic counselling. Taking family history is the first step in identifying individual with genetic risk. It is described as the “gateway to recognise inherited disorders in a patient” (Bennett, 2012). An ideal family history collects information on at least three generations. Ancestry history also forms an essential component when taking family history (Johnson et al., 2006). Positive family history can inform decisions about genetic carrier testing. There is often confusion between genetic carrier testing and screening (Nuffield Council on, 2003). Genetic carrier testing refers to testing of individuals to determine the presence or absence of the carrier status (Denayer et al., 1992). This testing could, for example, be in the context of family history of the autosomal recessive condition or relevant ancestry or ethnicity. On the other hand, genetic carrier screening involves offering or testing the whole population groups irrespective of individual risk (Castellani et al., 2010). Both genetic carrier testing and screening involve the analysis of blood, tissue or bodily fluid samples. Genetic counselling offers information about the risk to help women or prospective parents to make informed decisions.

Primary care providers may ideally positioned to discuss family and ancestry or ethnicity history as well as carrying out genetic carrier testing or screening. It is thus important to explore the opinions of primary care providers in providing preconception assessment of reproductive genetic risk. In addition, it is also useful to consider the women or couples’ interest in such preconception assessment as they are the target population. The subsequent section presents an overview

of primary care providers' and the target population's opinions on preconception assessment of reproductive genetic risk.

1.5 Opinions of primary care providers

Primary care is the first point of contact between the general population and the specialised health services. Every women of reproductive age presenting to the primary care settings are candidates for preconception care. Primary care providers; the GPs, midwives and practice nurses, have a critical role to play in educating, counselling, identifying and managing women with reproductive risks before conception. Traditionally, women consulted secondary care providers; obstetricians and gynaecologists, for established medical conditions which could affect pregnancy, for example, diabetes and epilepsy, or genetic clinics for established genetic conditions. They usually may not be attending secondary care for regular follow-up or for other complaints or issues such as for prescription of medications, vaccination, contraception or minor illnesses. In these circumstances, they will usually seek for advice from the primary care providers. This is where the opportunity for primary care providers to be involved in the healthcare of women in providing preconception assessment and information.

Realising this, national organizations have recommended that preconception care to be an essential part of primary care and encouraged primary care providers to offer preconception care for every potential health encounters (Cefalo et al., 1995, Johnson et al., 2006, Frey, 2006). Furthermore, the United Kingdom Human Genetics Commission has also emphasized that preconception genetic screening should be within the framework of a population screening programme (Denayer et al., 1992).

There have been several literatures on primary care providers' opinions on preconception assessment of reproductive genetic risk. An earlier

survey of GPs in the United Kingdom, two-thirds of the respondents indicated that identifying carrier couples to offer genetic counselling before conception as a very important benefit and believed that general practice is the most appropriate setting to carry it out (Boulton et al., 1996). In another survey, Mennie et.al. (1998) explored GPs' views about screening for cystic fibrosis, 78 percent of the respondents felt that it should be introduced to women seeking advice before pregnancy (Mennie et al., 1998). A Dutch study looking at the attitudes of GPs towards preconception cystic fibrosis screening, found more than half of the respondents have a positive attitude towards the screening while only a small proportion of the respondents were not willing to offer screening as they were afraid of psychological consequences on the carriers and family members (Poppelaars et al., 2004a).

1.6 Opinions of target population

Women also expressed their opinions on the benefits of preconception assessment of reproductive genetic risk and the involvement of primary care. In the South Oxfordshire, United Kingdom, Rose et.al. reported their experiences on setting up a special clinic with an emphasis on family history problems, genetic and preconception issues; the most common reason for patients' attendance to the clinic was, they were planning a pregnancy and concerned about genetic diseases. Fifteen percent of patients who attended were because they were concerned of diseases that could be passed on to their future children (Rose et al., 1999). With regards to cystic fibrosis, a Dutch study, reported that 97 percent of the couples that participated wanted to find out whether they were at risk of having a child with cystic fibrosis (Henneman et al., 2001b). This reflected the expectation of the couples to make informed decisions about having future children. In an interview where the participants were those who had experienced carrier identification through antenatal and newborn screening for sickle cell, thalassaemia and other haemoglobin variants diseases, indicated that they would have preferred to know their genetic risk status before pregnancy. One

of the reasons was it would help potential partners of the affected women be screened and thus enable the decisions on future reproduction, for example; opt not to get pregnant or would have had prenatal diagnosis (Locock and Kai, 2008). Further, in a Dutch study, women's interest of having preconception counselling and advice in health care system was explored and reported that about 60 percent of women who responded, were interested if such clinic did exist. The study also found that about 70 percent of the respondents would consider preconception counselling and advice if this was offered by their own GPs (Poppelaars et al., 2004b).

All the studies described above suggest that women are positive about preconception assessment of reproductive genetic risk and general practitioners' role in offering preconception counselling and advice.

1.7 Rationale for this thesis

Primary care is acknowledged to provide preconception risk assessment and care. Primary care providers recognised the importance of recommending reproductive genetic risk before conception. Women of reproductive age also realised the potential advantages of knowing genetic risk before pregnancy and favoured delivering it in the primary care settings. There is however gaps in the evidence about the effects of preconception care intervention carried out in the primary care settings. In particular, the evidence for preconception assessment of reproductive genetic risk currently, is also limited. While primary care is recognised as an ideal setting to provide preconception care, it is not clear whether it is acceptable to the GPs, which in this context, the GPs in the United Kingdom.

Firstly, this thesis seeks to examine the effectiveness of preconception care interventions in primary care and specifically examine the effectiveness of preconception assessment of reproductive genetic risk in clinical practice. This thesis also explores the attitudes and opinions of GPs as one of the primary care providers in the United Kingdom in providing preconception assessment of reproductive genetic risk.
The thesis hopes to identify potential preconception care interventions in primary care addressing specifically preconception assessment of reproductive genetic risk. This thesis hopes to elicit the opinions of GPs' regarding its development in the United Kingdom health infrastructure. Further, this thesis also hopes to explore the GPs' attitudes of preparedness in providing preconception assessment of reproductive genetic risk.

1.8 Thesis aim and objectives

The aim of this thesis is to help inform a strategy for the implementation of preconception assessment of reproductive genetic risk in primary care in the United Kingdom health infrastructure.

To achieve this aim, the objectives are;

1. To explore the development of preconception care, both general and specific to genetic risk, in the health care and other settings.
2. To examine the effectiveness of current preconception care interventions in the primary care settings.
3. To examine the effectiveness of preconception assessment of reproductive genetic risk in the health care settings.
4. To explore the attitudes and opinions of GPs to providing preconception assessment of reproductive genetic risk in primary care.

1.9 Organization of the thesis

Chapter 1 provides the introduction, the background of the thesis and the thesis aim and objectives.

Chapter 2 presents review of literatures on the development of preconception care in general, and specific to reproductive genetic risk in the health care and other settings. This chapter will also discuss potential opportunities and challenges related to the development of preconception interventions (mapped to objective 1).

Chapter 3 presents a systematic review of the effects of any preconception care interventions on improving pregnancy and reproductive health outcomes in the primary care settings (mapped to objective 2).

Chapter 4 presents a systematic review of the effects of preconception assessment of reproductive genetic risk of the commonest autosomal recessive conditions; thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease, in any health care settings (mapped to objective 3).

Chapter 5 describes the development of a questionnaire as a survey instrument to explore the attitudes and opinions of general practitioners to providing preconception assessment of reproductive genetic risk in primary care (mapped to objective 4).

Chapter 6 describes the survey methods and justification for the approach, taking account of the current literature of survey methodology and analysis (mapped to objective 4).

Chapter 7 presents the analysis and interpretation of the results of the questionnaire survey (mapped to objective 4).

Chapter 8 presents the principal findings of the thesis and its clinical and research implications.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

Chapter 1 has reported the overview of preconception care and in particular focussing on preconception assessment of reproductive genetic risk, and has introduced the direction of the whole thesis.

The objective of this chapter is to explore preconception care, in general and specific to reproductive genetic risk through reviewing relevant literatures as well as policy-related documents. Through this process, the approaches, potential opportunities and challenges related to the development of preconception care interventions in health care or other settings will be discussed.

2.2 Development of preconception care

Preconception care addresses women's health before conception that will enable women to enter pregnancy in optimal health and minimises health problems in future children for example; in folate supplementation and lifestyle modification such as smoking and alcohol moderation. Preconception care may be a promising approach to support informed reproductive decisions for future pregnancies in the case of genetic risk and maternal infections such as viral hepatitis B or C, or HIV infection (Rowley et al., 1997).

By 1980s, documented evidences from earliest studies that demonstrated relationship between women's health risks during pregnancy and the adverse pregnancy outcomes; for example; rubella infection (Miller et al., 1982), inadequate folate intake before pregnancy (Wake et al., 1996), maternal smoking and chronic illnesses (diabetes, hypertension) (Institute of Medicine, 1985) have fuelled the interest in setting up preconception care. There is opportunity that these health

risks can be identified, addressed and modified before pregnancy to reduce the risk of adverse pregnancy outcomes.

One of the earliest preconception care activity described in the literature was by Chamberlain in the United Kingdom in 1980. Chamberlain (1980) described preconception care a specialty service for women. The aim of this clinic is to provide counselling to women about health risk that could affect future reproductive outcomes. It was run by one consultant obstetrician and he was the only one providing advice and counselling. The preconception setting was known as pre-pregnancy clinic and was based in a hospital in London. Women with genetic risk were however excluded from the pre-pregnancy clinic as the hospital was already providing a weekly genetic clinic for them. This study reported that 56 women had attended the clinic in the first 18 months and majority of women who attended had existing maternal risks such as epilepsy and previous pregnancy-induced hypertension or previous poor reproductive outcomes such as congenital abnormalities. It demonstrated that women who attended were those actually concerned of future pregnancies due to existing reproductive risks. The most concerned risk reported were previous premature labour and its association with low birth weight (Chamberlain, 1980). The pre-pregnancy clinic may be potential approach to improve the women's future reproductive outcomes. The fact that it was run by a consultant who may already have interest and knowledge, a consistent and informative preconception counselling is expected. This study however has several limitations. Firstly, the clinic was set up only within 18 months; thus, the outcome of the women who had preconception counselling at the clinic was not known. Secondly, the clinic was based in the hospital; the question is whether this is practical to attract all women of reproductive age. It would be helpful if similar setting was placed in a primary care setting such as the general practice, however on the other hand, it could be easier to refer to the speciality concerned if identified maternal risks, if clinic is based at the hospital. Thirdly, this clinic did not provide counselling to those with genetic risk. Ideally,

genetics should also constitute preconception care counselling as it contributes to informed decisions on reproduction. Finally, this clinic was run by only one specialist. It would seem feasible if the patients were not of great load. Furthermore, there would be a break in the continuity of care if the specialist is away or not available. An ideal setting providing preconception counselling should also involve primary care providers.

In Hungary, a more integrated preconception initiative was carried out in 1984. This was a 27-year observational study, established in Budapest as a research project to assess the feasibility of preconception care. The project was called the Hungarian Preconception Service (HPS) which was established in 32 health care centres. The main aim of this initiative was to prepare prospective parents for a better pregnancy and reduce the occurrence of unfavourable pregnancy outcomes; for example; congenital abnormalities and preterm births (Czeizel, 2012).

The Hungarian Preconception Service was given free to women of reproductive age who were not pregnant at the time, no infertility and decision to participate has to be voluntary. The intervention described involved three essential components;

1. Screening for reproductive risk factors before conception for example; family history of genetic conditions, previous adverse pregnancy outcomes, existing or previous medical conditions, previous or current sexually transmitted diseases and vaccinations.
2. A three-month preparation before conception for example; lifestyle and behavioural modification and education courses of smoking, alcohol and drugs consumption, healthy diet and folate supplementation. At this point, any identified reproductive risks were treated or referred to appropriate specialities for example, genetic counselling clinic and special outpatient clinics for medical conditions.

3. Management of reproductive health issues and evaluation of the pregnancy outcomes of all women with confirmed pregnancy.

The first two components; screening for reproductive risk and advising on the three-month preparation before conception was carried out by qualified community nurses and midwives in the designated primary care centres. Following screening, the management of identified reproductive health issues was further carried out by the specialists in the respective specialities.

With regards to the outcomes, the Hungarian Preconception Service reported an improvement in the rate of women planning pregnancy. Following the intervention, there was significant reduction in the birth prevalence of neural tube defects (OR 0.07, 95% CI 0.04-0.13) and cardiovascular malformations (OR 0.42 95% CI 0.19-0.98) after folate-containing multivitamin supplementation as compared to no-folate-containing multivitamin folate The proportion of female smokers also decreased approximately 27 percent at three months preparation of smoking cessation counselling (Czeizel, 1999). Almost all women who participated went for rubella and hepatitis B screening and they were vaccinated if found seronegative. Genetic risk screening in the Hungarian Preconception Service was based on the pedigree obtained from couples. This includes previous child with congenital abnormalities or hereditary conditions. This service reported that the number of identified individuals has risen from eight percent in 1980 to 20 percent in 2000. All of them were referred to genetic counselling clinic. Among all who planned for pregnancy, half of them had early prenatal diagnosis whereby about five percent had future children with inherited genetic conditions. Affected couples decided to terminate pregnancy following prenatal diagnosis (Czeizel et al., 1992, Czeizel, 1992, Czeizel, 2012).

The Hungarian Preconception Service has demonstrated a comprehensive preconception care intervention that encompassed

assessment or screening of multiple reproductive health risk, education and counselling as well as management of the risks to secondary care. The intervention carried out by qualified nurses has improved the identification of reproductive risk. In addition, proper preparation before conception, such as folate supplementation and smoking, has reduced the prevalence of congenital abnormalities (Czeizel, 1999). This strategy at primary care level is promising however limited due to unavailable controlled data and evaluation of cost effectiveness of the intervention.

In the United States, one of the earliest preconception care intervention has focussed on health risks screening, counselling and treatment (Moos and Cefalo, 1987, Moos, 1989). Moos and Cefalo (1987) had developed a preconception health checklist in 1985 to help health care providers to conduct comprehensive preconception screening with the aim for appropriate counselling to take place with the women in a time-efficient manner. The checklist was a self-administered assessment screening questionnaire of reproductive health risks which includes medical history, family history of genetic conditions, nutrition, lifestyle, drugs or medication, and previous pregnancy history. The checklist has also a built-in educational feedback served as a reminder of actions for the women on how to improve pregnancy outcomes. This approach was initially introduced in the family planning clinics. Women were introduced and made aware of preconception care concepts during routine family planning visits. As a result, women with reproductive health risks were identified, counselled and managed appropriately earlier (Moos and Cefalo, 1987). Cefalo and Moos (1995) also reported an increased in planned pregnancy rate following the introduction of preconception care intervention (Cefalo et al., 1995). This initiative has moved public health organizations in the United States such as the Centers for Disease Control and Prevention (CDC), the March of Dimes and the American College of Obstetricians and Gynecologists to be committed to promote preconception care (Freda et al., 2006). In 2006, these organizations, through their collaborative efforts had led to

publish a national guidelines on preconception care (Johnson et al., 2006).

The United States approach to preconception care is notably escalating. This is stimulated by earlier research findings which underscored the limitations of antenatal care alone on improving reproductive outcomes. In addition, they recognized the importance to reach women of reproductive age to receive preventive measures before conception especially since almost 50 percent of the pregnancies are unplanned (Jones et al., 1988, Johnson et al., 2006). Nevertheless, the success of this intervention depends on the country's health infrastructure, socioeconomic and insurance systems (Van der Zee, 2013). There should also be comparative studies to demonstrate the quality of the interventions.

In the Netherlands, the earliest experience of preconception care was reported in the 1990s in clinic settings held within the gynaecologic or genetics department. Here, the care was mainly on gynaecological such as previous complicated obstetric history and genetic risk factors (Health Council of the Netherlands, 2007). Since then, the awareness and demand for more forms of preconception care has increased. In 2004 the Dutch Foundation for Preconception Care was developed with the aim to "promote easily accessible preconception consultation in the Netherlands". Organizations involved with this foundation have piloted more than 20 clinics in the primary care setting to offer preconception care. These clinics were run by trained midwives to assess preconception risks in couples who are then referred to respective specialists or secondary centres if risks are identified (Health Council of the Netherlands, 2007).

In 2009, further preconception initiatives were carried out by the municipal council of Rotterdam and the Erasmus University Medical Centre. This preconception intervention has focussed on relatively low socioeconomic population in two districts in the Netherlands using

campaigns on preconception care with specific modalities such as multi-lingual posters, leaflets, advertisements, and columns in the local media; followed by preconception education programme in groups and further emphasis on preconception care through individual preconception counselling by a midwife or a GP. This intervention also includes providing social services for prospective parents (van der Zee et al., 2011). From 1996, earlier interventions have demonstrated preconception care has helped to minimise risk factor in women at increased risk for a less favourable pregnancy outcome in the country. There was reduction in the rate of neural tube defects following increase in folate supplementation from 12.3 per 10000 children in 1997 to 6.3 per 10000 children in 2004 identified (Health Council of the Netherlands, 2007).

The primary care approach to preconception care reported in Netherland appears integrated highlighting the involvement of public modalities such posters and advertisements, preconception education and counselling by GPs and midwives as well as involvement of secondary or specialist care. It would seem feasible to carry out this strategy in the primary care setting. However, it is reported difficult to gauge the coverage and evidence for effectiveness as it still delivered in a small scale and not in a uniform manner (Temel et al., 2015).

Summary

Earliest experiences of intervening women of reproductive age before they conceive were directed to specific reproductive risks such as rubella vaccination, folate supplementation and diabetes (Garrard, 2006, Wald, 1991, Czeizel, 1993, Kitzmiller et al., 1998). Realising the importance of practical approach to preconception care in the primary care setting, preconception care intervention has to be more integrated and comprehensive encompassing assessment of multiple reproductive health risks, education and counselling as well as management of the risks.

The Hungarian Preconception Service, the national organizations in the United States such as the Centers for Disease Control and Prevention (CDC), the March of Dimes and the American College of Obstetricians and Gynecologists; and the Health Council of Netherlands have adopted a comprehensive preconception risk assessment which involved physical assessment, risk screening, education, counselling and management of the risk. Genetics and reproductive awareness are highlighted as one of the important areas in preconception risk screening (Johnson et al., 2006, Czeizel, 2012).

The Hungarian Preconception Service is one of the earliest interventions to report on the outcomes of preconception care that was carried out in relation to preconception genetics. With regards to evidence of effectiveness in the application of genetics in preconception care, it is still limited as other organizations were mainly reports on national recommendations.

There are earlier documented experiences of population-based and school-based genetic screening programs targeting on reproductive-aged individuals which includes women and men. Some of the programs were carried out entirely as a prevention programme on its own and not as a package of preconception care. There are also recent observational studies exploring reproductive decisions following assessment of reproductive genetic risk on women or couples considering pregnancy. The following section will discuss on earlier experiences of genetic screening programs internationally and also recent observational studies that addressed specifically on assessment of reproductive genetic risk in the preconception period.

2.3 Preconception assessment of reproductive genetic risk

2.3.1 Aim of preconception assessment of reproductive genetic risk

Most national organizations have recognised the importance of incorporating genetics into preconception care practice (Rowley et al., 1997, March of Dimes, 2008, Denayer et al., 1992). The need to provide preconception genetics interventions; that is, the assessment of reproductive genetic risk before conception, is realised because of its potential important benefits of future reproductive decisions and counselling to prospective parents (Hartley et al., 1997, Lafayette et al., 1999b, Fanos and Johnson, 1995b). In this instance, at-risk status for having an affected child can be identified early and this enables prospective parents to make informed reproductive decisions before pregnancy. Acquiring this information before pregnancy as compared to during antenatal period has the advantage of more reproductive options and couples are not pressed for time to make the decision. These options include not only prenatal diagnosis, which either followed by termination of pregnancy or continuing the pregnancy in the case of an affected child, but also options such as to make use of healthy donor gametes, adoption of another child, pre-implantation genetic diagnosis and in-vitro fertilization or even avoiding pregnancy (Jones et al., 2002, Wille et al., 2004a). In some cultures practicing consanguineous marriages, it could possibly result in adapting the choice of a partner (Lakeman et al., 2009, Teeuw et al., 2014)

2.3.2 International genetic screening programmes

The earliest population-based genetic screening program reported for autosomal recessive conditions was developed for Tay-Sachs disease in the United States in the 1970s (Kaback, 2000, ACOG, 2004). The screening was carried out among reproductive-aged women and men of Ashkenazi Jewish ancestry. The program reported reduction in the incidence of Tay-Sachs disease in the Jewish population by more than

90% within thirty years of its introduction. This was largely due to early prenatal diagnosis and termination of affected pregnancies (Kaback, 2000).

About the same time, a genetic screening program, the Cyprus Thalassaemia Control Program was developed for thalassaemia in Cyprus. Other Mediterranean countries such as Greece and Sardinia, Italy, which have high prevalence of thalassaemia, also adopted prevention programs. These countries reported significant reduction of children born with thalassaemia following the screening program (Angastiniotis and Hadjiminas, 1981, Cao and Kan, 2013). The prevention programs described in these countries were through premarital and preconception carrier assessment.

In countries that have religious and cultural reservations towards termination of pregnancy also have developed a nationwide pogramme. In 1997, the Regional Office of Eastern Mediterranean of WHO has supported carrying out preconception genetic risk assessment for haemoglobinopathies before marriage or premarital. The countries involved include Iran, Egypt and Bahrain (Alwan A, 1997). In Iran for example, the genetic assessment is carried out in premarital clinics where other preconception health care is also offered and discussed (Samavat and Modell, 2004).

In the Netherlands, the Health Council has considered preconception genetic risk assessment in particular for cystic fibrosis and haemoglobinopathies in view of the seriousness of both conditions in the country (Health Council of Netherlands, 2007). Currently, the assessment are offerred opportunistically among the high risk groups, individuals with positive family history and ethnicity or couples planning pregnancy (Health Council of Netherlands 2007).

The United Kingdom Human Genetics Commission acknowledged the importance of preconception genetic assessment would facilitate wider

reproductive choices and thus supporting reproductive decision-making in the prospective parents. It is being recommended within the framework of a population screening programme (Human Genetics Commission, 2011), however, not yet implemented nationally. In the South East Asia, thalassaemia is the commonest autosomal recessive genetic conditions. To date, nationwide reproductive genetic risk assessment is reported mainly during antenatal period (Banta, 2003, Fucharoen and Winichagoon, 2011).

Observational studies involving school-based genetic screening programs for Tay-Sachs disease and thalassaemia, also demonstrated encouraging results. The countries involved were Montreal in Canada and Marseille in France (Scriver and Mitchell, 2001, Lena-Russo et al., 2002). In Marseille, the participants were high school students (aged ≥ 16 years old) who volunteered and not confined to specific ethnicity, and the program consisted of education, carrier testing and reproductive counselling. Participants were followed up within twenty years and has reported early request for prenatal diagnosis from participants at risk and increased rate of early termination of affected pregnancies. This has resulted in a decrease in number of new cases of the conditions during the 20 years of follow-up (Lena-Russo et al., 2002). However, school-based genetic screening programs have not been implemented as school setting could raise concerns whether screening is well informed and voluntary as adolescent have limited ability to give true informed consent (Shoemaker et al., 2004). In addition, peer pressure might also influence one's decision (Ross, 2006). Further issues reported were whether confidentiality is maintained as this may involve parental decision and peers; the issues of stigmatisation and whether appropriate counselling is carried out before and after genetic screening (Denzin, 1970).

With regards to outcomes of genetic assessment in women or couples considering pregnancy, two recent studies demonstrated encouraging results. A study in Australia involving offering cystic fibrosis carrier

testing to 1000 individuals has resulted in 153 individuals being identified carriers and three carrier couples. All three reported to change their reproductive plans following the results; with two planned for in-vitro fertilization (IVF) and pre-implantation genetic diagnosis (PIGD) and one had an early prenatal diagnosis with termination of pregnancy of the affected foetus (Christie et al., 2009). Further larger study which involved 3200 individuals included women before pregnancy as well as in early trimester of pregnancy has also identified substantial number of carriers (106 individuals) and nine carrier couples; which three of the couples were preparing for pregnancy. Two couples requested for early prenatal diagnoses which resulted in one termination of affected pregnancy whereas the other two couples had planned for in-vitro fertilization (IVF) and pre-implantation genetic diagnosis (PIGD) in future (Massie et al., 2009).

The following section will discuss existing or potential challenges to the implementation of preconception care in general and specifically for preconception assessment of genetic risks. Two main challenges are regarding the target population and the primary care providers. Both will be discussed in the context of preconception care in general and preconception assessment of reproductive genetic risk.

2.4 Challenges of preconception care in general and preconception assessment of reproductive genetic risk

2.4.1 The target population

The inadequate interest of the target population to engage in preconception care may pose as a potential barrier. Earlier surveys of women demonstrated lack of awareness and interest to seek advice before pregnancy. A survey in the United Kingdom found that only less than 40% of the respondents considered preconception care essential and about more than 10% believed it to be of no importance (Wallace and Hurwitz, 1998). Further, in Netherlands, a survey of recently

married couples and planning for pregnancy, found that only 22% of the respondents agreed that they will consult their general practitioners for advice before they are pregnant (Poppelaars et al., 2004d). Even in the Hungarian Preconception Service (HPS) where preconception care was already offered, only 10% of all women with planned pregnancy took part in the program (Czeizel et al., 1992).

With regards to preconception assessment of reproductive genetic risk, in earlier studies, inadequate understanding and awareness of women or couples of its importance and consequences of the risk with genetic conditions were reported to contribute to them not participating in the preconception genetic screening programmes (Lemke et al., 1998, Henneman et al., 2002). When exploring women or couples about their opinion on preconception cystic fibrosis screening, fear of psychological consequences such as stigmatisations and relationships problems on affected individuals and their family members were reported as their negative intention to participate in the screening (Poppelaars et al., 2004e). These factors potentially pose barriers to the dissemination of preconception care. In the next section the role of primary care providers to deliver preconception care and difficulties faced will be discussed.

2.4.2 Primary care providers

As preconception care gained momentum over the past three decades, primary care providers are increasingly being urged to provide such care. In 1991, the House of Commons Health Committee (1992) proposed that preconception care be ‘identified as one of a ‘key area’ in maternal health care. The Centres for Disease and Control and Prevention (2006) has recommended to incorporate preconception care into practice in the United States and further published national guidelines to help primary care providers to deliver preconception health screening (Rowley et al., 1997).

In general, primary care providers were aware that a thorough health assessment prior to conception helps identify potential reproductive risks. One of earlier studies in the Netherlands, reported that majority (93%) of the respondents already considered providing preconception advice as part of their responsibilities as general practitioners (Gaytant et al., 1998). A survey of general practitioners and nurses in 42 general practices in the United Kingdom, reported that majority of the respondents recognised that preconception care is important to enhance better outcome for both mothers and future children (Wallace and Hurwitz, 1998). Furthermore, they agreed that preconception care should be offered opportunistically in the primary care settings (Wallace and Hurwitz, 1998, Heyes et al., 2004).

Although the importance of preconception care is well realised among primary care providers, implementation of this form of preventative program is still lacking. The difficulty of the primary care providers to reach or deliver preconception care to the targeted group posed an issue to the implementation of the services. Morgan (2004) reported that only about ten percent of pregnant patients came for preconception care before they become pregnant (Morgan et al., 2004). Heyes (2004) reported that getting the patients with already having reproductive risk to come to the preconception clinic is an obstacle (Heyes et al., 2004). The general practitioners believed that women did not perceive themselves to be at risk for a poor pregnancy outcome and, therefore, would not seek consultation before becoming pregnant (Van Der Pal-de Bruin et al., 2008). Furthermore, the subject of high occurrence of unplanned pregnancy contributed to difficulty in successfully implementing the programme (Czeizel, 1999). Lack of consultation time and inadequate appropriate knowledge and training among the primary care providers were also addressed as hindering factors in the delivery of the service (Gaytant et al., 1998, Heyes et al., 2004, Morgan et al., 2004). General practitioners also expressed dilemma that whether preconception care interventions truly linked with improved pregnancy outcomes if provided in the primary care settings (Heyes et al., 2004).

There were also conflicting views on who is the most appropriate to provide the care. Results of surveys on primary care providers and even women reported that general practitioners, practice nurses and community midwives were most preferred to deliver preconception care (Wallace and Hurwitz, 1998, Heyes et al., 2004, Poppelaars et al., 2004b).

2.4.3 Ethical, legal and social issues

When discussing in the area of genetics it is almost always impossible to avoid ethical, legal and social implications. The health care providers and community at large are worried about the effects of knowing genetic risk on a healthy individuals or families. These issues may vary for specific communities and countries because of cultural and religious background. (Clayton, 2003, WHO, 2006).

There are few concerns with regards to earlier experiences of the programs described. One, addressing specific population screening, for example; Ashkenazi Jewish communities for Tay-Sachs disease may have social or ethical implication such as stigmatisation and discrimination (Kaback, 2000). Secondly, another concern was the voluntariness of participation. Haemoglobinopathies screening in Cyprus and Iran was reported to be carried out premarital and was made mandatory (Angastiniotis and Hadjiminas, 1981, Samavat and Modell, 2004). World Health Organization (1998) has outlined that that reproductive-related genetic screening should be provided on a voluntary basis (Buhi and Goodson, 2007). Thirdly, the genetic screening programs were aimed to prevent further children born with Tay-Sachs disease and thalassaemia, hence, reduction in the incidence of the conditions (Angastiniotis and Hadjiminas, 1981, Samavat and Modell, 2004). Wert (2012) argued that when preconception assessment of reproductive genetic risk is concerned, the aim is to enhance well-informed reproductive decision rather than prevention (Wert et al., 2012). However, it would seem agreeable for countries with

high population frequency, and the conditions are associated with high morbidity and mortality (Wert et al., 2012).

Disclosing information to partners and also leaving them with possible reproductive options afterwards is seen as a potential confidentiality and social issues. In some countries where termination of pregnancy has legal or religious restriction also pose potential ethical and legal problems (Khoury et al., 2003, Fulda and Lykens, 2006).

2.5 Opportunities for preconception care in general and preconception assessment of reproductive genetic risk

Nevertheless, few studies reported that women would be motivated to participate if preconception care services are readily provided or offered. In a Dutch study, although women do not actively seek preconception advice, about 60% of the respondents demonstrated interest if there is specific preconception clinic in current health care system (Poppelaars et al., 2004b). In another survey, about 70% of women participated would consider preconception advice if actively offered by own general practitioner (Jones et al., 1988). In a recent study, most women have believed that optimizing the health of a mother prior to conception would benefit the overall health of the pregnancy despite pregnancy is planned or not (Frey and Files, 2006).

Women or couples have also begun to acknowledge the importance of preconception assessment of reproductive genetic risk. A study in the United Kingdom reported that the participants realised that family history recording allowed knowing risk of genetic conditions in future children and more importantly enabled pregnancy planning (Rose et al., 1999) and early identification of couples at genetic risk offered early genetic counselling (Czeizel, 1999a).

In Netherlands, a survey carried out on a population with high genetic risk, the Dutch Turks and Moroccan who practised consanguineous

marriages, more than half of the respondents thought that the best time to inform people about these risks was before marriage, and one-fifth thought this should happen before the first pregnancy (Teeuw et al., 2014).

2.6 Conclusion

The literatures offer background information in understanding the potential benefits of preconception care in general and particularly, preconception assessment of reproductive genetic risk. The potential challenges and opportunities to providing preconception care and preconception assessment of reproductive genetic risk have also been highlighted. More importantly, the literatures provide an insight of potential strategies or approaches to deliver preconception services. The evidence of these approaches, particularly in primary care, has not been systematically examined. It was imperative to systematically examine evidences of both preconception care and preconception assessment of reproductive genetic risk.

The following two chapters, Chapter 3 and 4 will report on systematic review on the effectiveness of preconception care interventions in the primary care setting and preconception assessment of reproductive genetic risk respectively. Considering this thesis is focussing on preconception assessment of reproductive genetic risk, GPs' views and preparedness to providing preconception assessment of reproductive genetic risk will be explored and this will be discussed in the later chapters.

CHAPTER 3

A SYSTEMATIC REVIEW OF THE EFFECTS OF PRECONCEPTION CARE INTERVENTIONS ON IMPROVING PREGNANCY AND REPRODUCTIVE HEALTH OUTCOMES IN PRIMARY CARE SETTING

3.1 Introduction

Previous chapters have highlighted that preconception care could be an opportunity to improve the health of women and future children. Involvement of primary care in the delivery of preconception care is emphasized by policymakers. Women have also expressed interest in discussing preconception issues with primary care practitioners. Yet, the evidence remains limited or unclear. Thus, there is a need for reviewing preconception care interventions in the primary care settings.

The objective of this chapter is to present a systematic review carried out to provide an up-to-date evidence of the effectiveness of preconception care interventions in primary care. Although the thesis focusses on preconception assessment of reproductive genetic risk, the nature of interventions identified in this review will potentially help to inform the provision of preconception care of reproductive genetic risk as it is relevant to preconception risk assessment in the primary care settings.

3.2 Background

Earlier, in Chapter 2, preconception care interventions directed on specific reproductive risk such as rubella vaccination, folate supplementation and diabetes control have reduced rate of major congenital abnormalities. Further, a preconception intervention involving a comprehensive preconception care assessment and management in a community-based setting by Czeizel et.al of over a 20 year period, also reported reduced rate of neural tube defects and cardiac malformations, improved maternal risk behaviour such as smoking, and

improved detection of genetic risk (Czeizel, 2012). However, earlier assessment was limited to observational methods.

An earlier systematic review published in 2002 examining the studies carried out between 1990 till 1999 to find evidence of preconception care interventions (Korenbrot et al., 2002). This review included all women of reproductive age whether planned or unplanned pregnancy, with no previous risk factors or already has existing risks such as diabetes or epilepsy. In addition, preconception care interventions carried out in all health care settings were included. This review has identified reduced prevalence of congenital anomalies with folate supplementation before and in early pregnancy, with dietary control of maternal phenylketonuria and with early management of hyperglycaemia (Korenbrot et al., 2002). The identified studies were mainly on specific reproductive risk and carried out in the secondary care settings. A further Cochrane review in 2009 assessed the effectiveness of pre-pregnancy health promotion which contained advice and education on health and lifestyle. This review reported encouraging evidence that these interventions promoted women to have healthier lifestyle but little evidence on improving pregnancy outcomes. Moreover, women in this review were limited to those with no pre-existing medical, obstetric or genetic risks (Whitworth and Dowswell, 2009).

In order to address comprehensiveness of preconception care interventions encompassing general or multifactorial reproductive risks in the primary care settings with a wider spectrum of women of reproductive age group, this systematic review was carried out to examine the evidences on improving reproductive health and pregnancy outcomes. In addition, this review may provide information on potential intervention strategies in particular addressing preconception care in genetics.

3.3 Objective

The objective of this review is to examine the effectiveness of preconception interventions on improving reproductive health and pregnancy outcomes in primary care.

3.4 Methods

The process for conducting this review was adapted from Cochrane Systematic Review of Interventions (Clayton et al., 1996).

3.4.1 Search strategy

Studies were systematically searched following four databases; MEDLINE, CINAHL, EMBASE and PsycINFO from July 1999 to end of 23 January 2013. The start dates for databases searches were set from July 1999 which ensued review carried out by Korenbrot (2002). The search strategies was generated following consideration of previous reviews (Poppelaars et al., 2004c, Whitworth and Dowswell, 2009) and relevant literatures, as well as consultation with a medical librarian. The detailed search is available in Appendix 3.1. A manual search of reference lists from included studies was also carried out for eligible records. This review was restricted to published articles and whose full texts were available in English.

3.4.2 Eligibility criteria

Intervention studies considered eligible for this review were randomised controlled trials (RCTs) and quasi-randomised studies. Only studies that clearly stated the interventions and had comparator arm were included. The comparator arm included ‘usual care’ or ‘alternative care’ or ‘not involving preconception care.’ Included subjects were women of reproductive aged between 18 to 45 years old, irrespective of their established medical, obstetric and genetic risk in primary care settings. The settings included were family or general practices, community health centres, community health services, community or outpatient clinics and ambulatory care services*.*

Interventions encompassed both primary and secondary prevention before pregnancy; the former included such as, advice on nutrition, lifestyle, folate intake, smoking cessation and alcohol moderation; and the latter included such as, screening for genetic disorders and gestational diabetes. Any reported outcomes, for examples; maternal risk behaviour, adverse pregnancy outcomes and measures of psychological distress were included.

3.4.3 Study identification

All retrieved records from the four databases were entered into the Endnote X6, the Endnote reference managing software. Any duplicates were initially removed. Every titles and abstracts identified were screened by the researcher (NH) and checked independently by a second author (NQ). These titles and abstracts were labelled ‘include’ or ‘exclude’. Full texts of studies potentially meeting the inclusion criteria, labelled as ‘include’ were assessed independently by two authors (researcher and second author) for relevance and inclusion. The researcher (NH) also hand searched the reference lists of all retrieved papers. Where disagreement existed, consensus was resolved through discussion.

3.4.4 Data extraction

Data extraction was carried out by the researcher (NH) and verified by the second author (NQ). Any disagreement was resolved through discussion. The data extraction form for the study description was informed by previous reviews. Where possible, the following descriptions of studies were documented:

1. study designs
2. characteristics of study participants (age, planning pregnancy)
3. inclusion and exclusion criteria
4. details of interventions (duration, follow-up, provided by whom)
5. details of comparator
6. settings of interventions
7. outcomes investigated
8. results of findings

3.4.5 Assessment of quality of studies

Assessment of quality of studies was carried out by the researcher and verified by the second author. Quality of studies checklist was constructed as outlined for the quality assessment for randomised controlled trials in the *Cochrane Handbook for Systematic Reviews of Intervention (Clayton et al., 1996).* Five domains were used in the criteria assessed. They were:

1. sequence generation
2. allocation concealment
3. blinding of participants, study personnel and outcome assessors
4. incomplete outcome data
5. selective reporting

For every included study, each domain was classified as ‘high’, ‘low’ or ‘unclear’ risk of bias to determine the quality of studies. Studies were

considered as highly susceptible of bias if 2 or more were classified as ‘high’ risk or 3 or more as ‘unclear’ risk of bias.

3.4.6 Data synthesis

Due to the heterogeneity in the nature of interventions and outcomes, the data was not pooled in a meta-analysis. Results of studies were reported separately as presented in each study; for dichotomous data, risk ratio or odds ratio with 95% confidence intervals; and continuous data was reported either as absolute difference (total or proportion of outcome in the intervention minus control group), change in mean score (before and after intervention in the intervention and control group) or change in total score (before and after intervention in the intervention and control group). P value or 95% confidence intervals were used to indicate effects of interventions.

3.5 Results

3.5.1 Description of included studies

4458 references were retrieved and screened. 1166 duplicates were removed. 3292 references were screened for eligible titles and abstracts. 23 full papers were retrieved; only nine studies met the inclusion criteria and were critically appraised (Figure 3). References for included studies are presented in Appendix 3.2.

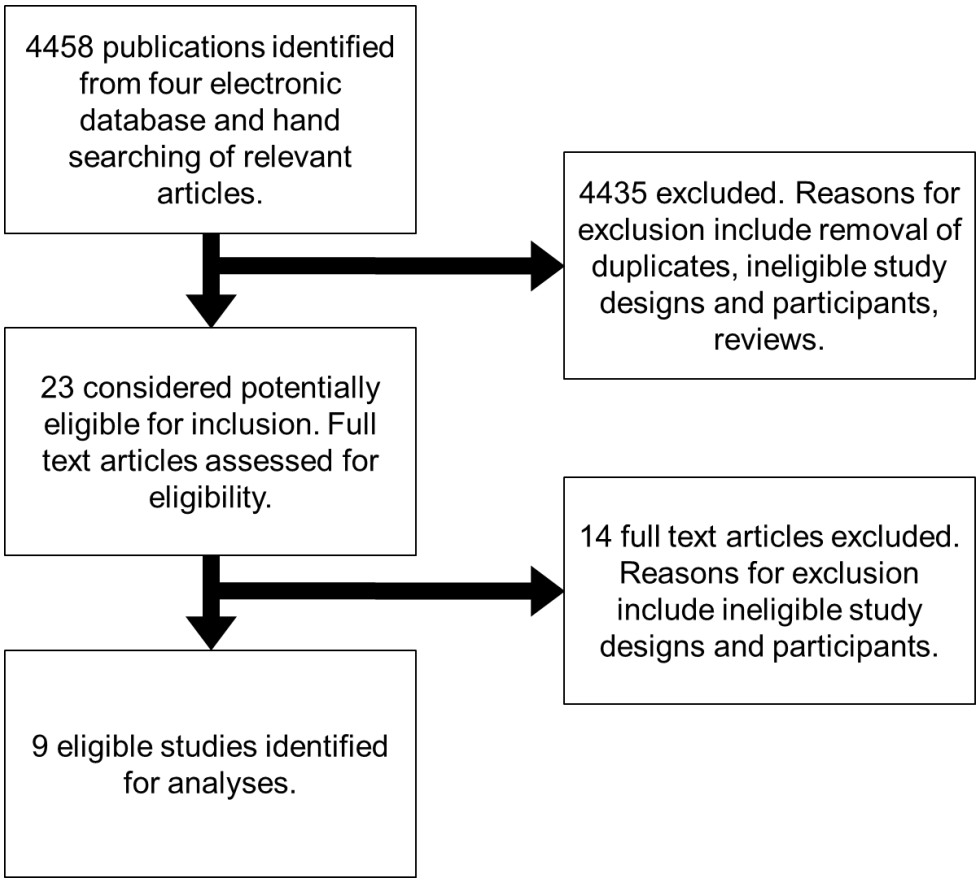


Figure 3 : Study flow of papers through review

Both the nature of interventions and the outcome measures varied across the nine studies. The intervention; is divided into two main groups; involving multifactorial reproductive health risks, as addressing nutrition, lifestyle, vaccination, infection prevention and genetic conditions in five studies; (Van der Zee, 2013, Lumley and Donohue, 2006, Elsinga et al., 2008, Hillemeier et al., 2008, Bastani et al., 2010) and single reproductive health risk, specifically folate supplementation and alcohol consumption in remaining four studies (Robbins et al., 2005, Floyd et al., 2007, Cena et al., 2008, Schwarz et al., 2008). The component of intervention included preconception health assessment, education and counselling. These interventions were delivered by various primary care-based health professionals; general practitioners (de Jong-Potjer et al., 2006, Elsinga et al., 2008), gynaecologists

(Robbins et al., 2005), nurses (Lumley and Donohue, 2006, Floyd et al., 2007), nutrition educators (Cena et al., 2008) and trained facilitators (Floyd et al., 2007, Hillemeier et al., 2008, Bastani et al., 2010) with computer-assisted counselling applied in one study (Schwarz et al., 2008). Period of interventions was grouped into two categories; brief, which involved a single session within a day and intensive; which involved more than one session and in some cases, over several weeks. The interventions were brief in five studies; from 30 to 60 seconds (Robbins et al., 2005), 15 minutes (Schwarz et al., 2008), to two hours of education and counselling over a single day (Lumley and Donohue, 2006, Cena et al., 2008, Bastani et al., 2010). In four studies interventions were more intensive with two studies involved risk assessment questionnaire followed by general practitioners' consultation and advice based on risk assessment and general risk factors for adverse pregnancy outcomes (de Jong-Potjer et al., 2006, Elsinga et al., 2008); a 2-hour group sessions on preconception health services, stress management, physical activity, smoking, gynaecologic infection, nutrition, and healthy eating demonstration over a 12-week period in one study (Hillemeier et al., 2008), and counselling and motivation sessions on alcohol moderation over a 14-week period (Floyd et al., 2007). In five studies, the interventions involved one to one counselling sessions whilst the other studies involved group intervention (Robbins et al., 2005, Lumley and Donohue, 2006, de Jong-Potjer et al., 2006, Elsinga et al., 2008, Schwarz et al., 2008) whilst the other studies involved group intervention (Floyd et al., 2007, Cena et al., 2008, Hillemeier et al., 2008, Bastani et al., 2010). The follow-up interval varied between two weeks to nine months (Robbins et al., 2005, Floyd et al., 2007, Cena et al., 2008, Hillemeier et al., 2008, Schwarz et al., 2008, Bastani et al., 2010) or follow-up ended on the birth of subsequent pregnancy (de Jong-Potjer et al., 2006, Lumley and Donohue, 2006, Elsinga et al., 2008). The primary care settings included were in primary care practices (de Jong-Potjer et al., 2006, Floyd et al., 2007, Elsinga et al., 2008, Schwarz et al., 2008), gynaecology outpatient clinics (Robbins et al., 2005), premarital clinics

(Bastani et al., 2010), community-based health centres, such as Women-Infant-Children clinics (Cena et al., 2008, Hillemeier et al., 2008) and one study was home visit (Lumley and Donohue, 2006). In six studies, participants recruited were limited to women planning pregnancy (de Jong-Potjer et al., 2006, Floyd et al., 2007, Elsinga et al., 2008, Hillemeier et al., 2008, Schwarz et al., 2008, Bastani et al., 2010) and the remaining included any reproductive women aged between 18 to 45 years old (Robbins et al., 2005, Lumley and Donohue, 2006, Cena et al., 2008).

Five broad categories of reproductive health outcomes were identified; improvement in maternal knowledge; improvement in self-efficacy and health locus of control; improvement in maternal risk behaviour; improvement in adverse pregnancy outcomes; and improvement in psychological outcomes.

3.5.2 Main findings

3.5.2.1. Improvement in maternal knowledge

Two studies reported an improvement in knowledge as a result of the intervention (Elsinga et al., 2008, Schwarz et al., 2008). The intervention used in the Schwarz study was brief and focussed on single health risk; a 15-minute computerised assisted counselling session of preconception folate supplementation combined with providing a bottle of free folate tablets to participants. This led to improved women's knowledge that folate can prevent birth defects (RR 1.72, 95%CI 1.32 to 2.23) (Schwarz et al., 2008). In the second study the intervention was intensive and involved preconception counselling on multifactorial health risks (Elsinga et al., 2008). In this study knowledge of pregnancy-related risk factors and preventive measures was evaluated in two groups; women who has never been pregnant and those who has been pregnant. The study reported significant improvement in total knowledge score between the intervention and control group in both women who has never been pregnant (difference in score: 11.3 (95%CI 4.6 to 18.0, $p<0.05$) and those who has been pregnant (difference in score 3.0; 95%CI 1.2 to 4.84, $p<0.05$) (Elsinga et al., 2008).

3.5.2.2. Improvement in self-efficacy and health locus of control

Two studies reported on self-efficacy and health locus of control (Hillemeier et al., 2008, Bastani et al., 2010)(21, 23). Interventions in both studies involved preconception health education addressing multifactorial reproductive health risks. The Hillemeier study, an intensive intervention led to significant improvement on self-efficacy towards eating healthier food (OR 1.757, p=0.008), physically active (OR 2.185, p=0.0001) and perceived higher preconception control of birth outcomes (OR 1.916, p=0.031) (Hillemeier et al., 2008). In the

Bastani study, which was a brief intervention also demonstrated significant improvement in exercise self-efficacy ($p<0.001$) and health locus of control scores ($p<0.001$ in internal health locus of control (internal HLOC) and $p= 0.003$ in external health locus of control (external HLOC)) (Bastani et al., 2010).

3.5.2.3. Improvement in maternal risk behaviour

Six studies reported improvement in self-reported maternal risk behaviour; three were brief interventions (Robbins et al., 2005, Cena et al., 2008, Schwarz et al., 2008) and the remaining studies were intensive (Floyd et al., 2007, Elsinga et al., 2008, Hillemeier et al., 2008). All brief interventions focussed on single health risk; preconception folate supplementation. In the intensive group, two studies involved multifactorial reproductive health risks intervention (Elsinga et al., 2008, Hillemeier et al., 2008) whilst another study focussed on single health risk of alcohol consumption (Floyd et al., 2007).

There was statistically significant improvement in self-reported folate intake before pregnancy in three studies that adopted single health risk intervention (Robbins et al., 2005, Cena et al., 2008, Schwarz et al., 2008) and two studies involving multifactorial reproductive health risks interventions (Elsinga et al., 2008, Hillemeier et al., 2008).

Maternal alcohol self-reported consumption appeared improved in one study that only focused on an intervention to reduce alcohol intake (Floyd et al., 2007). This was following five counselling sessions over a fourteen week period (Floyd et al., 2007)(28). Reduced risky drinking was reported at three time points: three months OR 1.79 (95%CI 1.28 to 2.51), six months, OR 1.64 (95%CI 1.15 to 2.33) and nine months, OR 1.54 (95%CI 1.09 to 2.18).

More women who received an intensive preconception risk assessment and counselling by general practitioners on multifactorial reproductive health risks in the Elsinga study also stopped smoking before pregnancy but this was not statistically significant (OR 3.04, 95%CI 0.95 to 9.69) (Elsinga et al., 2008).

3.5.2.4. Improvement in adverse pregnancy outcomes

Reported adverse pregnancy outcomes in the studies included were low birth weight, preterm delivery, congenital anomalies and prenatal death. Two studies, the Elsinga and the Lumley study, both involving multifactorial reproductive health risks intervention, reported adverse pregnancy outcomes (Lumley and Donohue, 2006, Elsinga et al., 2008). In the Elsinga study which involved an intensive intervention, women were followed-up until two months after subsequent delivery, and reported fewer total adverse pregnancy outcomes in the intervention group; 16.2% compared to the control group, 20.2% (OR 0.77, 95%CI 0.48 to 1.22) (Elsinga et al., 2008). The Lumley study, involving brief intervention of preconception counselling by an experienced midwife during home visit to women after first delivery, did not produce statistically significant findings but reported more infants born in subsequent pregnancy in the intervention group were low birth weight (less than 2500g: OR 1.14; 95%CI 0.55 to 2.38) and preterm (less than 37 weeks: OR 1.44; 95%CI 0.73-2.91) (Lumley and Donohue, 2006).

3.5.2.5. Psychological outcomes due to receiving information

Only one study reported psychological outcome which was anxiety following intervention (de Jong-Potjer et al., 2006). This study involved preconception education and counselling intervention of multifactorial reproductive health risks and delivered by general practitioners. Anxiety level was assessed using Spielberger State-Trait Anxiety Inventory (STAI) score and reported as mean score measured; before

intervention (STAI-1), immediately following intervention (STAI-2) and at first trimester of subsequent pregnancy (STAI-3). The results were, the mean STAI-1 score was 36.4. Following intervention, the mean STAI-2 score was lower, 32.8, a decrease of 3.6 points in anxiety-levels (95% CI, 2.4 – 4.8). Women were further followed-up after delivery of subsequent pregnancy and mean anxiety scores based on their memory of the first trimester of their pregnancy (STAI-3) score, was recorded. The mean STAI-3 score in the intervention group however, appeared higher, 38.7 (95%CI 37.9–39.5), when compared to baseline.

Table 3.1 summarised the characteristics of included studies. This is categorised into multifactorial reproductive health risk interventions and single reproductive health risk interventions.

Table 3.2 summarised the results of included studies.

Table 3.1 : Characteristics of included studies

A: MULTIFACTORIAL REPRODUCTIVE HEALTH RISK INTERVENTIONS

STUDY	DESIGN	PARTICIPANTS	NUMBER OF WOMEN RECRUITED	DURATION AND FOLLOW-UP	INTERVENTION ELEMENTS	COMPARATOR ELEMENTS	SETTINGS	OUTCOME MEASURES
Bastani 2010 Iran	RCT	Women 18-35 years old planning to conceive in the first year of marriage	Intervention group: 120 Control group: 120	one day; follow-up two weeks	Preconception health education: individual followed by group session of 8 to 12 women on healthy lifestyle and physical activity by researcher qualified in women's health. With routine premarital clinic sessions.	Routine premarital clinic sessions; covering screening of genetic conditions, drug abuse, sexually transmitted infections and family planning	Premarital counselling clinics	**Multidimensional Health Locus of Control (HLOC) score**: Internal HLOC and external HLOC **Physical exercise self-efficacy score**
Elsinga 2008 Netherlands	Cluster RCT at general practice level	Women aged 18-40 years old planning a pregnancy within a year	Intervention group: 30 GPs; Control group: 37 GPs 14915 women recruited	Single GP consultation; follow-up two months after subsequent delivery	Preconception care counselling by trained GPs on preconception specific and general risks; eg. genetics, infection, medication use, folate, alcohol, smoking. Brochures on preconception health were given.	Usual clinic consultation	General practices	**Knowledge**: Knowledge of pregnancy-related risk factors and 20 items on hazardous substances, prevention of infection, folate and timing of conception **Maternal risk behavioural change**: folate intake; alcohol and smoking **Adverse pregnancy outcomes**: Low birth weight, preterm delivery <37 weeks, congenital anomalies, perinatal death

STUDY	DESIGN	PARTICIPANTS	NUMBER OF WOMEN RECRUITED	DURATION AND FOLLOW-UP	INTERVENTION ELEMENTS	COMPARATOR ELEMENTS	SETTINGS	OUTCOME MEASURES
Lumley 2006 Australia	RCT	Women after delivery of first pregnancy	Intervention group: 777 Control group: 802	one day home visit; follow-up at delivery of subsequent pregnancy	Home visit by PPIS (pre-pregnancy information & counselling service) midwife; discussion on pre-pregnancy health; preparation for next pregnancy, taking family/genetic history, rubella vaccination, avoid cigarettes, alcohol, drugs. Also include discussion on experience of first labour, birth, postpartum	Discussion on experience of first labour, birth, postpartum	Home visit	**Adverse pregnancy outcomes**: low birth weight (<2,500g), difference of mean birth weight between the first and the second children; preterm birth
De Jong-Potjer 2006 Netherlands	Cluster RCT at general practice level	Women aged 18-40 years old planning a pregnancy within a year	Intervention group: 30 GPs; Control group: 37 GPs 14915 women recruited	Single GP consultation; follow-up immediately after consultation and two months after subsequent delivery	Preconception care counselling by trained GPs on preconception specific risk and general risk. Brochures on preconception health were given.	Usual clinic consultation	General practices	**Psychological stress due to receiving information**: Spielberger State-Trait Anxiety Inventory (STAI) score

B: SINGLE REPRODUCTIVE HEALTH RISK INTERVENTIONS

STUDY	DESIGN	PARTICIPANTS	NUMBER OF WOMEN RECRUITED	DURATION AND FOLLOW-UP	INTERVENTION ELEMENTS	COMPARATOR ELEMENTS	SETTINGS	OUTCOME MEASURES
Schwarz 2008 USA	RCT	Women aged 18-45 years old planning a pregnancy within a year	Intervention group: 227 women Control group: 219 women	15 minutes; follow-up 6 months	Computerized counselling on preconception folate supplement and provision of free 200 folate tablets	Computerized counselling on emergency contraception	Urgent care clinic	**Knowledge:** On folate can prevent birth defect **Maternal risk behavioural changes:** Folate intake
Cena 2008 USA	Cluster RCT	Any women aged 18 to 45 years old	Intervention group: 77 Control group: 78	one day; follow-up 4 weeks	Group education on folate-focused nutrition education by FSNE (Food Stamp Nutrition Education) program staff	Group education on resource management	Women-infant clinics; and Food Stamp Program offices	**Maternal risk behavioural changes**: On folate and folate-related food intake
Floyd 2007 USA	RCT	Women aged 18-44 years old planning to become pregnant in the next nine months	Intervention group: 416 Control group: 414	Fourteen weeks; follow-up at 3, 6 and 9 months	Four motivational interviewing counselling sessions by trained counsellors on alcohol and one contraception counselling by physician or family planning nurse	Brochures on alcohol use and women's health in general	Primary care practices	**Maternal risk behavioural changes**: Reduced on risky drinking – binge drinking (consume 5 or more standard drink/day; frequent drinking (8 or more drinks/week; (assessed using timeline follow back (TLFB) method); contraception
Robbins 2004 USA	RCT	Women aged 18-45 years old	Intervention group: 160 Control group: 162	30 to 60 seconds of counselling and booster call at 1 to 2 weeks; follow-up 2 months	Brief counselling by a physician based on a prepared script on 5 evidenced-based benefits of folate; free bottle of 30 tablets and pamphlet on folate by CDC; phone call at 1 to 2 weeks.	Brief counselling on 1 of 3 preventive health care; breast self-exam, seat belt use, sunscreen use, pamphlet on folate and a coupon for free folate tablets	Gynaecology outpatient clinics	**Maternal risk behavioural changes**: Self-reported frequency of folate intake

Table 3.2 : Results of included studies

STUDY	OUTCOME MEASURES	RESULTS
MULTIFACTORIAL REPRODUCTIVE HEALTH RISK INTERVENTIONS		
Bastani 2010 Iran	**Multidimensional Health Locus of Control (HLOC) score**	**Change in mean score (SD):** **Internal HLOC score** 6.3(5.5) versus 0.1(0.5),p<0.001 **External HLOC score** 0.7(2.6) versus 0.3(1.3), p= 0.003
	Physical exercise self-efficacy score	**Physical exercise self-efficacy score** 10.3(4.1) versus 2.1(5.4), p<0.001
Elsinga 2008 Netherlands	**Knowledge**	**Improvement in knowledge** In women never been pregnant difference in knowledge score 11.3 (95%CI 4.6-18.0) and who has been pregnant: 3.0 (95%CI 1.2-4.84)
	Maternal risk behavioural change	**Maternal risk behavioural change:** Folic acid use OR: 5.40 (95%CI 3.15–9.28) Alcohol: No binge drinking on ≥1 occasion before or during pregnancy OR: 1.52 (95%CI 0.64–3.60). No alcohol use during first 3 months of pregnancy OR: 1.68 (95%CI 1.03–2.75). Quit smoking before pregnancy OR: 3.04 (95%CI 0.95–9.69).
	Adverse pregnancy outcomes	**Adverse pregnancy outcomes** Total number of adverse pregnancy outcomes in the intervention group is 23/145(N); 16.2% as compared to control group 343/1740(N); 20.2%. OR 0.77(95% CI 0.48-1.22) Congenital anomalies 5/145(3.9%) versus 68/1740(4.5%). OR 0.88 (95% CI 0.35-2.21) Low birth weight OR 0.58 (95% CI 0.21-1.61)Preterm delivery<37 weeks OR 0.76 (95% CI 0.36-1.59) Perinatal death OR 0.86 (95% CI 0.11-6.55)
Hillemeier 2008 USA	**Self-efficacy**	**Improvement in self –efficacy** To eat healthier food OR 1.757, p= 0.008 Physically active OR 2.185, p< 0.0001 Preconceptional control OR 1.916, p= 0.031
	Maternal risk behavioural changes	**Maternal risk behavioural changes** Daily multivitamin with folate intake OR 6.595, p=0.0001

STUDY	OUTCOME MEASURES	RESULTS
De Jong-Potjer 2006 Netherlands	**Psychological stress due to receiving information** Mean score measured before intervention (STAI-1), immediately following intervention (STAI-2) and at first trimester of subsequent pregnancy (STAI-3)	**Psychological stress due to receiving information** Change in mean score between STAI-1 and STAI-2: 3.6 (95% CI, 2.4 – 4.8) in intervention group Mean scores of the STAI-3 were 38.7 (95% CI 37.9 – 39.5) in intervention group versus 38.5 (95% CI 37.7 – 39.3) in control group
SINGLE REPRODUCTIVE HEALTH RISK INTERVENTIONS		
Schwarz 2008 USA	**Knowledge** **Maternal risk behavioural changes**	**Knowledge** Improvement in knowledge on folate can prevent birth defect OR: 4.19 (95%CI 1.98-8.85) Knows that folate is important in the first few weeks OR 2.7 (95% CI 1.75-4.26) **Maternal risk behavioural changes** Folate intake increased in the last few months OR: 1.55 (95%CI 0.88-2.72)
Cena 2008 USA	**Maternal risk behavioural changes**	**Maternal risk behavioural changes** Mean folate intake from all sources (naturally occurring and synthetic) (µg DFE/d) increased in the 197.9±58.2 in the intervention group versus 46.8±85.4 in the control group. p=0.035
Floyd 2007 USA	**Maternal risk behavioural changes**	**Maternal risk behavioural changes** Reduced risky drinking at 3 months follow-up OR: 1.79 (95%CI 1.28-2.51) Reduced risky drinking at 6 month follow-up OR: 1.64 (95%CI 1.15-2.33) Reduced risky drinking at 9 month follow-up OR: 1.54 (95%CI 1.09-2.18)
Robbins 2004 USA	**Maternal risk behavioural changes**	**Maternal risk behavioural changes** Daily folate use increased 67% in the intervention group relative to baseline as compared to 54% in the control group. p=0.549. Weekly folate intake increased 68% in the intervention group relative to baseline as compared to 20% in the control group. p=0.008

3.6 Quality assessment of included studies

Overall, the reported methodological quality of the studies was generally moderate to poor. In general, the studies involving multifactorial reproductive health risks intervention had higher risk of bias as compared to studies of single reproductive health risk intervention. Allocation concealment was only described in two studies (Floyd et al., 2007, Schwarz et al., 2008). Blinding of the participants and personnel who delivered the intervention was not possible in majority of studies as interventions involved education and counselling. Documentation of participants who were lost to follow-up or refused follow-up was generally incomplete in studies involving multifactorial reproductive health intervention. One study reported 47% of women from the intervention group and 50% from the control group, who did not attend the follow-up assessment, were excluded from analyses (Hillemeier et al., 2008). In a further study, 43% of women from the intervention group who were lost to follow-up or did not become pregnant were also excluded from the analyses (Lumley and Donohue, 2006). In one study, only two to three percent of women recruited for preconception counselling actually attended within the study period (Elsinga et al., 2008). Attrition was not clearly described in studies involving single reproductive health risk (Robbins et al., 2005, Floyd et al., 2007, Cena et al., 2008). Results of studies with high levels of attrition should be interpreted with caution. Selective reporting was minimal in studies involving single reproductive health risk intervention; most data for pre-specified outcomes was reported (Robbins et al., 2005, Floyd et al., 2007, Schwarz et al., 2008). Results was clearly reported for the intervention group but insufficient data on the control group in one study involving multifactorial reproductive health risks intervention (Hillemeier et al., 2008). In addition, there may be reporting bias by the participants in studies where outcome measures were self-reported such as anxiety score (de Jong-Potjer et al., 2006) and studies indicating maternal risk behaviour outcomes (Robbins et al., 2005,

Floyd et al., 2007, Elsinga et al., 2008, Hillemeier et al., 2008, Schwarz et al., 2008).

Assessment of risk of bias is summarised in Table 3.3.
For detailed data extraction and quality assessment of each included studies are presented in Appendix 3.3.

Table 3.3 : Risk of bias of included studies

	MULTIFACTORIAL REPRODUCTIVE HEALTH RISKS INTERVENTION					SINGLE REPRODUCTIVE HEALTH RISK INTERVENTION			
	Bastani	**Elsinga**	**Hillemeier**	**Lumley**	**De Jong-Potjer**	**Schwarz**	**Cena**	**Floyd**	**Robbins**
Sequence generation	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear
Allocation concealment	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Blinding	High risk	High risk	High risk	High risk	High risk	Low risk	High	High risk	High risk
Incomplete outcome data	Unclear	High risk	High risk	High risk	High risk	Low risk	Unclear	Unclear	Unclear
Selective reporting	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk

3.7 Discussion

3.7.1 Summary of main findings

This review identified nine recent randomised controlled trials in primary care or community-based settings. However, there was variation in the characteristics of interventions evaluated in this review and results were heterogeneous. Five studies involving multifactorial reproductive health risk interventions (de Jong-Potjer et al., 2006, Lumley and Donohue, 2006, Elsinga et al., 2008, Hillemeier et al., 2008, Bastani et al., 2010) and these assessed maternal knowledge (Elsinga et al., 2008), self-efficacy and health locus of control (Hillemeier et al., 2008, Bastani et al., 2010), risk behaviour (Elsinga et al., 2008, Hillemeier et al., 2008) adverse pregnancy (Lumley and Donohue, 2006, Elsinga et al., 2008) and psychological outcomes (de Jong-Potjer et al., 2006). Further, there were four studies involving single reproductive health risk intervention reported on maternal knowledge (Schwarz et al., 2008) and risk behaviour (Robbins et al., 2005, Floyd et al., 2007, Cena et al., 2008, Schwarz et al., 2008). Considering the duration and nature of the nine interventions, four interventions were intensive and prolonged (Floyd et al., 2007, de Jong-Potjer et al., 2006, Elsinga et al., 2008, Hillemeier et al., 2008) and five were brief (Robbins et al., 2005, Lumley and Donohue, 2006, Cena et al., 2008, Schwarz et al., 2008, Bastani et al., 2010).

Irrespective of the nature of the interventions whether involved multifactorial or single reproductive risk, as well as intensity and duration of intervention, all demonstrated an improvement in maternal knowledge (Elsinga et al., 2008, Schwarz et al., 2008), self-efficacy and health locus of control (Hillemeier et al., 2008, Bastani et al., 2010). With regards to maternal risk behaviour, there was evidence for improvement in folate intake and alcohol consumption, however less convincing for smoking cessation (Elsinga et al., 2008, Hillemeier et al.,

2008, Schwarz et al., 2008). The evidence for the impact of multifactorial risk interventions on adverse pregnancy outcomes was inconclusive (Lumley and Donohue, 2006, Elsinga et al., 2008). One study reported impact on psychological wellbeing involving multifactorial health risks intervention and demonstrated no untoward short term anxiety but the evidence is less clear for a longer term effect (de Jong-Potjer et al., 2006).

3.7.2 Comparison with existing literature

Our review has added to the evidence by including recent relevant trials. Compared to a systematic review published in 1999 (Poppelaars et al., 2004c), a further nine randomised controlled studies were identified. Furthermore, compared to a more recent Cochrane review (Whitworth and Dowswell, 2009) that excluded women with pre-existing medical illnesses or genetic risk, this review has identified an additional five studies (de Jong-Potjer et al., 2006, Cena et al., 2008, Elsinga et al., 2008, Schwarz et al., 2008, Bastani et al., 2010). Unlike the previous reviews, this review focused on primary care or community-based settings. Although the studies in this review are too heterogeneous in terms of interventions involved, they indicate improved maternal knowledge and improved risk behaviour following interventions. Previous interventional studies that was carried out in hospital settings has demonstrated improved rate of adverse pregnancy outcomes such as reducing neural tube defect and congenital anomalies, following single reproductive health risk intervention of folate supplementation (Wake et al., 1996, Czeizel, 1993). Further, preconception control of hyperglycaemia was also associated with reduced risk of congenital anomalies in women with pre-existing diabetes (Kitzmiller et al., 1998) in similar hospital setting. In addition, observational studies, comprising health promotion and education to improve folate intake in women of childbearing age have also demonstrated improved awareness and reduced risk of neural tube defects (Berry et al., 1999, Watson et al., 2001). Another community-

based observational study, comprising a comprehensive preconception assessment and counselling on multifactorial reproductive health risks, demonstrated improved rates of adverse pregnancy outcomes, reduced infectious disease, and improved detection of genetic risk (Czeizel, 2012).

3.7.3 Strengths and limitations

To our knowledge, this is the first review to examine the effectiveness of preconception interventions in women in the primary care or community-based settings. Previous reviews have not focused on this setting and have excluded individuals with pre-existing medical conditions (Poppelaars et al., 2004c, Whitworth and Dowswell, 2009). However, there are some limitations related to the included studies for this review.

In two-thirds of the studies, participants were restricted to women planning pregnancy (de Jong-Potjer et al., 2006, Floyd et al., 2007, Elsinga et al., 2008, Hillemeier et al., 2008b, Schwarz et al., 2008, Bastani et al., 2010). Women planning pregnancy are potentially more motivated to change any risk behaviour in order to have uncomplicated pregnancies and healthy infant. This could contribute to the improvement of maternal behaviour. Thus, it is necessary to extend the study population to those even with unplanned pregnancy to evaluate the benefits of preconception care. This is crucial as unplanned pregnancies contribute to at least half of all pregnancies in England and Wales (Williamson et al., 1989, Lafayette et al., 1999a) and in the United States (Mitchell et al., 1993).

The overall quality of the evidence was moderate to poor, particularly in studies involving multifactorial health risks intervention requiring caution in interpreting the effectiveness of preconception interventions. Methodological flaws included lack of allocation concealment and missing outcome data due to attrition.

Furthermore, evidence from maternal risk behaviour and anxiety assessment relied on self-reported information which may not be reliable.

3.7.4 Implications for future practice

National and international policy document, such as UK Human Genetics Commission, NICE Maternity Guidelines, March of Dimes Foundation and Health Council of Netherlands, have highlighted the benefits of preconception risk assessment (Rowley et al., 1997, Denayer et al., 1992). With the introduction of the revised General Practitioner contract in 2004, each general practice was incentivised to produce a preconception risk assessment policy and incorporate preconception enquiry as part of certain disease domains, such as in diabetes management (Quality and Outcome Framework, 2004). Although the interventions of preconception education and counselling in this review were not supported by strong evidence, they seem plausible strategy for improving reproductive health and adverse pregnancy outcomes. The information would be useful to help planning to provide preconception care in primary care practice in future.

3.7.5 Implications for future research

For realistic implementation, preconception risk assessment in primary care for single risk factor interventions, and prolonged and intensive intervention would not be viable. Hence, future research needs to be pragmatic, integrating within the structure of current general practice or primary care setting comprising multifactorial risk assessment and interventions. Furthermore, appropriately developed interventions need to be evaluated in a controlled trial environment and future studies should recruit all eligible women, not merely those planning pregnancy in the forthcoming months. In this way this assessment would be accessible to all at-risk couples.

3.8 Conclusion

Overall, there is relatively limited evidence for the effectiveness of preconception interventions in primary care. Lack of evidence should not preclude recommending preconception intervention as a component of improving reproductive health. This review has synthesized potential key findings specifically in the areas of knowledge and risk behaviour modification. Despite possible sources of bias, this review also has identified possible opportunities from the nature of interventions that could inform future studies.

The following chapter will discuss systematic review carried out to examine specifically the effectiveness of preconception assessment of reproductive genetic risk in any health care setting.

CHAPTER 4

A SYSTEMATIC REVIEW OF THE EFFECTS OF PRECONCEPTION RISK ASSESSMENT FOR THALASSAEMIA, SICKLE CELL DISEASE, CYSTIC FIBROSIS AND TAY-SACHS DISEASE

4.1 Introduction

Previously, Chapter 3 discussed on systematic review of preconception care interventions in the primary care setting and found encouraging findings in improving maternal knowledge, self-efficacy and health locus of control, as well as maternal risk behaviour.

Further to this, as highlighted in Chapter 1 and Chapter 2, reproductive genetic risk assessment has constituted one of the main preconception care evaluation. The potential benefits of preconception assessment of genetic risk are also increasingly recognised, yet there is still limited evidence on its effectiveness in the health care settings. In line with the aim of this thesis and its focus on preconception assessment of genetic risk in primary care, it was important to address this issue.

The objective of this chapter is to present a systematic review carried out to examine the effects of preconception assessment of genetic risk. Because of limited studies in this area, particularly in primary care, the scope of this review included all health care settings. This review was also developed with the Cochrane Collaboration of Cystic Fibrosis and Genetic Disorders Group.

4.2 Background

As mentioned earlier in Chapter 1 of Introduction, the discussion of genetic conditions in this thesis will be confined to autosomal recessive conditions, namely, haemoglobinopathies such as Thalassaemia and Sickle Cell Disease, Cystic Fibrosis and Tay-Sachs disease. This is because of several reasons. Firstly, autosomal recessive conditions

bear carrier state property where only carries one copy of affected gene. Carriers are usually asymptomatic, they do not manifest clinically. However, future offspring can be affected if he or she inherits both affected genes from carrier couples of prospective parents. Thus, detecting carrier state before conception would allow informed decisions and offer a range of reproductive options (Denayer et al., 1992). Secondly, these conditions were more described in the literatures with regards to genetic screening services or programmes, for examples; thalassaemia (Angastiniotis and Modell, 1998, Samavat and Modell, 2004, Alswaidi and O'Brien, 2009), cystic fibrosis (Christie et al., 2009, Massie et al., 2009) and Tay Sachs disease (Zeesman et al., 1984, Mitchell et al., 1996). And thirdly, these conditions are recognised to cause significant public health burden (Buhi and Goodson, 2007).

Chapter 2 of Literature Review has discussed the benefits of preconception genetic carrier screening carried out in secondary schools (Zeesman et al., 1984; Mitchell et al., 1996; Lena-Russo et al., 2002), before marriage (Angastiniotis and Modell, 1998, Samavat and Modell, 2004, Alswaidi and O'Brien, 2009) and before couples conceive (Czeizel, 1999, Christie et al., 2009, Massie et al., 2009). Further, the benefits of family history recording as one of the components of the preconception health checks have been reported in previous observational community-based studies for a broader range of genetic conditions, in both the United Kingdom (Rose et al., 1999), and Hungary (Czeizel, 2012). The participants acknowledged that this intervention enabled pregnancy planning (Rose et al., 1999) and early identification of couples at reproductive genetic risk (Czeizel, 2012). However, these were observational studies and they are subjected to bias.

While a number of observational studies have reported the potential benefits of preconception genetic carrier screening, as with other screening programmes, assessment of genetic risk has potential

adverse effects. Genetic assessment for reproductive risk has been linked to psychological distress such as anxiety; however, the raised anxiety was reported as a transient phenomenon (Bekker et al., 1994, Archibald and Wilford, 2011). Further, it has been reported that carrier status may be associated with a poor perception of health (Henneman et al., 2002) and may have an impact on the carrier's relationships with their partner (Fanos and Johnson, 1995a). Social impacts such as stigmatisation and discrimination have also been reported (Kennen and Schmidt, 1978, Bonham et al., 2010). Despite these reported adverse effects, there are numerous psychological benefits including the support of informed decision-making and reproductive autonomy in prospective parents (Anido et al., 2005, Archibald and Wilford, 2011, Lewis et al., 2011).

With regards to the economic implications, as for other screening programmes, there is an opportunity cost for redistributing resources from medical care to preconception screening (WHO, 1968). Several economic appraisals of haemoglobinopathies screening in the antenatal and neonatal settings have indicated that these strategies are cost-effective (Zeuner et al., 1999, Davies et al., 2000).

At a policy level, preconception genetic risk assessment has also been recommended in the Netherlands, the United States of America and the United Kingdom (Health Council of Netherlands, 2007, March of Dimes, 2008, Denayer et al., 1992). This review aims to provide concrete evidence for preconception genetic risk assessment before widespread routine implementation in current health care settings.

4.3 Objective

The objective of this review is to examine the effectiveness of systematic preconception assessment of genetic risk in people of childbearing age for the identification of reproductive genetic risk of thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease.

4.4 Methods

The process in conducting this review followed the key steps as outlined in the Cochrane Systematic Review of Intervention Studies (Clayton et al., 1996). A protocol to conduct this review within the Cochrane Collaboration has also been developed and accepted by the Cochrane Cystic Fibrosis and Genetic Disorders Group. The protocol is currently being reviewed by the Editor of Cochrane Cystic Fibrosis and Genetic Disorders Group.

4.4.1 Search strategy

Studies were systematically searched following four databases; MEDLINE, CINAHL, EMBASE and PsycINFO from 1970 to end of August 2013. The start dates for database searches were set to when carrier screening or testing was first available. Based on WHO reports, earliest carrier status assessment was introduced for Tay-Sachs disease and haemoglobinopathies from the early 1970s (Angastiniotis et al., 1995, Kaback, 2000). Thus, relevant studies were searched in the databases from 1970 or the date of the database was first available if after 1970. The detailed search is available in Appendix 4.1.

The databases and the start dates of relevant studies:

1. Ovid MEDLINE (1970 until date);
2. Ovid EMBASE ((1974 until date);
3. CINAHL (1970 until date);
4. Ovid PsycINFO (1970 until date).

The search strategies was generated based on the guidelines in the Cochrane Systematic Review of Intervention Studies (Higgins and Green, 2011), relevant previous reviews published for Cochrane Cystic Fibrosis and Genetic Disorders Group, relevant literatures on the subject of preconception genetic risk assessment and consultation with information specialists of the Kleijnen Systematic Review as well as a medical librarian of the University of Nottingham. A manual search from reference lists of eligible published studies was also examined to identify further relevant and potential studies. Language was not restricted in the primary searching. However, no potentially eligible non-English language study was identified.

4.4.2 Eligibility criteria

Studies considered eligible for this review were intervention studies, randomised controlled and non-randomised. Before-and-after studies were also considered for inclusion.

Types of participants included in this review were all women of reproductive age between 16 to 50 years old with or without partners, accessing any health care services which include primary, secondary and tertiary care, in hospitals and community-based settings. Any health care services were included to anticipate limited number of retrieved studies if studies only focus on one setting for example, primary care. Community-based settings considered eligible encompassed family or general practices, community health centres, community health services, community or outpatient clinics and ambulatory care services. However, interventions implemented in school were not included. This is because in school-based studies the true effect of the intervention possibly could not be isolated due to the outcomes being assessed years down the line, and school-based studies may not be appropriate to identify at-risk individuals before pregnancy.

The study included any types of interventions concerning genetic risk assessment performed or offered at any time prior to conception. Here, the intervention was defined as a package of risk assessment including one or more of these components:

- family history assessment;
- assessment of ethnicity background;
- pre-carrier test counselling or education;
- genetic carrier testing;
- genetic carrier screening

The interventions involved four pre-specified conditions namely; thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease.

Types of outcomes assessed in this review were divided into primary and secondary outcomes.

Primary outcomes

1. Reproductive outcomes in at-risk individuals or couples identified during or after pregnancy:

i. Number of infants born with genetic conditions
ii. Number of infants born with congenital anomalies
iii. Number of infants born with low birth weight
iv. Number of infants born prematurely

2. Decisions about future conception and pregnancy in at-risk individuals or couples at any point after intervention:

i. Number of women or couples who would make use of prenatal diagnosis
ii. Number of women or couples who would make use of prenatal diagnosis and consider termination of pregnancy if the child is affected
iii. Number of women or couples who would consider pre-implantation genetic diagnosis and in vitro fertilization
iv. Number of women or couples who would conceive using donated gametes

v. Number of women or couples who would consider adoption
vi. Number of women or couples who would refrain from having any children

Secondary outcomes

Secondary outcomes are divided into two; measured during pregnancy following intervention and measured at the time of intervention.

1. During pregnancy following intervention:
    i. Gestational date of prenatal diagnosis in at-risk women
    ii. Gestational date of prenatal counselling in at-risk women or couples

2. At the time of intervention:
    i. Any objective measures of health-related quality of life resulting from preconception genetic risk assessment, using validated tools such as Short Form Health Survey 36 (SF36) and Health Questionnaire EQ-5D
    ii. Number of carrier women identified
    iii. Number of carrier women and partners, or couples identified
    iv. Any objective measures of quantifying psychological or social outcomes or both resulting from preconception genetic risk assessment using validated tools such as Spielberger State-Trait Anxiety Inventory (STAI), Perceived Stress Questionnaire (PSQ)
    v. Knowledge: Any measures of the women's or couples' or both, knowledge of reproductive genetic risk associated with carrier status for thalassaemia, sickle cell disease, cystic fibrosis or Tay-Sachs disease using validated self-reported questionnaire
    vi. Satisfaction: Any measures of the women's or couples' or both, satisfaction with the intervention using validated self-reported questionnaire

3. Cost of the intervention

Outcomes that measured the cost and effectiveness of the interventions were also considered during undertaking this review.

4.4.3 Study identification

All retrieved records from the four databases were entered into the Endnote X3, the Endnote reference managing software. Any duplicates were initially removed. Every titles and abstracts identified were screened by the researcher and checked independently by a second author. These titles and abstracts were labelled ‘include’ or ‘exclude’. Full texts of studies potentially meeting the inclusion criteria, labelled as ‘include’ were assessed independently by two authors (researcher (NH) and second author (NQ)) for relevance and inclusion. The researcher (NH) also hand searched the reference lists of all retrieved papers. Where disagreement existed, consensus was resolved through discussion. An author of the included titles and abstract were contacted for further information and clarification before including studies in the review.

4.4.4 Data extraction

Data extraction was carried out by the researcher (NH) and verified by the second author (NQ). Any disagreement was resolved through discussion. The data extraction form for the study description was developed based on the guidelines in the Cochrane Systematic Review of Intervention Studies (Higgins and Green, 2011), however customised to the objective of this review. Where possible, the following descriptions of studies were documented:

1. study designs
2. characteristics of study participants (age, planning pregnancy, ethnicity, cultural characteristics, geographic locations)
3. inclusion and exclusion criteria
4. details of interventions (duration, follow-up, provided by whom)
5. details of comparator (if applicable)
6. settings of interventions
7. outcomes investigated
8. results of findings

4.4.5 Assessment of quality of studies

Assessment of quality of studies was carried out by the researcher and verified by the second author. Primary investigators were contacted to clarify uncertainties in data reported in the included studies or any missing data which has a potential impact on the quality of studies.

According to the Cochrane guideline, for randomised control studies, criteria to assess the quality of eligible studies involved the following five domains:

1. sequence generation
2. allocation concealment
3. blinding of participants, study personnel and outcome assessors
4. incomplete outcome data
5. selective outcome reporting

For every included study, each domain was classified as ‘high’, ‘low’ or ‘unclear’ risk of bias to determine the quality of studies. Studies were considered as highly susceptible of bias if 2 or more were classified as ‘high’ risk or 3 or more as ‘unclear’ risk of bias.

As this review also considered non-randomised studies, two methodological quality checklists of non-randomised studies of interventions as outlined in the Cochrane Guideline, have been evaluated; Downs and Black instrument and the Newcastle-Ottawa scale (Deeks et al., 2003). For this systematic review, Downs and Black instrument was preferred as the tool was easy to use and items in the checklist were in agreement with this review to synthesize the evidence. The Downs and Black instrument contains 27 ‘yes’-or-'no’ questions across five sections. The five sections include questions about:

1. Overall quality of the study (10 items)
2. External validity; the ability to generalize findings of the study (3 items)
3. Study bias; to assess bias in the intervention and outcome measure(s) (7 items)
4. Confounding and selection bias; to determine bias from sampling or group assignment (6 items)
5. Power of the study; to determine if findings are due to chance (1 item)

4.4.6 Data synthesis

Due to the differences in the study designs, nature of interventions and outcomes, the data was not pooled in a meta-analysis. Outcome measures were reported separately for the two included studies. Results were presented as reported in each study. Outcome measures for knowledge and anxiety were presented as mean score of all the participants or change in mean score as reported in the two studies. P value of < 0.05 was considered as significant. Results on outcomes such as uptake of screening, feeling worried, recall of test-results,

understanding of test-results, reproductive intentions and satisfaction were reported as proportion. Where possible, odds ratio and 95% confidence interval will be presented or calculated.

4.5 Results

4176 references were retrieved and screened. 1492 duplicates were removed. 2684 references were screened for eligible titles and abstracts. Six full papers of potentially eligible studies were retrieved. After reviewing full text documents, only two studies met the inclusion criteria and were critically appraised.

4.5.1 Description of included studies

Table 4.1 summarised the characteristics and findings of included studies. The details of the two included studies are presented in the Appendix 4.3.

Table 4.1 : Characteristics of included studies

	Henneman 2002 Netherlands	Lakeman 2008 Netherlands
Aim of study	To assess the impact of offering preconception cystic fibrosis carrier couple screening	To study psychological outcomes, knowledge, recall and understanding of test-results, satisfaction and reproductive intentions in preconception carrier screening for cystic fibrosis and haemoglobinopathies in a multi-ethnic population in Netherlands, in which a couple's eligibility for cystic fibrosis and/or haemoglobinopathies was based on both partners' ancestry
Study design	Non-randomised study involving two different approaches in the interventions; firstly, looking at the mode of invitation for screening and the other was comparing three modes of information giving	Non-randomised, before-and after study
Eligibility criteria	Age: 20 – 35 years old Individual who had a partner with whom they were planning a pregnancy, irrespective of whether this would be in the near future or at a later date	Age: 20 – 35 years old Individual who had a partner with whom they were planning a pregnancy, irrespective of whether this would be in the near future or at a later date
Exclusion criteria	Pregnancy, positive family history of cystic fibrosis, age younger than 18 years old, having fertility and psychosocial problems	Pregnancy, inability to read and write in Dutch, positive family history of cystic fibrosis and/or haemoglobinopathies
Recruitment procedure	Names and addresses of potential participants were obtained from the practice register and population register and either invited by own general practitioners and Municipal Health Service. Recruitment period: May 1997 to December 2000	Names and addresses of potential participants were obtained from the practice register and population register and either invited by own general practitioners and Municipal Health Service. Recruitment period: January to December 2005
Setting	Community-based	Community-based
Intervention	First approach of intervention involved mode of invitation, individuals were sent either invitation letters by the Municipal Health Service (MHS) or by their general practitioners. Both letters were identical, but signed by the Director of Municipal Health Service and the latter written and signed by the general practitioners respectively. In this intervention, the primary outcome was uptake of screening. The second approach involved three types of information giving regarding carrier couple screening for cystic fibrosis; pre-carrier test education provided during a group session, individual pre-carrier test consultation by the general practitioner and the third group was sent a brochure about cystic fibrosis and carrier testing. No face-to-face session involved with the third group. The group session was provided by the researcher (L.H).The interventions were then followed by the actual carrier testing.	Target individuals were sent invitation for screening, information leaflet and decisional questionnaire which have a question on individual's ancestry, to screen for eligibility. Decisional questionnaire were self-reported. Eligible participants with their partner were required to visit their general practitioner for pre-carrier test consultation followed by offering carrier testing. Samples were taken and actual testing of the samples only carried out after receiving signed informed consent form. A brochure on information about clinical and genetic aspects of the conditions, test procedure, test sensitivity was provided to take home. *step-wise cystic fibrosis carrier testing; one partner tested first and the second was tested only if the first partner's result was positive. For haemoglobinopathies carrier testing, both partners were tested.

	Henneman 2002 Netherlands	Lakeman 2008 Netherlands
Main outcomes	Main outcomes were reported by participants using a validated structured questionnaire completed at three different measurement points; 1: before pre-carrier test education or consultation 2: within one week after consultation but before test-results 3: six months after receiving carrier test-results	Main outcomes were reported by participants using a validated structured questionnaire completed at four different measurement points; 1: 30 min before pre-carrier test consultation 2:within one week after consultation but before test-results 3: one week after receiving carrier test-results 4: three months after receiving carrier test-results
Psychological outcomes (anxiety level feeling worried)	Not applicable Measured at 3	Measured at 1,2,3,4 Measured at 3,4
Knowledge outcomes	Measured at 1,2,3	Measured at 1,2,3
Recall of test-results	Measured at 3	Measured at 3,4
Understanding of test-results	Measured at 3	Measured at 2,3,4
Reproductive intentions	Measured at 2,3	Measured at 2,4
Satisfaction	Measured at 3	Measured at 3,4
Study population	Invitation n=38291 Response n=1160 (580 couples) Eligible n=1118 (559 couples) Tested n= 1118 (559 couples)	Invitation n=9453 Response n=1566 Eligible n=556 Tested n=87 individuals and providing 72 couple for testing 47 couples eligible for testing of cystic fibrosis only, 6 for haemoglobinopathies only, and 19 for both

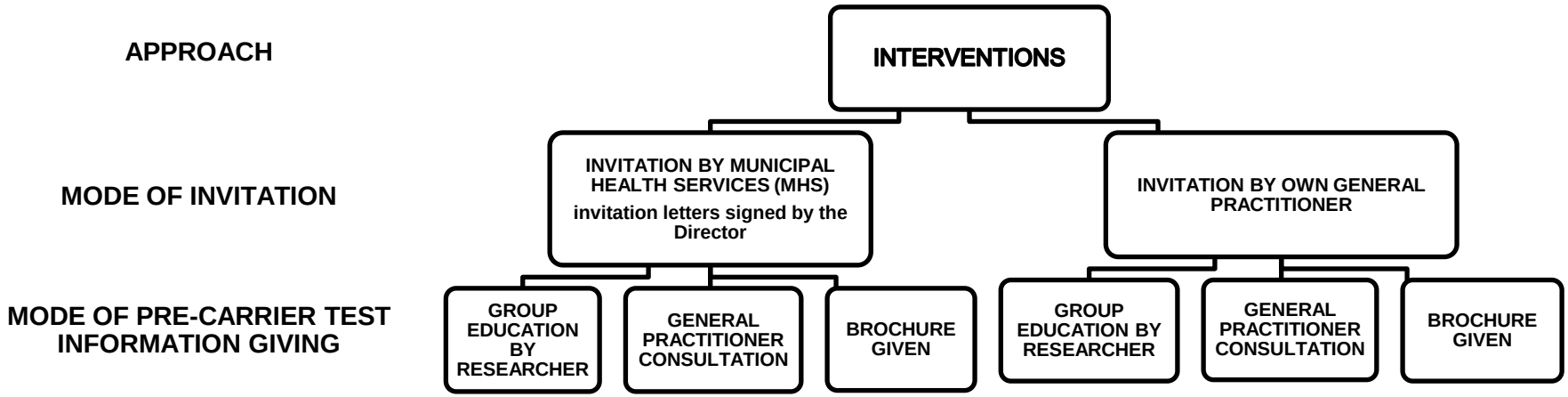
Both, the Henneman and the Lakeman studies were diverse in their study design, methodology and intervention. They were non-randomised; in one study, there were two different approaches in the interventions; firstly, looked at the mode of invitation for screening and the other was comparing three modes of information giving (Henneman et al., 2002) and the other was before-and-after intervention study (Lakeman et al., 2008). Both studies were community-based and conducted in the Netherlands. In both studies, participants recruited were individuals aged 20 to 35 years old, with a steady partner with whom they were planning a pregnancy irrespective of whether it is in

near future or later. In other words, eligible participants involved both couples.

Henneman (2002) assessed the acceptability and effects of offering preconception cystic fibrosis carrier couple screening. In this study, two different approaches in the interventions were described; one looked at the mode of invitation for screening and the next, compared three types of information giving regarding carrier couple screening for cystic fibrosis. With regards to the mode of invitations, individuals were sent either invitation letters by the Municipal Health Service (MHS) or by their general practitioners. Both letters were identical, but signed by the Director of Municipal Health Service and the latter written and signed by the general practitioners respectively. In this intervention, the primary outcome was uptake of screening.

The second approach involved three types of information giving regarding carrier couple screening for cystic fibrosis; pre-carrier test education provided during a group session, individual pre-carrier test consultation by the general practitioner and the third group was sent a brochure about cystic fibrosis and carrier testing. No face-to-face session involved with the third group. The group session was provided by the researcher (L.H).The interventions were then followed by the actual carrier testing. The primary outcomes evaluated for these interventions were psychological outcome, knowledge regarding cystic fibrosis, recall and understanding of test-results, reproductive intentions, and satisfaction. All outcomes were obtained from a self-reported questionnaire which was completed at three different measurement points; before pre-carrier test education or individual consultation (1), within one week after the consultation but before the results (2), and six months after receiving the test-results (3). The self-reported questionnaire was previously validated (Henneman et al., 2001b).

Figure 4 : Illustrates the different approaches in the interventions (Henneman 2002)



The Lakeman study involved offering preconception ancestry-based carrier couple screening for both cystic fibrosis and haemoglobinopathies. This unique targeted ancestry approach was based on a validated decisional instrument (Lakeman et al., 2006). The nature of the screening was participant-driven, where couples' eligibility to do screening for cystic fibrosis and haemoglobinopathies were based on self-reported ancestry enquired in the decisional instrument. Eligible couples had individual pre-carrier test consultation by their general practitioners followed by the actual carrier testing. Primary outcomes evaluated in this study were psychological outcome and knowledge about inheritance. These outcomes were measured before-and-after the introduction of the intervention. There were also other outcomes assessed; recall of test-results, understanding of test-results, reproductive intentions and satisfaction. However, these were measured only after intervention. All outcomes were obtained from a self-reported questionnaire which were completed at four different measurement points; about 30 minutes before pre-carrier test consultation by their general practitioners (1), within one week after the consultation but before the results (2), one week (3) and three months (4) after receiving the test-results. The questionnaire was previously validated (Lakeman et al., 2006).

4.5.2 Main findings

4.5.2.1. Uptake of screening

Only the Henneman study reported this outcome. Response rate of participants offered for group education was higher when invited by the general practitioners (11.9% 95%CI 10.2-13.8) as compared to invitation by the Municipal Health Service (9.2% 95%CI 8.4-10.0).

For participants offered consultation by general practitioners, response rate was similar irrespective of the mode of invitation; MHS 24.7% 95%CI 22.1-27.4); general practitioner (24.7% 95%CI 19.1-30.9).

4.5.2.2. Psychological outcomes

In the Henneman study, participants were asked to indicate whether they felt worried while waiting for their test-results which were asked at six months follow-up. The study reported that overall, only 8 out of 826 participants (<1%) reported worry; 4 of whom were carriers. Participants who attended educational group session and those who received brochure were likely to be more worried than those who attended a general practitioner's consultation ($p<0.04$).

In the Lakeman study, anxiety level was assessed before-and-after the intervention at four measurement points as described earlier, by using a 6-item short form of Spielberger Strait-Trait Anxiety Inventory (STAI) on a 4-point scale. In this scale, a score of 1 indicated low level of anxiety and a score of 4 indicated high level of anxiety. Here, the results of STAI were reported as mean scores. This study reported no further worsening of anxiety level following intervention; the mean scores at four measurement points were 1.6, 1.5, 1.3 and 1.3 respectively, ($p<0.001$).

The participants were also asked to indicate whether they felt worried while waiting for their test-results; only 31 out of 116 participants (27%) reported worry.

4.5.2.3. Knowledge outcomes

The Henneman study compared knowledge outcome of participants following the three preconception interventions on information giving as mentioned previously. This was assessed using five multiple choice questions on cystic fibrosis and carrier inheritance at three measurement points; before (1) and after (2) pre-carrier test group education or individual general practitioner consultation, and six month after the receipt of test-results (3). The study reported that, at all three

measurement points, the knowledge score were significantly higher for participants who attended the group education session than those who received general practitioners' consultation ($p<0.001$). The increase in knowledge score within one week following group education was significantly higher than after general practitioner consultation ($p=0.001$). When compared at 6 months after test-results, knowledge score of participants who attended the general practitioners' consultation was similar to those who did not have personal education while those who had the group education were higher.

Lakeman (2008) assessed participants' knowledge using five item questionnaire about inheritance of cystic fibrosis and haemoglobinopathies, measured at three measurement points as described earlier. This study reported that the knowledge score significantly increased from before pre-carrier test consultation (knowledge score=2.8) to after consultation (knowledge score=3.7), ($P<0.05$). However decreased at one week after receiving test results (knowledge score=2.8, $p<0.001$).

4.5.2.4. Recall of test-results

Recall of test results was assessed at six-month follow-up in the Henneman study while the Lakeman (2008) study assessed at three-month follow-up. In both studies majority of the participants were able to recall their test-results. 771 out of 826 (93%) participants in the Henneman study and the Lakeman study was 113 out of 120 (94%) participants.

4.5.2.5. Understanding of test-results

To assess understanding of test-results, participants were asked on their residual risks following their own test-results, for example; risk of having a child with cystic fibrosis or haemoglobinopathies.
In the Henneman (2002) study, understanding of test-results were measured at six months follow-up and reported that overall more than half of the participants had a correct understanding of residual risk; 536 out of 826 participants (64%). The participants who attended the group education (72%) were more likely than those who attended the general practitioners' consultation (47%), or those who received brochures (58%), to correctly understand their test results (OR 1.7, 95% CI 1.1-2.6).

In the Lakeman (2008) study, understanding of test-results was measured at one week and three months following test results. The proportion of participants who correctly understood their residual risk was 53% and 39% respectively.

4.5.2.6. Reproductive intentions

Participants' reproductive intentions in the Henneman (2002) study were obtained following the information giving interventions and at six months follow-up. Results were reported as following all interventions. When asked in situation if both partners were found to be carriers, overall, 36% of the participants thought they would refrain from having children; 87% would make use of prenatal diagnosis if pregnant; and of those who opt for prenatal diagnosis, 68% would consider termination of pregnancy if the child is found to have cystic fibrosis. There were still a small proportion that was undecided; 28%, 9% and 25% respectively, in all three situations. At six months follow-up, those identified carriers reported no impact of the test-results on their reproductive plans.

The Lakeman (2008) study also reported about the same results; 27% of the participants thought they would refrain from having children; 89% would make use of prenatal diagnosis if pregnant; and 68% would consider termination of pregnancy if the child is found to have cystic fibrosis.

4.5.2.7. Satisfaction

The Henneman (2002) study reported high satisfaction rate; overall, majority would recommend carrier assessment to others (88%) and 95% would have the test if they decide to test again. The Lakeman (2008) study also reported similar results; 75% and 91% respectively.

Table 4.2 summarizes the results reported for both included studies.

Table 4.2 : Results of included studies

Outcomes	Henneman 2002	Lakeman 2008
Uptake of screening	**Outcome:** Response rate of participants **Results:** Response rate of participants offered for group education was higher when invited by the general practitioners (11.9% 95%CI 10.2-13.8) as compared to invitation by the Municipal Health Service (9.2% 95%CI 8.4-10.0). For participants offered consultation by general practitioners, response rate was similar irrespective of the mode of invitation; MHS 24.7% 95%CI 22.1-27.4); general practitioner (24.7% 95%CI 19.1-30.9).	Not applicable
Psychological outcomes	**Outcome**: Proportion of participants feeling worried about test-results following interventions. **Results:** Overall, only 8 out of 826 participants (<1%) reported worry; 4 of whom were carriers. Participants who attended educational group session and those who received brochure were likely to be more worried than those who attended a general practitioner's consultation (p<0.04).	**1.Outcome**: Proportion of participants feeling worried about test-results at three month following test-results. **Result**: 31 out of 116 participants (27%) reported worry. **2.Outcome**: Mean Spielberger Strait-Trait Anxiety Inventory (STAI) anxiety score of participants measured at all four points **Results:** Mean scores at four measurement points were 1.6, 1.5, 1.3 and 1.3 respectively, (p<0.001).
Knowledge outcomes	**Outcomes**: Mean knowledge score and change in knowledge score between all measurement points, on five multiple choice questions on cystic fibrosis and carrier inheritance. **Results:** At all three measurement points, the knowledge score were significantly higher for participants who attended the group education session than those who received general practitioners' consultation (p<0.001). The increase in knowledge score within one week following group education was significantly higher than after general practitioner consultation (p=0.001). When compared at 6 months after test-results, knowledge score of participants who attended the general practitioners' consultation was similar to those who did not have personal education while those who had the group education were higher.	**Outcome**: Mean knowledge score between point 1,2 and 3, on five multiple choice questions on cystic fibrosis and carrier inheritance **Results**: Mean knowledge score significantly increased from before pre-carrier test consultation (knowledge score=2.8) to after consultation (knowledge score=3.7), (P<0.05). However decreased at one week after receiving test results (knowledge score=2.8, p<0.001).

Outcomes	Henneman 2002	Lakeman 2008
Recall of test-results	**Outcome**: Proportion of participants who were able to recall rest-results measured at six month following test-results. **Results**: Overall, 771 out of 826 (93%) participants had correct recall of test-results	**Outcome**: Proportion of participants who were able to recall rest-results measured. **Results**: 113 out of 120 (94%) participants. had correct recall of test-results
Understanding of test-results	**Outcomes:** Proportion of participants who had correct understanding of residual risk following their own test results measured at six months following test-results. **Results**: Overall, 536 out of 826 participants (64%) had correct understanding. The participants who attended the group education (72%) were more likely than those who attended the general practitioners' consultation (47%), or those who received brochures (58%), to correctly understand their test results (OR 1.7, 95% CI 1.1-2.6).	**Outcomes**: Proportion of participants who had correct understanding of residual risk following their own test results measured at point understanding of test-results was measured at one week and three months following test **Results**: The proportion of participants who correctly understood their residual risk were 53% and 39% respectively
Reproductive intentions	**Outcomes**: Proportion of participants' reproductive intentions after at within one week following intervention. **Results**: Overall, 36% thought they would refrain from having children (OR 0.99 95%CI 0.62-1.60); 87% would make use of prenatal diagnosis if pregnant (OR 41.5 95%CI 31.2-55.1) p<0.0001; and of those who opt for prenatal diagnosis, 68% would consider termination of pregnancy if the child is found to have cystic fibrosis (OR 2.3 95%CI 1.89-2.81) p<0.0001	**Outcome**s: Proportion of participants' reproductive intentions after at within one week following intervention **Results**: 27% thought they would refrain from having children (OR 0.99 95%CI 0.62-1.60); 89% would make use of prenatal diagnosis if pregnant (OR 41.5 95%CI 31.2-55.1) p<0.0001; and 68% would consider termination of pregnancy if the child is found to have cystic fibrosis (OR 2.3 95%CI 1.89-2.81) p<0.0001.
Satisfaction	**Outcomes:** Proportion of participants 1. that would recommend carrier assessment to others 2. would have the test if they decide to test again. **Results**: 88% would recommend carrier assessment to others and 95% would have the test if they decide to test again.	**Outcomes**: Proportion of participants 1.that would recommend carrier assessment to others 2. would have the test if they decide to test again. **Results**: 75% would recommend carrier assessment to others and 91% would have the test if they decide to test again.

4.6 Quality assessment of included studies

Table 4.3 shows the assessment of quality of included studies using Downs and Black checklist.

In general, both studies were liable to high risk of bias as both studies were non-randomised. However, there are certain research questions which may not necessarily always be answered by randomised controlled trials, for example, studies involving genetic screening as they potentially have ethical implications.

The overall quality of both studies were good; aim of study as well as interventions, participants and main outcomes were explicitly described. External validity of study was also good. However, the studies were subjected to methodological bias; non randomised, blinding was not possible and difficulties of controlling confounding factors such as differences in the care of the participants.

In addition, both studies were also at risk of response bias as the outcomes measured were self-reported.

Table 4.3 : Quality assessment of included studies (Downs and Black checklist)

	Henneman 2002	Lakeman 2008
1. Aim of the study clearly described	Yes	Yes
2. Main outcomes to be measured clearly described in the Introduction or Methods section	Yes	Yes
3. Characteristics of the patients included in the study clearly described	Yes	Yes
4. Interventions of interest clearly described	Yes	Yes
5. Principal confounders in each group of subjects to be compared clearly described	No	No
6. Main findings of the study clearly described	Yes several papers	Yes
7. Random variability for the main outcome provided	Yes	Yes
8. Important adverse reported	Yes	Yes
9. Characteristics of patients lost to follow-up clearly described	No	No
10. Actual probability values reported for the main outcomes	Yes	No
11. Subjects asked to participate in the study representative of the entire population from which they were recruited	Yes	Yes
12. Subjects agreed to participate representative of the entire population from which they were recruited	Yes	Yes
13. Staff, places, and facilities representative of the participants' environment	Yes	Unable to determine
14. Attempt made to blind participants	No	No
15. Attempt made to blind those measuring the main outcomes of the intervention	No	No
16. Data dredging results stated clearly	Unable to determine	No
17. Analyses adjusted for different lengths of follow-up, same time period between the intervention and outcome the same , follow-up was the same for all participants	Yes	Yes
18. Statistical tests used to assess the main outcomes appropriate	Yes	Yes
19. Compliance with the intervention/s reliable	Unable to determine	Yes
20. Accurate outcome measures	Yes	Yes
21. Participants in different intervention groups recruited from the same population	Yes	Yes
22. Participants in different intervention groups recruited over the same time	Yes	Yes
23. Participants randomised to intervention groups	No	No
24. Adequate allocation concealment	No	No
25. Adequate adjustment for confounders	No	No
26. Participants lost to follow-up taken into account	Yes	Yes

	Henneman 2002	Lakeman 2008
27. Study has sufficient power to detect a clinically important effect where the probability value for difference being due to chance <5%	No	No

4.7 Discussion

4.7.1 Summary of main findings

This review identified two studies that reported on the effects of interventions of preconception assessment of reproductive genetic risk. The interventions involved assessment of two autosomal genetic conditions, cystic fibrosis and haemoglobinopathies. However, there was a considerable variation in the nature of the interventions. In the Henneman (2002) study, the focus was looking at the uptake of screening based on different mode of invitations and also examine the outcomes of different modes of information giving; pre-carrier test group education, individual general practitioner consultation and giving a brochure. Whereas the focus in the Lakeman (2008) study was to assess the effects of offering preconception carrier couple screening based on ancestry.

With regards to uptake of screening, there was no difference in the response rate of participants invited by the Municipal Health Service (MHS) or by their own general practitioners. Previous study about cervical cancer screening reported higher response rate in the group invited by own general practitioners (Hermens et al., 2000). The Henneman study has demonstrated an added important finding; an invitation by the MHS could reduce the extra workload of general practitioners to invite (Henneman et al., 2002). Furthermore, the response rate of participants for pre-carrier test general practitioners' consultation were more than those offered group education. The reason for this may be that couples preferred to consult and discuss with their

own general practitioner individually and not during group discussion where there were bound to have other couples. This could indicate that the general practitioners potentially ideal to assess and screen as well as provide genetic information to the target population. This finding potentially has an implication to extend the role of general practitioners and primary care.

Genetic assessment for reproductive risk has been previously linked to psychological distress such as anxiety and worry (Bekker et al., 1994, Archibald and Wilford, 2011), however, in both studies, only a small proportion of participants reported worriedness while waiting for test-results following pre-carrier test education or consultation (Henneman et al., 2002, Lakeman et al., 2008). Further the Lakeman (2008) study reported no worsening of anxiety level following preconception ancestry-based carrier couple screening. The reason for this may be that both couples had pre-carrier test education or counselling together, sharing the information together likely to reduce problems in relationships (Watson et al., 1992a).

With regards to knowledge, both studies reported significant improvement from before and just after pre-carrier test education or counselling. The importance of sufficient knowledge was reported to help in informed decision-making when undergoing genetic screening (Marteau et al., 2001, Stefansdottir et al., 2010). The Henneman (2002) study reported the increase within one week following group education was significantly higher than after general practitioner consultation ($p=0.001$). This may be due to the differences between the education session delivered, person providing the education or the difference among the participants. The group sessions potentially have protected time to carry out, not like the general practitioners where counselling was carried out during their practice, thus may have more time to explain and discuss. The researcher who provided the group education may have a special interest in this subject and research thus contribute to the content of information given. Finally, the participants who

attended the group session may be motivated and supported by other participants in the group. However, the increase in knowledge was not sustained following three or six months of intervention.

In both studies, majority of the participants could recall their test-results. With regards to understanding their residual risk, both studies reported satisfactory results. In the Henneman (2002) study, overall more than half of the participants had a correct understanding of residual risk; 536 out of 826 participants (64%). The participants who attended the group education (72%) were more likely than those who attended the general practitioners' consultation (47%), or those who received brochures (58%), to correctly understand their test results (OR 1.7, 95% CI 1.1-2.6). These results could be related to the results of knowledge.

With regards to reproductive intentions if both partners have positive test-results, both studies demonstrated that the participants would make use of available reproductive options. This has implication that the interventions potentially could facilitate informed reproductive decision.

Overall, satisfaction reported in both studies was high. Participants acknowledged the importance of reproductive genetic risk assessed before conception and would recommend to others.

4.7.2 Strengths and limitations

This is the first review to examine the effects of preconception assessment of reproductive genetic risk in the four specified autosomal recessive genetic conditions. However, evidence to support the benefits of preconception assessment of reproductive genetic risk is restricted. There were only two studies eligible for this review and the nature of both studies was different. The limitations to interpret the direct effect of interventions were also related to methodological bias; both studies were non randomised studies, and confounders were not clearly reported. Furthermore, participants recruited in both studies were those

planning pregnancy. It is important to include those with unplanned pregnancies as unplanned pregnancies contribute to at least half of all pregnancies reported in the United States (Finer and Zolna, 2011) and England and Wales (Lafayette et al., 1999a).

There were also potential limitations with regards to the outcomes reported. In the Henneman (2002) study as, not all outcomes were reported individually for each intervention. Some were reported as overall; for example, recall of test-results, understanding of residual risk, reproductive intentions and satisfaction; following all intervention but only at certain time of measurement. In addition, these outcomes were reported only after interventions. Similarly, In the Lakeman (2008) study only knowledge and anxiety score were reported before-and-after interventions. The rest were reported only after intervention, however different in the time of measurement (Lakeman et al., 2008). On the other hand, recall of test-results, understanding of residual risk, reproductive intentions and satisfaction inevitably appropriate to be asked only following pre-carrier test consultation or education.

4.7.3 Implications for future practice

The national and international organizations, such as UK Human Genetics Commission and the Health Council of Netherlands, have acknowledged and recommended preconception assessment of reproductive genetic risk (Health Council of Netherlands, 2007, Denayer et al., 1992). However, this is not carried out routinely and there is still existing uncertainties of the benefits of assessing reproductive genetic risk preconception as reported previously (Bekker et al., 1994, Archibald and Wilford, 2011, Wert et al., 2012). This review may provide an insight into the beneficial aspects of assessing reproductive genetic risk preconception. In fact, the preferred mode of invitation for offering screening was also highlighted. The review has demonstrated that preconception assessment and education have positive benefits and implications on the target populations' emotion, knowledge, recall and

understanding of test-results and satisfaction. These would potentially support informed reproductive decision-making. The information gathered would be useful to help health care providers planning to provide preconception screening and counselling in future.

4.7.4 Implications for future research

The preliminary findings of both studies have demonstrated promising results. However, further prospective cohort studies would help assess the actual effect of pre-carrier test group education or counselling and carrier testing; particularly its effect on reproductive decisions. Furthermore, there is a need for broader definitions of target population, not only on women planning pregnancy. Future interventions should involve currently practiced health care providers such as general practitioners and nurses in providing pre-carrier test information giving rather than a researcher as described in this study. Pre-carrier test education and counselling should also include other common reproductive genetic risk conditions such as sickle cell disease and Tay-Sachs disease.

4.8 Conclusion

This review highlights the paucity of research examining the effects of preconception assessment of reproductive genetic risk, thus it is difficult to conclude concrete evidence addressing the effects of preconception assessment of genetic risk in people of childbearing age. Nevertheless, this review has highlighted encouraging outcomes. More research is needed to explore further the long term effects, and interventions should involve broader range of health care professionals such as nurses and public health staffs, and also define participants to include also those with unplanned pregnancy.

CHAPTER 5
DEVELOPMENT OF PRECONCEPTION ASSESSMENT OF REPRODUCTIVE GENETIC RISK IN PRIMARY CARE QUESTIONNAIRE

5.1 Introduction

The conclusions in systematic reviews in Chapter 3 and Chapter 4 have highlighted a range of approaches and encouraging outcomes which resulted from preconception care interventions in general such as; improvement in maternal knowledge and self-efficacy as well as maternal risk behaviour, and specific to preconception assessment of reproductive genetic risk for example; making use of expanded reproductive options, increased understanding of test-results and satisfaction. Clearly, there is still lack of evidence to support the implementation of preconception assessment of reproductive genetic risk in the primary care setting. However, the seriousness of the autosomal recessive conditions such as; haemoglobinopathies and cystic fibrosis, and their relatively high prevalence has prompted the United Kingdom Human Genetics Commission to recommend preconception assessment of reproductive genetic risk in primary care health system. In line with objective 4 of this thesis, exploring the attitudes and opinions of GPs in the United Kingdom to preconception assessment of reproductive genetic risk was considered important to improve the impact of this thesis. A questionnaire survey was carried out to achieve this objective. It is hoped that the results of the survey and the positive benefits highlighted from the systematic reviews would be useful to provide an understanding to developing preconception assessment of reproductive genetic risk in the UK health infrastructure.

There are three phases of work in relation to questionnaire survey discussed in this thesis. They are;

1. Developing the questionnaire
2. Implementing the questionnaire survey
3. Analysis and results of questionnaire survey

The objective of this chapter, Chapter 5 is to describe the development of the new questionnaire as the survey instrument. A new questionnaire was developed as there was lack of existing questionnaire as indicated while carrying out literature reviews, which fully addressed GPs' opinions and attitudes on preconception assessment of reproductive genetic risk in primary care. The following phases of work which are implementing the questionnaire survey and; analysis and results of questionnaire survey will be discussed in Chapter 6 and Chapter 7 respectively.

5.2 Background

The assessment of reproductive genetic risk, to date, focuses mainly on the antenatal and newborn periods (Qureshi et al., 2004). In particular, reproductive genetic screening or testing, which often occurs during pregnancy leaves the couple or prospective parents with restricted reproductive options (Dormandy et al., 2008). As highlighted in previous chapters, identifying carriers or risk of carrier state before pregnancy can provide a more appropriate timeframe for informed decision-making and expands reproductive options (Jones and Fallon, 2002, Wille et al., 2004b).

Realising this, there is growing interest to offer preconception assessment of reproductive genetic risk within the healthcare infrastructure (Czeizel, 1992). In particular, the importance of primary care or general practice involvement is increasingly highlighted (Heyes et al., 2004, Morgan et al., 2004, Denayer et al., 1992).The GPs are the gatekeeper to secondary care, thus, their possible roles are identifying individuals at genetic risk, providing support and counselling, and referring to specialists when appropriate (Qureshi and Raeburn, 1993). Before a formal program of preconception assessment of reproductive genetic risk is introduced or implemented in the primary care setting, it is essential that studies are undertaken to explore the GPs' readiness to

run the program, identify resources and needs to facilitate the delivery of the program and also to understand their experiences and potential barriers to providing the service.

To address this, a questionnaire survey was undertaken aimed to explore GPs' opinions and attitudes to providing reproductive genetic risk assessment to women or couples of reproductive age before conception, in the existing primary care practice.

5.3 Objective

This survey has six specific objectives. The objectives are;

1. To explore GPs' current experiences on preconception assessment of reproductive genetic risk.
2. To explore potential approach on how to deliver preconception assessment of reproductive genetic risk in primary care.
3. To explore potential setting within primary care to deliver preconception assessment of reproductive genetic risk.
4. To identify potential resources needed to support the delivery of preconception assessment of reproductive genetic risk in primary care.
5. To explore potential barriers to providing preconception assessment of reproductive genetic risk in current practice.
6. To explore the attitudes of GPs about their preparedness to providing preconception assessment of reproductive genetic risk assessment in current practice.

5.4 Methods

A questionnaire was devised to address the six objectives of this survey study. The development of questionnaire consists of generating items or statements for the questionnaire, and determining the format of questionnaire. This involves;

1. A review of literatures that addressed the six objectives specified to help generate items for questionnaire.
2. Focus group data to complement the literature review in generating items for questionnaire.
3. Experts' review for face and content validity.
4. Pilot testing; questionnaire sent to a group of GPs for them to complete and comment for face and content validity.

The term 'questionnaire item' will be used in the discussion throughout this thesis to indicate items or statements in the questionnaire.

5.4.1 Generating questionnaire items from literature review

Jaeger (1984) described the use of literature review is "almost inevitable in developing questionnaire". Literature review aimed to identify key issues and gaps in current topic being studied (Jaeger, 1984).

For this study, the literature review has provided a starting point in the initial development of the questionnaire. Information from published literatures was used to generate specific questionnaire items. The literatures reviewed have involved studies not just specifically on preconception assessment of reproductive genetic risk but also on preconception care in general, population-based carrier screening programs, and assessment of common genetic conditions in general for example, breast cancer. All the studies have focussed on aspects of opinions and attitudes of a range of primary care providers where

majority were GPs, and also included practice nurses, health visitors, midwives as well as obstetricians and gynaecologist that were based in outpatient clinics. It was necessary to broaden the range of literatures to inform the questionnaire items as existing literatures on preconception assessment of reproductive genetic risk in the primary care settings alone were still limited. Where possible, the actual questionnaires of the studies were obtained for references. For this study, two actual questionnaires were retrieved; one from the author himself (Poppelaars et al., 2004a) and the other was accessed online (Heyes et al., 2004).

During the literature review, a number of studies were identified that addressed the opinions and attitudes of primary care providers towards providing either preconception assessment of reproductive genetic risk, genetic screening for common genetic conditions and providing preconception care.

Certain questionnaire items that were used in the previous studies have also helped to inform the questionnaire items for my survey.

The following are themes for the questionnaire identified from the literatures and in relation to the objectives of this study. The questionnaire items developed are grouped into these themes:

1. GPs' current experiences
2. Approach on how to deliver the service
3. Potential settings in primary care
4. Potential resources
5. Potential barriers
6. Attitudes of GPs on their preparedness

Table 5.1 shows relevant studies from literature review that had helped in the generation of questionnaire items.

Table 5.1 : Relevant studies from literature review considered for generating questionnaire items

LITERATURES		THEMES: QUESTIONNAIRE ITEMS					
Author Year of publication Journal	**Title of study**	**Current experiences**	**Approach to deliver**	**Primary care settings**	**Resources**	**Barriers**	**Attitudes of preparedness**
Watson et.al. 1991 British Journal of General Practice	Attitudes to carrier screening for cystic fibrosis: a survey of health care professionals, relatives of sufferers and other members of the public						√
Boulton et.al.1996 British Journal of General Practice	The views of general practitioners on community carrier screening for cystic fibrosis		√				√
Mennie et.al. 1998 J Med Screen	Attitudes of general practitioners to screening for cystic fibrosis				√	√	√
Suchard et.al. 1999 British Journal of General Practice	General practitioners' views on genetic screening for common diseases						√
Acheson et.al. 2000 Genetics in Medicine	Family history-taking in community family practice: Implications for genetic screening		√				
Poppelaars et.al. 2004 Family Practice	Current practice and future interest of GPs and prospective parents in pre-conception care in The Netherlands						√
Morgan et.al. 2004 Genetics in Medicine	Practice patterns of obstetrician-gynecologists regarding preconception and prenatal screening for cystic fibrosis	√					√
Heyes et.al. 2004 Family Practice	Preconception care: practice and beliefs of primary care workers	√		√	√	√	
McCahon et.al. 2009 Clinical Genetics	General practitioners' attitudes to assessment of genetic risk of common disorders in routine primary care						√

Current experiences

Morgan (2004) explored obstetricians and gynaecologists' experiences on practicing on preconception screening for cystic fibrosis. There were two types of practices described; took family genetic history routinely when taking full medical history and took family genetic history routinely if the woman is planning pregnancy (Morgan et al., 2004).

Heyes (2004) explored primary care providers' experiences about providing preconception care in general. The respondents reported have provided opportunistically in routine clinic, family planning and well women clinics. A small proportion of the respondents reported having written policy on preconception care at their practice (Heyes et al., 2004).

Approach on how to deliver

Boulton (1996) explored the GPs' views on potential approach to offer carrier screening for cystic fibrosis and reported that majority agreed to offer screening when the individuals seek family planning advice (Boulton et al., 1996). In another study, Acheson (2000) reported that the family history was mainly discussed by the GPs at patients' first visits and also during well care rather than illness visits (Acheson et al., 2000).

Primary care settings

Heyes (2004) surveyed primary care providers' experiences of providing preconception care in the clinic settings. The respondents reported that they have provided in routine clinics, dedicated preconception clinics, family planning and well woman clinic (Heyes et al., 2004). These replies given by the respondents informed the potential settings to provide preconception assessment of reproductive genetic risk in primary care.

Resources

Mennie (1998) reported potential support mentioned by GPs include information giving before and after carrier testing and training (Mennie et al., 1998). In a study by Heyes (2004), refresher courses and evidence-based guidelines were suggested as resources to assist in the general practices (Heyes et al., 2004).

Barriers

In a study by Mennie (1998), screening for carrier was perceived to do more harm than good (Mennie et al., 1998). Heyes (2004) reported that barriers to providing preconception care include poor contact or difficult to capture women planning to conceive, lack of resources and lack of training (Heyes et al., 2004)

Attitudes of GPs focussing on their preparedness to provide the service

Five studies were identified that reported GPs' attitudes on preparedness of offering screening for reproductive genetic risk. All studies were on carrier screening for cystic fibrosis (Watson et al., 1991, Boulton et al., 1996, Mennie et al., 1998, Morgan et al., 2004, Poppelaars et al., 2004d). There was a range of questions pertaining to GPs' preparedness. They were asked on willingness to provide carrier screening routinely (Watson et al., 1991, Boulton et al., 1996, Mennie et al., 1998, Poppelaars et al., 2004d); pre-carrier test counselling post-carrier test counselling and disclosure of test-results In addition, the two studies reported preparedness to offer screening only in specific situations such as, when is requested by the patients, couples planning pregnancy, positive family inheritance of genetic conditions, if the partners are known carriers or has cystic fibrosis and patients or her partners are in high risk ethnic group ((Morgan et al., 2004, Poppelaars et al., 2004d)

Further, in two studies exploring GPs' attitude about providing screening for common genetic conditions, reported that they were

willing to take family history and offer counselling if given necessary training and information of assessing genetic risk ((Suchard et al., 1999b, McCahon et al., 2009).

To further inform the content of the questionnaire, focus group was carried out with groups of primary care providers and women of reproductive age. Focus group data was analysed using a framework approach.

5.4.2 Using focus group data to inform questionnaire items on preconception assessment of reproductive genetic risk in primary care

5.4.2.1. Introduction

Focus group is defined as ‘’a group of individuals selected and assembled by researchers to discuss and comment on, from personal experience, the topic that is the subject of the research’’ (Powell and Single, 1996). It is ‘’a method to gather information and to obtain an understanding or insight of a specific subject from a range of views from different groups of people’’ (Morgan and Kreuger, 1993). Kruger (1994) also described focus groups as ‘’a carefully planned discussion designed to obtain perceptions on a defined area of interest in a permissive, non-threatening environment’’ (Kreuger, 1994). Interaction, which is its unique characteristic, allows participants to explore and discuss the topic in great detail as well as clarify their views (Liamputtong, 2011).

Focus groups can offer an avenue for work at various steps of the research process, for example, obtaining information, generating hypothesis, generating new concepts to hypothesis testing and refining already known concepts (Kreuger, 1994).

Focus group has been used for developing surveys, in particular to generate questionnaire items as well as improving the contents of questionnaire items in surveys (O'Brien, 1993). O'Brien (1993) described his accounts of using focus groups to develop questionnaire items. His study involved exploring gays and bisexual men about their experiences and views regarding Acquired Immunodeficiency Syndrome (AIDS) to develop items for questionnaire survey, which later became a community project (O'Brien, 1993).

In this study, the primary aim of the focus group was to elicit participants' attitudes and ideas about preconception care particularly on the topic of preconception assessment of reproductive genetic risk.
The themes gathered from focus group analysis using a framework approach were then mapped to the themes identified from literature review. Following this, questionnaire items were derived.

5.4.2.2. Methods

In this study, the focus groups were made up of one group of primary care providers involving three GPs, a midwife and two health visitors; and six groups of women in the reproductive age group. The responses from primary care providers unfortunately were limited; there were only one group involved in the focus group. The demographic details of the participants will be presented later in this chapter. It was important to have both the perspectives of primary care providers and the women to inform the contents of the questionnaire. This is because information provided by the GPs, health visitors and midwife are important as they are potentially involve in the management of women's health in primary care. This has helped provide understanding in the management of issues of interest from a different angle. Focus groups data of women was necessary to explore their opinion on preconception assessment of genetic risk who may take up the service. Results from the analysis are used to inform questionnaire items.

5.4.2.3. Data collection

The preliminary process of planning and recruitment for the focus groups was initiated by the members of Collaboration for Leadership in Applied Health Research and Care – Nottinghamshire, Derbyshire and Lincolnshire - Action Before Conception (CLAHRC-NDL-ABC) study; Exploratory study of acceptability, feasibility and effectiveness of preconception health assessment intervention in primary care. The initial activity of the CLAHRC-NDL-ABC study was already taken place before I began my PhD. The main aim of exploratory phase of CLAHRC-NDL-ABC study was to explore the feasibility of preconception health assessment as an intervention for preconception care assessment. For this process, focus groups were involved. The objectives were to explore and identify current practice, attitudes, beliefs and information needs concerning preconception care in general and assessment among women and primary care providers. In this CLAHRC-NDL-ABC study, preconception care assessment encompassed a variety of risks such as medical conditions, drugs abuse, infections and lifestyle risk such as smoking and alcohol. Reproductive genetic risk assessment constitutes one of preconception care assessment in the CLAHRC-NDL-ABC study.

I first obtained a Research Passport or an Honorary Research Contract to qualify to undertake research activities within the National Health Service (NHS), before getting involved in the exploratory phase of the study. With timing of Research Passport, it allowed me to take the role of an assistant moderator. During the focus groups, I have made field notes and captured as much information on the topic of interest, particularly on preconception assessment of reproductive genetic risk. I also observed the group dynamics and the terminologies and words used in the discussion. Written notes were summarised and distributed among other involved members of CLAHRC-NDL-ABC study, to help give input and improve on the qualitative data. The disadvantage was I had no control in the discussion of the focus groups. Besides assistant

moderator, I had helped to improve the interview guide for the focus group as well as helped to refine preconception health assessment as an intervention for the CLAHRC-NDL-ABC study.

The focus groups were audio taped and transcribed by the CLAHRC-NDL-ABC study members. Transcripts were cross-checked by the assigned CLAHRC-NDL-ABC study members to ensure their reliability. I was given permission by the lead researcher the study to review the transcripts. I reviewed and analysed the transcripts independently in line with the objectives of my thesis. This was really important to ensure the authenticity of the analyses. At this point, no involvement or input from the members of the CLAHRC-NDL-ABC study as it was necessary to extract the data based on the objectives of my study and particularly focussed on the issues of interest.

5.4.2.4. Data analysis

Focus group data analysis was guided by framework analysis methodology. Framework analysis was chosen for a range of reasons. First, it is suitable to analyse a cross-sectional data, in particular, for this study that has specific research objectives (Ritchie and Lewis, 2003). Secondly, interpretations of participants' experiences are transparent (Ritchie and Lewis, 2003), thus, allows me to understand and interpret directly. Finally, it is better adapted to a study that has a limited time frame (Ritchie and Lewis, 2003).

The management and analysis of data was carried out manually on paper. The initial framework was derived from research objectives and prior literature review that addressed the objectives of the survey. To recap, the themes identified from research objectives (relevant to preconception assessment of reproductive genetic risk) and literature review are:

1. GPs' current experiences.
2. Approach on how to deliver the service.
3. Potential settings in primary care to carry out the service.
4. Potential resources.
5. Potential barriers.
6. Attitudes of GPs on their preparedness to offer the service.

The first step was the data familiarisation. The transcripts were read two to three times to get familiarised with the information. During this process, focus group data was collated and assigned to themes; this is demonstrated in Appendix 5.1 and Appendix 5.2. These themes which derived were guided by the initial framework. Guided by the themes in the framework, chunks of data that have meaningful descriptions were highlighted. Following this, the data was organised and mapped to the themes in the framework. These were adjusted accordingly when going through the transcripts again. I re-examined to ensure the clarity of the original data reflects the themes. Adjustment was made accordingly if needed.

For the purpose of this chapter to describe the development of the questionnaire, the results of focus group data in accordance with the objectives of this questionnaire survey are presented. Relevant findings from the focus groups of primary care providers were incorporated with the findings from the six focus groups of women.

Further, with regards to analysis, all themes were able to be retrieved from focus group except, the attitudes of GPs on their preparedness to offer the service. This is because there was insufficient focus group data that addressed or discussed on preparedness of the GPs.

The following section presents the results of focus groups; first is the characteristics of the participants, and secondly is the thematic analysis.

5.4.2.5. Results of focus groups

Characteristics of the participants

Focus group of primary care providers

There were six primary care providers involved in this focus group. There were three GPs, with aged ranged between 40 to 50 years old. Two of them were practicing in rural, Chesterfield and North West Derbyshire while one GP was practicing in Derby City. The remaining participants involved were a midwife and two health visitors, aged ranged between 30 to 50 years old and all were working in North West Derbyshire practice.

Focus group of women

There were six focus groups of women with a total of 26 involved in the analysis. The women were from a mixture of different ethnic background for example; Indians, Pakistani, African and European Whites. Age of the participants ranged between 18 to 45 years old with majority already had children. One participant was pregnant and seven have not conceived at the time of the interview. Six participants reported graduate degrees, thirteen had vocational qualifications or advanced education, and five had secondary education. The remaining reported elementary education. The focus groups were conducted at community or public centres and general practice. The summary of the participants is shown in Table 5.2.

Table 5.2 : Summary of participants

Focus group (FG)	Characteristics of Participants			
Location	**Age**	**Parity**	**Ethnicity**	**Education level**
FG1 College canteen, Nottingham 5 participants	26-45 years	3 women have 2 children. 2 women have 3 children.	5 Sikh	1 Degree 2 NVQ/equivalent 2 GCSE/equivalent
FG2 General practice, Derby Lane 6 participants	26-35 years	1 woman was pregnant. 4 women have no children.	4 Pakistani 1 Indian	1 Degree 3 NVQ/equivalent 1 GCSE
FG3 Nottingham Women's Community Centre 3 participants	18-35 years	2 women have 1 child. 1 woman has 2 children.	2 European White 1 African	Elementary
FG4 General practice, New Mills 4 participants	17-35 years	3 women have 1 child. 1 woman has 2 children.	4 European White	1 Degree 2 NVQ/equivalent 1GCSE
FG5 General practice, New Mills 5 participants	18-35 years	1 woman has 1 child. 4 women have 2 children.	5 European White	1 Degree 4NVQ/equivalent
FG6 Sherwood Community Centre 4 participants	18-45 years	1 woman has 2 children. 3 women have no children.	4 Pakistani	2 Degree 2 NVQ/equivalent

*GCSE: General Certificate of Secondary Education

*NVQ: National Vocational Qualifications

Thematic analysis

Theme 1

Experiences of preconception practices

During the focus group with the primary care providers, the participants stated that preconception advice in general, was being offered opportunistically. One GP expressed that it was uncommon to offer routinely unless requested specifically for preconception advice by patients. In addition, family planning clinic was mentioned as the setting where he had offered preconception care. With regards to preconception genetic assessment and advice, one GP stated that they took the opportunity when seeing patient in the high risk group. The midwife experienced that women who had a family history of genetic conditions would have been informed through genetic counselling or told by their family members.

In the focus group of women, one participant mentioned that the GPs' consultations were usually guided by the patients' requests. She had expressed that she would prefer the GPs to have a proactive role rather just providing preconception advice and care only when requested by patients.

> ***GP 2, Chesterfield***
>
> *"I don't think that it is something that we advertise but we will see anyone…"*
>
> *"….things that is badged as preconception, I often used to do in family planning, if they were an ethnic minority you would do the haemoglobin screening…."*
>
> *"…… I can think of two in the last couple of years who specifically made an appointment and consulted me about that……"*

Midwife, North West Derbyshire

"Ones that have got issues and the genetic problems in the family, they could have had genetic counselling or families pass on that information"

Woman (focus group 4), white, Derbyshire

"I don't think they should wait either to be approached by someone for it, it should automatically be offered. Because sometimes you'll go into a GP for information and you don't get it unless you ask for it, it's not always there at hand…"

Theme 2

Potential approaches, settings and resources to deliver preconception assessment of reproductive genetic risk in practice

All the primary care providers recognised the importance of offering preconception genetic risk assessment in the practice. Women also acknowledged that knowing genetic risk before conceive would help in deciding options for having future children.

One GP mentioned that preconception assessment of genetic risk could be offered during family planning visits or rather opportunistically, when consulting with women enquiring about matters related to pregnancy or reproduction.

Similarly, the women also expressed their opinion that preconception assessment and advice could be offered in general practice particularly during visits for contraception and family planning clinics. The women acknowledged that this has an advantage to capture women in the younger age group.

One woman suggested sending out information sheet routinely when women reach certain age; which in this case, at reproductive age.

GP 2, Chesterfield

things that is badged as preconception, I often used to do in family planning…."

Woman (focus group 4), White, Derbyshire

"I think approaching GPs and family planning clinics and maybe hospitals where people are having, you know, are wanting children and are having to go for testing or whatever, I think doing it that way might work"

Woman (focus group 5), White, Derbyshire

"You could do when you're going for contraception, that's good, actually, that would be a good way of … "

Woman (focus group 3), African, Nottingham

"…as a routine procedure to send information sheet at certain age group…"

Theme 3

Barriers to developing preconception assessment of reproductive genetic risk

In the context of preconception advice in general, the GPs agreed that it is regarded as a rare encounter and believed that women are not forthcoming to discuss about preconception issues, thus, only few coming to seek advice before conceive.

GP 1, Northwest Derbyshire

" ….. I don't think I remember many people coming and asking me for advice before trying to get pregnant….."

GP 2, Chesterfield

" ….. Perhaps they don't want to be so public about it as to discuss it with a professional, before embarking on trying to get pregnant…."

Further barriers mentioned by the participants were potential negative implications generated by genetic risk assessment. This includes psychosocial harm, stigmatisation and relationship issues. One of the GPs was concerned about his rapport with his patients if starting to discuss about hereditary conditions. One participant in the women focus group actually was worried with potential stigmatisation and stress in family relationships.

GP 2, Chesterfield

"…… nobody wants to think that something bad might happen to them….."

"….. I would be worried about my relationship with those people in the future if I started talking a lot about congenital abnormalities, hereditary diseases. Well, we're already married. We are going to try for a baby anyway….."

GP 3, Derby City

"….if you provide this as a universal approach used for everyone, there is going to be some background harm that could happen if you tap some anxiety that was underneath the surface…."

Woman (focus group 4), white, Derbyshire

"It just causes so many problems, though, you know..."

"…like, if you think, if you've been in a long term relationship with someone and you think, right, let's plan to have a child but, you know, if you go and test and see if someone's a carrier, either you or your partner's a carrier of something and you have a child

and then that child's got whatever you carried, then it's going to be, you know, a blame game, well it's your fault, you carried it, you know, you carried that faulty gene so it's your fault that he turned out like that, so I don't think I would, I think I'd leave it so that we couldn't blame"

There was some resistance to adding preconception care in the current primary care system. One GP mentioned that it is possibly going to add to their existing workload and there should be a balance among other health areas.

GP 1, Northwest Derbyshire

"Do we need to be doing this as a national thing?"

"…Which I guess is where you are heading with this. I can see how that would work but I think in terms of what you were saying about what happens next – if you raise the expectation, there has got to be a way to meet the expectation without too much sacrifice to other health areas that are currently there".

The following section describes the process of generating questionnaire items from literature review and focus group data.

5.5 Generation of questionnaire items from incorporation of literature review and focus group qualitative data

This stage involved incorporating the themes and information from the literatures and focus group data to inform the contents of each questionnaire item.

Referring to the themes as below which were described earlier, questionnaire items were derived:

1. GPs' current experiences.
2. Approach on how to deliver the service
3. Potential setting in primary care
4. Potential resources
5. Potential barriers
6. Attitudes of GPs on their preparedness

The following section below describes the themes and the questionnaire items generated for each theme. Segments or aspects from the literatures reviewed and focus groups data in relation to the appropriate themes are presented. Variables in questionnaire items that derived from the literatures and focus group were indicated in bold. The rationale for deciding on the variables is described.

Theme 1: GPs' current experiences.

Here, the GPs were asked about their experiences of assessing reproductive genetic risk before conception. Two important aspects of assessment that were asked are discussing family history and discussing genetic carrier testing with women of childbearing age group. In addition, in this domain, GPs were asked about their practices within the last three months to indicate their recent experiences.

***Rationale*:** This information would help identify potential settings or situations that the GPs are likely to offer preconception assessment of

reproductive genetic risk with women of childbearing age before they conceive.

Table 5.3 : GPs' current experiences

<table>
<tr><td>THEME 1</td><td colspan="2">EXPERIENCES (in the last three months)
a. Discussing family history of reproductive genetic risk
b. Discussing preconception advice about genetic carrier testing</td></tr>
<tr><td>Literature Review</td><td>Focus Group</td><td>Questionnaire Items</td></tr>
<tr><td rowspan="2">Morgan 2004

Respondents described “took family genetic history routinely when taking full medical history” and “took family genetic history routinely if the woman is planning pregnancy”

Heyes 2004

Respondents reported “have provided preconception care opportunistically in routine clinic, family planning and well women clinics”.</td><td rowspan="2">General Practitioner 2, Chesterfield

“….things that is badged as preconception, I often used to do in family planning, if they were an ethnic minority you would do the haemoglobin screening….”</td><td>Discussing family history of reproductive genetic risk

1. I have discussed this during routine consultation
2. I have discussed this to women planning a pregnancy
3. I have discussed this during visit for contraception
4. I have discussed this during visit for family planning</td></tr>
<tr><td>Discussing preconception advice about genetic carrier testing

1. I have discussed this during routine consultation
2. I have discussed this to women planning a pregnancy
3. I have discussed this during visit for contraception
4. I have discussed this during visit for family planning
5. I have discussed to this women with known family history of genetic conditions
6. I have discussed this with women of certain ethnicity background (e.g. African, Asian, European</td></tr>
</table>

Both studies Morgan (2004) and Heyes (2004) described respondents have experienced providing either preconception genetic assessment or preconception care in general, in routine clinic, either when taking full medical history or when the women were planning to conceive. Further, the focus group of primary care professionals revealed had experienced

discussing preconception genetic screening in family planning clinics and when encountered an ethnic minority patients.

Theme 2: Potential approaches

***Rationale*:** Before preconception reproductive genetic risk assessment is to be developed formally in primary care practice, it is essential that we consider an appropriate and reasonable approach to carry out the assessment. Two important aspects of assessment that were asked are approaches to obtain family history and to offer genetic carrier testing with women of childbearing age group in the primary care practice.

Table 5.4 : Potential approaches

<table>
<tr><th>THEME 2</th><th colspan="2">APPROACHES
a. To obtain family history of reproductive genetic risk
b. To offer genetic carrier testing</th></tr>
<tr><th>Literature Review</th><th>Focus Group</th><th>Questionnaire Items</th></tr>
<tr><td rowspan="2">Boulton 1996)
explored the general practitioners' views on potential approach to offer carrier screening for cystic fibrosis and reported that majority agreed of offering screening when the individuals seek family planning advice

Acheson 2000
This study reported that family history was discussed by during patients' first visits at a primary care clinic.</td><td rowspan="2">Woman (focus group 5), White, Derbyshire
"You could do when you're going for contraception, that's good, actually, that would be a good way of …"

Woman (focus group 4), White, Derbyshire
"I think approaching GPs and family planning clinics and maybe hospitals where people are having, you know, are wanting children and are having to go for testing or whatever, I think doing it that way might work"</td><td>To obtain family history of reproductive genetic risk
1. From all women of childbearing at registration by means of self-completed family history questionnaire
2. From women enquiring about preconception advice
3. From women enquiring family planning advice</td></tr>
<tr><td>To offer genetic carrier testing
1. To offer all women of childbearing at registration
2. From women enquiring about preconception advice
3. From women enquiring family planning advice</td></tr>
</table>

The focus groups suggested offering preconception assessment when women come for family planning advice such as contraception and

women wanting to conceive. The study by Acheson mentioned family history was discussed at patients' first visits. At this point, the statement "by means of self-completed family history questionnaire" was added in the item as self-completed family history screening questionnaires potentially could help identify those patients at risk to allow a more detailed assessment and counselling when consulting the general practitioner.

Theme 3: Potential settings

Rationale: It is important to elicit primary care providers' and the women's views regarding the settings in the practice appropriate to provide preconception reproductive genetic risk assessment

Table 5.5 : Potential settings

THEME 3	SETTINGS	
Literature Review	**Focus Group**	**Questionnaire Items**
Heyes 2004 Respondents reported "have provided **opportunistically in routine clinic, also in more focussed settings such as dedicated preconception clinics, family planning and well women clinics".**	***Woman (focus group 4), White, Derbyshire*** "I think approaching general practitioners and **family planning clinics** and maybe hospitals where people are having, you know, are wanting children and are having to go for testing or whatever, I think doing it that way might work"	Potential setting appropriate to provide preconception assessment of genetic risk 1. A dedicated clinic 2. Well woman clinic 3. Family planning clinic 4. During routine consultation

Family planning clinic was mentioned in both literature and focus group. Other settings mentioned were dedicated preconception clinic, well women and in routine clinic.

Theme 4: Potential resources

Rationale: It is important to elicit potential resources that could improve the delivery of preconception reproductive genetic assessment in primary care. This will help to inform future strategies to implement preconception assessment of reproductive genetic risk in primary care.

Table 5.6 : Potential resources

THEME 4	RESOURCES	
Literature Review	**Focus Group**	**Questionnaire Items**
Mennie 1998 This study assessed potential support that the general practitioners would need to offer cystic fibrosis screening in the general practice, most indicated that **information giving support** before and after testing would be necessary and others were **administrative and training support.** ***Heyes 2004*** The respondents stated that they would appreciate **refresher courses** and suggested **evidence-based guidelines** to assist them in their practice.	***Woman (focus group 3), African, Nottingham*** "…As a 'routine' procedure to **send information sheet** at certain age group…" "You can actually go and pick up a **leaflet** beforehand or say when you are a certain age they would just send it out to you as standard or something, I don't know. I know it would cost a bit but you know… I was thinking a lot of the information that would serve.... I mean I did -- I read it. I like to know these things. I read it all pretty much straight away. and I was thinking -- I wish I'd known about that before, I wish I'd known about that…" ***Woman (focus group 4), White, Derbyshire*** "I think they should just make it a **leaflet, you know, like when you go into your GP**, there's a wall of leaflets and there should be something that you can pick up of it, it would make it easier because you might not want the world to know that you're planning a pregnancy, but just to slip by and pull out a leaflet, nobody needs to know. "	**Potential resources that will improve the delivery of preconception assessment genetic risk in your practice.** 1. Appropriate training for the general practitioners 2. National guidelines for general practitioners 3. Information leaflets on preconception genetic risk assessment given at registration to all women of childbearing age

Both the literatures and focus groups indicated that information giving supports are needed such as information leaflets. Other resources needed were training support and practice guidelines.

Theme 5: Potential barriers

***Rationale*:** It is important to identify potential barriers to offering or providing preconception assessment of reproductive genetic risk in the general practice. The rationale is to elicit factors that could impede the delivery of preconception assessment of reproductive genetic risk if it is introduced formally in the general practice. This information would help to identify difficulties which would help to consider range of approaches to overcome the barriers of the delivery of preconception reproductive genetic risk assessment in primary care in future.

Table 5.7 : Potential barriers

THEME 5	POTENTIAL BARRIERS	
Literature Review	**Focus Group**	**Questionnaire Items**
Mennie 1998 In this study, a small proportion of respondents believed that screening for carrier will do **more harm than good** ***Heyes 2004*** Barrier **reported in this study were difficulties to capture women planning to conceive, lack of resources** (e.g. money) and **lack of training**.	***General Practitioner 1, Northwest Derbyshire*** "….. I **don't think I remember many people coming** and asking me for advice before trying to get pregnant….." "Do we need to be doing this as a national thing? Which I guess is where you are heading with this. I can see how that would work but I think in terms of what you were saying about what happens next – if you raise the expectation, there has got to be a way to meet the expectation **without too much sacrifice to other health areas that are currently there**" ***General Practitioner 2, Chesterfield*** "….. I would be worried about my **relationship** with those people in the future if I started talking a lot about congenital abnormalities, hereditary diseases. Well, we're already married. We are going to try for a baby anyway….." ***Woman (focus group 4), White, Derbyshire*** "…if you go and test and see if someone's a carrier…whatever you carried…it's going to be a **blame game**… "	**Potential barriers for developing preconception genetic risk assessment in your practice.** 1. Very few women coming for advice before trying to conceive 2. It is difficult to capture the target group 3. I am worried about ethical implication of preconception genetic risk assessment eg. stigmatisation of carriers 4. I am concerned that discussing hereditary diseases to couples who are trying for a baby will cause more harm (e.g. affect doctor-patient relationship , emotional disturbances to couples) 5. I do not have adequate training to provide preconception reproductive genetic assessment 6. Setting up a service will require substantial time and work

Barriers in carrier screening and providing preconception care described in both Morgan (2004) and Heyes (2004) studies were: more harm; difficult to capture women planning to conceive; lack of resources and lack of training. With regards to focus groups, the GPs expressed that they had not encountered that many women seeking for

preconception advice whereas the women expressed concerns over relationships and stigmatisation.

Theme 6: GPs' Preparedness

In 2009, the National Screening Committee of United Kingdom (NSC) has commissioned the Human Genetics Commission to explore the need for preconception genetics screening. As a result, the Human Genetics Commission recommended that preconception genetic screening should be in the framework of screening programmes in primary care (Human Genetics Commission 2011). Hence, it was important to explore primary care providers' perception of their role and in this context, the GPs. GPs' preparedness towards this recommendation is important to help motivate the introduction and deliver the practice of assessing genetic risk in primary care.

Rationale: Theme 6 was added as it was necessary to increase the scope of the questionnaire to elicit how prepared are the GPs to offer and counsel about preconception reproductive genetic risk assessment before incorporating into their practice. This information would help to give an idea the component of genetic consultation that the GPs are more confident dealing with, together finding the gaps that could limit them from offering. This is also important to inform the strategy of a formal preconception assessment in the primary care practice.

The questionnaire items were mainly informed by studies in the literature review.

Table 5.8 : GPs' Preparedness

THEME 6	PREPAREDNESS
Literature Review	**Questionnaire Items**
Mennie 1998 Respondents reported they were **prepared to carry out pre-test counselling and disclosure of results** in their primary care practice; and also, **to undertake counselling of positive results.** ***Suchard 1999*** Respondents were reported that they felt **sufficiently prepared to take family histories** and draw pedigrees, **to counsel about the genetic test results and if given the necessary training** and information, they were willing to take family histories and to counsel about the results respectively ***Poppelaars 2004*** Respondents reported they were **willing to offer preconception cystic fibrosis screening, routinely to couples planning pregnancy.** ***Morgan 2004*** Respondents reported that they were **willing to offer screening only in specific situations such as, when is requested by the patients, positive family inheritance of genetic conditions, if the partners are known carriers or has cystic fibrosis and patients or her partners are in high risk ethnic group**. ***Mc Cahon 2009*** The respondents were willing to **take family history routinely** and some reported they were **willing to take family history if given necessary training**.	**Your preparedness to offer preconception assessment of genetic risk in your practice.** 1. I am prepared to take family history of genetic conditions from all women of childbearing age routinely when taking medical history 2. I am prepared to offer genetic carrier testing to at-risk women of childbearing age 3. If appropriate to the consultation, I am prepared to offer genetic carrier testing to women of childbearing age 4. Given the necessary training and information, I am prepared to counsel about genetic carrier testing results

Besides the questionnaire items, the demographic items were also devised.

5.6 Demographic items

Demographic items were included in the questionnaire as this helped in describing the participants' characteristics. The variables included in the demographic section were age, gender, years of experience, description of practice, practice list size and whether practice has a preconception care protocol. These variables were based from literature review for examples: age, years of experiences, practice list size and whether have local guidelines on genetic assessment; these variables were tested for predictors of general practitioners' attitudes of preparedness (Poppelaars et al., 2004d, McCahon et al., 2009).

The following section describes the designing of the format of questionnaire.

5.7 Deciding the questionnaire format

In general the questionnaire comprised of three main components. The first component is the introduction, secondly is the actual questionnaire items and the third component is the demographic items.
Please refer to Appendix 5.3 for full description of the questionnaire.

Component 1: Introduction

The introduction is on the first page of the questionnaire aimed to highlight the purpose and the importance of carrying out the survey. This component also described the instructions on how to reply to the questions and approximate time to complete the questionnaire.

Component 2: Actual questionnaire items

The questionnaire items components are divided into four main parts. Every part has headings which gives brief explanation on how to address the following questionnaire items. The four main headings are:

1. Participants' experiences of discussing preconception assessment on reproductive genetic risk. This includes

discussing family history of reproductive genetic risk and genetic carrier testing.

2. Participants' opinions on potential barriers to developing preconception reproductive genetic risk assessment in current practice.
3. Participants' opinions on potential approaches to deliver and resources required to improve on the delivery of preconception reproductive genetic risk assessment in current practice.
4. Participants' attitudes on preparedness to providing preconception assessment of reproductive genetic risk in current practice.

All the questionnaire items were closed-response type. This format of closed-response type was preferred due to two factors; the time taken for the participants to complete the questionnaire will be less as compared to responding to open-ended question (Polgar and Thomas, 2000, Buckingham and Saunders, 2004) and responses could be easily coded and analysed (Polgar and Thomas, 2000). The response format for each item was a 5-point scale of agreement ranging from 'strongly agree' on one end to 'strongly disagree' on the other with 'don't know' in the middle. Each level on the scale was assigned a numeric value starting at 1 and incremented by one for each level. This format is useful to determine the responses' opinions and attitudes (Bourque and Fielder, 1995, Buckingham and Saunders, 2004). Further, free text response was included in this questionnaire to give opportunities to the participants to express their opinions or suggestions on preconception assessment of genetic risk. This allowed gathering important information or helped identifying new issues which was not covered in the questionnaire items.

Component 3: Demographic items

The demographic items component consisted of a categorical format for categorical variables and free spaces for continuous variables.

Appreciation statement and the researcher's contact detail concluded the questionnaire.

The following section described the layout of the questionnaire.

5.8 Deciding the questionnaire layout

Careful attention was given to the details of the layout, for example; question ordering, spacing, and font size. This was to ensure that the questionnaire was easy to read, understand and to complete. This was crucial to maintain the respondents' compliance and interest (Lydeard, 1991).

Generally, the questionnaire items of the same topic were grouped together for each four parts. This is to ensure that questionnaire items were listed in a logical manner. Further, later responses to questionnaire items were checked not to be biased by earlier questions. The main headings were in capital letters, bolded and font size 14. Brief explanations following each heading were bolded and font size 12. The questionnaire items were typed in font size 12 and not bolded. This is to distinguish the headings and explanations from the questions itself. All the questionnaire and demographic items were numbered. The 5-point scales were arranged horizontally for every question. With regards to the wordings, words with double meaning, double negatives and jargons were avoided. The whole questionnaire was an 8-page questionnaire and every page was numbered. The number of pages was limited to emphasize that it could be completed within a short time. This was important as to avoid sense of disinterest the first instance of receiving the questionnaire.

At this juncture, the draft questionnaire was ready for assessment of validity.

5.9 Assessing the validity of the questionnaire

It is essential to establish accuracy and applicability to relevant target participants when developing new questionnaire (Polgar and Thomas, 2000, Lydeard, 1991). For this questionnaire, assessment of face and content validity was undertaken. Face validity refers to whether the study instrument, which in this case, the questionnaire, represents the proposed concept or theme the questionnaire intended to measure (Litwin, 1995). Content validity is the extent to which the items of the study instrument adequately cover areas of importance and interest with no irrelevant content (Litwin, 1995). In the initial step, the draft questionnaire was sent to two academic personnel and experts in primary care genetics from the University of Nottingham. Both were also practicing GPs. In addition, the questionnaire was also sent to a GP who was a research fellow at the University of Oxford. The experts were consulted to address and comment on the validity of every questionnaire items and to assess the clarity of the wordings of the questionnaire items. Where required, new questionnaire items were added as suggested by the experts. The GP from the University of Oxford emailed her responses while face to face discussion with the experts from the University of Nottingham was made to review the questionnaire.

Following discussion with the experts, the questionnaire items were revised or added appropriately.

5.10 Revision of draft after experts' review

Following experts' review and feedback, revision was advised for the following. The table below (Table 5.9) summarized the revision described.

1. Practice patterns: The questionnaire item, "I have discussed this during visit for contraception" and "I have discussed this during visit for family planning" was considered confusing. To avoid

confusion, it was decided to put “I have discussed this during visit for contraception” and to omit the other as this term was more focused.

2. Potential approaches: The expert recommended adding the questionnaire item “Women enquiring about menstrual problems” in the part. This was to add to options for opportunistic consultation to women in childbearing age group with regards to preconception assessment.

3. Potential resources: In the questionnaire item “National guideline for GPs” the expert recommended to add example, in the case, NICE (National Institute for Health and Care Excellence) guideline was suggested.

Table 5.9 : Revision of draft after experts' review

Theme	Questionnaire Items	
	Draft 1 (before experts' review)	**Draft 2 (after experts' review)**
Experiences	1. I have discussed this during routine consultation 2. I have discussed this to women planning a pregnancy 3. I have discussed this during visit for contraception 4. I have discussed this during visit for family planning	1. I have discussed this during routine consultation 2. I have discussed this to women planning a pregnancy 3. I have discussed this during visit for contraception
Potential approaches	**To obtain family history of reproductive genetic risk** 1. From all women of childbearing at registration by means of self-completed family history questionnaire at registration 2. From women enquiring about preconception advice 3. From women enquiring family planning advice	**To obtain family history of reproductive genetic risk** 1. From all women of childbearing at registration by means of self-completed family history questionnaire at registration 2. From women enquiring about preconception advice 3. From women enquiring family planning advice 4. Women enquiring about menstrual problems
	To offer genetic carrier testing 1. To offer all women of childbearing at registration 2. From women enquiring about preconception advice 3. From women enquiring family planning advice	**To offer genetic carrier testing** 1. To offer all women of childbearing at registration 2. From women enquiring about preconception advice 3. From women enquiring family planning advice 4. Women enquiring about menstrual problems
Potential resources	1. Appropriate training for the general practitioners 2. National guidelines for general practitioners 3. Information leaflets on preconception genetic risk assessment given at registration to all women of childbearing age	1. Appropriate training for the general practitioners 2. National guidelines for general practitioners eg. NICE **3.** Information leaflets on preconception genetic risk assessment given at registration to all women of childbearing age

Next, the second draft of the questionnaire was piloted with a group of seven GPs who were practicing in the United Kingdom. The questionnaire had to be mailed to two GPs and written comment was obtained. The other five completed the questionnaire individually, in my presence, and the questionnaire was reviewed for content and comprehension of every questionnaire items, as well as presentation of the questionnaire items taking into consideration its readability and format. The time to complete the questionnaire was also assessed.

Following suggestions by the GPs, only minor amendment to the layout was made to improve on the presentation between the headings and the brief explanation. The layout was revised to; the main headings in capital letters, bolded and font size 14; the brief explanations bolded and font size 12; and the questionnaire items were typed in font size 12 and not bolded. There was no additional suggestion or amendment to questionnaire items at this stage.

5.11 Strengths and limitations of research methods used

Relevant information and questionnaire items gathered from the literature review and focus group enhances the comprehension of the questionnaire being developed. The focus group data was considered appropriate to generate questionnaire items. It provides opportunity to get wider opinion from different groups of people. Nonetheless, the richness of the data could be improved if the following actions are taken.

Firstly, taking the role as the main moderator would help me to be involved actively in the focus group discussion. I could take control of the discussion and tailored to the objectives of my study. Focus group provides a wealth of information, but it could be improved if one to one interview is carried out on issues around reproductive genetic conditions. There are possibilities that the presence of others in the

focus group may make it difficult to disclose information of a personal experience involving ethical, legal and social aspects related to genetic conditions.

Secondly, there was only one group of primary care providers involved where only three GPs participated. The reason for only three GPs was attributed to poor response to participate. Although, they provide a breadth of information, the quality of the data could be improved if there was more than one focus group of GPs which preferably more diverse in demographic, considering that the study population for the survey is GPs. It would also be helpful to get the views of other primary care providers such as the health visitors and midwives who may be involved in women's health and this focus group could be conducted separately. It could be argued that discussion can be dominated by the GPs if not carried out separately, whereby, this was observed during this study.
In the analysis of focus group, it is noted that most coded data is identified as GP participant. This was because the discussion was mainly dominated by the GPs. Nevertheless, the aim of focus group was to inform questionnaire survey of GPs, thus findings most of the data extracted from focus group originated from GPs is an advantage.

With regards to focus group of women, there was considerable number of groups. The ethnicity in each group was more or less homogenous. This has allowed the discussion on exploring the opinions and problems about reproductive genetic conditions faced by specific ethnic group without causing any harm or stigmatization. The groups appeared heterogeneous especially in age, parity and education level and this has provided better understanding of the issues across the diverse in the participants. However, issues on genetics can be personal, some of the participants may not disclose their real feelings towards the topic, or they refuse to share their experience either because they felt hindered by other participants who have higher education level or by older participants. This was observed during the focus group. However, on the other hand, it could be argued that every group was more or less

homogenous in ethnicity; it did not portray or provide much perspective on ethnicity sensitivity.

5.12 Conclusion

This chapter gives an account of the systematic process in developing the questionnaire. It was important to ensure that the contents of the questionnaire addressed the objectives of this study. The following chapter will discuss the methodology; recruitment and data collection, carried out for the questionnaire survey study.

CHAPTER 6
METHODS IN QUESTIONNAIRE SURVEY

6.1 Introduction

The objective of Chapter 6 is to describe the methods used in the questionnaire survey. This includes identifying participants, data collection, improving participants' response rate and methods to analyse the data.

6.2 The sampling frame and study population

This survey was carried out within the National Health Service (NHS) of Nottinghamshire and Derbyshire, United Kingdom.

The sampling frame was drawn from databases of general practices within the Primary Care Trusts of Nottinghamshire County, Nottingham City, Derbyshire County and Derby City. The most updated list was retrieved in July 2012 from the National Health Service (NHS) Information Centre website. The four PCTs were chosen as sampling frame because of easy accessibility. These PCTs were already involved in the CLAHRC-NDL-ABC study. The study population are the GPs working in general practices within the Primary Care Trusts of Nottinghamshire County, Nottingham City, Derbyshire County and Derby City.

6.3 Ethical consideration

Approval to carry out this study was sought form three main bodies;

1. Research Governance of the University of Nottingham
2. National Health Service (NHS) Research and Development (R&D) department
3. Medical School Ethics Committee of the University Of Nottingham

The proposal of the study was initially entered into The Integrated Research Application System (IRAS), a single online system for applying for permissions and approvals for health and social care or community research in the United Kingdom. The approval bodies were contacted approximately at the time of completing the IRAS to seek for advice on how to proceed. I was informed by the NHS Research and Development (R&D) department that the study does not require Research Ethics Committee review as it was a survey and not involving patients. The protocol was reviewed by the Research Governance and the Medical School Ethics Committee of the University of Nottingham.

First, the research protocol and relevant documents such as cover letter, participant information sheet and reminder letter as well as the draft questionnaire were submitted to the Research Governance of the University of Nottingham. All of the documents were reviewed thoroughly and underwent three amendments before the study could be approved. Further, the approved protocol was reviewed by the NHS Research and Development (R&D) department and Medical School Ethics Committee of the University Of Nottingham. Only one revision was made to the questionnaire following recommendations by the Ethics Committee. The whole process took approximately eight months before approval to commence the study.

6.4 Methods

6.4.1 Study design

The study design was a cross-sectional survey using self-administered postal questionnaire.

Cross-sectional surveys have been used for descriptive studies primarily aim to “gather reliable and unbiased data from a representative of respondents” (McColl et al., 2001). Surveys intend to “explore aspects of situation, seek explanation and provide data for testing hypotheses from selection of a sample of people from a pre-determined population or population of interest, followed by collection of information from those individuals and making quantitative inferences in relation to the population of interest” (McColl et al., 2001, Kelley et al., 2003). They are preferred to collect quantitative information on peoples’ knowledge, attitudes and behavioural intentions (Fink, 2002). Also, surveys have been described as “real life snapshots of the population” where data was gathered (Kelley et al., 2003).

In the context of this study, the survey aims to capture information or data on the opinions and attitudes of the GPs towards preconception assessment of reproductive genetic risk. Further, it also allows testing of hypothesis that the GPs, who are the population of interest; were prepared to offering preconception assessment of reproductive genetic risk in the primary care practices.

Although postal questionnaires are widely used to collect data in health research, there was a general consensus that postal questionnaires of GPs may have low response rates (McColl et al., 2001, Kelley et al., 2003, Thorpe et al., 2009) and it was reported a significant problem in the United Kingdom (Sibbald et al., 1994). Thus, improving response rate was important to ensure the quality of the data collected. The following section describes the methods to structure and disseminate

the questionnaire survey incorporating strategies to enhance responses from the target population.

6.4.2 Questionnaire survey composition

The questionnaire survey package was composed of:

1. Cover letter
2. Participant Information Sheet
3. Questionnaire
4. Returned-stamped self-addressed envelope

6.4.2.1. Cover letter

A cover letter is a formal introductory letter accompanying a document. The cover letter accompanying the questionnaire should explain the purpose of the study and emphasised the importance of a response from the targeted individuals as well as providing an assurance of confidentiality and expressing gratitude to the participants for their assistance (Dillman, 1978, Buckingham and Saunders, 2004).

A number of studies have explored specific characteristics of a cover letter that could enhance response rates as well as credibility of the questionnaire. To achieve success of the survey, the objective of the study and the reason why responses are important should be stated (McColl et al., 2001, Turocy, 2002). The cover letter should also provide an estimate time required to complete to encourage participation (McColl et al., 2001, Turocy, 2002). To enhance credibility and further enhance participation, the cover letter should be printed on departmental-letterhead (Burns et al., 2008) with the researchers' signature (Edwards et al., 2002). The response to survey increased when each cover letter was signed (Edwards et al., 2002). In addition, Paxson (1995) also stated that a reasonably high response rate may be

achieved when the name of the researcher is used on the correspondence (Paxson et al., 1995).

For this study, the cover letter (Appendix 6.1) was designed as outlined stating the following:

1. Objectives of the study
2. Reason why the participants' responses are important in the study
3. Emphasis on confidentiality of the participants
4. Estimated time required to complete the questionnaire
5. Researcher's contact details
6. Thanking the participants for completing the questionnaire and stating that incentive will be given at the end of cover letter

The objectives and the reason for participation was clearly stated in the cover letter to emphasize that the GPs participation was important to the achieve success of the survey. In addition, the cover letter provided an estimate time required to complete as well mentioned incentive to be given to the first 100 respondents, to encourage participation. The cover letters was signed by the academic advisor who is also a GP (Nadeem Qureshi) and me as researcher. The cover letters were printed on University letterhead.

6.4.2.2. Participant Information Sheet

Sudman (1983) suggested that in surveys involving professionals, a cover letter could be accompanied by more extensive supporting document to provide more detailed information about the study (Sudman, 1983). Participant information sheet was used in addition to cover letter to provide more detail on the objectives of the study, to emphasise the importance of obtaining responses from the general practitioners and contact details of the researchers in case, the participants needed further information and clarification with regards to the questionnaire (Appendix 6.2)

6.4.2.3. Questionnaire

Besides the format (Chapter 5), to further improve the presentation of the questionnaire, several important steps were adopted to encourage responses. Previous studies have highlighted the importance of colour and brightness in the visual presentation of questionnaires (Edwards et al., 2002, Burns et al., 2008).The questionnaires for this study were printed on A4-sized coloured paper (green) to enhance visual appeal. It was an 8-page; printed on both sides and stapled together to facilitate use and completion (Burns et al., 2008).

6.4.2.4. Return-stamped self-addressed envelope

The use of return-stamped self-addressed envelope has been demonstrated to gain response rate (Edwards et al., 2002). For this, each participant was provided a return-stamped self-addressed envelope in which to return the completed questionnaire to the researcher.

6.4.2.5. Questionnaire survey package

The cover letter, participant information sheet, return-stamped self-addressed envelope and the questionnaire were arranged in that order and fit in a 25×35cm-sized envelope. This constituted the questionnaire survey package.

6.4.2.6. Other measures to enhance responses

Incentives

Edwards (2009) and. has reported that using incentives versus no incentives has shown to have positive impact on response rates. There was a significant increase in response rate when using monetary

incentive (Edwards et al., 2009). The incentive offered in this study was a £5 voucher to the first 100 general practitioners who completed and returned the questionnaire, and this was stated in the cover letter and participant information sheet. The offering of incentives in this study was approved by the Medical School Ethics Committee of the University of Nottingham.

Face-to-face invitation to participate

In addition, I took the opportunity to attend two Protected Learning Time (PLT) events in December, 2012. These events were Continuing Professional Development (CPD) learning activities that were held for general practices' staffs, including GPs in Nottingham. During these events, I introduced to the GPs about the concept of preconception assessment of reproductive genetic risk and further invited them to participate in the questionnaire survey.

Timing of disseminating the questionnaire

In order to improve on participation, specific issues for example, the timing of the second mailing was chosen after the Christmas and New Year vacations to avoid clashing with the GPs' busy periods.

6.5 The decision to choose type of survey administration method

The reason for choosing self-administered postal survey for this study was to gather information from a large group of GPs using most economical approach, importantly taking into consideration budget and time.

In general, there are three types of administering questionnaire survey; self-administered via postal, interviewer-administered via face-to-face or telephone and self-administered via internet. I will discuss the advantages and disadvantages of each approach in the following

section. I will then summarise my reasons for choosing self-administered postal survey.

Self-administered postal survey

When conducting survey, one must function within the constraint of budget, time and experience. The decision to choose self-administered postal questionnaire for this study was due to several advantages (McColl et al., 2001, Kelley et al., 2003):

1. This method has allowed covering a wider geographic coverage; which is all the general practices in the PCTs of Nottinghamshire and Derbyshire.
2. Data can be collected within short periods of time. This is particular important as the duration of my PhD is limited.
3. It is relatively inexpensive when compared to other types of survey, such as face-to-face survey and easier to implement considering limited availability of research budget to conduct this study.
4. Postal questionnaire survey allowed GPs to complete the questionnaires at their own convenient time, thus, protected time for the questionnaire was not necessary.
5. There was little chance for personal bias as there was no contact between the researcher and the participants.

Interviewer-administered questionnaire (face to face, telephone)

Interviewer-administered questionnaire with physicians have been reported to have higher response rates; 65% to 80% as compared to postal questionnaire. This approach also enables data to be collected rapidly as well as minimise potential missing data (Shosteck and Fairweather, 1979, Dillman, 2000). Hence, this improves the quality of data. Nevertheless, this approach has been associated with substantial time such as for travelling and cost incurred.

Even though interviewer-administered questionnaire has better response rates, self-administered questionnaire was still preferred as it is easier to implement. The time and cost needed to implement are relatively less (McColl et al., 2001). All the questionnaires can be sent within the same day and practically received by the participants within four to five days period. Furthermore, the cost of travelling to every general practices is negligible.

The advantage to the participants is self-administered questionnaire can be completed at the their convenience without being bothered by the researcher; thus avoiding potential interviewer-bias (McColl et al., 2001). The participants' responses to the questionnaire are also not influenced by the researcher. Furthermore, the participants are free from any commitment for an appointment as interviewer-administered questionnaire uses a considerable length of time.

Internet-based questionnaire

Internet-based questionnaire was introduced as a survey technique in the late 1990s as an additional approach to data collection (Janssens et al., 2014). There is no doubt that this approach is gaining popularity nowadays especially when most GPs have access to internet. There are several advantages related to this approach. Firstly, internet-based questionnaire allows automatic transfer of data into a database, and hence, eliminates the need for manual inputting and avoid potential error on data entry (van Gelder et al., 2010). As data entry is performed by the participants, this approach may offer potential cost saving for staff. Furthermore, it reduces cost of stationary and postage (Sinclair et al., 2012).

On the other hand, creating survey on-line required specialized knowledge (Shannon and Bradshaw, 2002) and hence, possible more time as well as skills is required. There are methodological issues

reported with creating internet-based questionnaire for example; the designing and formatting an on-line questionnaire to simplify data collection and data entry (Janssens et al., 2014). There is also a variation in individual respondents' computer hardware and software, thus, one has to design accordingly and compatible with the participants' computer program (Janssens et al., 2014). Furthermore, there may be a possibility of losing of data through a brief server failure (Shannon and Bradshaw, 2002) or problems in downloading the whole questionnaire (Janssens et al., 2014).

With regards to response rate, internet-based questionnaire was reported to have a variable response rates ranging from 9% to 94% (Janssens et al., 2014). In fact, few studies involving questionnaire survey among physicians demonstrated more responses to postal questionnaire as compared to internet-based questionnaire (Kim et al., 2000, Raziano et al., 2001).

Although, internet-based questionnaire may offer advantages, indeed, there is a compromise in deciding between self-administered postal questionnaire and internet-based questionnaire. I had to balance the pros and cons before making a decision considering my time constraint and limited manpower. One of the factors that has led to the decision of self-administered postal questionnaire and not internet-based, is because of the reason of ensuring that one GP to represent a practice. I may have difficulty to disseminate questionnaire via internet because any GP is eligible to participate. If use internet-based, I might have to pre-select a particular GP to represent the practice. This may lead to selection bias. Adding to this, I was unaware of any available method that is confidential to process an internet-based questionnaire if send through a third person for example the practice manager before distributing to a GP of that practice.

6.6 Selection of study population

There were a total of 285 practices in the sampling frame. The entire general practices within the PCTs of Nottinghamshire County, Nottingham City, Derbyshire County and Derby City were retrieved from the National Health Service (NHS) Information Centre website and any duplicated names of the practices were checked and removed before carrying out the survey.

In the UK, the implementation of preconception screening in the general practice could be incentivised by the Quality Outcome Framework (QOF). Because of this, it is crucial to ensure maximal response as possible from practices across the counties for this survey study. Thus, it was agreed that at least one GP from every practice is needed to participate. This would potentially reduce response bias of GPs who may have special interest in the topic being studied.

The questionnaires were sent to all 285 practices. Any one GP from every practice was invited to represent their practice. This would encourage voluntary involvement of any GPs in the practice to respond to the survey. Each practice received a single questionnaire survey package ensuring that the practices would have equal opportunity to participate.

6.7 Commencing the questionnaire survey

The standard approach for data collection in postal surveys as described in the Dillman method was used as a guide. The Dillman method is often regarded as the standard for many postal surveys (Thorpe et al., 2009). Furthermore, it was reported that the method appeared to help obtain high survey response rate (Hoddinott and Bass, 1986). The Dillman method involves five components (Dillman, 2000):

1. Appropriate development of questionnaire
2. The use of four contacts by, with an additional ‘special’ contact (e.g. certified mail, telephone call) and recommended by first-class mail
3. The use of return envelopes with real first-class stamps
4. A personalized correspondence
5. A token of financial incentive that is sent with the survey request.

With regards to the first, the development of questionnaire, this was already discussed earlier in Chapter 5.

Although the Dillman method was used to enhance participation from GP there were however, few revisions to the method of disseminating the questionnaire following review from the Research Governance of the University of Nottingham as well as due to budget constraint. The use of four contacts in the mailings, which was proposed in the original protocol, was revised to three contacts following protocol review from Research Governance of the University of Nottingham. Further, due to budget constraint, the use of first-class mail and return envelopes with real first-class stamps was revised to using second class mail. In addition, incentive was also decided to send only when participants returned completed questionnaire instead of sending with the survey package.

Follow–up is another essential component to that has positive influence on response rates (Dillman, 2000, Edwards et al., 2009). It was reported that the best predictor of response in surveys of the public was the number of follow-up mailings (Barclay et al., 2002). In particular, postal questionnaire survey of general practitioners, reminders and follow-up mailings have been reported to be effective (Barclay et al., 2002). In this study, follow-ups following the first mail-out took the form of letter reminders and second mailings with duplicate cover letter, participant information sheet and questionnaire with return-stamped

envelope; which will be mentioned in detail in the data collection section.

6.7.1 Data collection

The data collection took place between October 2012 and February 2013. It involved:

1. Mailing out the first batch of questionnaire survey packages
2. Follow-up with letters of reminder to non-responders
3. Mailing out the second batch of questionnaire survey packages to non-responders following reminders

The first batch of survey packages was sent to all the 285 practices in the four counties mentioned earlier. The questionnaire survey package was addressed to the general practice in the first batch of mailing. The return of completed questionnaires indicated the GPs' consent to participate which was stated clearly in the cover letter (Appendix 6.1).
To give the GPs adequate time to reply, reminder letters (Appendix 6.3) were sent approximately six weeks after the first mailing.

The second mailing of the survey packages was sent in mid-January 2013. The timing of the second mailing was chosen after the Christmas and New Year vacations to avoid clashing with the GPs' busy periods. This was specifically chosen to improve on participation. In addition, before mailing out the second batch, telephone calls were made to the practices to encourage more responses (Dillman, 1978). Attempts to speak personally to the practice managers were made before the final mailing to notify about the questionnaire survey and emphasized on participation from the GPs. Practice managers are preferred as they are the prime person that organised the practices and they may be appropriate to disseminate the questionnaire to the GPs in the practice. Only 88 practice managers were able to be contacted.

For this batch, an additional cover letter addressed to the Practice Manager was also attached (Appendix 6.4). The cover letter provided brief information about the study and requested assistance to hand over the questionnaire to any one GP in the practice. A photocopied £5 voucher was also stapled to the cover letter. The aim was to attract the Practice Managers and hence, the GPs.

A 'Thank You' card and a £5 voucher were sent to the GPs who had participated in the survey.

6.8 Methods of analysis

All data collected were entered in Statistical Package for the Social Sciences (SPSS) version 16.0 database and double checked by the researcher (NH) to avoid any errors. Before carrying out the analyses, the data were checked again. Statistical advice was sought before conducting the analyses to ensure the appropriateness of the statistical tests applied.

Descriptive statistics were calculated for all variables. Frequencies and percentages were calculated for all categorical variables whilst continuous variables were analysed for means and standard deviations (SD).

Chi-squared test and independent t-test was used to assess whether differences existed between two variables for categorical and continuous data respectively.

The following describes the methods of analysis with regards to each objective of the questionnaire survey.

Objective 1 : To explore GPs' experiences on preconception assessment of reproductive genetic risk

Each questionnaire item was initially explored independently. This involved straight description of the proportion of the each scale of agreement; however, to facilitate interpretation of results, 5 point were collapsed to 3 point scale; agree (from strongly agree and agree), don't know, and disagree (from disagree and strongly disagree), resulting in 3 categorical variables. Frequencies and percentages were calculated for all enquired experiences of discussing family history of reproductive genetic risk and discussing preconception advice on genetic carrier testing in women of childbearing age.

Further, Chi-squared tests were computed to assess whether differences existed between GPs' experiences and their preparedness to offer and provide preconception assessment of reproductive genetic risk in their practice.

Objective 2 : To explore GPs' opinions on potential approach to deliver preconception assessment of reproductive genetic risk in primary care

Each questionnaire item was initially explored independently. This involved straight description of the proportion of the each scale of agreement; however, to facilitate interpretation of results, 5 point were collapsed to 3 point scale; agree (from strongly agree and agree), don't know, and disagree (from disagree and strongly disagree), resulting in 3 categorical variables. Frequencies and percentages were calculated for all inquired approach to deliver preconception assessment of reproductive genetic risk in primary care.

Objective 3 : To explore GPs' opinions on appropriate settings in primary care practice to deliver preconception assessment of reproductive genetic risk

Each questionnaire item was initially explored independently. This involved straight description of the proportion of the each scale of agreement; however, to facilitate interpretation of results, 5 point were collapsed to 3 point scale; agree (from strongly agree and agree), don't know, and disagree (from disagree and strongly disagree), resulting in 3 categorical variables. Frequencies and percentages were calculated for all enquired settings in primary care practice to deliver preconception assessment of reproductive genetic risk.

Objective 4 : To identify potential resources needed to improve the delivery of preconception assessment of reproductive genetic risk in primary care

Each questionnaire item was initially explored independently. This involved straight description of the proportion of the each scale of agreement; however, to facilitate interpretation of results, 5 point were collapsed to 3 point scale; agree (from strongly agree and agree), don't know, and disagree (from disagree and strongly disagree), resulting in 3 categorical variables. Frequencies and percentages were calculated for all enquired resources needed to improve the delivery of preconception assessment of reproductive genetic risk in primary care practice.

Objective 5 : To explore potential barriers to developing preconception assessment of reproductive genetic risk in primary care

Each questionnaire item was initially explored independently. This involved straight description of the proportion of the each scale of agreement; however, to facilitate interpretation of results, 5-point were

collapsed to 3-point scale; agree (from strongly agree and agree), don't know, and disagree (from disagree and strongly disagree), resulting in 3 categorical variables. Frequencies and percentages were calculated for all enquired barriers to developing preconception assessment of reproductive genetic risk in primary care practice.

Objective 6 : To explore GPs' preparedness to offer and provide preconception assessment of reproductive genetic risk in primary care

These variables of preparedness were treated as the outcomes of interest. The 5-point scales of agreement for preparedness were collapsed to 2-point scale; and were recoded as prepared and less prepared. Here, 'Strongly agree' and 'agree' were recoded to 'prepared' and 'don't know', 'disagree' and 'strongly disagree' were recoded to 'less prepared'. Frequencies and percentages were calculated for all enquired questionnaire items for preparedness to offer and provide preconception assessment of reproductive genetic risk in primary care practice.

For univariate analyses, chi-squared test and independent t-test was used for categorical and continuous data respectively to assess whether differences existed between every questionnaire items for preparedness and demographic variables. Chi-squared test was computed to assess differences between GPs' preparedness and their experiences on preconception assessment of reproductive genetic risk.

Binary logistic regression was used to study the association between GPs' responses to preparedness (offer and provide preconception assessment of reproductive genetic risk) and demographic variables. Demographic variables are age, gender, number of years of experience as GP, practice list size and whether practice has a preconception protocol.

Guided by the literatures, the following variables; location of practice (urban/rural/inner-city), type of practice (group/solo) and availability of preconception care protocol that covered family history taking and genetic carrier testing are regarded as predictor variables (Poppelaars et.al., 2004c, McCahon et.al., 2009). Age, gender, number of years of experience as GP and practice list size are regarded as confounding variables. In building the models, the predictor variables were tested to determine association with GPs' preparedness. Results are presented as unadjusted odds ratio with 95% confidence interval. These were then adjusted for age, gender, number of years of experience as GP and practice list size as confounders and presented as adjusted odds ratio with 95% confidence interval.

For all univariate analysis and logistic regression the level of statistical significance, $p<0.05$ was used as the criteria for statistical significance.

Analysing free text-response type questions

Free text-response type questions offer insights or issues not captured in the closed-response type. Here, the free text-response type was put in two main themes related to facilitators and barriers. The analyses are presented descriptively in the results section.

6.9 Strengths and limitations

Research and Development approval

The review process for approval from Research and Development was relatively long, thus there was a time constraint in completing the PhD. During the process, the original protocol to carry out the study was required to be revised to accommodate the recommendations made by the approval bodies. In the original protocol, it was proposed to carry out piloting the fieldwork or data collection to a group of GPs before the actual data collection as this was deemed necessary in actual research methods. The reason was to anticipate problems of the actual mailing,

so that this could be revised before carrying out the actual survey. However, contacting GPs numerous times was considered coercive by the Research Governance and Research and Development department. Hence, piloting the fieldwork was not carried out. Adding to this, the mailing was also reduced to three contacts: first mail-out; reminder and second mail-out.

Study population

Inviting one GP to represent each practice within the PCTs in Nottinghamshire and Derbyshire allows equal opportunity of every practice in to participate. More importantly, it is to ensure maximal responses of practices are achieved. As a result, this would have an impact if preconception assessment of genetic risk services is to be introduced at practice level. Further, if allowing any GP from the sampling frame would have a skewed result to specific PCT and the GP who responded may have an interest on the topic. However, it could be argued that allowing only one GP to represent a practice may have a potential to limit generalisability of this study.

Response rate

Self-administered postal questionnaire survey was relatively easy to administer. Nevertheless, poor questionnaire response rate was a disadvantage. Several measures were planned such as; cover letters, providing return-stamped self-addressed envelope and incentives; at the outset to anticipate poor response, and were carried out to enhance participation from the GPs. The second batch of questionnaire survey package was addressed to the practice managers of the non-responded practices with a cover letter to the practice manager (Appendix 6.4), along with other documents. Attempts to contact the practice managers personally were also made to improve participation.

Methods of analysis

The logistic regression model allows one to study on the association of the outcome variables to a set of possible predictor variables with the

adjustment of confounders. Hence, the use of logistic regression was applied as part of the statistical analysis in this survey.
However, if the study size is small as a result of poor response, this potentially has limited value; small study size would result in a wide confidence interval.

6.10 Conclusion

A high response rate was important to ensure the success of the study; whether the results of the survey is reflective those of the target population (Burns et al., 2008). Several measures were planned and carried out to ensure participation from the GPs at the outset. This includes from meticulously developing the questionnaire to disseminating the questionnaire. There was however challenges faced during the process which resulted in suboptimal response.

The following chapter presents the analyses and results of the questionnaire survey study.

CHAPTER 7
RESULTS OF SURVEY

7.1 Introduction

This chapter presents the results of the questionnaire survey. The results are presented in four sections.

In general, **Section 1** presents the response rates and descriptive analysis. Cross tabulations were used to assess the association between location of practice areas and the availability of preconception protocol that covered family history or genetic carrier testing in the practice.

Section 2 presents the association between the four outcomes of preparedness with the respondents' experiences of discussing family history and preconception advice on genetic carrier testing. The four outcomes of preparedness are; preparedness to take family history of genetic conditions from all women of childbearing age group routinely, preparedness to offer genetic carrier testing to at-risk women, preparedness to offer genetic carrier testing if appropriate to the consultation and preparedness to counsel genetic carrier testing results if given training and information.

Section 3 presents the association between preparedness of the participated GPs in offering and providing preconception assessment of reproductive genetic risk across all demographic variables. Logistic regression analysis, assessing the effects of the predictor variables on the four outcomes of preparedness in offering and providing preconception assessment of reproductive genetic risk is presented.

The final **Section 4** presents the analysis of free text responses.

The following (Table 7.1) is the summary of the survey results chapter.

Table 7.1 : Summary of the survey results chapter.

Structure of the survey results chapter	
Section 1	Response rates. Descriptive analysis of demographic variables. Descriptive analysis of all variables in questionnaire items. Association between location of practice areas and the availability of preconception protocol that covered family history or genetic carrier testing.
Section 2	Association between respondents who are prepared and less prepared with experiences of discussing family history and preconception advice on genetic carrier testing variables.
Section 3	Logistic regression analysis, univariate and multivariate, to assess the effects of demographic variables on the four outcomes of preparedness.
Section 4	Analysis of free text responses

7.2 Results of survey

Section 1

7.2.1 Response rate

A total of 285 questionnaires were sent to 285 general practices.
In total 95 (33.3%) general practitioners; who represented 95 practices responded to the survey and returned completed questionnaires.

Table 7.2 summarised the response rates. In the first batch of mail-out, 48 completed the questionnaires (16.8%). Following reminder letters to 237 of non-responders to the first mail-out, 10 (3.5%) returned completed questionnaire. Finally, additional 37 (13.0%) general practitioners returned completed questionnaires following the second batch of mail-out.

Table 7.2 : Response rates of participants (by number of practices)

Response rates of participants (N = 285)	
Completed survey package	**Response rates n (%)**
First mail-out	48 (16.8)
Following reminder letters	10 (3.5)
Second mail-out	37 (13.0)
Total	95 (33.3)

Table 7.3 summarised the response rates from the four Primary Care Trusts. The highest proportion was from GPs in Nottingham City (44.4%) followed by Derbyshire (32.6%) and Nottinghamshire (31.9%) counties. The lowest proportion (18.8%) was the Derby City Primary Care Trust.

Table 7.3 : Response rates by Primary Care Trusts area

Primary Care Trusts area	**Response rates n (%)**
Nottinghamshire County (N=97)	31 (31.9)
Nottingham City (N=61)	27 (44.3)
Derbyshire County (N=95)	31 (32.6)
Derby City (N=32)	6 (18.8)

*N: the total number of practices in every Primary Care Trust.

The proportion indicates the proportion of respondents from each Primary Care Trust.

7.2.2 Demographic characteristics of GPs and general practices

Table 7.4 shows the demographic characteristics of the respondents.

The mean age of GP was 45.7 (SD 8.9) years old; a higher proportion was female (57.4%). They had practised as GPs for a mean of 15.6 (SD 8.5) years. About 58% of the respondents described their practice as urban. 23.2% described their practice as inner city and 16.8% as rural. The mean practice list size was 8529.2 (SD 7439.2)

Sixteen (17%) of the respondents reported having protocol on preconception care in their practice. Of the practices which have the protocol, ten practices has preconception care protocol covering family history of reproductive risk and only two practices covering genetic carrier testing. The practices were predominantly urban and inner city, five and three respectively, and two from rural practice. Six other practices have protocol on preconception care however did not cover either family history of reproductive risk or genetic carrier testing.

Table 7.4 : Demographics

Characteristics	Value (N=95)*
N (%)	
Gender	
Male	40 (42.1)
Female	54 (56.8)
Missing	1 (1.1)
Location of practice	
Rural	16 (16.8)
Urban	55 (57.9)
Inner city	22 (23.2)
Missing	7 (2.1)
Type of practice	
Solo	8 (8.4)
Group	86 (90.5)
Missing	1 (1.1)
Preconception care protocol available,	16 (17.0)
Covered family history, n (%) **	10 (62.5)
Rural #	2 (20.0)
Urban#	5 (50.0)
Inner city#	3 (30.0)
Covered genetic carrier testing, n (%) **	2 (12.5)
Rural#	0
Urban#	0
Inner city#	2 (100.0)
Mean (SD)	
Age, mean	45.7 (8.9)
Missing	3 (3.2%)
Number of years as a general practitioner, mean	15.6 (8.5)
Missing	3 (3.2%)
Practice list size per 1000, mean	8529.2 (7439.2)
Missing	2 (2.1%)

* 95 GPs representing 95 practices

** number (n) is based on whether preconception care protocol is available

The proportion indicates the proportion of each area of practices that has preconception protocol covering family history of reproductive risk or genetic carrier testing

7.2.3 GPs' experiences on preconception assessment of reproductive genetic risk

GPs were asked about their experiences of discussing family history of reproductive genetic risk and discussing preconception advice on genetic carrier testing in women of child bearing age in the last three months. Table 7.5 shows the proportion of respondents who had experienced or not, of discussing family history of reproductive genetic risk and discussing preconception advice on genetic carrier testing in women of child bearing age in the last three months .

With regards to discussing family history, over half of the GPs that responded (55.8%) indicated that they had discussed family history of reproductive genetic risk with women planning a pregnancy and approximately one third (37.6%) had discussed during routine consultation. Discussing family history of reproductive genetic risk with women during visit for contraception was the least practiced (17.0%). About a quarter (25.8%) of the respondents reported not discussing in any consultation in the last three months.

In discussing preconception advice about genetic carrier testing within the last three months, 44.1% indicated that they had discussed with women known to have family history of genetic conditions, whereas approximately a third had discussed with women of certain ethnicity background (30.5%) and with women planning a pregnancy (33.3%), respectively. 20.2% of the respondents indicated they had discussed preconception advice about genetic carrier testing during routine consultation. Only 11.6% of the respondents discussed during women's visit for contraception. The proportion of respondents who had not discussed in any consultation in the last three months was 26%, which was approximately similar to the experiences of not discussing family history.

Nevertheless, in both situations about 70% of the respondents actually disagreed to the statement that they never discussed during any other consultations within the last three months. This may indicate that they had discussed but perhaps during other consultations not mentioned in the questionnaire items. Only a small proportion of the respondents, between 1.1% till 6.5%, indicated that they were uncertain of their experiences in the last three months in all the situations.

Table 7.5 : Experiences

Questionnaire Items		Yes	No	Don't know
Experiences of discussing family history of reproductive genetic risk	During routine consultation	35 (37.6)	54 (58.1)	4 (4.3)
	Missing	2 (2.1)		
	With women planning a pregnancy	53 (55.8)	40 (42.1)	2 (2.1)
	Missing	0		
	With women during visit for contraception	16 (17.0)	76 (80.9)	2 (2.1)
	Missing	1 (1.1)		
	Never discussed during any consultations	24 (25.8)	67 (72.0)	2 (2.2)
	Missing	2 (2.1)		
Experiences of discussing preconception advice on genetic carrier testing	During routine consultation	19 (20.2)	72 (76.6)	3 (3.2)
	Missing	2 (2.1)		
	With women planning a pregnancy	31 (33.3)	61 (64.9)	2 (2.1)
	Missing	1 (1.1)		
	With women during visit for contraception	11 (11.6)	83 (87.4)	1 (1.1)
	Missing	0		
	With women with known family history of genetic conditions	41 (44.1)	46 (49.5)	6 (6.5)
	Missing	2 (2.1)		
	With women of certain ethnicity (Asian, African, European)	29 (30.5)	60 (63.2)	6 (6.3)
	Missing	0		
	Never discussed during any consultations	25 (26.6)	66 (70.2)	3 (3.2)
	Missing	1 (1.1)		

7.2.4 GPs' opinions on potential approach to deliver preconception assessment of reproductive genetic risk in the primary care setting

The GPs were asked to indicate their opinions on two components of preconception assessment of reproductive genetic risk; firstly on approach to obtain family history and secondly, on approach to offer genetic carrier testing in general practice.

Table 7.6 (1) and Table 7.6 (2) show the proportion of respondents who agreed on the potential approaches to deliver preconception assessment of reproductive genetic risk in the primary care setting.

Majority of the respondents agreed that obtaining family history (95.8%) and offering genetic carrier testing (77.7%) from women seeking preconception advice would be a preferred approach to carry out preconception assessment of reproductive genetic risk in the primary care setting. Majority also favoured obtaining family history from all women of childbearing age at registration by means of self-completed family history questionnaire (81.9%). However, this was not the case in offering genetic carrier testing, where only a third indicated that it was appropriate to offer to all women of childbearing age at registration (34%).

Approximately half of the respondents preferred taking family history of reproductive genetic risk from women enquiring family planning advice (54.7%). Only 35.1% considered that offering carrier testing was appropriate when women seek for family planning advice.

Assessing reproductive genetic risk in women enquiring about menstrual problems is the least agreed (15.8% and 8.5% respectively).

Table 7.6 (1): Potential approach to obtain family history

Obtaining family history of reproductive genetic risk from;	Agree, N (%)*
Women seeking preconception advice	91 (95.8)
Missing	0
All women of childbearing age at registration by means of self-completed family history questionnaire	77 (81.9)
Missing	1 (1.1)
Women enquiring family planning advice	52 (54.7)
Missing	0
Women enquiring about menstrual problems	15 (15.8)
Missing	0

Table 7.6 (2): Potential approach to offer genetic testing

Offering genetic carrier testing to:	Agree, N (%)*
Women seeking preconception advice	73 (77.7)
Missing	1 (1.1)
Women enquiring family planning advice	33 (35.1)
Missing	1 (1.1)
All women of childbearing age at registration	32 (34.0)
Missing	1 (1.1)
Women enquiring about menstrual problems	8 (8.5)
Missing	1 (1.1)

* The denominator depends on the total number of respondents who completed each questionnaire item.

7.2.5 GPs' opinions on appropriate settings in primary care practice to deliver preconception assessment of reproductive genetic risk

The GPs were asked to indicate which settings in primary care practice would be suitable to deliver or provide preconception assessment of reproductive genetic risk. Four suggested primary care setting were listed.

Table 7.7 shows the proportion of respondents who agreed on the settings listed.

The results indicate that family planning clinic (69.6%) was the most preferred setting to deliver preconception assessment of reproductive genetic risk. This is followed by a dedicated preconception clinic, where about half indicated that (52.2%) it would be suitable. Approximately only one-third agreed on providing the assessment in well woman clinic (43.5%) or during routine clinic consultation (34.4%) respectively.

Table 7.7 : Settings

Primary care settings	Agree, N (%)*
A family planning clinic	64 (69.6)
Missing	3 (3.2)
A dedicated clinic	48 (52.2)
Missing	3 (3.2)
A well woman clinic	40 (43.5)
Missing	3 (3.2)
In a routine clinic consultation	32 (34.4)
Missing	2 (2.1)

* The denominator depends on the total number of respondents who completed each questionnaire item.

7.2.6 Potential barriers to developing preconception assessment of reproductive genetic risk in the primary care setting

The GPs were asked to indicate their perceived barriers to developing preconception assessment of reproductive genetic risk in the primary care setting.

Six suggested barriers were listed. Table 7.8 demonstrates the proportion of respondents who agreed whether these barriers play a role in developing preconception assessment of reproductive genetic risk in the primary care setting.

Majority of the respondents indicated, the potential challenges would be that very few women coming for advice before conceive (90.5%) and also difficult to engage these women as target group for preconception advice (76.8%). Further, approximately two-thirds of the respondents considered that not adequately trained to provide preconception reproductive genetic assessment (64.2%) as a barrier. 63.2% also believed that an additional service would involve substantial time and work.

Interestingly, only less than half considered that preconception genetic risk assessment has potential ethical implications (46.3%) and can cause more harm (12.6%).

Table 7.8 : Barriers

Barriers	Agree, N (%)*
Very few women coming for advice before trying to conceive	86 (90.5)
It is difficult to capture the target group	73 (76.8)
I do not have adequate training to provide preconception reproductive genetic assessment	61 (64.2)
Setting up a service will require substantial time and work	60 (63.2)
There is potential ethical implications of preconception genetic risk assessment (e.g. stigmatisation of carriers)	44 (46.3)
Discussing hereditary diseases with couples who are trying for a baby will cause more harm (e.g. emotional disturbances to couples)	12 (12.6)

* No missing data

* The denominator depends on the total number of respondents who completed each questionnaire item.

7.2.7 GPs' opinions on resources to improve the delivery of preconception assessment of reproductive genetic risk in the primary care setting

The GPs were asked to indicate resources that could facilitate the delivery of preconception assessment of reproductive genetic risk in the primary care setting. Three suggested resources were listed. Table 7.9 shows the proportion of respondents who agreed whether the resources have a role to improve the delivery of preconception assessment of reproductive genetic risk in the primary care setting.

Overall, majority of the respondents agreed that further resources were required to improve the delivery of preconception assessment of reproductive genetic risk. The respondents believed that training program for GPs was essential (92.6%). In addition, the respondents agreed that national guideline documents for GPs (82.1%) as well as information leaflets on preconception assessment of reproductive genetic risk for the women given at registration (88.4%) were required

to facilitate the delivery of preconception assessment of reproductive genetic risk if it were implemented in the primary care setting.

Table 7.9 : Resources

Potential resources	Agree, N (%)*
Training programs for the general practitioners	87 (92.6)
Missing	1 (1.1)
Information leaflets on preconception assessment of reproductive genetic risk for women of childbearing age, given at registration	84 (88.4)
Missing	0
National guidelines for the general practitioners (e.g. NICE guidelines)	78 (82.1)
Missing	0

* The denominator depends on the total number of respondents who completed each questionnaire item.

7.2.8 GPs' preparedness to offer and provide preconception assessment of reproductive genetic risk in women of child bearing age group in the primary care practice

GPs' preparedness to offer and provide preconception assessment of reproductive genetic risk in women of child bearing age group in the primary care practice was explored in four situations of preparedness. Table 7.10 provides the proportion of respondents who were prepared and less prepared in the four specified situations.

Majority of the respondents agreed that if appropriate to the consultation, they would be prepared to offer genetic carrier testing to women of childbearing age (74.2%). About two thirds (62.8%) were prepared to offer genetic carrier testing to at-risk women of childbearing age group. 65% of the respondents were willing to counsel about genetic carrier testing results if given the necessary training and information. Additionally, approximately half of the respondents were

prepared to take family history of genetic conditions routinely during obtaining medical history (55.9%).

Generally, in all four situations of preparedness the proportion of respondents who were prepared was higher than the less prepared indicating that the majority of the respondents were prepared to offer and provide preconception assessment of reproductive genetic risk. Further, the result indicates that a higher proportion were prepared if there is an indication, for example, assessment of women prior to their planning for a pregnancy and if the GPs have undergone appropriate training with regards to genetic assessment.

Table 7.10 : Preparedness

Statement of Preparedness	**Prepared N (%)**	**Less prepared N (%)**
I am prepared to take family history of genetic conditions from all women of childbearing age group routinely when taking medical history	52 (55.9)	41 (44.1)
Missing, n (%)	2 (2.1)	
I am prepared to offer genetic carrier testing to at-risk women of childbearing age group	59 (62.8)	35 (37.2)
Missing, n (%)	1 (1.1)	
If appropriate to the consultation, I am prepared to offer genetic carrier testing to women of childbearing age group (e.g. planning a pregnancy)	69 (74.2)	24 (25.8)
Missing, n (%)	2 (2.1)	
Given the necessary training and information, I am prepared to counsel about genetic carrier testing results	61 (64.9)	33 (35.1)
Missing, n (%)	1 (1.1)	

* The denominator depends on the total number of respondents who completed each questionnaire item.

The following section, Section 2, analyses were carried out to investigate the association between respondents who were prepared and less prepared in the four situations of preparedness, in offering and providing preconception assessment of reproductive genetic risk with their experiences of providing preconception assessment of reproductive genetic risk in the last three months.

Section 2

7.2.9 Association between GPs' preparedness to take family history of genetic conditions routinely when taking medical history with their experiences of discussing family history and preconception advice on genetic carrier testing

Respondents who had discussed family history of reproductive genetic risk during routine consultation in were significantly more prepared as compared to those who had not in the previous three months (p=0.04). Those who had experienced discussing preconception advice on genetic carrier testing with women during visit for contraception were also significantly more prepared to take family history of genetic conditions routinely from all women of childbearing age when taking medical history (p=0.008).

Table 7.11 shows the results of analyses between respondents who were prepared and less prepared with their experiences in providing preconception assessment of reproductive genetic risk in the last three months.

Table 7.11 : Association between GPs' preparedness to take family history of genetic conditions routinely when taking medical history with their experiences of discussing family history and preconception advice on genetic carrier testing

GPs' experiences		Prepared N (%)	Less prepared N (%)	p value (Chi-square)
Discussing family history of reproductive genetic risk	During routine consultation, N (%)			
	Yes	26 (51.0)	12 (30.0)	0.04*
	No	25 (49.0)	28 (70.0)	
	Missing, n (%)	4 (4.2)		
	With women planning a pregnancy, N (%)			
	Yes	31 (59.6)	21 (51.2)	0.42
	No	21 (40.4)	20 (48.8)	
	Missing, n (%)	2 (2.1)		
	With women during visit for contraception N (%)			
	Yes	12 (23.1)	6 (15.0)	0.33
	No	40 (76.9)	34 (85.0)	
	Missing, n (%)	3 (3.2)		
Experiences of discussing preconception advice on genetic carrier testing	During routine consultation N (%)			
	Yes	13 (25.0)	9 (22.5)	0.78
	No	39 (75.0)	31 (77.5)	
	Missing, n (%)	3 (3.2)		
	With women planning a pregnancy N (%)			
	Yes	18 (34.6)	14 (35.0)	0.97
	No	34 (65.4)	36 (65.0)	
	Missing, n (%)	3 (3.2)		
	With women during visit for contraception N (%)			
	Yes	11 (21.2)	1 (2.4)	0.008*
	No	41 (78.8)	40 (97.6)	
	Missing, n (%)	2 (2.1)		
	With women with known family history of genetic conditions N (%)			
	Yes	29 (56.9)	17 (42.5)	0.18
	No	22 (43.1)	23 (57.5)	
	Missing, n (%)	4 (4.2)		
	With women of certain ethnicity (Asian, African, European) N (%)			
	Yes	18 (34.6)	16 (39.0)	0.66
	No	34 (65.4)	25 (61.0)	
	Missing, n (%)	2 (2.1)		

*P< 0.05

7.2.10 Association between GPs' preparedness to offer genetic carrier testing to at-risk women of childbearing age with their experiences of discussing family history and preconception advice on genetic carrier testing

The results indicate that there is significant difference between respondents who had discussed family history of reproductive genetic risk during routine consultation (p=0.001) and with women planning a pregnancy (p=0.014) in the last three months than who had not. Those who had discussed were significantly more prepared to offer genetic carrier testing to at-risk women of childbearing age than those who had not discussed during the previous three months.

Table 7.12 shows the results of analyses between respondents who were prepared and less prepared with their experiences in providing preconception assessment of reproductive genetic risk in the last three months.

Table 7.12 : Association between preparedness to offer genetic carrier testing to at-risk women of childbearing age with their experiences of discussing family history and preconception advice on genetic carrier testing

General practitioners' experiences		Prepared	Less prepared	p value Chi-square
Discussing family history of reproductive genetic risk	During routine consultation, N (%) Yes No	 32 (56.1) 25 (43.9)	 7 (20.0) 28 (80.0)	 0.001*
	Missing, n (%)	3 (3.2)		
	With women planning a pregnancy, N (%) Yes No	 39 (66.1) 20 (33.9)	 14 (40.0) 21 (60.0)	 0.014*
	Missing, n (%)	1 (1.1)		
	With women during visit for contraception, N(%) Yes No	 14 (24.1) 44 (75.9)	 4 (11.4) 31 (88.6)	 0.13
	Missing, n (%)	2 (2.1)		
Experiences of discussing preconception advice on genetic carrier testing	During routine consultation N (%) Yes No	 16 (27.6) 42 (72.4)	 6 (17.1) 29 (82.9)	 0.25
	Missing, n (%)	2 (2.1)		
	With women planning a pregnancy N (%) Yes No	 22 (37.9) 36 (62.1)	 11 (31.4) 24 (68.6)	 0.53
	Missing, n (%)	2 (2.1)		
	With women during visit for contraception N (%) Yes No	 9 (15.3) 50 (84.7)	 3 (8.6) 32 (91.4)	 0.35
	Missing, n (%)	1 (1.1)		
	With women with known family history of genetic conditions N (%) Yes No	 29 (50.9) 28 (49.1)	 18 (51.4) 17 (48.6)	 0.96
	Missing, n (%)	3 (3.2)		
	With women of certain ethnicity (Asian, African, European) N (%) Yes No	 22 (37.3) 37 (62.7)	 13 (37.1) 22 (62.9)	 0.99
	Missing, n (%)	1 (1.1)		

*P <0.05

7.2.11 Association between GPs' preparedness to offer genetic carrier testing to women of childbearing age if appropriate to consultation with their experiences of discussing family history and preconception advice on genetic carrier testing

The results demonstrates that respondents who had discussed family history of reproductive genetic risk with women planning a pregnancy in the last three months were significantly more prepared to offer genetic carrier testing to women of childbearing age if appropriate to consultation ($p=0.035$).

Table 7.13 shows the results of analyses between respondents who were prepared and less prepared with their experiences of discussing family history and preconception advice on genetic carrier testing in the last three months.

Table 7.13 : Association between preparedness to offer genetic carrier testing to women of childbearing age if appropriate to consultation with experiences of discussing family history and preconception advice on genetic carrier testing

General practitioners' experiences		Prepared	Less prepared	p value Chi-square
Discussing family history of reproductive genetic risk	During routine consultation, N (%) Yes No	 32 (47.8) 35 (52.5)	 7 (29.2) 17 (70.8)	 0.11
	Missing, n (%)	4 (4.2)		
	With women planning a pregnancy, N (%) Yes No	 43 (62.3) 26 (37.7)	 9 (37.5) 15 (62.5)	 0.035*
	Missing, n (%)	2 (2.1)		
	With women during visit for contraception N (%) Yes No	 15 (22.1) 53 (77.9)	 3 (12.5) 21 (87.5)	 0.31
	Missing, n (%)	3 (3.2)		
Experiences of discussing preconception advice on genetic carrier testing	During routine consultation N (%) Yes No	 16 (23.5) 52 (76.5)	 6 (25.0) 18 (75.0)	 0.89
	Missing, n (%)	3 (3.2)		
	With women planning a pregnancy N (%) Yes No	 26 (38.2) 42 (61.8)	 7 (29.2) 17 (70.8)	 0.43
	Missing, n (%)	3 (3.2)		
	With women during visit for contraception N (%) Yes No	 9 (13.0) 60 (87.0)	 3 (12.5) 21 (87.5)	 0.95
	Missing, n (%)	2 (2.1)		
	With women with known family history of genetic conditions N (%) Yes No	 34 (50.7) 33 (49.3)	 13(54.2) 11 (45.8)	 0.78
	Missing, n (%)	4 (4.2)		
	With women of certain ethnicity N (%) Yes No	 25 (36.2) 44 (63.8)	 9 (37.5) 15 (62.5)	 0.91
	Missing, n (%)	2 (2.1)		

*P <0.05

7.2.12 Association between GPs' preparedness to counsel genetic carrier testing results to women of childbearing age if given necessary training and information with their experiences of discussing family history and preconception advice on genetic carrier testing

The result demonstrates that respondents who had discussed family history of reproductive risk to women planning a pregnancy were significantly more prepared to counsel genetic carrier testing results to women of childbearing age if given appropriate training and information ($p=0.04$). Respondents who had discussed preconception advice on genetic carrier testing during routine consultation and with women of certain ethnicity were also significantly more prepared to counsel genetic carrier testing results ($p=0.005$).

Table 7.14 shows the result of analyses between respondents who were prepared and less prepared with their experiences of discussing family history and preconception advice on genetic carrier testing in the last three months.

Table 7.14 : Association between preparedness to counsel genetic carrier testing results to women of childbearing age if given the necessary training and information with respondents' experiences in providing preconception assessment of reproductive genetic risk in the last three months

General practitioners' experiences		Prepared	Less prepared	p value Chi-square
Discussing family history of reproductive genetic risk	During routine consultation, N (%) Yes No	 29 (49.2) 30 (50.8)	 10 (30.3) 23 (69.7)	 0.08
	Missing, n (%)	3 (3.2)		
	With women planning a pregnancy, N (%) Yes No	 39 (63.9) 22 (36.1)	 14 (42.4) 19 (57.6)	 0.04*
	Missing, n (%)	1 (1.1)		
	With women during visit for contraception N (%) Yes No	 14 (23.3) 46 (76.7)	 4 (12.1) 29 (87.9)	 0.19
	Missing, n (%)	2 (2.1)		
Experiences of discussing preconception advice on genetic carrier testing	During routine consultation N (%) Yes No	 18 (30.0) 42 (70.0)	 4 (12.1) 29 (87.9)	 0.05
	Missing, n (%)	2 (2.1)		
	With women planning a pregnancy N (%) Yes No	 25 (41.7) 35 (58.3)	 8 (24.2) 25 (75.8)	 0.09
	Missing, n (%)	2 (2.1)		
	With women during visit for contraception N (%) Yes No	 10 (16.4) 51 (83.6)	 2 (6.1) 31 (93.4)	 0.15
	Missing, n (%)	1 (1.1)		
	With women with known family history of genetic conditions N (%) Yes No	 33 (55.9) 26 (44.1)	 14(42.4) 19 (57.6)	 0.21
	Missing, n (%)	3 (3.2)		
	With women of certain ethnicity (Asian, African, European) N (%) Yes No	 29 (47.5) 32 (52.5)	 6 (18.2) 27 (81.8)	 0.005*
	Missing, n (%)	1 (1.1)		

*P <0.05

In the following section, Section 3, analyses were carried out to investigate the association between respondents who were prepared and less prepared in offering and providing preconception assessment of reproductive genetic risk, with demographic variables. Logistic regression analyses, assessing the effects of the demographic variables on the four outcomes of preparedness in offering and providing preconception assessment of reproductive genetic risk are presented.

Section 3

7.2.13 Logistic regression analysis; Univariate and Multivariate analysis

Logistic regression analyses were used to predict the outcome variables; which are GPs' preparedness to offer and provide preconception assessment of reproductive genetic risk in women of child bearing age group in the four specified situations, according to demographic variables. To recap, the four outcome variables are; preparedness to take family history of genetic conditions from all women of childbearing age group routinely, preparedness to offer genetic carrier testing to at-risk women, preparedness to offer genetic carrier testing if appropriate to the consultation and preparedness to counsel genetic carrier testing results if given training and information.

The demographic variables are age, gender, years of experience as a GP, location of practice, type of practice, practice list size, availability of protocol on preconception care in the practice that covered taking family history of reproductive genetic risk or protocol on preconception genetic carrier testing.

Univariate analyses were performed individually for all demographic variables, with each four outcome variables. The analyses demonstrate

that all independent variables are statistically insignificant to predict respondents' preparedness.

The variables age, gender, years of experience as a GP and practice list size were regarded as confounders. The variables location of practice, type of practice and availability of preconception care protocol that covered family history and genetic carrier testing were regarded as predictive variables (Poppelaars et.al., 2004c, McCahon et.al., 2009). The confounders were entered into the model to get the adjusted odds ratio. The variable, "Availability of preconception care protocol that covered genetic carrier testing" was not included in the logistic regression analyses as the numbers were extremely small and has resulted in a very wide confidence interval.

Results are presented separately for each outcome variable.

7.2.14 Logistic regression analyses between preparedness to take family history of genetic conditions routinely from all women of childbearing age when taking medical history routinely with demographic variables

Table 7.15 shows the results of the analyses.
The proportion of female GPs (55.8%) who were prepared appeared more than the male GPs (44.2%) although not statistically significant. With regards to location of practice, the highest proportion of GPs who were prepared was from urban practice (55.8%), followed by inner city (27.5%) and rural practice (13.7%). GPs that had preconception protocol on family history of reproductive risk, a high proportion, 71.4% were more prepared as compared to only 28.6% who did not have the protocol. Nevertheless, both results did not reach statistical significant. There was no significant difference between the GPs' age, years of experience and practice list size, between those who were prepared and less prepared.

Table 7.15 : Logistic regression analyses between preparedness to take family history of genetic conditions routinely from all women of childbearing age when taking medical history routinely with demographic variables

Factors	Prepared	Less Prepared	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p value
Age, mean (SD)	45.9 (8.9)	45.1 (8.5)	1.01(0.96-1.06)	1.11 (0.98-1.26)	0.67
Missing, n (%)	4 (4.2)				
Gender, N (%)					
Female	29 (55.8)	24 (58.5)	reference	Reference	0.79
Male	23 (44.2)	17 (41.5)	1.12 (0.49-2.56)	1.23 (0.52-2.95)	
Missing, n (%)	2 (2.1)				
Number of years as a GP, mean (SD)	15.4 (8.8)	15.7 (8.5)	0.99 (0.95-1.05)	0.90 (0.79-1.03)	0.87
Missing, n (%)	4 (4.2)				
Location of practice, N (%)					
Rural	7 (13.7)	9 (22.0)	reference	reference	0.27
Urban	30 (58.8)	25 (61.0)	1.54 (0.51-4.74)	1.98 (0.59-6.62)	
Inner city	14 (27.5)	7 (17.0)	3.00 (0.76-11.86)	2.537 (0.559-11.53)	
Missing, n (%)	3 (3.2)				
Type of practice, N (%)					
Group	47 (90.4)	39 (95.1)	reference	Reference	0.39
Solo	5 (9.6)	2 (4.9)	2.07 (0.38-11.29)	2.01 (0.34-11.78)	
Missing, n (%)	2 (2.1)				
Practice list size per 1000, mean (SD)	8103.7 (8196.5)	9236.2 (6400.9)	1.00 (1.00-1.00)		0.48
Missing, n (%)	3 (3.2)				

Factors	Prepared	Less Prepared	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p value
*Preconception care protocol that covered family history taking available					
No	4 (28.6)	2 (44.4)	Reference	Reference	0.63
Yes	5 (71.4)	5 (55.6)	2.00 (0.24-16.36)	1.37 (0.04-51.28)	Fischer's exact test
*Preconception care protocol that covered genetic carrier testing available					
No	6 (85.7)	8 (88.9)	Not available as sample is too small		0.85
Yes	1 (14.3)	1 (11.1)			Fischer's exact test

* Based on availability of preconception care protocol

OR = odds ratio

CI = confidence interval

**Adjusted for age, gender, years of experience as a GP, practice list siz

7.2.15 Logistic regression analyses between preparedness to offer genetic carrier testing to at-risk women of childbearing age with demographic variables

Table 7.16 shows the results respondents who were prepared and less prepared and demographic variables.

The results demonstrate that age, gender, years of experience as a GP, location of practice, type of practice and practice list size did not appear to have statistically significant associations with respondents' preparedness to offer genetic carrier testing to at-risk women of childbearing age. The odds of respondents in practices that have preconception protocol on family history appeared to be prepared two times higher however results did not reach statistically significance (OR 2.33 (0.28-18.97)).

Table 7.16: Logistic regression analyses between preparedness to offer genetic carrier testing to at-risk women of childbearing age with demographic variables

Factors	Prepared	Less prepared	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p value
Age, mean (SD)	45.8 (8.5)	45.5 (9.6)	1.01 (0.96-1.05)	1.03 (0.93-1.14)	0.88
Missing, n (%)	3 (3.2)				
Gender, N (%)					
Female	30 (50.8)	24 (68.6)	Reference	Reference	0.09
Male	29 (49.2)	11 (31.4)	2.11 (0.87-5.07)	2.13 (0.86-5.29)	
Missing, n (%)	1 (1.1)				
Number of years as a general practitioner, , mean (SD)	15.6 (7.96)	15.4 (9.53)	1.01(0.96-1.05)	0.98 (0.88-1.08)	0.91
Missing, n (%)	3 (3.2)				
Location of practice, N (%)					
Rural	10 (17.2)	6 (17.1)	reference	Reference	0.67
Urban	36 (62.1)	19 (54.3)	1.14 (0.36-3.61)	1.32 (0.39-4.51)	
Inner city	12 (20.7)	10 (28.6)	0.66 (0.18-2.48)	0.83 (0.19-3.71)	
Missing, n (%)	2 (2.1)				
Type of practice, N (%)					
Group	55 (93.2)	31 (88.6)	Reference	Reference	0.44
Solo	4 (6.8)	4 (11.4)	0.56 (0.13-2.41)	0.55 (0.11-2.64)	
Missing, n (%)	1 (1.1)				
Practice list size, mean (SD)	9035.7 (6421.1)	7689.9 (8914.3)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.40
Missing, n (%)	2 (2.1)				
*Preconception care protocol that covered family history taking available					
No	3 (30.0)	3 (50.0)	Reference	Reference	0.42
Yes	7 (70.0)	3 (50.0)	2.33 (0.28-18.97)	0.62 (0.02-22.95)	

Factors	Prepared	Less prepared	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p value
*Preconception care protocol that covered genetic carrier testing available					
No	8 (80.0)	6 (100.0)	Not available as sample is too small		0.24 Fischer's exact test
Yes	2 (20.0)	0			

* Based on availability of preconception care protocol

OR = odds ratio

CI = confidence interval

**Adjusted for age, gender, years of experience as a general practitioner and practice list size

7.2.16 Logistic regression analyses between preparedness to offer genetic carrier testing to women of childbearing age if appropriate to the consultation with demographic variables

None of the results was significant indicating that age, gender, years of experience as a general practitioner, location of practice, type of practice, practice list size and preconception care protocol on family history and genetic carrier testing, did not have association with respondents whether they were prepared or less prepared to offer genetic carrier testing to women of childbearing age if appropriate to consultation. The odds of respondents in practices that have preconception protocol on family history appeared two times higher however the results did not reach statistically significance (OR 2.33 (0.29-18.96)).

Table 7.17 : Logistic regression analyses between preparedness to offer genetic carrier testing to women of childbearing age if appropriate to the consultation with demographic variables

Factors	Prepared	Less prepared	Adjusted Odds Ratio (95% CI)	Unadjusted Odds Ratio (95% CI)	p value
Age, mean (SD)	45.5 (9.1)	46.1 (8.2)	0.99 (0.94-1.05)	1.09 (0.94-1.280	0.77
Missing, n (%)	4 (4.2)				
Gender, N (%)					
Female	39 (56.5)	14 (58.3)	Reference	Reference	0.88
Male	30 (43.5)	10 (41.7)	1.08 (0.42-2.76)	1.24 (0.46-3.35)	
Missing, n (%)	2 (2.1)				
Number of years as a general practitioner, , mean (SD)	15.1 (8.8)	16.9 (8.1)	0.97 (0.92-1.03)	0.89 (0.77-1.04)	0.35
Missing, n (%)	4 (4.2)				
Location of practice, N (%)					
Rural	11 (16.2)	5 (20.8)	Reference	Reference	
Urban	39 (57.4)	15 (62.5)	1.12 (0.35-3.98)	1.71 (0.46-6.33)	
Inner city	18 (26.4)	4 (16.7)	1.93 (0.42-8.82)	1.67 (0.32-8.81)	0.66
Missing, n (%)	3 (3.2)				
Type of practice, N (%)					
Group	62 (89.9)	23 (95.8)	Reference	Reference	
Solo	7 (10.1)	1 (4.2)	2.59 (0.30-22.28)	2.20 (0.23-20.85)	0.37
Missing, n (%)	2 (2.1)				
Practice list size per 1000, mean (SD)	8141.4 (6214.9)	9433.3 (10324.8)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.46
Missing, n (%)	3 (3.2)				
*Preconception care protocol that covered family history taking available					
No	3 (30.0)	3 (50.0)	Reference	Reference	Fischer exact test
Yes	7 (70.0)	3 (50.0)	2.33 (0.29-18.96)	(0.12-282.96)	0.42

Factors	Prepared	Less prepared	Adjusted Odds Ratio (95% CI)	Unadjusted Odds Ratio (95% CI)	p value
*Preconception care protocol that covered genetic carrier testing available					
No	8 (80.0)	6 (100.0)	Not available as sample is too small		0.50 Fischer exact test
Yes	2 (20.0)	0			

* Based on availability of preconception care protocol

OR = odds ratio

CI = confidence interval

**Adjusted for age, gender, years of experience as a general practitioner and practice list size

7.2.17 Logistic regression analyses between preparedness to counsel genetic carrier testing results if given necessary training and information with demographic variables

The results show that there was no significant association between respondents who were prepared and less prepared to counsel genetic carrier testing results to women of childbearing age given appropriate training and information, with the demographic variables.

Table 7.18 : Logistic regression analyses between preparedness to counsel genetic carrier testing results if given necessary training and information with demographic variables

Factors	Prepared	Less prepared	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	p value
Age, mean (SD)	45.2 (8.66)	46.7 (9.24)	0.98 (0.93-1.03)	0.99 (0.91-1.09)	0.42
Missing, n (%)	3 (3.2)				
Gender, N (%)					
Female	32 (52.5)	22 (66.7)	Reference	Reference	0.18
Male	29 (47.5)	11 (33.3)	1.81 (0.75-4.38)	1.88 (0.76-4.67)	
Missing, n (%)	1 (1.1)				
Number of years as a general practitioner, , mean (SD)	15.2 (8.61)	16.3 (8.51)	0.98 (0.94-1.04)	0.99 (0.89-1.09)	0.56
Missing, n (%)	3 (3.2)				
Location of practice, N (%)					
Rural	11 (18.0)	5 (15.6)	Reference	Reference	
Urban	37 (60.7)	18 (56.3)	0.93 (0.28-3.09)	1.06 (0.30-3.72)	0.76
Inner city	13 (21.3)	9 (28.1)	0.61 (0.15-2.37)	0.63 (0.14-2.85)	
Missing, n (%)	2 (2.1)				
Type of practice, N (%)					
Group	57 (93.4)	29 (87.9)	Reference	Reference	0.36
Solo	4 (6.6)	4 (12.1)	0.51 (0.12-2.18)	0.54 (0.11-2.59)	
Missing, n (%)	1 (1.1)				
Practice list size per 1000, mean (SD)	8672.3 (6567.3)	8269.1(8915.2)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.81
Missing, n (%)	2 (2.1)				

Factors	Prepared	Less prepared	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	p value
*Preconception care protocol that covered family history taking available					
No	4 (44.4)	2 (28.6)	Reference	Reference	
Yes	5 (55.6)	5 (71.4)	0.50 (0.06-4.09)	0.31 (0.01-6.75)	0.52 Fischer exact test
*Preconception care protocol that covered genetic carrier testing available					
No	7 (77.8)	7 (100.0)	Not available as sample is too small		
Yes	2 (22.2)	0			0.18 Fischer exact test

* Based on availability of preconception care protocol

OR = odds ratio

CI = confidence interval

**Adjusted for age, gender, years of experience as a general practitioner and practice list size

7.2.18 Summary of results of logistic regression

The results of logistic regression to demonstrate variables that predict all four outcomes of preparedness, whether unadjusted or adjusted, none of the results was significant indicating that; respondents practicing in urban and inner city were not significantly more likely to be prepared compared to respondents practicing in the rural; respondents in group practice were not significantly more likely to be prepared compared to respondents practicing solo and availability of preconception care protocol that covered family history were not predictive of respondents preparedness.

The following Section 4 presents the analyses of free text responses that were written by the respondents to indicate suggestions or additional views of the questionnaire items.

Section 4

7.3 Analysis of free text responses

Free texts from respondents offered at every questionnaire items were considered as free text responses, and were analysed. Two major themes were derived from the free text responses; facilitators and barriers.

Facilitators

Incentives were repeatedly mentioned to motivate general practitioners when introducing new health care service in the practice. The respondents also suggested enhanced health care services to help in the delivery of preconception assessment of reproductive genetic risk. Further, the respondents also suggested the nurses to take charge of

preconception services, besides the GPs, as strategy to facilitate the service.

Barriers

Time factor was consistently mentioned in the free text response, particularly time with regards to the consultation of preconception assessment of reproductive genetic risk. In addition, one of the respondents was also concerned of time taken for genetic test results to return which may potentially affect the management of the patient. The respondents also cited that introducing new services would imply additional cost and funding.

Table 7.19 summarizes the analysis of the free text response and examples of the free texts.

Table 7.19 : Analysis of the free text response

Themes	Categories	Free text-response
Facilitators	**Incentives**	*" ….will there be funding to lost opportunity time"* *"It's not all about financial incentives and although unfortunately that seems to be what the GPs want"*
	Enhanced health care organization	*"May need to be enhanced service…"*
	Delegate task	*"Nurse led clinic would be most effective use of resources"* *"Midwife preconception clinic"* *"…practice nurse discusses preconceptual risk.."*
Barriers	**Consultation time**	*"Time within the consultation, even with adequate training, it is not a discussion that can be had in ten minutes"* *"…genetic risk assessment can take as long as 30 minutes with preconception advice"* *"Genetic testing of blood only via genetics service which incurs a wait and fee"*
	Cost/Funding	*"Possibility of additional cost to NHS when we really need cost cutting"* *"Not too sure of genetic testing, funds?*

7.4 Discussion

7.4.1 Strengths and limitations

Response rates

Despite this study incorporated several strategies that potentially would have an impact on the return of the questionnaire, the response rate was poor, 34%. This was lower than the mean response rate reported in a recent review of published primary care journals looking at GPs' response to postal questionnaire survey, which was 47% (Creavin et al., 2011). A number of factors may have influenced the outcome; it may be the level of interest to this topic was still low and the GPs may not consider the issue of preconception assessment of reproductive genetic risk relevant to their practice. Adding to this, the sampling was from at least one GP in each practice, thus, the issue of 'passing the responsibility to others' to complete the survey may end up to not completing it. Poor response may also be due to the GPs' busy schedule. As a result, the quality of this study may have been affected by the poor response rate.

Firstly, it has led to small sample size, thus it was difficult to interpret the results, in particular the calculation of logistic regression models which resulted in wide confidence intervals. Secondly, it potentially limits the generalisability of collected data due to non-response bias. Non-response bias occurs when the answers of respondents may differ from potential answers of those who did not respond to the survey; GPs who replied may have interest or motivated in genetic medicine, the results potentially is skewed to positive replies. Ideally, every non respondent should be contacted; however, this was not always possible.

Although this study has been limited by the small sample size, some information gathered in this survey have nonetheless, offer an insight

for potential future interventions in preconception assessment of reproductive genetic risk.

Demographic characteristics

The demographic profiles of the respondents were approximately similar to the profile of the GPs in the United Kingdom as a whole, with the exception, the proportion of male and female GPs. According to the National Survey of General Practitioners, in 2006, 60% of the GPs were male compared with 42.6% in this study. Nationally, the mean age of GPs was 47.0 years (SD 9.3), compared with the mean age of 45.7 years (SD 8.9) in this study. The mean number of years working as GPs reported in National Survey of General Practitioners was 16.0 years (SD 9.2) compared with 15.6 years (SD 8.5) in this study. The proportion of solo practitioners was 5% nationally; approximately similar to this study 8%. The mean practice list size across all respondents in this study was 8,530 as compared to 8,653 as reported nationally in 2006. Although the demographic profile were about similar to the profile of GPs in the United Kingdom, the findings may not be broadly generalise as this study was only limited to general practices within PCTs of Nottinghamshire, Nottingham City, Derby City and Derbyshire. This may be due to the geographic settings (urban, inner city, rural) that may differ with other PCTs.

Majority of general practices which participated were located in the urban and inner city areas. Firstly, the population of reproductive age group in the United Kingdom, aged 20-45 years old, majority lived in urban and the inner city areas whereas, the rural population is predominantly aged between 45 and 64 years old (DEFRA, 2012). Secondly, populations of ethnic minority groups from the South East Asian, Mediterranean and the Africans, recognised to inherit autosomal recessive genetic conditions in were concentrated in the inner cities (Modell and Kuliev, 1993, Hickman et al., 1999). Adding to this, very few of the practices have a written protocol on preconception care and particularly covering family history and genetic carrier testing (10% of all practices).The practices which had both family history and genetic

carrier testing components in the preconception care protocol were predominantly inner city practices.

These results may suggest that assessment of reproductive genetic risk in women before conception is still not widely recognised or practised. It could be argued that the GPs working in urban and inner city areas are more aware of the issues around reproductive genetic assessment such as preconception and antenatal screening because these areas have higher proportion of population at risk.

Analysis of preparedness

The univariate analyses demonstrates that generally, majority of the respondents were more prepared to offer preconception assessment of reproductive genetic risk if there is an appropriate indication such as with women planning a pregnancy (74.2%) and with women at reproductive genetic risk (62.8%), or if GPs were given adequate training and information (65%). In addition, the respondents' preparedness was reflected by their previous experiences. The respondents' preparedness to offer and provide preconception assessment of reproductive genetic risk however, was not significantly associated with their age, gender, years of experience as a general practitioner, the location of practice area, practice description whether solo or group and practice list size. The availability of preconception protocol on family history and genetic carrier testing also did not significantly have association with the respondents' preparedness. These findings may suggest that the GPs realised the potential benefits of preconception assessment of reproductive genetic risk and were prepared to deliver in primary care. It is likely that they were more prepared if preconception risk assessment is relevant to the women.

The logistic regression models did not demonstrate the association between predictor variables and the outcomes of preparedness. Predictor variables would help researchers to understand GPs preparedness to engage with preconception assessment of

reproductive genetic risk interventions. The statistically insignificant results are possibly due to inadequate power of the study. It would be desirable to investigate other variables or predictors which were not asked in the survey that could have an impact on the outcomes of preparedness; for example, previous training in genetics or reproductive genetics, and previous CME (Continuous Medical Education) attendance on genetics or reproductive genetics; level of knowledge, level of confidence, place of training, clinical genetic services facilities and ethnicity of the GPs (Suchard et al., 1999a). These factors would give additional information on how to facilitate GPs preparedness to engage with preconception assessment of reproductive genetic risk interventions. Adding to this, perhaps a larger study is worthwhile to generate more precise estimate of effect.

Free text analyses

The free text responses have provided additional important information on issues to consider when recommending preconception assessment of reproductive genetic risk in general practice, in particular, the suggestion on enhanced health care services, an independent organization to help improve the delivery of future interventions. Financial incentives through Quality and Outcomes Framework could be one of the ways to facilitate GPs when promoting new health care service. However, preconception consultation of genetic risk is considered requiring a longer time in the clinic. Introducing new health care program would incur additional cost to the NHS.

7.4.2 Comparison with existing literatures

Previous studies have reported GPs' experiences of providing consultation on preconception care in general (Heyes et al., 2004, Mennie et al., 1993) but not specifically to preconception assessment of reproductive genetic risk. Further, a substantial number of them actually had initiated the consultation on preconception care in routine clinics (Heyes et al., 2004, Janz et al., 2002). When reported specifically on

preconception assessment of reproductive genetic risk, this study has highlighted encouraging respondents' experiences. Fifty-six percent of the respondents reported doing family history consultations mainly with women planning a pregnancy, whereas, when discussing genetic carrier testing, the highest proportion was with women known family history of genetic conditions (44%), followed by women planning pregnancy (33%) and those with certain ethnicity background (30.5%). This seems plausible as women planning pregnancy are the target population to be offered any form of preconception care, and this includes assessment of reproductive genetic risk. Women with known family history of genetic conditions and of certain ethnicity, for examples, Asians and Mediterranean, are in the at-risk group. Family and ethnicity history are an expected component in genetic assessment (Bennett, 2012), thus, discussing genetic carrier testing is almost inevitable in this at-risk group.

Interestingly, there were a small proportion of respondents who had discussed family history (37.6%) and giving preconception advice on genetic carrier testing (20.2%) during routine consultation. This proportion is lower than previous study which reported about 56% of the participated GPs had provided opportunistically during clinic, but on general preconception advice (Heyes et al., 2004).

As a substantial proportion of respondents had discussed family history and giving preconception advice on genetic carrier testing mainly to women planning pregnancy, it was not a surprise that majority of the respondents, their preferred approach to obtain family history and offer genetic testing are to women who are seeking preconception advice, 96% and 78% respectively. This certainly offers an opportunistic approach. Nevertheless, women were reported not actively coming for preconception advice, whether for general advice (Heyes et al., 2004) or specific for reproductive genetic risk assessment (Poppelaars et al., 2003). This study demonstrated similar findings that majority, 91% of

the respondents still believed that accessing this target group of women, a major obstacle.

Another important finding was about 82% of the respondents favoured the suggestion of self-completed family history questionnaire to be given to all women of childbearing age in the practice. This could be obtained at first registration or from existing patients who have not had family history taken before. This approach could be an avenue to capture women who are at reproductive genetic risk, even if they do not plan to conceive. In this approach, following information gathered from the self-completed family history questionnaire, women can then be offered information about genetic risk in detail and also genetic testing during consultation with their GPs. Information leaflets on preconception risk can be offered in the general practice to enhance awareness about the importance preconception assessment as agreed by 88% of the respondents.

With regards to preferred primary care setting to provide preconception assessment of reproductive genetic risk, the highest proportion, 70% of the respondents had indicated that family planning clinic as the appropriate setting. In the United Kingdom, family planning clinics serve as a contraception clinic where they provide advice and information on contraception to women (http://www.nhs.uk/Conditions/contraception-guide [accessed 5 December 2013]). Although, majority favoured family planning clinics, only a small proportion of the respondents reported discussing family history (17%) and preconception advice about genetic carrier testing (11.6%) during women's visits for contraception. This result was about similar to previous survey on preconception care in general, where only about 10% of participated GPs had provided preconception advice in the clinics (Heyes et al., 2004). In addition, only about half (54%) of the respondents preferred the approach to obtain family history and 35% to offer genetic carrier testing from women enquiring family planning advice.

There may be few possible explanations for this. Firstly, the proportion of at-risk women who consulted for contraception during the time of this study may be low and hence, only small percentages of GPs had discussed family history and genetic carrier testing. Secondly, contraception advice may be provided by other primary care providers such as the nurses. Thirdly, women rarely visit for contraception in routine general practice consultation. Furthermore, having to discuss solely on preconception assessment of reproductive genetic risk during this visits may be seen as irrelevant by the women. Finally, it may simply due to inadequate attention to preconception care by the GPs during family planning or contraceptive visits.

With regards to barriers, the most widely acknowledged by the respondents are very few women come for preconception advice before pregnancy (90.5%) and the difficulty to reach these women (76.8%). Lack of time (63.2%) and inadequate training (64.2%) still contribute the main barriers when introducing new services in a health care system, similar to previous other studies on preconception care and genetic conditions (Heyes et al., 2004, McCahon et al., 2009). About half (46.3%) still believed that genetic assessment is associated with ethical implication such as stigmatisation. Nevertheless, interestingly only a small proportion of the respondents (12%) believed that genetic assessment could cause more harm. This finding was similar to previous study where 13% (Poppelaars et al., 2004a) and 3% (Mennie et al., 1998) respectively, of participated GPs were concerned of the cystic fibrosis screening to cause more harm. Stigmatisation and discrimination has been consistently mentioned in the national policies as the main concern when recommending any genetic risk assessment programs (Nuffield Council on, 2003, Health Council of the Netherlands, 2007, Human Genetics Commission, 2011). This may remain as a continuing issue with regards to screening for reproductive genetic risk. Nonetheless, preconception assessment of reproductive genetic risk is seen to do more good than harm. This may indicate that women or prospective parents are more aware of the benefits of knowing

reproductive genetic risk before having any children (Wert et al., 2012). Henneman (2003) reported, preconception assessment of reproductive genetic risk for cystic fibrosis did not cause further anxiety (Henneman et al., 2003).

The attitudes of preparedness from the survey reflects earlier studies that the vast majority of participated GPs recognised the importance of providing preconception care assessment and education (Gaytant et al., 1998, Wallace and Hurwitz, 1998, Heyes et al., 2004) and GPs agreed that primary care setting is most appropriate to offer the service (Wallace and Hurwitz, 1998, Heyes et al., 2004).

7.5 Conclusion

The findings from the survey study has provided an understanding of GPs' attitudes, potential facilitators and gaps in the delivery of preconception assessment of reproductive genetic risk in primary care. However, it is limited due to small study size. The credibility of this study could be enhanced by improving the study design, questionnaire as the survey instrument and carrying out in a larger scale.

The following chapter, the final chapter presents the conclusions of this thesis. This chapter will discuss the main findings of thesis; strength and limitations of this thesis; implications for future practice; and implications for future research in the United Kingdom. In addition, international applicability of this thesis will also be discussed, with Malaysia as an example.

CHAPTER 8
CONCLUSION

8.1 Introduction

Improving preconception care can result in improved maternal health and pregnancy outcomes (Rowley et al., 1997, Atrash et al., 2006). Preconception care can offer a window of opportunity to provide information for women or prospective parents allowing informed decisions on a broader range of reproductive options (Solomon et al., 2008b) Enhancing reproductive decision making is regarded as the primary aim of preconception care for reproductive genetic risk (Wert et al., 2012). The existing antenatal assessment is seen as suboptimal in terms of enabling full reproductive decision making (Jans et al., 2012, Solomon et al., 2008b).

The aim of this thesis is to identify the opportunity for preconception care with assessment of reproductive genetic risk as the main focus in the primary care setting. The role of primary care in delivering preconception care is increasingly recognised (March of Dimes, 2002, Health Council of the Netherlands, 2007). The views of primary care providers are clearly important to understand potential gaps in delivering preconception care, specifically in reproductive genetic risk. Two systematic reviews examining evidences of effectiveness of interventions for preconception care and preconception assessment of reproductive genetic risk were carried out to achieve the aim. A questionnaire survey study involving GPs was carried out to explore their views and attitudes. It is hoped that the results of the survey and the positive benefits highlighted from the systematic reviews would be useful to provide an understanding to developing preconception assessment of reproductive genetic risk in the United Kingdom health infrastructure.

In this concluding chapter, I will present the aim and key findings of each chapter of the thesis. I will futher discuss the strengths and limitations, and will conclude by providing recommendations for future research and discussing clinical implications for practice in the United Kingdom based on results of this thesis. In addition, I will also discuss opportunities to deliver preconception care and specifically preconception assessment of reproductive genetic risk in Malaysia.

8.2 Main findings of thesis

Chapter 1 provides the general introduction of this thesis, aim and objectives, and background rationale to carrying out the work for this thesis.

Chapter 2 discusses the potential opportunities and challenges of preconception care in general and specifically in reproductive genetic risk, from review of existing literatures as well as policy-related documents. This chapter has offered information and understanding to the challenges related to its implementation in the United Kingdom and other countries like the Hungary, Netherlands and the United States, as well as the Mediterranean countries such as Cyprus and Greece.

Chapter 3 presents the systematic review examining the effectiveness for preconception care strategies to improve pregnancy and reproductive outcomes in primary care. In line with the aim of this thesis, this review was carried out to assess preconception intervention strategies that incorporate genetic assessment of reproductive risk as part of comprehensive preconception care assessment. The aim of this review is also to explore interventions with practical and systematic approach that can be utilised in primary care.

This review concluded that there is still limited robust evidence for the effectiveness of preconception care interventions in primary care.

There was variation in the characteristics of interventions evaluated and the results were heterogeneous. The results of this review indicated that both multifactorial and single reproductive health risk interventions improved maternal knowledge, self-efficacy towards healthy lifestyle and risk behaviour, irrespective of the duration of intervention. However, there was no clear indication of improvement in adverse pregnancy outcomes. In two-thirds of the included studies, participants were restricted only to women planning pregnancy. Reaching out only to women who are planning pregnancy would result in missed opportunities for preventative strategy.

Chapter 4 presents the systematic review, using Cochrane methodology, examining the evidence of effectiveness for preconception assessment of reproductive genetic risk. As there is little research in this area particularly in primary care, the scope of this review has included any health care settings instead of only primary care settings. The scope of diseases for this review was confined to autosomal recessive genetic conditions, namely; haemoglobinopathies which include thalassemia and sickle cell disease, cystic fibrosis and Tay-Sachs disease; as these diseases are common and high prevalent worldwide.

It was not possible to draw clear conclusions regarding the effectiveness of preconception assessment of reproductive genetic risk, as this review identified only two interventional studies and only on two specific genetic conditions, haemoglobinopathies and cystic fibrosis. Furthermore both studies were of different methodological design and of limited quality. Nevertheless, these studies have demonstrated that preconception assessment (carrier testing) and education have positive benefits and implications on the target populations' knowledge, psychological wellbeing, recall and understanding of test-results and satisfaction. With regards to knowledge, both studies reported significant improvement from before and just after pre-carrier test education or counselling.

Chapter 5, 6 and 7 presents the questionnaire survey exploring the attitudes and opinions of GPs in the Nottinghamshire and Derbyshire.
It is encouraging to discover that the present GPs in my study were already offering or providing preconception advice on reproductive genetic risk opportunistically particularly, with women planning pregnancy, with positive family history of genetic conditions or with women of certain ethnicity background. Even if they are not offering or providing preconception advice on reproductive genetic risk, majority of them indicated that they are prepared to offer and provide the advice or service, especially to women at-risk or women planning a pregnancy. In addition, the GPs indicated that they are also prepared to provide genetic counselling if they are given appropriate training and information. This indicates that the GPs are willing to take an active role to introduce the service in their practice. Certainly this is a positive indicator in the initial step to recommending preconception assessment of reproductive genetic risk in primary care.

It was agreed by most GPs in my study that family planning clinic is the preferred setting in primary care to deliver preconception assessment of reproductive genetic risk. There is a need to re-emphasize the role of family planning clinic to the GPs as well as other primary care providers and to all women of reproductive age in the United Kingdom. Since the GPs' primary concern is difficulty to capture women to go for preconception care assessment, thus, it would seem feasible to reach them through family planning clinics.

8.3 Strengths and limitations of thesis

The reviews in Chapter 3 and Chapter 4 examined the evidence for effectiveness of interventions in preconception care focussing on preconception assessment of reproductive genetic risk in primary care setting. Systematic reviews aim to "collect and synthesize relevant evidence to inform real-world health care decisions for patients, health

care providers, and policymakers, as well as to identify future research needs" (Higgins and Green, 2011). Evidently, strong methodologic approaches increase the transparency, consistency and scientific rigor of these reports (Higgins and Green, 2011). This is the key strength of systematic reviews. However, the use of robust methodology has led to limited number of eligible studies being identified for these reviews.
Systematic review may not always provide the evidence to developing preconception genetic interventions within the health care systems, but what I've learnt is looking at within the context of the settings, situations and community targeted in each intervention as well as potential outcomes and benefits that each intervention is able to demonstrate.
Adding to this, the reviews have highlighted positive benefits in the improvement of maternal knowledge on preconception care and preconception genetics. The importance of sufficient knowledge would potentially help to support women or prospective parents informed decision-making when undergoing genetic screening (Marteau and Lerman, 2001, Stefansdottir et al., 2010). This is important when informed decision-making is regarded as the primary aim and focus of preconception assessment of reproductive genetic risk.

Although there is lack of robust evidence, these reviews could inform future research in preconception interventions. It also helps to inform potential strategy for developing preconception assessment of genetic risk in primary care such as potential target population and potential setting to implement it.

The survey was carried out to explore the GPs' attitudes and opinions on preconception assessment of reproductive genetic risk if this intervention is to be introduced in the general practices in the United Kingdom. This survey has been limited by poor response rate. Although the demographic profiles are approximately similar to the profiles of GPs, there is a concern about generalising the findings to the entire GPs in the United Kingdom as it only involved two counties, Nottinghamshire and Derbyshire. Adding to this, the questionnaire was

replied by only one GP for each practice. Nonetheless, the findings gathered in this survey have offered invaluable information for potential future interventions in preconception assessment of reproductive genetic risk. It is hoped these findings could be translated into primary care practice in the United Kingdom in future. This will be discussed in subsequent section; the 'Implications for future practice'.

8.4 Implications for future practice in primary care in the United Kingdom

I acknowledged that the impact of this thesis is limited due to poor trial evidence in the systematic reviews as well as poor response in the questionnaire survey. Nevertheless, the findings have generated some insights how this might be used to inform or translated into primary care practice. Furthermore, preconception care has already taken place in some parts of the world based on evidences from large observational studies, especially in the developed countries such as the United States and the Netherlands. There is a possibility to recommend it in the NHS United Kingdom.

8.4.1 Recommending family planning clinic

One of the key findings in my survey is recommending utilizing family planning clinic to reach women prior to pregnancy. Family planning clinic could be used as a potential starting point to introduce and implement preconception care.

In the United Kingdom, family planning clinic seems to be a feasible setting to capture women of childbearing age, especially when we consider that preconception interventions should be offered and accessible to all or at risk women. There is a need to re-emphasize and delineate the role of family planning clinics within the health infrastructure in the United Kingdom. According to the National Health Service, a family planning clinic provides reproductive health services

which involve fertility, preparing for pregnancy and preventing pregnancy or contraception, and prevention of gynaecologic malignancy and infection (http://www.nhs.uk/Conditions/contraception-guide/Pages/contraception-clinic-services.aspx). This allows family planning clinic a unique ability to reach any women of childbearing age. It also often attracts younger women who primarily come for contraception advice, thus, this setting may potentially offer opportunity for reproductive advice (Gold, 2005). A routine health risk assessment could be proposed as part of preconception care package in this setting to identify women at reproductive genetic risk when they come for any reproductive health advice or treatment at this clinic. A self-administered family history questionnaire, given to women at registration could be recommended to assist in the assessment process. In addition, as time especially during routine consultation is a problem that is commonly voiced by the GPs in the survey, family planning clinic may provide a protected time and opportunity to discuss preconception risk and reproductive issues, along with other women's health issues.

8.4.2 GPs' preparedness

Optimizing the delivery of preconception care practices in primary care will require integration across the various groups of primary care providers (Ross, 2012) and strong commitment of the primary care team to carry out and to sustain adherence to the service.

GPs are the main gatekeepers in the primary care setting, and they could be supported by other primary care providers such as, practice nurses and midwives (Roland et al., 2012). Are the GPs prepared to deliver if implemented nationally or at a population level? According to my study, the GPs appear to have positive attitude to preparedness to offering and providing the service. This may suggests GPs' acceptance of the service in primary care. In this context, improving their awareness

and knowledge would be the logical initial step when recommending the intervention. This includes education and training on the importance of addressing preconception health in general and specific in reproductive genetic risk among all women of childbearing age and risk screening. Nevertheless, GPs expressed that lack of training in this area is a limitation. It is essential that continuous medical education for the GPs or other primary care providers that covers the assessment and counselling of reproductive genetic risk be developed to improve and sustain their knowledge and practices. Education and training module such as the PEGASUS (Professional Education for Genetic Assessment and Screening) should include issues such as family history, consanguinity, the timing for preconception risk assessment, genetic carrier screening and interpretation of results. In the case of haemoglobinopathies, cystic fibrosis and Tay-Sach disease, possible reproductive options and detection of signs of possible genetic conditions should be added in the module.

8.4.3 Facilitating service provision

Besides enhancing the role of GPs, service provision in general, needs to be addressed. Primary care providers including GPs need appropriate resources. In the context of preconception assessment of reproductive genetic risk, the recommendation would be to develop of consolidate the existing clinical professional guidelines, such as the National Institute for Health and Care Excellence (NICE) guideline, such as that covers fertility, pregnancy and childbirth, which most GPs in the survey acknowledged.

The women and prospective parents need to be aware and understand of the importance of preconception care in general and preconception assessment of reproductive genetic risk (Solomon et al., 2008a, Jans et al., 2012). Information leaflets and electronic media on preconception care incorporating reproductive genetic risk would help to achieve their awareness. Another possible suggestion is to deliver general education

about timing of conception and pregnancy-related health risks in family planning clinics or even in schools. Integrating reproductive health messages into the existing health promotion campaign in the clinic for example, the campaigns for cervical screening or breast cancer screening campaigns could be beneficial.

With regards to the delivery of preconception assessment of reproductive genetic risk, it should not be regarded as a separate entity but should incorporate into the existing reproductive health infrastructure in primary care practice. These could either be linked to a specific preconception care package, maternity package which would include preconception, antenatal and postnatal, or women's care package for example, Pap smear and breast-self-examination. In fact, in the latest WHO policy report 2012, the WHO has outlined reproductive genetic conditions as one of the areas to be addressed in preconception care package (WHO, 2012)

Funding and incentives are two important resources to consider when introducing new health care service in the primary care settings. The introduction of Quality and Outcomes Framework (QOF) in the United Kingdom has incentivised general practices to engage in management of diseases and preventative activities (Dixon et al., 2011). With regards to preconception screening, only preconception screening for diabetes and epilepsy have taken place in the United Kingdom (www.bma.org.uk/ap.nsf/Content/QOFbrief0908). In addition, one of the Quality Outcome Framework (QOF) also includes enhanced health care services, in which case could help to provide and improve the delivery of preconception care interventions in general practice.

The systematic reviews have highlighted that majority of the target population in the primary studies was women planning pregnancy. It is possible that women who are planning pregnancy are more likely to be interested in preconception care and motivated to achieve improved knowledge and risk behaviour change. Possibly to the women, this is

seen as important to achieve improved preconception health and ultimately would benefit informed decisions and their pregnancy outcomes. One might argue that is it worthwhile to address preconception interventions only to women planning pregnancy? After all, they are motivated and potentially would have better outcome in reproductive health. On the other hand, this may not be fair. Interventions should be offered and accessible to all or at risk women. Nevertheless, targeting women planning pregnancy in the intervention at the initial development might be a logical and desirable idea.

8.5 Potential challenges of delivering preconception care and specifically reproductive genetic risk in the United Kingdom

There is opportunity that working preconception care into the existing family planning clinic services would create a platform for improved reproductive health care. This family planning clinic setting is potentially capable to capture women of reproductive age group. However, critical challenges to working this out need to be addressed.

Firstly, the challenge would be to establish what a preconception care package should consist of, so that it is more applicable and realistic to women who use family planning clinic services. This is important because traditionally family planning clinic services offer contraceptive services to avoid becoming pregnant. Although women come to family planning clinics for contraceptive services, this could be an opportunity to inform and educate them about preconception care. Adding to this, there should be a method to inform these women of the role of family planning clinic such as through electronic media, advertisement on public transport or free pamphlet from clinics or even superstores.

With regards to the implementation of this service, there should be a protocol for providing preconception care in the family planning clinic setting so that so that it is offered universally in the NHS infrastructure. The challenge at this point is that, there is still paucity of strong

evidence to recommend at policy level. Implementation could be based on existing large observational studies that have demonstrated positive impact of preconception care such as reduction in the prevalence of neural tube defects (Czeizel, 1993).

Next, the challenge would be to have sufficient professional human resources to run preconception health. This is important because at any point GPs would also have to handle other clinical services. One possible suggestion is to extend the role of other primary care providers besides the GPs to provide preconception care. If this is run in the family planning clinic, midwives and practice nurses could be involved in the assessment of reproductive risk as well as giving information on preconception care. Further to this, there should be additional training for primary care providers both in clinical such as like the PEGASUS (Professional Education for Genetic Assessment and Screening) as well as administration training. There should be coordination and access with other specialists such as gynaecologist, geneticist or genetic counsellors to refer women who are at health risk.

An expansion to include preconception care would mean potential additional cost. Thus, securing adequate funding is necessary to facilitate successful integration of preconception care into family planning clinic settings. The development of such intervention not just relies on adequate financial allocation but also, appropriate mobilization of financial resources for that matter. Local primary care organizations such as the Primary Care Trust (PCT) should explore the feasibility and cost-effectiveness of providing preconception care to the population, directing appropriate resources and funding into general practices.

When introducing preconception care and preconception on reproductive genetic risk nationally, there will also be potential challenges on sustainability of the intervention. This would mean that there should be a body within the NHS infrastructure such as the National Screening Committee to organize and sustain its

implementation. They could be in charge of quality control, make plans to evaluate and to monitor effectiveness of the intervention. One possible suggestion with regards to evaluating effectiveness is to develop key indicators for example, number of adverse pregnancy outcomes or congenital abnormality with regards to preconception care; and number of preconception genetic testing, number of carrier detected and number of referrals for genetic counselling to demonstrate the results of this intervention in particular on preconception care of genetics.

Above all, the government as policy maker has vital role to approve, ensure enforcement and to sustain this intervention nationally. It is hoped that with better resources, organization, manpower and training could provide a valued preconception care service to any women of reproductive age.

When discussing genetics it usually raises ethical, legal and social implications. They are still considered as the key concern when developing genetic risk assessment at national or population level (Clayton, 2003, Fulda and Lykens, 2006) even if the benefits of the intervention are maximised. Generally, the health care providers and community at large are worried about the effects of knowing genetic risk on a healthy individuals or families. These issues may vary for specific communities and countries because of cultural and religious background (Clayton, 2003, WHO, 2006). Across the countries, WHO (2006) reported possible detrimental effects of genetic assessment in general which are (WHO, 2006):

1. Anxiety raised by information that cannot be used to make positive personal choices about treatment measures or limited choices for preventive measures.
2. Social stigmatization of people with genetic risk or genetic conditions.
3. Undue pressure on individual choices.

4. Confidentiality issues whereby disclosing information to the partner or family members may conflict the affected person's confidentiality.
5. Misuse of the information and discrimination based on the test results after disclosure to third parties, such as insurers and employers.
6. Health disparities such as poor access to genetic services for example genetic counselling or genetic education, in general and specific to genetic screening or testing or early antenatal diagnosis.
7. Health disparities due to limited health professionals with adequate genetic training.
8. Legal or religious restrictions for the termination of pregnancies affected with genetic conditions.

These possible effects could be relevant in the United Kingdom.

In relation to preconception genetic assessment, confidentiality issues especially disclosing information to partners and also leaving them with possible reproductive options afterwards has been recognised as a potential social implications. Disparities with the health services following reproductive screening, for example, availability of early antenatal diagnosis, as well as legal or religious restriction to termination of pregnancy are also potential problems (Khoury et al., 2003, Fulda and Lykens, 2006).

8.6 Implications for future research in the United Kingdom

The conclusion from systematic reviews shows that there is a need for more interventional studies and trials on preconception care, especially in primary care applying more pragmatic approach based on current structure of primary care and available resources. It seems appropriate to suggest studies of intervention that involves multifactorial risk assessment incorporating all women of reproductive age. One

suggestion is to test on the effectiveness of a preconception care package consists of multifactorial risk assessment in a family planning clinic and targeting on all women of reproductive age over usual consultation in the common general practice. Taking into consideration the limitation of GPs, for example; understaff and time; future studies should also recruit other potential primary care providers for example, practice nurses or midwives to offer preconception care.

With regards to preconception genetics, suggested studies would be to examine strategies for preconception genetic risk assessment which include education, counselling and screening or testing as the intervention for the target population. One possible suggestion is to test the effectiveness with regards to different nature of delivery, different primary care settings and who can most effectively delivers the interventions.

With regards to effectiveness of these interventions, possible outcome measures should include uptake of the intervention, number of referrals for carrier testing, reproductive decisions (eg. number of infants born with hereditary genetic conditions), psychological outcomes (eg. anxiety, depression) and social outcomes (eg. stigmatisation) and possibly understanding of carrier status.

The questionnaire survey also has several methodological limitations. To optimize the impact of the survey, it should be implemented on a larger scale, not just confined to two counties, so that the results potentially would be generalisable. The survey instrument should be improved with additional variables that are hypothesized to have effect on the GPs' preparedness such as number of continuous medical training or courses on preconception care or genetics (Suchard et al., 1999a) and number of consultation on preconception genetics in the last three months (Suchard et al., 1999a).

Adding to this the survey which originally was administered to GPs should also involve other primary care providers such as the nurses and midwives. This is because they are also potentially involve in delivering preconception care.

Cost-benefit and cost-effectiveness should also be carried out as part of outcomes of studies on preconception interventions.

To enhance the impact of the intervention on preconception care and preconception assessment of reproductive genetic risk, qualitative studies should be carried out involving women and primary care providers to explore intervention feasibility and acceptability. It would be helpful to explore their views on the benefits and limitations of the intervention as they are the main stakeholders.

8.7 Opportunities in Primary Care in Malaysia

Having explored the implications for recommending practice of preconception care focussing in the assessment of reproductive genetic risk in the United Kingdom, I will now look at the applicability of the recommendations in my practice in Malaysia. There is opportunity to introduce preconception care and in particular, preconception assessment of reproductive genetic risk in Malaysia.

In Malaysia, thalassaemia is considered the most prevalent autosomal recessive condition and it poses an increasing public health problems (George, 2001). Approximately 3.5-4% of Malaysians are carriers of β-thalassemia (Ministry of Health Malaysia, 2009, George and Ann, 2010). In 2009, there were about 4,700 registered thalassaemia patients with majority were β-thalassemia major (Hishamshah, 2012). The Malaysian National Thalassaemia Prevention and Control Programme gained the Ministry of Health approval in the late 2004 (Ministry of Health Malaysia, 2009). At present, screening for

reproductive genetic risk is carried out antenatally, nationwide. Opportunistic screening is either carried out through positive family history or voluntary (Ministry of Health Malaysia, 2009).

The implication of carrying out screening for thalassaemia antenatally, gives the women or prospective parents limited reproductive options. The options include doing prenatal diagnosis and prepare oneself antenatally and, or postnatally if the future child is found to have thalassaemia major. They could also continue with the pregnancy without prenatal diagnosis. In Malaysia, termination of pregnancy has legal consequence. In 1989, according to the penal code, it is only allowed to terminate pregnancy within 120 days of conception if the pregnancy poses a threat to the women's life or to her physical and mental health greater than would the termination of pregnancy (The Penal Code (Amendment) Act 1989 (Act A727). Apart from legal issues, termination of pregnancy is not permissible by the most Malaysians due to religious and cultural concerns (Wong et al., 2011).

With the increasing number of thalassaemia in Malaysia, there is a place that identification of carriers should take place before women conceive. It gives prospective parents more reproduction options where termination of pregnancy is not permissable. A recent study carried out locally reported that majority of the participants expressed positive attitude towards premarital genetic screening (Wong et al., 2011).

8.8 How to develop preconception care within the primary care infrastructure in Malaysia

8.8.1 Introduction

The primary care in Malaysia is provided by an integrated system of health clinics and community clinics in the public sector. Both health clinics and community clinics cover maternal, which include antenatal and postnatal and also child health. Some of the community clinics are managed by midwives in rural areas. According to a recent report by Mohamed Noh (2011), the number of health clinics is 812 and 1919 community clinics nationally in 2010. This organization of public sector is under the directive of Ministry of Health of Malaysia (Mohamad Noh, 2011), so any interventions or programmes developed by the government will be implemented systematically in all health clinics and community clinics.

There is also considerable number of private clinics that offers primary care facilities. Most women also go to private clinics to seek advice on reproductive issues. The policies of private clinics are managed individually by private organization.

8.8.2 Opportunities and challenges

The role of family planning services to improve reproductive and women's health in Malaysia is as similar as in the United Kingdom. It could be a potential setting to introduce preconception health assessment as part of reproductive health care. Preconception health assessment should include identifying women at reproductive genetic risk.

With regards to the implementation of preconception assessment of genetic risk, one important suggestion highlighted by a local study (Wong et al., 2011) is to introduce the intervention before marriage or

premarital intervention. Implementation of national premarital screening has been extensively reported in many countries where autosomal recessive genetic conditions, namely thalassaemia, is most prevalent (Angastiniotis and Hadjiminas, 1981, Samavat and Modell, 2004). It is reported that the driving force for the acceptance of this programme is public awareness specifically knowing the importance and role of premarital screening, availability of effective genetic education and counselling, high consanguinous marriage, availability of genetic services and supports by religious organizations and policy makers or government (WHO, 2006). This could be pertinent in Malaysia who has high prevalent of thalassaemia and evidence of consanguinous marriage in certain ethnic group (Wong et al., 2011).

In Malaysia, there are two types of legal marriage, civil and Muslim marriages. Under the Malaysian law, in any types, couples who are going to wed will need to register formally with appointed government or religious Registrar (www.malaysianbar.org.my). This may be a potential setting to introduce premarital genetic screening as part of preconception health assessment. There are potential limitations; the appointed government or religious authorities has to agree to undertake this intervention; the public's acceptance of carrying genetic screening before marriage may have social implications such as stigmatisation, individual's religion and cultural constraint may contribute as barriers. Inadequate efficient funding and inefficient access or network to health facilities for testing, genetic education and counselling may limit the running of the intervention.

However, it seems possible to link preconception assessment of reproductive genetic risk through family planning services or through premarital screening in Malaysia. Foremost, is to formulate a strategy appropriate to the local epidemiology, current service infrastructure and available funding and resources. There is a need to collaborate the policy makers or respective authorities in the government. The government could take the primary role to arrange a thalassaemia

carrier screening programme to create awareness and help organise screening through either family planning services or premarital registration.

The empowerment of women and family members through education is an important facet of this intervention, thus information can be conveyed to the public by electronic media, advertisements, pamphlets, posters or public forum. There should be a network of family planning and premarital services with the primary care facilities for example, the health clinics and community clinics or even hospitals. A constant effort has to be made to educate and train primary care providers to emphasize on the continuing burden of thalassaemia, to improve the genetic education or counselling and to understand the application of genetics to public health and its associated ethical, religion, legal and social issues.

However, there is concern over public and private sector where variation in practice, inequality in the distribution of health resources and workload might exist. This may lead to standard of care may not be uniform throughout. There is also concern over continuity of care of the target population. Nevertheless, this should not be the barrier to implement preconception assessment of reproductive genetic risk. With respect to this, the first logical step would be to introduce to the Ministry of Health and implement it in the public sector.

Another possible suggestion is to introduce intervention through linkage with other relevant programmes. Relevant to reproductive health, existing programme in Malaysia is Adolescent Health which is community based and covers sexual and reproductive health as documented in the 10th Malaysian Plan (10th Malaysian Plan, 2011). It would seem beneficial for the adolescent to be aware of genetic risk as they are in the reproductive age group and majority may not yet conceived, however, the downside is this programme mainly involved

school-age individuals and there will be issues on informed consent and stigmatization among peers.

8.8.3 Future research in Malaysia

It will be my interest to explore the perspectives of primary care providers in the public and private sector as well as women of childbearing age in Malaysia with regards to introducing preconception care involving reproductive genetic risk as the main focus.

My study, the questionnaire survey, could be replicated to explore the attitudes and opinions of GPs as well as other primary care providers that managed the health clinics or community clinics for example, nurses and midwives. The questionnaire items and methodology will need to adapt to the structure of primary care in Malaysia. As the first step, the content of the questionnaire could be improved with prior qualitative studies such as qualitative interview or focus groups with primary care providers exploring their views on barriers and facilitators to the developing preconception care involving reproductive genetic risk. This would help to understand the pathway of health services and how preconception care could be provided. Interviewing about the issues around referrals and counselling would help to understand the available resources and service provision following identified women who are at risk.

With regards to target population, conducting focus group of women of childbearing age in Malaysia would help to understand the facilitators and barriers of implementing preconception assessment of reproductive genetic risk in the community.

8.9 Learning points through this PhD thesis

The whole process has been a learning experience and hard work, but the overall satisfaction has been the knowledge and research skills that I have acquired. The PhD programme has given me the opportunity to develop and carry out a robust systematic review and also practical experience in mixed research methods. During this thesis, I have discovered substantially interesting issues related to my research and this has opened up to realise the depth of the knowledge that would be very useful and applicable in future health care management.

The findings in my thesis has offered valuable information on the potential benefits of preconception care and preconception assessment of reproductive genetic risk, however, strong evidence on its effectiveness is still limited. This needs to be addressed in future research. Despite the continuing challenges to develop this intervention in primary care, it is encouraging to discover that GPs are prepared to deliver preconception assessment of reproductive genetic risk in their practice. This offers an opportunity to implement intervention in primary care.

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APPENDICES

Appendix 3.1 : Search strategy for Systematic Review 1

MEDLINE search terms

1 preconception care.mp. or exp Preconception Care/

2 (preconcep$ adj2 care).tw.

3 (preconcep$ adj2 assess$).tw.

4 preconception health.mp.

5 (preconcep$ adj2 health).tw.

6 preconception care/ or reproductive health services/

7 (prepregnan$ adj2 care).tw.

8 prepregnancy care.mp.

9 (prepregnan$ adj2 health).tw.

10 (prepregnan$ adj2 assess$).tw.

11 exp Genetic Counseling/ or preconception health.mp.

12 (preconcep$ adj4 genetic).tw.

13 genetic screening.mp.

14 (genetic adj2 screen$).tw.

15 or/1-14

16 primary care.mp. or exp Primary Health Care/

17 family practice.mp. or exp Family Practice/

18 general practice.mp.

19 exp Community Health Services/ or exp Community Health Centers/ or community clinics.mp. or exp Outpatient Clinics, Hospital/

20 ambulatory care facility.mp. or exp Ambulatory Care Facilities/

21 or/16-20

22 15 and 21

23 limit 22 to (English language and humans)

24 limit 23 to yr="1998 -Current"

EMBASE search terms

1	preconception care.mp. or exp Preconception Care/
2	(preconcep$ adj2 care).tw.
3	preconception assessment.mp.
4	(preconcep$ adj2 assess$).tw.
5	preconception health.mp.
6	(preconcep$ adj2 health).tw.
7	preconception care/ or reproductive health services/
8	(prepregnan$ adj2 care).tw.
9	prepregnancy care.mp.
10	(prepregnan$ adj2 health).tw.
11	(prepregnan$ adj2 assess$).tw.
12	exp Genetic Counseling/
13	genetic screening.mp.
14	(preconcep$ adj4 genetic).tw.
15	(prepregnan$ adj4 genetic).tw.
16	or/1-15
17	primary care.mp. or exp Primary Health Care/
18	family practice.mp. or exp Family Practice/
19	general practice.mp.
20	exp Community Health Services/ or exp Community Health Centers/ or community clinics.mp. or exp Outpatient Clinics, Hospital/
21	ambulatory care facility.mp. or exp Ambulatory Care Facilities/
22	or/17-21
23	16 and 22
24	limit 23 to (english language and humans and yr="1998 - Current")
25	limit 24 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or multicenter study or randomized controlled trial) [Limit not valid in EMBASE; records were retained]

PsycINFO search terms

1	preconception care.mp. or exp Preconception Care/
2	(preconcep$ adj2 care).tw.
3	(preconcep$ adj2 assess$).tw.
4	preconception health.mp.
5	(preconcep$ adj2 health).tw.
6	reproductive health services.mp.
7	(prepregnan$ adj2 care).tw.
8	prepregnancy care.mp.
9	(prepregnan$ adj2 health).tw.
10	(prepregnan$ adj2 assess$).tw.
11	exp Genetic Counseling/
12	genetic screening.mp.
13	(preconcep$ adj4 genetic).tw.
14	(prepregnan$ adj4 genetic).tw.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 11 or 12 or 13 or 14
16	primary care.mp. or exp Primary Health Care/
17	family practice.mp. or exp Family Practice/
18	general practice.mp.
19	exp Community Health Services/ or exp Community Health Centers/ or community clinics.mp. or exp Outpatient Clinics, Hospital/
20	ambulatory care facility.mp. or exp Ambulatory Care Facilities/
21	16 or 17 or 18 or 19 or 20
22	15 and 21
23	limit 22 to (human and English language)

CINAHL search terms

S1	MH preconception care
S2	TX preconception health
S3	TX preconception assessment
S4	TX reproductive health service
S4	MW pre-pregnancy care
S6	TX pre-pregnancy care
S7	TX pre-pregnancy health
S8	TX pre-pregnancy assessment
S9	TX preconception family history
S10	TX preconception genetic assessment
S11	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
S12	TX primary care
S13	TX primary health care
S14	TX family practice
S15	TX general practice
S16	TX community health clinic
S17	TX community health centre
S18	TX community health service
S19	TX outpatient clinic
S20	TX ambulatory care
S21	TX ambulatory care facility
S22	S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21
S23	S11 and S22
S11 and S22	Limiters - Published Date from: 19990101-20101231; English Language; Exclude MEDLINE records; Human

Appendix 3.2 : References to studies included in Systematic Review 1

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Appendix 3.3 : Full data extraction and assessment of quality of each included studies

Bastani 2010

Methods	Design: Randomised controlled trial Randomisation: block randomisation Follow-up: 2 weeks post intervention
Participants	Women (18-35 years old), attending premarital counselling clinic in west Tehran; 240 women randomised; 120 (intervention) and 120 (control). Inclusion criteria: healthy with no identifiable health risk factors (self-reported); intending to conceive in their first year of marriage; and literate in Farsi. Exclusion criteria: Women with any medical or health problems during the recruitment period.
Interventions	Intervention: Nature: A 1-day workshop on health education programme Delivered by: Investigators qualified in health education and women's health Setting: Premarital counselling clinics in west Tehran, Iran. Details: Preconception health education programme consists initial individual meeting on advice regarding healthy lifestyle and physical activity and address participants' concern, then followed one hour after, of 2-hour session of 8-12 women covering on benefits of health lifestyle, physical activity, consequences of overweight and underweight and implications to pregnancy outcomes. The sessions also include routine clinic premarital sessions. Control: Routine clinic premarital sessions, no special healthy lifestyle training. *Premarital session covers reproductive health issues; family planning, HIV/AIDS, sexually transmitted disease and screening of genetic conditions and drug abuse.
Outcomes	Health locus of control – internal and external (HLOC) using Multidimensional Health Locus of Control scales and physical exercise self-efficacy using Health-Specific Self-Efficacy scales. Both scales were already tested for reliability and validity in previous Iranian studies. These variables were measured before and 2 weeks post intervention for both groups of women.

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Yes	Described as block randomisation method.
Allocation concealment?	Unclear	Insufficient information given to determine concealment.
Blinding?	No	It was not feasible to blind the participants and health educators.
Incomplete outcome data adequately addressed?	Unclear	240 participants randomised, 210 (87%) of whom were included in the analyses (intervention group = 109, control group = 101). 30 women did not complete the post-intervention questionnaires; it was reported that data were missing in some categories in the excluded women.
Free from selective reporting?	Yes	Data have been provided for all outcomes proposed in the methods/outcomes section.
Free from other bias?	Yes	Baseline comparability: There were no significant differences in the baseline characteristics of both groups. Similarly, with the non-respondents were also not statistically significant. Validation of measures: The scales used has been previously tested for reliability and validity in Iranian studies

Elsinga 2008

Methods	Design: Cluster randomised controlled trial, Randomisation occurred at the GPs level. Randomisation: randomisation stratified Follow-up: Trial was followed three times within a 3-year period
Participants	Women aged 18-40 years old attending for care with 67 GPs which were randomised; 30 (intervention) and 37 (control). Inclusion criteria: All women planning pregnancy. Exclusion criteria: GPs reviewed the selected women and excluded for the following reasons: completed family, subfertility or infertility, sterilisation, insufficient knowledge of the Dutch language, pregnancy and adverse social circumstances. A total of 27,226 women over the 3-year study period were invited for PCC, however, 12,306 women were excluded based on the exclusion criteria. Of 14,915 women eligible, only 6,782 responded to the offer. Of interested responders, 725 intended to get pregnant within one year and 1095 within one to five years. Eligible women who responded were sent risk assessment questionnaire and only 491 returned. Of these only 348 (2.3%) actually attended PCC within the 3-year period. For the first year, participants were all eligible women. For the second year, participants were limited to new eligible women, non-responders from the first year and responders who had shown interest but contemplating pregnancy between one in five years. For the third year, participants were limited to new eligible women, non-responders from the second year and responders who had shown interest in the second year but contemplating pregnancy between one in five years and interested in the first year but did not specified the time to conceive. Insufficient information on women in the control group.
Interventions	Intervention: Nature: A 3-year study whereby annual PCC is offered to eligible women in the year 2000, 2001 and 2002. Brochures (VSOP) on general information were also given Delivered by: GPs participated in PCC project 'Parents to Be'. Setting: Primary health care centres in Netherlands Details: Annual invitation for PCC to women aged 18-40 years old. Risk assessment questionnaire were sent to those eligible and interested for PCC and those contemplating pregnancy within a year. Participants and partners were scheduled appointments for PCC after completed questionnaires. GP discussed risk factors to woman and partner, individually based on risk assessment and provide information on general risk factors for adverse

	pregnancy outcome. These include infection prevention, medication use, folate intake, alcohol, smoking, nutrition, occupational hazards and genetic risk assessment. Couples also receive brochures (VSOP) on general information. Control: Standard care by GPs (no routine invitation for PCC)
Outcomes	Assessment of knowledge of pregnancy-related risk factors and preventive measures, behavioural changes before and during pregnancy and adverse pregnancy outcomes. Assessment of knowledge – assessed among a randomisation of half of women eligible prior to PCC, post intervention, knowledge was assessed in all women who attended PCC and random selection of half of women receiving standard care. Insufficient information on the actual timing of knowledge assessment. Knowledge assessed consists of 20 essential items covering hazardous substances, prevention of infection, folate and timing of conception. Assessment of behavioural changes and pregnancy outcomes were assessed within two months after delivery. Adverse pregnancy outcomes analysed were miscarriage, extrauterine pregnancy, stillbirth, premature birth, low birth weight and congenital anomalies.

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Yes	Described as stratified cluster randomisation.
Allocation concealment?	Unclear	Insufficient information given to determine concealment.
Blinding?	No	It is not possible to blind the participating GPs and women; they were aware of the assignments.
Incomplete outcome data adequately addressed?	No	Intention –to –treat analysis could not be performed as actual PCC attendance was lower than expected.
Free from selective reporting?	Yes	Data have been provided for assessment of knowledge. With regards to behavioural changes and pregnancy outcome measures, there were only 150 pregnancies after receiving PCC, of these only 114 participants completed the questionnaires and included in the analyses.
Free from other bias?	No	Baseline comparability: Groups differed at baseline characteristics. The difference in country of birth and educational level could have affected the results.

Hillemeier 2008

Methods	Design: Randomised controlled trial Randomisation: stratified randomisation Follow-up: 14 weeks after baseline risk assessment
Participants	692 women aged 18-35 years old were recruited from 15 low-income, rural communities 473 assigned to intervention group and 219 in control. Inclusion criteria: capable of becoming pregnant in future. Exclusion criteria: history of tubal ligation, hysterectomy, or other known cause of infertility and non-English speaking.
Interventions	Intervention: Nature: Consists of six 2-hour group sessions over a 12-week period. Delivered by: Group facilitators who were trained by study investigators. Setting: Community based health settings. Details: Strong healthy women intervention consists of 6 biweekly organized group sessions beginning 2 weeks after risk assessment; Content areas addressed in this intervention were preconception health services, stress management, smoking, preventing gynaecologic infection, nutrition and healthy eating demonstration, physical activity. Sessions involved setting of expectation, homework assignments, relaxation techniques, healthy eating demonstrations and social support. Participants who were unable to attend certain sessions were provided with session materials and given the opportunity for a short make-up session. Follow-up post intervention were scheduled 14 weeks after the initial baseline assessment. Control: No active intervention
Outcomes	Measures assessed were self-efficacy (4-point scale), behavioural intent (7-point scale) and behaviours associated with content areas addressed in the sessions. Biomarker indicators for health status were also collected; height, weight, waist circumference, BMI, BP, glucose and HDL-cholesterol.

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Yes	Stratified randomisation performed according to site.
Allocation concealment?	Unclear	Insufficient information to determine concealment
Blinding?	No	It was not feasible to blind the group facilitators and the participants.
Incomplete outcome data adequately addressed?	Yes	692 women randomised, only 362 completed the study included in the analyses. Levels of attrition is 48%. Analytic sample for the pretest–posttest findings presented includes those women who attended both the baseline and follow-up risk assessments. Women who did not attend the follow-up risk assessment were excluded because posttest data were not available; 47% of participants in the intervention group and 50% of the women in the control group did not attend the follow-up risk assessment.
Free from selective reporting?	Unclear	Results of statistical analysis (of pre-post intervention) are presented in the paper, but no original data have been provided (n values, CI, and results compared with control)
Free from other bias?	Yes	Baseline comparability: No significant baseline differences between groups.

Schwarz 2008

Methods	Design: Randomised controlled trial Randomisation: computer-generated sequence Follow-up: 6 months post intervention
Participants	Women aged 18-45 years recruited from waiting areas of two urgent care clinics. Inclusion criteria: capable of becoming pregnant Exclusion criteria: if the woman was unlikely to become pregnant in the next year, currently pregnant, had undergone a hysterectomy or tubal ligation, had an intrauterine device in place, had a partner who had undergone a vasectomy, or was aged 45 years, did not have a telephone or were relocating. 446 women randomised; 227 (intervention) and 219 (control).
Interventions	Intervention: Nature: one-time, short computerized counselling Delivered by: computer module; consists of video segments of a doctor addressing questions regarding folate supplementation Setting: semiprivate space in clinic while waiting to see clinicians Details: 15-min computerized counselling about preconception folate supplementation and women were given a bottle of 200 free folate tablets (400mcg) with written instruction of one tablet daily Control: Computerized counselling about emergency contraception Participants were randomly assigned after completed baseline computerised survey consisting of sociodemographic and reproductive variables as well as the woman's knowledge and use of folate supplements.
Outcomes	Knowledge on folate can prevent birth defect and use of folate supplements were assessed before and 6 months post-intervention Post-intervention – phone interview of 30 items on knowledge regarding folate

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Yes	Described as randomisation performed by computer-generated sequence
Allocation concealment?	Yes	Allocation was concealed from research assistants until after the participant had completed the baseline survey and received the computerized counseling intervention.
Blinding?	Yes – research assistants No - participants	The research assistants were blinded about the participants' placement, however not feasible to blind the participants
Incomplete outcome data adequately addressed?	Yes	446 women randomised, only 265 completed follow-up; 138 (intervention) and 127 (control). Intention-to-treat (ITT) analysis was performed that included all randomized women; in this analysis, women who were lost to follow-up were assumed to have no knowledge or use of folate supplements.
Free from selective reporting?	Yes	Data have been provided for all outcomes proposed in the methods/outcomes section.
Free from other bias?	Unclear	Insufficient information on baseline comparability. The computerized survey was pilot-tested in study's target population.

Cena 2008

Methods	Design: Cluster randomised controlled trial Randomisation: not reported Follow-up: 4 weeks post intervention
Participants	15 recruitment sites were randomly assigned from 5 counties in California to either the intervention or control group. All women recruited from a given site were assigned the same treatment to reduce contamination bias. 157 women aged 18 to 45 years old were eligible for the study. Inclusion criteria: non-pregnant women, low-income (≤185% of federal poverty level). Exclusion criteria: women who had formal nutrition education programs during the previous years.
Interventions	Intervention: Folate-focused nutrition education lesson which involved group discussions, participatory activities, worksheets, visual aids, cooking demonstrations, and instructor explanations. The education was delivered by FSNE (Food Stamp Nutrition Education) program staff Control: Education about resource management Upon enrolment, participants completed demographic questonaire, the Block Dietary Folate Equivalents (DFE) screener and food behaviour checklist (FBC)
Outcomes	Changes of folate intake and food-related behaviours. Five types of folate intake were assessed; natural food folate, synthetic folate from fortified food and supplements, total synthetic folate and total folate from all sources Participants completed DFE screened and FBC 4 weeks following the group lesson.

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information on sequence generation
Allocation concealment?	Unclear	Insufficient information to determine concealment
Blinding?	No	It was not possible to blind the study participants or those administering the intervention.
Incomplete outcome data adequately addressed?	Yes	Of 157 women recruited, 2 were lost to follow-up. Data on analyses were reported on 155 women; 77 (intervention) and 78 (control). Data was adjusted for baseline.
Free from selective reporting?	Yes	Data have been provided for all outcomes proposed in the methods/outcomes section
Free from other bias?	Unclear	Insufficient information on baseline characteristics on both groups

Floyd 2007

Methods	Design: Randomised controlled trial Randomisation: computer generated randomisation Follow-up: Participants were contacted at 3, 6 and 9 months post intervention
Participants	830 women aged 18-44 years old randomised; 416 (intervention) and 414 (control). Inclusion criteria: capable of becoming pregnant and planning to become pregnant in the next nine months and engaged in risky drinking (defined as-have had 8 drinks/week or >5 drinks on one occasion) and had vaginal intercourse during previous 3 months without using effective contraception Exclusion criteria: infertility
Interventions	Intervention: Nature: Intensive counselling sessions Delivered by: 21 trained counsellors and 6 contraceptive care providers; physicians and family planning nurses Setting: community-based settings; suburban primary care practices Details: Four motivational interviewing counselling sessions by trained counsellors on increasing the participants' commitment to change and one contraception counselling visit with health care provider to discuss medical history and contraception options. Delivered over 14 weeks, 2 to 3 weeks between sessions, each session were 45 to 60 min Control: Brochures on alcohol use and women's health in general, and referral guide to local resources
Outcomes	Outcome measures assessed were; • Risky drinking – binge drinking (consume 5 or more standard drink/day; shown to be deleterious to fetal development) and frequent drinking (8 or more drinks/week; reported has effects on growth and neurodevelopment) • Effective contraception • At risk of alcohol-exposed pregnancy Participants were contacted at 3, 6 and 9 months Outcome measures were assessed using timeline followback (TLFB) method (shown to be reliable and valid) which can repord daily drinking, vaginal intercourse and contraceptive practices. Participants provide TLFB report at baseline, 3, 6 and 9 months

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Yes	computer generated randomisation – Microsoft Visual Basic 6.0 Professional Edition
Allocation concealment?	Yes	A card indicated the group status were sealed in an envelope and mailed to the study sites. The envelopes were boxed in numeric order.
Blinding?	No	It was not possible to blind the study participants or those administering the intervention.
Incomplete outcome data adequately addressed?	Yes	830 women randomised, 665 participants completed at 3 month, 604 completed at 6 month and 593 completed the whole study. At the end of the study, 237 were lost to follow-up. The authors stated that they could not be located. Level of attrition (28%). Intention-to-treat analysis was carried out, in which all participants lost to follow up were treated as treatment failure
Free from selective reporting?	Yes	Data have been provided for all outcomes proposed in the methods/outcomes section
Free from other bias?	Yes	Baseline comparability: No significant baseline differences between both groups

Lumley 2006

Methods	Design: Randomised controlled trial Randomisation: random number tables and balance block randomisation Follow-up: recruitment began in 1982 till 1991, follow-up till the end of 1994
Participants	Inclusion criteria: Women after first pregnancy were recruited 1579 were randomised, however only 786, 392 (intervention) and 394 (control) completed the study. 793 women who did not complete were either refused, decide not to have another child, pregnant before the meeting midwife, moved or lost to follow-up
Interventions	Intervention: Nature: Home visit to individual women after delivery of first pregnancy Delivery by: PPIS (pre-pregnancy information & counselling service) midwife who was an experienced one Setting: Women attending local MCH centres with first child received home visits Details: The PPIS midwife delivering the intervention made a home visit to discuss first pregnancy's labour, birth and postpartum experience as well as pre-pregnancy health intervention during the early month after the first birth; consists of identification of current problem, preparation for next pregnancy, taking family/genetic history and arrange for referral if necessary, arrange for rubella vaccination, advice to avoid cigarettes and alcohol or other drugs Control: PPIS midwife discuss on first pregnancy's labour, birth and postpartum experience and to answer any raised issue Women were followed up till birth of second pregnancy; within three years after recruitment
Outcomes	Difference of mean birth weight between the first and the second children, gestational age at birth, preterm birth grouped as 20–27 weeks, 28–31 weeks, and 32–36 weeks; low birth weight (<2,500 g), perinatal deaths and birth defects.

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Yes	Described as sequence of allocation from random number tables and balance block randomisation
Allocation concealment?	Yes	Insufficient information given to determine method of concealment, however, allocation occurred before the midwife delivering the intervention (PPIS midwife) met the participants
Blinding?	No	Not feasible, participating midwife and women were aware of the assignments
Incomplete outcome data adequately addressed?	Unclear	1579 were randomised, however only 786 women completed the study and included in the analyses. Data were missing in some categories.
Free from selective reporting?	Yes	Data have been provided for all outcomes proposed in the methods/outcomes section.
Free from other bias?	Unclear	Baseline comparability: No significant baseline differences between groups. The interval between intervention and conception may have affect the results.

De Jong-Potjer 2006

Methods	Design: Cluster randomised controlled trial Randomisation: Computer-generated randomisation Follow-up: The trial was within a 3 year period. Participants were followed-up immediately after the intervention and after the first trimester of pregnancy
Participants	54 practices in Netherlands randomised; 27 practices each in intervention and control group. Comparable numbers of women were selected in the intervention and control group. Women included were those interested in preconception counselling and were planning pregnancy within one year
Interventions	Intervention: GP-initiated preconception counselling; discussed individual risk factors of both partners based on the risk assessment as well as general risk factors (genetic counselling, infection prevention, medication use, folate use, alcohol, smoking) Control: Usual care All women interested were asked to complete risk assessment questionnaire and six-item short-form Spielberger State Trait Anxiety Inventory (STAI)
Outcomes	Anxiety level following preconception counselling (PCC) and in first trimester of pregnancy. [Change in mean STAI score between intervention and control gp]. STAI were completed prior to intervention (STAI-1), immediately following PCC (STAI-2) or usual care. All women who had been pregnant between April 2000 and April 2003 were sent to complete the STAI on the basis of their memory of first trimester of pregnancy two months after their pregnancy ended (STAI-3). Mean change of STAI-3 in both groups were analysed.

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation
Allocation concealment?	Unclear	Insufficient information to determine concealment
Blinding?	No	It was not possible to blind the study participants or those administering the intervention.
Incomplete outcome data adequately addressed?	Unclear	466 women eligible, however only 353 attended PCC sessions and further 223 women completed STAI-2 (questionnaire post intervention). Outcome data were available for the 223 women who completed STAI-2. During the study, 4,062 pregnancies occurred, only 3,693 eligible for the study, however, 2,276 (56%)questionnaires completed adequately were analysed for STAI-3.
Free from selective reporting?	Unclear	Insufficient information on the results of control group. Results were reported on reduction in STAI-1 and STAI-2 score for the intervention group.
Free from other bias?	Unclear	Baseline comparability: Groups differed at baseline in terms country of birth and educational level could have affected the results. GP also excluded women if taking part in the study was thought to be too burdensome due to emotional bias may have been affected the results.

Robbins 2004

Methods	Design: Randomised controlled trial Randomisation: Not reported Follow-up: 2 months post intervention by telephone
Participants	Women aged 18-45 years old, 332 were randomised; 160 (intervention) and 162 (control). Exclusion criteria: women who were currently pregnant, were visiting for preconception or non routine care, were unable to speak and understand English, or had had a hysterectomy or tubal ligation or a previous pregnancy that was affected by an NTD.
Interventions	Intervention: 30-60 sec brief counselling by a physician covering 5 evidenced-based benefits of folate and a free bottle of 30 folate tablets and a pamphlet by CDC addressing benefits of folate. Then a booster phone call from research nurse emphasizing benefits on folate 1 to 2 weeks after. Control: 30-60 sec brief counselling by the physician on 1 of 3 preventive health behaviour; BSE, seat belt and sunscreen use. The control gp also received pamphlet and coupon for free bottle of 30 folate tablets. However, physicians were not prohibited from including folate in the advice to control patients.
Outcomes	Daily and weekly use of folate tablets were asked 2 months after the intervention by telephone.

Risk of bias

Item	Review authors' judgement	Description
Adequate sequence generation?	Unclear	Described as women were assigned randomly. No other details given.
Allocation concealment?	Unclear	Insufficient information given to determine concealment.
Blinding?	No	Participating clinical staffs and women were aware of the assignments.
Incomplete outcome data adequately addressed?	Unclear	332 participants randomised, 279 (87%) of whom are included in the analyses (intervention group = 139, control group = 140). Follow-up telephone contact was unsuccessful for 40 women, and 3 women refused to complete the follow-up interview.
Free from selective reporting?	*Yes*	Data have been provided for all outcomes proposed in the methods/outcomes section.
Free from other bias?	Unclear	Outcome measures were self-report. Possibility of contamination of the control group; physicians seeing women in both the intervention and control groups.

* Note: 'Yes' indicates a 'low risk of bias'; 'No' indicates a 'high risk of bias'; 'Unclear' indicates an 'uncertain risk of bias'.

Appendix 4.1 : Search strategy of Systematic Review 2

MEDLINE search strategy
Ovid MEDLINE(R) Daily Update
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1970 to present

1. exp Thalassemia/
2. thalass?emia.ti,ab,ot,hw.
3. ((erythroblastic or erythro-blastic or hypochromic or cooley$ or mediterranean) adj2 an?emia$).ti,ab,ot,hw.
4. (h?emoglobin adj2 disease$).ti,ab,ot,hw.
5. exp Hemoglobinopathies/
6. hereditary persistence of f?etal h?emoglobin.ti,ab,ot,hw.
7. (h?emoglobin adj2 (H or F or D or E) adj2 disease$).ti,ab,ot,hw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Anemia, Sickle Cell/
10. Sickle Cell Disease.ti,ab,ot,hw.
11. (sickle cell adj2 (an?emia$ or disease$ or disorder$)).ti,ab,ot,hw.
12. (h?emoglobin adj2 (S or C or SC)).ti,ab,ot,hw.
13. ((drepanocytosis or drepanocytic) adj2 an?emia).ti,ab,ot,hw.
14. 9 or 10 or 11 or 12 or 13
15. Cystic Fibrosis/
16. cystic fibrosis.ti,ab,ot,hw.
17. CF.ti,ab.
18. mucoviscidosis.ti,ab,ot,hw.
19. (fibrocystic adj3 disease$).ti,ab,ot,hw.
20. (pancreas$ adj2 (fibrosis or cystic disease$)).ti,ab,ot,hw.
21. 15 or 16 or 17 or 18 or 19 or 20
22. Tay-Sachs Disease/
23. Tay Sachs.ti,ab,ot,hw.
24. ((familial or infantile) adj2 amaurotic idiocy).ti,ab,ot,hw.
25. TSD.ti,ab.
26. (GM2 adj2 gangliosidosis).ti,ab,ot,hw.
27. 22 or 23 or 24 or 25 or 26
28. Heterozygote/
29. trait$.ti,ab,ot,hw.
30. carrier$.ti,ab,ot,hw.
31. 28 or 29 or 30
32. 8 or 14 or 21 or 27 or 31
33. (Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$).ti,ab,ot,hw.
34. Maternal Health Services/

35. ((pregnan$ or conception or family) adj3 plan$).ti,ab,ot,hw.
36. (Pre-marital or Premarital or Pre-marriage or Premarriage).ti,ab,ot,hw.
37. ((Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.
38. ((Pre-marital or Premarital or Pre-marriage or Premarriage) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.
39. 33 or 34 or 35 or 36 or 37 or 38
40. (carrier$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.
41. (genetic$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.
42. (heterozygot$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.
43. Genetic Services/
44. family history.ti,ab,ot,hw.
45. 40 or 41 or 42 or 43 or 44
46. (h?emoglobin adj2 electrophoresis).ti,ab,ot,hw.
47. Cystic Fibrosis Transmembrane Conductance Regulator/ or sweat test.ti,ab,ot,hw.
48. ((CFTR gene mutation$ or CFTR mutation$ or Hexoaminidase-A or Hexoaminidase A or HEX-A or H?emoglobin F or H?emoglobin A2 or H?emoglobin S) adj3 (test$ or analys$ or screen$ or profil$)).ti,ab,ot,hw.
49. 46 or 47 or 48
50. 32 or 45 or 49
51. 39 and 50
52. exp animals/ not humans.sh.
53. 51 not 52
54. limit 53 to yr="1970-Current"

PsycINFO search strategy
1970 to present

1. thalassemia.ti,ab,ot,hw.
2. thalassaemia.ti,ab,ot,hw.
3. ((erythroblastic or erythro-blastic or hypochromic or cooley* or mediterranean) adj2 anaemia*).ti,ab,ot,hw.
4. ((erythroblastic or erythro-blastic or hypochromic or cooley* or mediterranean) adj2 anemia*).ti,ab,ot,hw.
5. ((haemoglobin or hemoglobin) adj2 disease*).ti,ab,ot,hw.
6. ((haemoglobin or hemoglobin) adj2 (H or F or D or E) adj2 disease*).ti,ab,ot,hw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Sickle Cell Disease/
9. (sickle cell adj2 (anaemia* or disease* or disorder*)).ti,ab,ot,hw.
10. ((haemoglobin or hemoglobin) adj2 (S or C or SC)).ti,ab,ot,hw.
11. 8 or 9 or 10
12. Cystic Fibrosis/
13. cystic fibrosis.ti,ab,ot,hw.
14. CF.ti,ab.
15. mucoviscidosis.ti,ab,ot,hw.
16. (fibrocystic adj3 disease*).ti,ab,ot,hw.
17. 12 or 13 or 14 or 15 or 16
18. Tay Sachs Disease/
19. Tay Sachs.ti,ab,ot,hw.
20. ((familial or infantile) adj2 amaurotic idiocy).ti,ab,ot,hw.
21. TSD.ti,ab.
22. (GM2 adj2 gangliosidosis).ti,ab,ot,hw.
23. 18 or 19 or 20 or 21 or 22
24. heterozygote.ti,ab,ot,hw.
25. trait*.ti,ab,ot,hw.
26. carrier*.ti,ab,ot,hw.
27. 24 or 25 or 26
28. 7 or 11 or 17 or 23 or 27
29. (Preconcept* or Pre-concept* or Prepregnan* or Pre-pregnan*).ti,ab,ot,hw.
30. (Pre-marital or Premarital or Pre-marriage or Premarriage).ti,ab,ot,hw.
31. maternal health service*.ti,ab,ot,hw.
32. maternal care.ti,ab,ot,hw.
33. ((pregnan* or conception or family) adj3 plan*).ti,ab,ot,hw.
34. ((Preconcept* or Pre-concept* or Prepregnan* or Pre-pregnan*) adj2 (care or counsel* or advice* or advise or inform*)).ti,ab,ot,hw.

35. ((Pre-marital or Premarital or Pre-marriage or Premarriage) adj2 (care or counsel* or advice* or advise or inform*)).ti,ab,ot,hw.
36. 29 or 30 or 31 or 32 or 33 or 34 or 35
37. (genetic* adj3 (screen* or test* or counsel* or assess* or detect* or diagnos* or inform* or analys*)).ti,ab,ot,hw.
38. (carrier* adj3 (screen* or test* or counsel* or assess* or detect* or diagnos* or analys*)).ti,ab,ot,hw.
39. (heterozygot* adj3 (screen* or test* or counsel* or assess* or detect* or diagnos* or analys*)).ti,ab,ot,hw.
40. genetic service*.ti,ab,ot,hw.
41. family history.ti,ab,ot,hw.
42. 37 or 38 or 39 or 40 or 41
43. ((haemoglobin or hemoglobin) adj2 electrophoresis).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
44. Cystic Fibrosis Transmembrane Conductance Regulator/ or sweat test.mp.
45. 43 or 44
46. 28 or 42 or 45
47. 36 and 46
48. exp Animals/
49. human.mp.
50. 48 and 49
51. 48 not 50
52. 47 not 51
53. limit 52 to yr="1970-Current"

EMBASE search strategy
1974 to present

1. exp thalassemia/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]
2. exp delta thalassemia/ or exp beta thalassemia/ or exp thalassemia major/ or exp alpha thalassemia/ or exp thalassemia intermedia/ or exp sickle cell beta thalassemia/ or exp thalassemia minor/
3. thalass?emia.ti,ab,ot,hw.
4. ((erythroblastic or erythro-blastic or hypochromic) adj2 an?mia$).ti,ab,ot,hw.
5. (h?emoglobin adj2 disease$).ti,ab,ot,hw.
6. hemoglobinopathy/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]
7. hereditary persistence of f?etal h?emoglobin.ti,ab,ot.
8. (h?emoglobin adj2 (h or d or e) adj2 disease$).ti,ab,ot,hw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp sickle cell anemia/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]
11. sickle cell disease.ti,ab,ot,hw.
12. (h?emoglobin adj2 (s or c)).ti,ab,ot,hw.
13. 10 or 11 or 12
14. exp cystic fibrosis/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]
15. cystic fibrosis.ti,ab,ot,hw.
16. CF.ti,ab.
17. 14 or 15 or 16
18. exp Tay Sachs disease/cn, di, ep, et, pc [Congenital Disorder, Diagnosis, Epidemiology, Etiology, Prevention]
19. Tay Sachs.ti,ab,ot,hw.
20. ((familial or infantile) adj2 amaurotic idiocy).ti,ab,ot,hw.
21. TSD.ti,ab.
22. 18 or 19 or 20 or 21
23. exp heterozygote/ or exp heterozygote detection/
24. trait$.ti,ab,ot,hw.
25. carrier$.ti,ab,ot,hw.
26. 23 or 24 or 25
27. 9 or 13 or 17 or 22 or 26
28. (Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$).ti,ab,ot,hw.
29. (Pre-marital or Premarital or Pre-marriage or Premarriage).ti,ab,ot,hw.
30. ((pregnan$ or conception or family) adj3 plan$).ti,ab,ot,hw.

31. ((Preconcept$ or Pre-concept$ or Prepregnan$ or Pre-pregnan$) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.
32. ((Pre-marital or Premarital or Pre-marriage or Premarriage) adj2 (care or counsel$ or advice$ or advise or inform$)).ti,ab,ot,hw.
33. 28 or 29 or 30 or 31 or 32
34. (carrier$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.
35. (genetic$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.
36. (heterozygot$ adj3 (screen$ or test$ or counsel$ or assess$ or detect$ or diagnos$ or inform$ or analys$)).ti,ab,ot,hw.
37. Genetic Service$.ti,ab,ot,hw.
38. family history.ti,ab.
39. 34 or 35 or 36 or 37 or 38
40. (h?emoglobin adj2 electrophoresis).ti,ab,ot,hw.
41. Cystic Fibrosis Transmembrane Conductance Regulator.ti,ab,ot,hw.
42. sweat test.ti,ab.
43. ((CFTR gene mutation$ or CFTR mutation$ or Hexoaminidase-A or Hexoaminidase A or HEX-A or H?emoglobin F or H?emoglobin A2 or H?emoglobin S) adj3 (test$ or analys$ or screen$ or profil$)).ti,ab,ot,hw.
44. 40 or 41 or 42 or 43
45. 27 or 39 or 44
46. 33 and 45
47. animal/
48. human/
49. 47 and 48
50. 47 not 49
51. 46 not 50
52. limit 51 to yr="1970-Current"

CINAHL search strategy
1970 to present

SI. (MH "Thalassemia") OR (MH "beta-Thalassemia") OR (MH "alpha-Thalassemia") OR (MH "delta-Thalassemia")

S2. (MH "Hemoglobinopathies")

S3. (MM "Anemia, Hypochromic")

S4. (MH "Anemia, Sickle Cell") OR (MH "Sickle Cell Trait")

S5. (MH "Cystic Fibrosis") OR "mucoviscidosis"

S6. (MH "Tay-Sachs Disease")

S7. (MH "Prepregnancy Care")

S8. (MH "Genetic Screening")

S9. (MH "Family Assessment") OR (MH "Family History")

S10. "hemoglobin electrophoresis"

S11. "cystic fibrosis transmembrane conductance regulator"

S12. "sweat test"

S13. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S8 OR S9 OR S10 OR S11 OR S12

S14. S7 AND S13

S15. Limiters - Published Date from: 19700101-current

Appendix 4.2 : References to studies included in Systematic Review 2

1. HENNEMAN, L., BRAMSEN, I., VAN DER PLOEG, H. M., ADÈR, H. J., VAN DER HORST, H. E., GILLE, J. J. P. & TEN KATE, L. P. 2001. Participation in preconceptional carrier couple screening: characteristics, attitudes, and knowledge of both partners. *Journal of Medical Genetics,* 38**,** 695-703.

2. HENNEMAN, L., BRAMSEN, I., VAN DER PLOEG, H. M. & TEN KATE, L. P. 2002. Preconception cystic fibrosis carrier couple screening: impact, understanding, and satisfaction. *Genetic Testing,* 6**,** 195-202.

3. HENNEMAN, L., BRAMSEN, I., VAN KEMPEN, L., VAN ACKER, M. B., PALS, G., VAN DER HORST, H. E., AD, X00E, R, H. J., VAN DER PLOEG, H. M. & TEN KATE, L. P. 2003. Offering preconceptional cystic fibrosis carrier couple screening in the absence of established preconceptional care services. *Community Genetics,* 6**,** 5-13.

4. LAKEMAN, P., PLASS, A. M. C., HENNEMAN, L., BEZEMER, P. D., CORNEL, M. C. & TEN KATE, L. P. 2008. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. *Genetics in Medicine,* 10**,** 820-30.

Appendix 4.3 : Full data extraction of each included studies

Henneman Study: Preconception cystic fibrosis carrier couple screening: impact, understanding and satisfaction

General information

Date of data extraction	15 May 2013
Study title	Preconception cystic fibrosis carrier couple screening: impact, understanding, and satisfaction
Country of origin	Netherlands

Study characteristics

Aim of the study	To assess the impact, understanding, and satisfaction among participants in a preconception cystic fibrosis carrier couple screening program
Study design	Non-randomised study involving two interventions
Study inclusion	Individual who had a partner with whom they were planning to have children
Study exclusion	Pregnancy, positive family history of cystic fibrosis, age younger than 18 years old, having fertility and psychosocial problems
Recruitment procedure	Names and addresses of potential participants were obtained from the practice register and population register and invited by own general practitioners and Municipal Health Service respectively
Duration of study	May 1997 to December 2000

Participant characteristics
Characteristics of participants at the beginning of the study

Age	20 – 35 years old (invited by mail either by Municipal Health Services (MHS) or own general practitioners)
Number of participants pre-intervention	1118 participants (559 couples) eligible for participation. Of the 580 couples who responded, 559 couples gave written consent to have the test.

Intervention 1

Nature of intervention	Pre-carrier test educational group session followed by carrier testing
Delivered by	One study researcher
Description of intervention	1. An invitation letter with an information leaflet was sent to eligible couple. Information leaflet described clinical and genetic aspects of cystic fibrosis, carrier prevalence, implication of a positive carrier testing, methods of carrier testing and information on test sensitivity 2. Participants attended educational session; session consist more detailed education eg. reproductive choices, advantages and disadvantages of screening 3. Couples were offered testing at the end of the session; mouthwash sample for mutation analysis. One partner was tested first, if positive only the second partner was tested 4. A brochure about cystic fibrosis was given further 5. Test results were sent to couples by mail within 8 weeks 6. Duration of session was 45 min. Held on 2-3 evenings in one week
Study instrument	All participants were asked to complete individually a questionnaire at three different measurement; Q1: before pre-carrier test education or consultation Q2: within one week after consultation but before test result Q3: six months after receipt of carrier test result
Integrity of intervention	Validity of information leaflet Described the clinical and genetic aspects of cystic fibrosis, carrier prevalence in the population, implication of positive carrier screening test, how testing take place and sensitivity of the test. Validity of questionnaire Questionnaire was developed and tested for homogeneity specifically for this study. Contents included socio-demographics, familiarity with the disease, knowledge of the disease, health locus of control, perceptions and attitudes on carrier testing which derived from Health Belief Model. Reliability analysis was performed.

Intervention 2

Nature of intervention	Pre-carrier test individual consultation delivered by general practitioners.
Delivered by	18 general practitioners were involved. A manual for cystic fibrosis consultation was given to participating general practitioners to use as guide during consultation.
Description of intervention	1. An invitation letter with an information leaflet was sent to eligible couple. Information leaflet described clinical and genetic aspects of cystic fibrosis, carrier prevalence, implication of a positive carrier testing, methods of carrier testing and information on test sensitivity 2. Couples attended general practitioner consultation. This session specifically for preconception cystic fibrosis carrier screening. The session consist more detailed education eg. reproductive choices, advantages and disadvantages of screening 3. Couples were offered testing at the end of the consultation; mouthwash sample for mutation analysis. One partner was tested first, if positive only the second partner was tested 4. A brochure about cystic fibrosis was given further 5. Test results were sent to couples by mail within 8 weeks unless objected by couples, copies of positive results were sent to their general practitioner. 6. Positive result were confirmed by second testing.

Intervention 3

Nature of intervention	No personal education. Participants were sent a brochure on information on cystic fibrosis and carrier testing

Lakeman study : Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and haemoglobinopathies in the Netherlands

General information

Date of data extraction	14 May 2013
Study title	Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and haemoglobinopathies in the Netherlands
Country of origin	Netherlands

Study characteristics

Aim of the study	To study psychological outcomes, knowledge, recall and understanding of test-results, satisfaction and reproductive intentions in preconception carrier screening for cystic fibrosis and haemoglobinopathies in a multi-ethnic population in Netherlands, in which a couple's eligibility for cystic fibrosis and/or haemoglobinopathies was based on both partners' ancestry
Study design	Non-randomised, before-and after study
Study inclusion	Individual who had a partner with whom they were planning a pregnancy, irrespective of whether this would be in the near future or at a later date
Study exclusion	Pregnancy, inability to read and write in Dutch, positive family history of cystic fibrosis and/or haemoglobinopathies
Recruitment procedure	Names and addresses of potential participants were obtained from the practice register and population register and invited by own general practitioners and Municipal Health Service respectively
Duration of study	January to December 2005

Participant characteristics
Characteristics of participants at the beginning of the study

Age	20 – 35 years old
Ancestry	Western (European, North American, Australian) and non-western (Turkey, Surinam, Morocco, South-east Asian) participants
Married	50 individuals married
Parity	34 individuals with children
Number of participants pre-intervention	490 participants eligible for participation
Number of participants post-intervention	72 couples (N=143 individuals); 47 couples eligible for testing of cystic fibrosis only, 6 for haemoglobinopathies only, and 19 for both
Number of participants included in analysis	Q1: n=143 (100%) Q2: n=139 (97%) Q3: n=116 (81%) Q4: n=120 (84%) 110 participants completed all Q1- Q4
Number of withdrawals, lost to follow-up	33 individuals (23%) lost to follow-up. No information about reasons in this group.

Intervention and setting

Description of intervention	Participants with their partner were required to visit their general practitioner for pre-carrier testing consultation. During this consultation, the general practitioner assessed the couple's eligibility for cystic fibrosis and haemoglobinopathies testing based on a decisional instrument already developed. Advantages and disadvantages of screening were discussed. The general practitioner then offered testing. Samples were taken if the couples agreed. A brochure on information about clinical and genetic aspects of the conditions, test procedure, test sensitivity was provided to take home, accompanied by an informed consent form which had to be returned within one week to the researcher to consent to analyses of the samples. Cystic fibrosis carrier testing was carried out step-wise: one partner was tested first and the second was tested only if the first partner's test result was positive. For haemoglobinopathies carrier testing, both partners were tested.
Study instrument	All participants were asked to complete individually a questionnaire at four different measurement; Q1: 30 min before pre-carrier test consultation Q2:within one week after consultation Q3: one week after receiving carrier test results Q4: three months after receiving carrier test results
Integrity of intervention	Validated of decisional instrument

Appendix 5.1 : Thematic analysis of focus group of primary care providers

Themes	Subthemes	Codes
Conceptualising preconception care	Defining preconception care	Educating women before they enter into pregnancy (GP1) Making sure they are going into it knowing they are fit and well (GP1) Reducing the problems that they may have before pregnancy (GP2)
	Unclear about roles; Family planning and pre-pregnancy planning is seen as two different entities	It's a gap between family planning and pre-pregnancy planning (GP2) You would be talking family planning but you would also be talking pre-pregnancy planning and it didn't work. (GP3)
Experience in providing preconception advice	Offer opportunistic	We will see anyone (GP2)
	Specifically for genetic screening – offer opportunistic screening	Things that are badged as pre-conception, do in family planning (GP2) If ethnic minority, would do the haemoglobin screening (GP2)
	Patient seeking preconception advice regarded as rare	Not many coming and asking me for advice before trying to get pregnant (GP1) Very few consulted within couple of years (GP2)
	Women are not forthcoming	Women don't want to discuss it with a professional before embarking on trying to get pregnant (GP2) Women don't want to discuss if no issue (GP2)
Relevance of PGRA to the work of GPs	Relevance of carrying out risk assessment preconception may depend on the prevalence	How many problems there are actually out there? (GP2)

	of the problems, availability of intervention and whether intervention will benefit patients	What's the prevalence of these problems get detected? (GP2) What's the benefit? (GP2) People would want to do things if it is going to make a difference (GP1)
	Will not disregard other heath interventions that already taken place	Without much sacrifice to other health areas that are currently in place (GP1)
	Perceived rarity of the problems	How common is children born with genetic conditions in day to day practice (GP1)
Generate morale/ethical issues/harm	Perception of harm produced by genetic risk assessment is a barrier	Nobody wants to think that something bad might happen to them (GP2) Worried about my relationship with patients who are already planning for a baby (GP2) Might induce anxiety (GP3)
Ambiguities about offering PGRA	GPs realised there is potential for PGRA but at the same time expressed ambivalence about acceptance and whether really change people's decisions	There is opportunity but how hard do we push people and how much is modifiable if people are already to … (GP2)
Motivating PGRA	Awareness is present if there is existing genetic problems in family	Ones that have got issues and the genetic problems in the family, they could have had genetic counselling or families pass on that information (MW)
	Challenges of reaching women who have never had a pregnancy unless they have had problems in previous pregnancies or chronic health problems Suggest to target women planning to get married and offer through pre-marriage counselling	To connect people who are thinking about trying for a baby is to connect people who are thinking about trying to get married and connect with the minister or imam or the leader who might have some kind of interest in pre-marriage counselling and then offer a service, a referral service from there (GP1)

Appendix 5.2 : Thematic analysis of focus groups of women

Themes	Subthemes	Codes
Experiences of seeking preconception care	Means of experiencing preconception advice or care	Went to see a nurse before we conceived our first…(FG 4) Found out stuff on the internet…. (FG 3) Because sometimes you'll go into a general practitioner for information and you don't get it unless you ask for it, it's not always there at hand… (FG 4)
Perceptions and attitudes to assessment of reproductive genetic risk before conception	Motivation	I agree with that … (FG 1) … But you see, the thing is, and this is where my problem was, you wait until you are up 12 weeks pregnant usually, or, no, a bit before that , 8 weeks pregnant maybe, to see your midwife for the first time. By which time a lot of the really key stuff, developmental stuff for your baby has already happened… (FG 3) See, knowing about your family history, I suppose, and genetic history, that's always quite handy just for future reference (FG 4)
	Hesitancy and reservation to the role of assessment of reproductive genetic risk before conception	I don't think you should review but I think if you've got something in your family history that ... you know, (relative) researched and looked into the potential… (FG 4) … and I think that's a much better idea to do it pre perhaps but I think, personally for me, if we decided to try for a baby, I probably wouldn't even take that up … (FG 4) I think I would be I'm more a mind of I'd like to know, personally, I wouldn't like

		to -, say there was something in my family history, I'd like to know if I was a carrier or whatever before getting pregnant because I couldn't get pregnant and then them say there's something wrong with your child, you know, I'd feel awful for having this baby that has something wrong with it and I've not taken the chance to find out if, you know, I could have stopped it somehow…. (FG 4) …. in theory, I think oh yes, it's all very good and I should do that but, in reality, I think I don't do any of it, so ……. but only because I've had no bad experiences so it's easy to say that….. You wouldn't get any genetic testing but when somebody close to you or something happens it makes you think, oh actually... (FG 5)
Barriers	Unplanned	My daughter wasn't planned, didn't plan at 19 to become a mum, so I never thought of discussing anything like this… (FG 5)
	Generate harm/morale issues	No because it could stop you having kids couldn't it, when that are actually you could have perfectly fine children. (FG 3) I mean, I was offered some screenings, but I turned them down because I just thought, if I turned up and they told me there was something wrong, I don't want that to change my mind of carrying a baby. (FG 4)
	Stigmatisation	It just causes so many problems, though, you know, like, if you think, if you've been in a long term relationship with someone and you think, right, let's

		plan to have a child but, you know, if you go and test and see if someone's a carrier, either you or your partner's a carrier of something and you have a child and then that child's got whatever you carried, then it's going to be, you know, a blame game, well it's your fault,…. (FG 4)
Opportunities	Enhance awareness and offering of preconception genetic assessment	I think approaching GPs and family planning clinics and maybe hospitals where people are having, you know, are wanting children and are having to go for testing or whatever, I think doing it that way might work. (FG 4) You could do when you're going for contraception, that's good, actually, that would be a good way of … (FG 5)

Appendix 5.3 : Questionnaire – final version

WHAT DO YOU THINK ABOUT PRECONCEPTION ASSESSMENT OF GENETIC RISK IN PRIMARY CARE?

This survey is about exploring your opinion of assessing reproductive genetic risk before pregnancy.

Identifying women and partners at reproductive risk of having children with genetic conditions is important information for General Practitioners. Assessing genetic risk before pregnancy includes exploring family history and ethnicity and genetic carrier testing.

In April 2011, a consensus panel of Human Genetics Commission (HGC) has highlighted the importance of doing preconception reproductive genetic screening. Women have reported that offering genetic screening during antenatal period, which is the current practice, is perhaps too late for them to make appropriate reproductive decisions.

There are two components to preconception assessment of genetic risk:

- **Identifying family history of genetic conditions**
- **Carrier testing for common genetic conditions, such as, Sickle Cell Anaemia, Thalassaemia, Cystic Fibrosis and Tay-Sachs disorder**

We would value your opinion about offering assessment of preconception genetic risk in your practice.

The questionnaire should take no more than 15 minutes to complete.

The first 100 completed questionnaires returned will receive a gift voucher.

<u>Filling in the questionnaire</u>

Most questions are attempting to elicit your strength of opinion. An example is shown below;
To respond, please circle the number which most closely corresponds to your opinion; if you feel **strongly agree** with the statement below, you could circle **1** in the statement as shown.
Example:

I like to learn about new things	strongly agree	Agree	uncertain	disagree	strongly disagree
	1	2	3	4	5

PART A: YOUR CURRENT EXPERIENCE OF PRECONCEPTION PRACTICE

A1. You may already be providing preconception advice during consultations. It would be helpful to know your experiences of discussing *family history of reproductive genetic risk* (e.g. Down's syndrome, recurrent abortions) with women of child bearing age in the last THREE months.

		strongly agree	agree	don't know	disagree	strongly disagree
1.	I have discussed this during routine consultation	1	2	3	4	5
2.	I have discussed this with women planning a pregnancy	1	2	3	4	5
3.	I have discussed this during visit for contraception	1	2	3	4	5
4.	I have never discussed this during any consultations	1	2	3	4	5

Other experience(s)? Please indicate:

……

A2. You may already be providing preconception advice during routine consultation. It would be helpful to know your experiences of discussing preconception advice about *genetic carrier testing* (e.g. thalassaemia, sickle cell anaemia, cystic fibrosis) to women of child bearing age in the last THREE months.

		strongly agree	agree	don't know	disagree	strongly disagree
1.	I have discussed this during routine consultation	1	2	3	4	5
2.	I have discussed this to women planning a pregnancy	1	2	3	4	5
3.	I have discussed this during visit for contraception	1	2	3	4	5
4.	I have discussed this with women with known family history of genetic conditions	1	2	3	4	5

		strongly agree	agree	don't know	disagree	disagree
5.	I have discussed this with women of certain ethnicity background (e.g. African, Asian, European)	1	2	3	4	5
6.	I have never this discussed during any consultation	1	2	3	4	5

Other experience(s)? Please indicate:

……

PART B: BARRIERS

B1. The statements below describe potential barriers to developing preconception genetic risk assessment in primary care. Do you agree with the following statements?

		strongly agree	agree	don't know	disagree	strongly disagree
1.	Very few women coming for advice before trying to conceive	1	2	3	4	5
2.	It is difficult to capture the target group	1	2	3	4	5
3.	There is potential ethical implications of preconception genetic risk assessment (eg. stigmatisation of carriers)	1	2	3	4	5
4.	Discussing hereditary diseases with couples who are trying for a baby will cause more harm (eg. emotional disturbances to couples)	1	2	3	4	5

		strongly agree	agree	don't know	disagree	strongly disagree
5.	I do not have adequate training to provide preconception reproductive genetic assessment	1	2	3	4	5
6.	Setting up a service will require substantial time and work	1	2	3	4	5

Other barrier(s)? Please indicate:

……

PART C: DELIVERING PRECONCEPTION GENETIC ASSESSMENT IN PRACTICE

C1. Several approaches have been suggested to deliver preconception genetic risk assessment in the general practice. Family history and genetic carrier testing are two components of preconception reproductive genetic assessment. Could you give your opinion of the approach as described below:

Family history could be obtained from;

		strongly agree	agree	don't know	disagree	strongly disagree
1.	All women of childbearing age at registration by means of self-completed family history questionnaire	1	2	3	4	5
2.	Women enquiring about preconception advice	1	2	3	4	5
3.	Women enquiring about family planning advice	1	2	3	4	5
4.	Women enquiring about menstrual problems	1	2	3	4	5

Other approaches to collect family history:

.....

Genetic carrier testing could be offered to;

		strongly agree	agree	don't know	disagree	strongly disagree
1.	All women of childbearing age at registration	1	2	3	4	5
2.	Women seeking preconception advice	1	2	3	4	5
3.	Women enquiring family planning advice	1	2	3	4	5
4.	Women enquiring about menstrual problems	1	2	3	4	5

Other approaches to offer preconception genetic carrier testing:

.....

C2. Introducing new services into general practice has often required additional resources. Which of the following resources do you think could improve the delivery of preconception genetic risk assessment in your practice?

		strongly agree	agree	don't know	disagree	strongly disagree
1.	Appropriate training for general practitioners	1	2	3	4	5
2.	Clear national guidelines for general practitioners eg. NICE	1	2	3	4	5
3.	Information leaflets on preconception genetic risk assessment given at registration to women of childbearing age	1	2	3	4	5
4.	No need for additional resources	1	2	3	4	5

Any other resource(s)? Please indicate:

.....

.....

C3. If there were plans to incorporate preconception genetic risk assessment routinely in general practice, could you indicate which of the following settings may be appropriate to provide genetic risk assessment?

		strongly agree	agree	don't know	disagree	strongly disagree
1.	A dedicated clinic	1	2	3	4	5
2.	Well woman clinic	1	2	3	4	5
3.	Family planning clinic	1	2	3	4	5
4.	During routine consultation	1	2	3	4	5

Any other setting(s)? Please indicate:

.....

PART D: YOUR PREPAREDNESS TO OFFER PRECONCEPTION GENETIC CARRIER ASSESSMENT

D1. The statements below seek to explore how prepared you are to offer preconception reproductive genetic assessment in your practice.

		strongly agree	agree	don't know	disagree	strongly disagree
1.	I am prepared to take family history of genetic conditions from all women of childbearing age group routinely when taking medical history	1	2	3	4	5
2.	I am prepared to offer genetic carrier testing to at-risk women of childbearing age group	1	2	3	4	5
3.	If appropriate to the consultation, I am prepared to offer genetic carrier testing to women of childbearing age group (eg. planning a pregnancy)	1	2	3	4	5
4.	Given the necessary training and information, I am prepared to counsel about genetic carrier testing results	1	2	3	4	5

Any other comments:
If you do not agree with any of the statements above, please state your reasons and can you suggest when is the most appropriate?

……

Finally, just a little information about you:

1.	Your year of birth	……..	
2.	Your gender	□ Female □ Male	
3.	Number of years as a GP	……..	
4.	How would you describe your practice	□ Rural □ Urban □ Inner city □Others (please indicate)	□Solo practice □Group practice □Others (please indicate)
5.	Your approximate practice list size	……	
6.	Does your practice have a formal written protocol regarding preconception care? If yes to question 6, please proceed to question 7 and 8	□ Yes □ No	
7.	If yes, does the protocol cover collection of family history of reproductive risk?	□ Yes □ No	
8	If yes, does the protocol cover genetic carrier testing?	□ Yes □ No	

Thank you for your help. Please return the completed questionnaire in the enclosed stamped addressed envelope provided. My return post details are listed below:

Dr. Norita Hussein
Division of Primary Care
School of Community Health Sciences
University of Nottingham
D1422, D Floor
Queens Medical Centre
FREEPOST
Nottingham, NG7 2UH

If you would like feedback on the findings of the survey, please provide your address below.

Name:

Address:

Appendix 5.4 : Questionnaire – draft format before actual survey

WHAT DO YOU THINK ABOUT PRECONCEPTION GENETIC RISK ASSESSMENT IN PRIMARY CARE?

This survey is about exploring your opinion of preconception genetic risk assessment.

Identifying women and partner at reproductive risk of having children with genetic conditions is important information for General Practitioners. Assessing genetic risk before pregnancy included family and ethnicity history and genetic carrier screening. Recently in April 2011, a consensus panel of Human Genetics Commission (HGC) has highlighted the importance of doing reproductive genetic screening before pregnancy. Women have reported that offering genetic screening during antenatal period, which is the current practice, is perhaps too late for them to make appropriate decisions. There are two components to preconception genetic screening:

- **Identifying family history of genetic conditions**
- **Carrier testing for common genetic condition, such as, Sickle Cell, Thalassaemia, Cystic Fibrosis and Tay Sachs disorder**

We would value your opinion about offering preconception genetic risk in your practice.

The questionnaire should take about 15 to 20 minutes to complete.

The first 100 of returned completed questionnaire will be given a gift voucher.

<u>Filling in the questionnaire</u>

Most questions are attempting to elicit your strength of opinion. An example is shown below;
To respond, please circle the number which most closely corresponds to your opinion; if you feel **strongly agree** with the statement below, you could circle **1** in the statement as shown.
Example:

I like to learn about new things	strongly agree	agree	uncertain	disagree	strongly disagree
	1	2	3	4	5

PART A: YOUR CURRENT EXPERIENCE OF PRECONCEPTION PRACTICES

You may already be providing preconception advice during your consultation. It would be helpful to know your experiences of discussing preconception advice about *family history of reproductive genetic risk* (e.g. Down's syndrome, recurrent abortions) to women of child bearing age in the last THREE months.

		strongly agree	agree	don't know	disagree	strongly disagree
1.	I have discussed during routine consultation	1	2	3	4	5
2.	I have discussed to women planning a pregnancy	1	2	3	4	5
3.	I have discussed during visit for contraception	1	2	3	4	5
4.	I have discussed during visit for family planning	1	2	3	4	5
5.	I have never discussed during any consultation	1	2	3	4	5

Other experience(s)? Please indicate:

……

You may already be providing preconception advice during routine consultation. It would be helpful to know your experiences of discussing preconception advice about *genetic carrier screening* (e.g. thalassaemia, sickle cell, cystic fibrosis) to women of child bearing age in the last THREE months.

		strongly agree	agree	don't know	disagree	strongly disagree
6.	I have discussed during routine consultation	1	2	3	4	5
7.	I have discussed to women planning a pregnancy	1	2	3	4	5
8.	I have discussed during visit for contraception	1	2	3	4	5
9.	I have discussed during visit for family planning	1	2	3	4	5
10.	I have discussed to women with known family history of genetic conditions	1	2	3	4	5
11.	I have never discussed during any consultation	1	2	3	4	5

Other experience(s)? Please indicate:

……

PART B: BARRIERS

The statements below are described potential barriers for developing preconception genetic risk assessment service in your practice. Do you agree with the following statements?

		strongly agree	agree	don't know	disagree	strongly disagree
1.	Women do not come for advice before trying to conceive	1	2	3	4	5
2.	I am worried about ethical implication of preconception genetic risk assessment eg. stigmatisation of carriers	1	2	3	4	5
3.	I do not have adequate knowledge to provide preconception genetic risk assessment	1	2	3	4	5
4.	I am concerned that providing genetic advice will jeopardise doctor-patient relationship	1	2	3	4	5
5.	Setting up a service will require substantial time and work	1	2	3	4	5

Other barrier(s)? Please indicate:

……

PART C: DELIVERING PRECONCEPTION GENETIC ASSESSMENT IN PRACTICE

Several approaches have been suggested to deliver preconception genetic risk assessment in the general practice. Family history and genetic carrier screening are two components of preconception reproductive genetic assessment. Could you give your opinion of the approach as described below:

Family history could be obtained from;

		strongly agree	agree	don't know	disagree	strongly disagree
1.	All women of childbearing age at registration by means of self-completed family history questionnaire	1	2	3	4	5
2.	Women enquiring about preconception advice	1	2	3	4	5
3.	Women enquiring about family planning advice	1	2	3	4	5
4.	Women enquiring about menstrual problems	1	2	3	4	5

Other approaches to collect family history:

.....

Genetic carrier screening could be offered to;

		strongly agree	agree	don't know	disagree	strongly disagree
1.	All women of childbearing age at registration	1	2	3	4	5
2.	Women enquiring preconception advice	1	2	3	4	5
3.	Women enquiring family planning advice	1	2	3	4	5
4.	Women enquiring about menstrual problems	1	2	3	4	5

Other approaches to offer preconception genetic carrier screening:

.....

Introducing new services into general practitioner has often required additional resources. Which of the following resources do you think will improve the delivery of preconception genetic risk service in your practice?

		strongly agree	agree	don't know	disagree	strongly disagree
1.	Appropriate training for general practitioners	1	2	3	4	5
2.	Clear national guidelines for general practitioners eg. NICE	1	2	3	4	5
3.	Information leaflets on preconception genetic risk assessment given at registration to women of childbearing age	1	2	3	4	5
4.	No need for additional resources	1	2	3	4	5

Any other resource(s)? Please indicate:

.....

If there were plans to incorporate preconception genetic risk assessment routinely in general practice, could you indicate which of the following setting is appropriate to provide genetic risk assessment?

		strongly agree	agree	don't know	disagree	strongly disagree
1.	A dedicated clinic	1	2	3	4	5
2.	Well woman clinic	1	2	3	4	5
3.	Family planning clinic	1	2	3	4	5
4.	During routine consultation	1	2	3	4	5

Any other setting(s)? Please indicate:

.....

PART D: YOUR PREPAREDNESS OF OFFERING PRECONCEPTION GENETIC CARRIER SCREENING.

The statements below seek to explore how prepared you are to offer preconception genetic carrier screening in your practice.

		strongly agree	agree	don't know	disagree	strongly disagree
1.	I am prepared to offer genetic carrier screening routinely to any women of childbearing age group	1	2	3	4	5
2.	I am prepared to advise about genetic carrier screening results	1	2	3	4	5
3.	I am prepared to discuss psychosocial issues if the results are positives	1	2	3	4	5

Finally, just a little information about you:

1. Your year of birth ……..

2. Your gender □ Female

   □ Male

3. Number of years as a GP ……..

4. How would you describe your practice □ Rural □ Urban □ Inner city □Others (please indicate) □ Solo practice □Group practice □ Others (please indicate)

5. Your approximate practice list size ……

6. Does your practice have a formal written protocol regarding preconception care? □ Yes □ No

7. If yes, does the protocol cover component of genetic risk assessment or carrier screening? □ Yes □ No

Thank you for your help. Please return the completed questionnaire in the enclosed stamped addressed envelope provided. My return post details are listed below:

Dr. Norita Hussein
Division of Primary Care
School of Community Health Sciences
University of Nottingham
FREEPOST
Nottingham, NG7 2RD

If you would like feedback on the findings of the survey, please provide your address below.

Name:

Address:

Appendix 6.1 : Cover Letter

Dear Doctor,

This is kindly to request you to assist in a study that we are conducting at the School of Community Health Sciences, University of Nottingham titled, Preconception Genetic Risk Assessment in Primary Care. The purpose of this study is to explore your opinion of offering a formal preconception genetic risk assessment in primary care practice. The findings from this study may help us understand the feasibility of delivering the service in primary care setting.

We would very much appreciate if you could spare some time to complete the questionnaire which should only take about 15-20 minutes of your time. Your participation is important in obtaining useful information for this study.

We have enclosed the following documents for your consideration;

- Information sheet
- A questionnaire

If you have any questions or concerns about completing the questionnaire or about participating in this study, please do not hesitate to contact us, Dr. Nadeem Qureshi at Nadeem.Qureshi@nottingham.ac.uk or 01158231439 and Dr. Norita Hussein at mzxnh1@nottingham.ac.uk or 01158230463.

If you choose to participate, kindly return the completed questionnaire to us in the enclosed self-addressed, postage-paid envelope. Your return of the questionnaire indicates your consent to participate in the study.
All information given on the questionnaire will be kept strictly confidential and anonymous.

We will send you one of the high street vouchers should you be one of the first 100 to return a completed questionnaire.

Thank you very much for taking the time to consider this request.

Yours sincerely,

Dr. Nadeem Qureshi,
Clinical Associate Professor of Primary Care,
School of Community Health Sciences,
University of Nottingham.

Dr. Norita Hussein,
Division of Primary Care,
School of Community Health Sciences,
University of Nottingham.

Appendix 6.2 : Participant Information Sheet

(Final version 1.0: 2 Nov 2011)

Title of Study: Preconception Genetic Risk Assessment in Primary Care.

Name of Researcher(s): Associate Professor Nadeem Qureshi.
Dr. Norita Hussein.
Professor Joe Kai.

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Please read this information sheet which should hopefully tell you everything you need to know. If there is anything that is not clear and would like clarification, please do not hesitate to contact a member of the research team, Dr. Norita Hussein on 01158230463. Alternatively, please email at mzxnh1@nottingham.ac.uk.

What is the purpose of the study?

Identifying women at reproductive risk of having children with genetic conditions is relevant in primary care. Presently, it is mainly performed during antenatal period. Recently, a consensus panel of Human Genetics Commission (HCG) has highlighted the importance of doing reproductive genetic screening in women preconception. Women have mentioned that genetic screening in antenatal is perhaps too late for them to make appropriate decision. The purpose of this study is to explore your opinion of offering a formal preconception genetic risk assessment in your practice. Your response will help us understand the anticipated difficulties and how best to put into primary care practice.

Why have I been invited?

You are being invited to take part because you are a general practitioner practicing in primary care setting in Nottingham and Derby and we feel it is really important that we gather your opinion and suggestion to offering a formal preconception genetic risk assessment in primary care practice. We are hoping that you will be willing to take part in this study as your response will help us inform effective way of delivering the service in your setting.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to complete the enclosed questionnaire - If you complete and return the enclosed questionnaire this will be taken as you giving your consent to take part. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

We would like you to fill out a questionnaire which includes questions regarding your professional experiences and opinions of reproductive genetic screening in your practice. There are no 'right' or 'wrong' answers and the questionnaire should take about 15 to 20 minutes of your time to complete. A stamped addressed envelope is provided to make it easier to send back the questionnaire to us once you have completed it.

Expenses and payments

Participants will not be paid inconvenience allowance to participate in the study. However, if you are one of the first 100 participants who send a completed survey back to the research team, you will be given a £5 Love2shop gift voucher. This can be spent in hundreds of high street stores and more details can be found at http://www.highstreetvouchers.com/gift-vouchers

What are the possible disadvantages and risks of taking part?
Apart from the time required to complete the survey, no known disadvantages or risks are associated with taking part.

What are the possible benefits of taking part?

We hope that the information we get from this study will help form the basis of the development of an implementation model for preconception genetic risk assessment in primary care.

What if there is a problem?

If you have any questions or queries about any aspects of this study, you can contact the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet.
If you remain unhappy and wish to complain formally, you can do this by contacting the secretary of the University of Nottingham Medical School Research Ethics Committee, Louise Sabir, Division of Therapeutic and MM, D Floor, South Block, QMC Campus, Nottingham University Hospitals, NG7 2UH: email louisesabir@nottingham.ac.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to monitor the quality of the study. All will have a duty of confidentiality to you as research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office and on a password protected database.

Your questionnaire will only be identifiable by a unique code. This means that you cannot be recognised from the data you provide in the questionnaire. The unique number and any identifiable information will be kept securely by the researchers.
Data from the survey cannot be accessed by anyone other the researchers. A username and password is needed for the researchers to access survey data and will not be given out to anybody else.

Your personal data (GP address, telephone number, email address) will be kept separately from your questionnaire and deleted as soon as we have contacted you to send one of the high street vouchers, should you be one of the first 100 to respond to the questionnaire or to contact you about the findings of the study, should you request. All other data (research data) will be kept securely in the University of Nottingham for 7 years. After this time your data will be disposed of securely. All precautions will be taken to maintain your confidentiality during this time only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and that this information may still be used in the analysis.

What will happen to the results of the research study?

Once the study has been completed, we will produce reports that will describe the results of the study as a whole. Reports will also be written up as part of a doctorate

qualification (PhD). Results will be published in formats including academic and medical research journals and medical conference presentations.
If you would like to obtain the results of the study once they have been published, please email Dr. Norita Hussein on mzxnh1@nottingham.ac.uk anytime before May 2013 and the results will be sent to you via email.
Please note that you will not be identified in any report or publication that is written as part of this study.

Who is organising and funding the research?

This research is being organised and funded by the University of Nottingham.

Who has reviewed the study?

All research involving NHS staff is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the University of Nottingham Medical School Ethics Committee in accordance with the revised NRES (National Research Ethics Service) guidance.

Further information and contact details

If you have decided to take part and would like to discuss this further or you would like further information before making a decision please contact:

Dr. Norita Hussein by phone on 01158230463 or by email at mzxnh1@nottingham.ac.uk .

The chief investigator for this study is:
Associate Professor Nadeem Qureshi
Division of Primary Care
School of Community Health Sciences
The University of Nottingham
NG7 2RD
Phone**:** 01158466917
Fax**:** 01158230214
Email**:** nadeem.qureshi@nottingham.ac.uk

Thank you very much for considering taking part in the study.

Appendix 6.3 : Reminder letter

Dear Doctor,

Approximately two weeks ago, we sent you a letter and a questionnaire inviting you to participate in our study titled, Preconception Genetic Risk Assessment in Primary Care. At the time of sending this letter, we have not yet received your questionnaire. This reminder is to give you the opportunity to take part in our study. Your views are important to us and we would very much appreciate your reply.

If you have already completed and returned your questionnaire, we would like to express our gratitude and please accept our apologies for mailing you again. However, we will send you another copy of the questionnaire and a self-addressed, postage-paid envelope if we do not hear from you within this one to two weeks.

If you have any more questions or need help filling in the questionnaire, please do not hesitate to contact us; Dr. Nadeem Qureshi at Nadeem.Qureshi@nottingham.ac.uk. or Dr. Norita Hussein at mzxnh1@nottingham.ac.uk .

Thank you very much for taking the time to consider this request.

Yours sincerely,

Dr. Nadeem Qureshi,
Clinical Associate Professor of Primary Care,
School of Community Health Sciences,
University of Nottingham.

Dr. Norita Hussein,
Division of Primary Care,
School of Community Health Sciences,
University of Nottingham.

Appendix 6.4 : Cover letter to Practice Managers

14 February 2013

Dear Practice Manager,

Re: Questionnaire Survey on 'Preconception Assessment of Reproductive Genetic Risk in Primary Care'

We are writing to let you know that we are conducting a survey to explore the General Practitioners' views of assessing reproductive genetic risk before pregnancy.

We would be very grateful if you could help us giving this questionnaire survey to **any** General Practitioner in your practice. For your information, we only require **one** General Practitioner to represent each practice to participate in the survey. Attached are the cover letter to the GP, Participant Information Sheet and the Questionnaire. We will also be giving a gift voucher to those who participate. Example of the voucher that we will be sending is attached.

We would like to thank you for taking the time to assist us in distributing this questionnaire.

Yours sincerely,

Dr. Norita Hussein
Division of Primary Care
School of Community Health Sciences
The University of Nottingham