

# **Thalassaemia prevention in Maldives: effectiveness of primary, secondary and tertiary prevention interventions**

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## Abstract

### *Background*

Republic of Maldives (Maldives) is an island nation in the Indian Ocean with a population of 344, 023. Maldives has one of the world's highest carrier rates of the  $\beta$ -thalassaemias in the world:  $\beta$ -thalassaemia carriers 16-18%,  $\alpha$ -thalassaemia carriers 2.1%, HbE carriers 0.9%, HbS carriers 0.13% and HbD carriers 0.43%. It has been more than 20 years since the establishment of free genetic screening for carriers and treatment for thalassaemia majors. Patient registration and free treatment for thalassaemia majors were established in 1994. Prenatal diagnosis has been allowed since 1999.

However, during 2001-2012, approximately 28 new major cases are recorded annually. As at August 2014, a cumulative total of 803 thalassaemia cases were registered in Maldives. Currently, 563 thalassaemia patients were living: which is approximately 1.6/1000 population. A large proportion of 459 people of the total thalassaemia major population were transfusion dependent  $\beta$ -thalassaemia majors in Maldives. The eldest of the major population was 36 years and the median age of the total population was around 13 years. According to the thalassaemia register of Maldives Blood Services (MBS), 288 thalassaemia majors were residing in the capital Male' while the other half lives in outer atolls.

The high number of new cases each year indicates that thalassaemia prevention program is not effective and research into the area is a starting point to improve the program. The aim of this study was to **explore and evaluate the effectiveness of thalassaemia prevention interventions in Maldives**. The Population prevention model articulated by Leavell and Clark was used to attain a holistic picture of the program activities. As such, three levels (primary, secondary and tertiary) of prevention interventions were explored. Primary prevention included

health education, genetic screening and counselling. Secondary prevention included prenatal diagnosis. Tertiary prevention included treatment of people living with thalassaemia in Maldives.

### *Methods*

The three levels required different participants and study approaches. Therefore, this study was divided into three sub studies; each targeting a different intervention level. A generic qualitative approach using face-to-face in-depth interviews was used for studies one and two. Both studies were underpinned by a constructivist paradigm. Participants of study one were Maldivians who married and had thalassaemia major child/children without screening for thalassaemia and Maldivians who married and had thalassaemia major child/children in spite of knowing their carrier status. Study one examined two different aspects, hence, it was divided into two parts (study 1a and 1b). Study 1a included 22 participants and study 1b included 23 participants. The second study included Maldivians who undertook prenatal diagnosis and termination of pregnancy due to thalassaemia. Study two included 21 participants. Purposive sampling was used to select informants for these two studies. All interviews were conducted in Maldivian local language (Dhivehi) and later translated and transcribed to English for analysis. Thematic analysis was used for the two studies and NVivo was used for data management.

The third study was a cross-sectional study conducted using SF-36 survey to evaluate the Health Related Quality of Life (HRQoL) of transfusion dependent thalassaemia patients in Maldives. The target population was thalassaemia majors who were 14 years and over and were registered at Maldives Blood Services (MBS). All thalassaemia majors had to register with MBS by law. I was able to access 74.4% of the target population. The SF-36 survey form was translated to the local language

and it was administered with an additional form to collect participant characteristics. In addition, patient records of MBS were also collected and analysed. The HRQoL scores were calculated as advised on RAND website. Simple linear regression was computed for HRQoL scores to evaluate the association with predictor variables.

## **Results**

Findings of the first part of the first study showed that participants did not undergo carrier tests due to lack of awareness and poor understanding related to the dynamics of thalassaemia propagation. Findings of the second part of the first study showed that genetic make-up was not a barrier to marriage and access and quality of genetic counselling participants received was poor. The main reasons for not doing prenatal diagnosis were cost and religious beliefs. The consequences of having thalassaemia major children were emotionally and economically devastating for both groups. Religion was the main coping strategy they used.

The findings of the second study, presented as themes, showed that Maldivians undertook prenatal diagnosis for reasons including ‘I desire the joy of pregnancy’, ‘Our wish is not a choice’, ‘If I didn’t, others would blame me’, ‘It is the ethical decision’, ‘Encouragement and recommendation’, ‘Experience with thalassaemia major children’, ‘Religion allows it’ and ‘We want a ‘Saviour Child’. The barriers to prenatal diagnosis included cost, travel, limited time, procedural, fear, distress and hope and wishful thinking. Maldivians heavily relied on *Fatwa* (a consensus edict of Islamic scholars) and scholars’ advice in prenatal diagnosis and termination decisions. All participants in this group believed in fatwa, but had difficulty accepting the actions (termination of pregnancy) that follows. Hence, many participants were torn between fatwa and their moral beliefs.

A total of 145 participants of age 14-33 years took part in the third study. The

mean HRQoL scores from highest to lowest were 87.3 (Social Functioning), 83.7 (Physical Functioning), 77.5 (Emotional Wellbeing), 75.0 (Role Physical), 71.5 (Role Emotional), 68.8 (Bodily Pain), 64.4 (Vitality) and 62.3 (General Health). Education, gender, number of transfusions, presence of co-morbidities, age of first transfusion, compliance to iron chelation therapy, type of iron chelation therapy, marital status, average haemoglobin level, transport and residential island showed a significant association with HRQoL scores while age, household income, serum ferritin level, onset of anaemia, accommodation type, employment, frequency of transfusion and iron chelation therapy type did not show any significant association with HRQoL scores.

### *Conclusions*

Primary prevention related findings showed that primary prevention efforts should look into knowledge, attitude and behaviour of the thalassaemia carrier population in Maldives. Prenatal diagnosis was limited due to socio-cultural and personal barriers. Many overcame those barriers, however, and undertook it with much effort. Religion was both a positive and a negative factor that both impedes and helps prenatal diagnosis decisions of thalassaemia carriers in Maldives. The HRQoL ratings of Maldivian thalassaemia major participants were good in comparison to other countries in the literature. Participants' age did not show a significant association with any HRQoL scores, but the maximum age of 33 years among participants (and 36 years in the MBS registry) is a main concern as it is well below the life expectancy of Maldivians. Overall, the thalassaemia prevention program of Maldives has many strengths that need to be fostered and weaknesses that need improvements.

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## List of Abbreviations

|          |                                                             |
|----------|-------------------------------------------------------------|
| Maldives | Republic of Maldives                                        |
| MBS      | Maldives Blood Services                                     |
| WHO      | World Health Organization                                   |
| UNESCO   | United Nations Education, Science and Cultural Organization |
| HRQoL    | Health Related Quality of Life                              |
| SHE      | Society for Health Education                                |
| PF       | Physical Functioning                                        |
| RP       | Role Physical                                               |
| RE       | Role Emotional                                              |
| BP       | Bodily Pain                                                 |
| VT       | Vitality                                                    |
| SF       | Social Functioning                                          |
| EH/MH    | Emotional Health/Mental Health                              |
| GH       | General Health                                              |
| CVS      | Chorionic Villus Sampling                                   |
| CMC      | Christian Medical College (Vellore)                         |
| IGMH     | Indhira Gandhi Memorial Hospital                            |
| NSPA     | National Social Protection Agency                           |
| MFDA     | Maldives Food and Drug Authority                            |
| HPA      | Health Protection Agency                                    |
| NGO      | Non Governmental Organization                               |
| GDP      | Gross Domestic Product                                      |
| GNI      | Gross National Income                                       |
| PPP      | Purchasing Power Parity                                     |
| MVR      | Maldivian Rufiyaa (currency of Maldives)                    |
| Hb       | Haemoglobin                                                 |
| UK       | United Kingdom                                              |
| USA      | United States of America                                    |
| UAE      | United Arab Emirates                                        |
| TIF      | Thalassaemia International Federation                       |
| MRI      | Magnetic resonance imaging                                  |

## **Publications arising from this thesis**

The following manuscripts are included in this thesis and are being submitted for publication as outlined below.

1. Waheed F, Fisher C, Awofeso A, Stanley D (2015) Thalassaemia in Maldives: Reasons for not Screening and its Consequences. *Journal of Community Genetics*. (Submitted) (Chapter 4).
2. Waheed F, Fisher C, Awofeso A, Stanley D (2015) Why do Maldivians marry and have children in spite of positive thalassaemia carrier status. *Journal of Community Genetics*. (Submitted) (Chapter 5).
3. Waheed F, Fisher C, Awofeso A, Stanley D (2015) Reasons for undertaking prenatal diagnosis for thalassaemia in Maldives. *Journal of Prenatal Diagnosis*. (Submitted) (Chapter 6).
4. Waheed F, Fisher C, Awofeso A, Stanley D (2015) Socio-cultural barriers faced by Maldivians who undertake prenatal diagnosis for Thalassaemia. *Journal of Prenatal Diagnosis*. (Submitted) (Chapter 7).
5. Waheed F, Fisher C, Awofeso A, Stanley D (2015) Ethical conflicts and Islamic fatwa on prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives. *Journal of Prenatal Diagnosis*. (Submitted) (Chapter 8).
6. Waheed F, Fisher C, Awofeso A, Stanley D (2015) Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives: A cross-sectional study. *Journal of Quality of Life Research*. (Submitted) (Chapter 9).
7. Waheed F, Fisher C, Awofeso A, Stanley D (2015) Predictors of Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives: A cross-sectional study. *Journal of Quality of Life Research*. (Submitted) (Chapter 10).

## Statement of Contribution

The author of this thesis (Fazeela Waheed) is solely responsible for the review of the literature, planning, data collection, translation, transcription, data entry, data analysis and interpretation and writing of this thesis under the supervision of Professor Colleen Fisher (coordinating Supervisor), Professor Niyi Awofeso and Dr David Stanley (co-supervisors).

The thesis contains seven different papers prepared for publication and all papers are co-authored. The percentage contribution of each author for each paper is provided below with the bibliographic details.

1. **Paper one:** Waheed F (80%), Fisher C (10%), Awofeso A (5%), Stanley D (5%). Thalassaemia in Maldives: Reasons for not Screening and its Consequences. Journal of Community Genetics. 2015. (Submitted)
2. **Paper two:** Waheed F (80%), Fisher C (10%), Awofeso A (5%), Stanley D (5%). Why do Maldivians marry and have children in spite of positive thalassaemia carrier status. Journal of Community Genetics. 2015. (Submitted)
3. **Paper three:** Waheed F (80%), Fisher C (10%), Awofeso A (5%), Stanley D (5%). Reasons for undertaking prenatal diagnosis for thalassaemia in Maldives. Journal of Prenatal Diagnosis. 2015. (Submitted)
4. **Paper four:** Waheed F (80%), Fisher C (10%), Awofeso A (5%), Stanley D (5%). Socio-cultural barriers faced by Maldivians who undertake prenatal diagnosis for Thalassaemia. Journal of Prenatal Diagnosis. 2015. (Submitted)

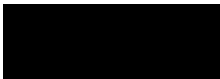
5. **Paper five:** Waheed F (80%), Fisher C (10%), Awofeso A (5%), Stanley D (5%). Ethical conflicts and Islamic fatwa on prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives. *Journal of Prenatal Diagnosis*. 2015. (Submitted)
6. **Paper six:** Waheed F (80%), Fisher C (10%), Awofeso A (5%), Stanley D (5%). Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives: A cross-sectional study. *Journal of Quality of Life Research*. 2015. (Submitted)
7. **Paper seven:** Waheed F (80%), Fisher C (10%), Awofeso A (5%), Stanley D (5%). Predictors of Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives: A cross-sectional study. *Journal of Quality of Life Research*. 2015. (Submitted)

We confirm that permission has been obtained from all co-authors and they have no reservations in including the above manuscripts in this thesis.

Signature: 

Date: 23<sup>rd</sup> December 2015

Professor Colleen Fisher, Coordinating Supervisor, School of Population Health

Signature: 

Date: 23<sup>rd</sup> December 2015

Fazeela Waheed, PhD candidate



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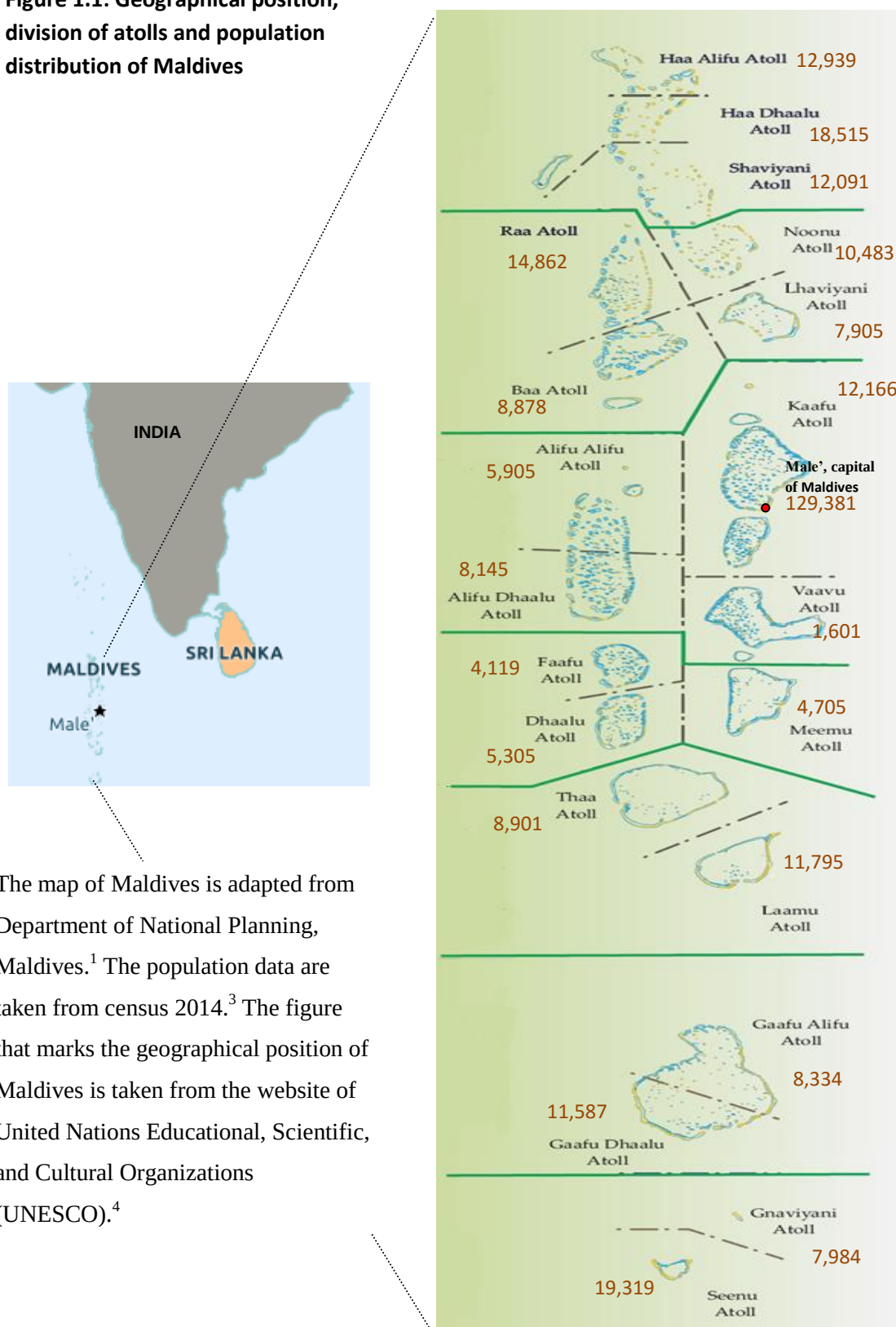
## Chapter 1: Introduction

Maldives is an archipelago in the Indian Ocean, about 300 miles southwest of the southern tip of India and 450 miles west of Sri Lanka.<sup>5</sup> It is 820 kilometres in length and 130 kilometres in width.<sup>6</sup> The total area of Maldives including sea is 115,300 sq. km and the exclusive economic zone covers an area of 859,000 sq. km.<sup>7</sup> Maldives has 1192 low lying coral islands divided into 20 atolls for administrative purposes.<sup>7</sup> One hundred and eighty eight of those islands are inhabited and 104 islands are uninhabited.<sup>7</sup> Population of the islands ranges from few a 100s to 100,000 in the capital Male'.<sup>3</sup> According to the 2014 census reports of Maldives, the local Maldivian population at the end of 2014 was 344, 023 with an annual population growth rate of 1.65 percent.<sup>3</sup> The original ancestry of the Maldivian population is not clear, but genetic research shows a clear genetic link between South Indians and Maldivians, indicating a large population of the Maldivian ancestors are from South India.<sup>8</sup> Maldives has one ethnic group and all Maldivians are Sunni Muslim by law.<sup>9</sup> Dhivehi is the National language, though English is the main language of the national curriculum and it is frequently used in other government communications.<sup>7</sup> The geographical position, division of atolls and population distribution are shown in Figure 1.1.

Maldives is an upper middle income in the South East Asia (SEA) region.<sup>10</sup> Country development indicators shows that Maldives has a literacy rate of 98%.<sup>11</sup> Its economy is mainly based on earnings from tourism, fisheries, agriculture and import duties.<sup>12</sup> The Gross Domestic Product (GDP) growth rate of Maldives at the end of 2013 was 3.7% with a GDP per capita of US\$3,846.<sup>7</sup> The Gross National Income (GNI) per capital based on purchasing power parity (PPP) in 2013 was \$9,890. The currency of Maldives, Maldivian Rufiyaa (MVR) has a floating exchange rate

(MVR16 is approximately US\$1). Public television, radio and cellular telecommunication are widely available throughout Maldives. It is estimated that 637,339 cellular phone lines were registered in Maldives as at 2014.<sup>7</sup>

**Figure 1.1: Geographical position, division of atolls and population distribution of Maldives**



The map of Maldives is adapted from Department of National Planning, Maldives.<sup>1</sup> The population data are taken from census 2014.<sup>3</sup> The figure that marks the geographical position of Maldives is taken from the website of United Nations Educational, Scientific, and Cultural Organizations (UNESCO).<sup>4</sup>

The administration of health services in Maldives operates along four tiers, ascending from island, atoll, regional to central level. The health system consists of a main National tertiary hospital (Indhira Gandhi Memorial Hospital [IGMH]), six regional hospitals, atoll hospitals, health centres and health posts. Other major services and programs that are under Ministry of Health and contribute to the health system of Maldives include the Health Protection Agency (HPA), Maldives Blood Services (MBS), National Social Protection Agency (NSPA), National Drug Authority and Maldives Food and Drug Authority (MFDA).<sup>13</sup> In addition, the health system includes a significant number of private health care organisations, Non Governmental Organisations (NGOs), private pharmaceutical outlets and a few traditional medical clinics.

Maldives has a physician ratio of 14.2/10,000 population and a nursing and midwifery workforce of 50.4/10,000 population.<sup>10</sup> Density of hospitals per 100,000 population in Maldives is 6.7; which is a quite high number compared to the other countries in the region. The high number of hospitals and health workforce is the result of dispersed population in small islands and high number of primary and secondary level health infrastructure within Maldives. The physician workforce is trained overseas and most of the nursing and midwifery workforce is trained locally. Total health expenditure as a percentage of GDP is 11.4% in Maldives.<sup>10</sup> The government contribution for health is 57.1% (16% of the total government expenditure) while the other 42.9% is private contribution for health expenditure (mainly out of pocket payments).<sup>10</sup> Social security expenditure as a percentage of general government expenditure on health in Maldives is 56.5%.<sup>10</sup>

Maldives has made notable progress in the area of health in recent decades. Latest health indicators show remarkable improvements compared to most South Asian countries. Life expectancy of Maldivians at birth is recorded as 77 years for males and 79 years for females.<sup>10</sup> The World Health Statistics Report of 2015 shows that Maldives has one of the lowest under- five mortality rates in South East Asia; 9.9 per 1000 live births which is second lowest in the region, next to Democratic People's Republic of Korea.<sup>10</sup> The regional average of under five-mortality rate is 46.9 per 1000 live births. The same report shows that Maldives is among the highest on the immunization scale for under one year olds with a percentage covering 99% of the one year olds in most vaccination categories.<sup>10</sup> Furthermore, maternal mortality rate is also low for Maldives (31 per 100, 000 live births) in comparison with regional average of 190 per 100,000 live births.<sup>10</sup> The improvements in the health indicators of Maldives are partly attributable to its small population, the expansion of health services to the rural population in the outer atolls and coordinated efforts to improve immunization uptake, communicable and non-communicable diseases control and improvements in maternal and child health status.

Nevertheless, many challenges lie ahead for the health sector of Maldives. Like many other South East Asian and South Asian countries, hemoglobinopathy related genetic disorders is a major challenge for Maldives. Maldives falls on to the tropical belt where hemoglobinopathy related disorders are most common (see Figure 1.2). Specifically, thalassaemia and its variants are common in Maldives. In 2014, it was reported that approximately 1.6/1000 of the total population has thalassaemia major trait.<sup>14</sup> The aim of this research was to explore and evaluate the

effectiveness of thalassaemia prevention interventions in Maldives. The objectives of this study were:

- (1) Explore the reasons for couples marrying without testing for thalassaemia in Maldives.
- (2) Explore the reasons why carriers of thalassaemia in Maldives marry and have children despite knowing their carrier status.
- (3) Explore the reasons that motivate at risk Maldivian couples to undertake prenatal diagnosis and termination of pregnancy for thalassaemia.
- (4) Explore the barriers and facilitators that are faced by Maldivian couples who undertake prenatal diagnosis and termination of pregnancy for thalassaemia.
- (5) Explore the potential ethical conflicts with an Islamic view of prenatal diagnosis and selective termination of pregnancy for thalassaemia in Maldives.
- (6) Evaluate the Health Related Quality of Life of transfusion-dependent thalassaemia patients who are 14 years and above in Maldives.
- (7) Determine the predictors of Health Related Quality of Life of transfusion-dependent thalassaemia patients who are 14 years and above in Maldives.

### **Structure of the thesis**

Seven papers based on this research were written and submitted for publication in peer reviewed journals. The thesis is divided into 11 chapters, including seven papers with each as a separate chapter. Chapters are as follows in numerical order:

1. **Chapter 1:** Introduction to the topic and thesis
2. **Chapter 2:** Literature review with details of the issues related to the topic in reference to current literature
3. **Chapter 3:** Methodology used for this research. Research methodology is divided into two parts- qualitative and quantitative. The qualitative part is presented as methods, research perspective, sample selection and population, data collection, data analysis and rigour. The quantitative part describes method, research instrument, participants, data collection, data analysis, and reliability and validity. In addition, ethical procedures followed for the study are explained as the last part of this chapter.
4. **Chapter 4:** First paper-based on the first objective of the study, to “Explore the reasons for couples marrying without testing for thalassaemia in Maldives.”  
  
**Reference:** Waheed F, Fisher C, Awofeso A, Stanley D. Thalassaemia in Maldives: Reasons for not Screening and its Consequences. Journal of Community Genetics. 2015. (Submitted)
5. **Chapter 5:** Second paper-based on the second objective of the first study, to “Explore the reasons why carriers of thalassaemia in Maldives marry and have children despite knowing their carrier status.”  
  
**Reference:** Waheed F, Fisher C, Awofeso A, Stanley D. Why do Maldivians marry and have children in spite of positive thalassaemia carrier status. Journal of Community Genetics. 2015. (Submitted).
6. **Chapter 6:** Third paper-based on the first objective of the second study, to “Explore the reasons that motivate at risk Maldivian couples to undertake prenatal diagnosis for thalassaemia.”

**Reference:** Waheed F, Fisher C, Awofeso A, Stanley D. Reasons for undertaking prenatal diagnosis for thalassaemia in Maldives. Journal of Prenatal Diagnosis. 2015. (Submitted)

7. **Chapter 7:** Fourth paper-based on the second objective of the second study, to “Explore the barriers that are faced by the Maldivian couples who undertake prenatal diagnosis for thalassaemia.”

**Reference:** Waheed F, Fisher C, Awofeso A, Stanley D. Socio-cultural barriers faced by Maldivians who undertake prenatal diagnosis for Thalassaemia. Journal of Prenatal Diagnosis. 2015. (Submitted)

8. **Chapter 8:** Fifth paper- based on the third objective of the second study, to “Explore the potential ethical conflicts with Islamic view of prenatal screening and diagnosis for thalassaemia in Maldives.”

**Reference:** Waheed F, Fisher C, Awofeso A, Stanley D. Ethical conflicts and Islamic fatwa on prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives. Journal of Prenatal Diagnosis. 2015. (Submitted)

9. **Chapter 9:** Sixth paper- based on the first objective of the third study, to “Evaluate the Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives.”

**Reference:** Waheed F, Fisher C, Awofeso A, Stanley D. Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives: A cross-sectional study. Journal of Quality of Life Research. 2015. (Submitted)

10. **Chapter 10:** Seventh paper- based on the second objective of the third study, to “Determine the Predictors of Health Related Quality of Life of

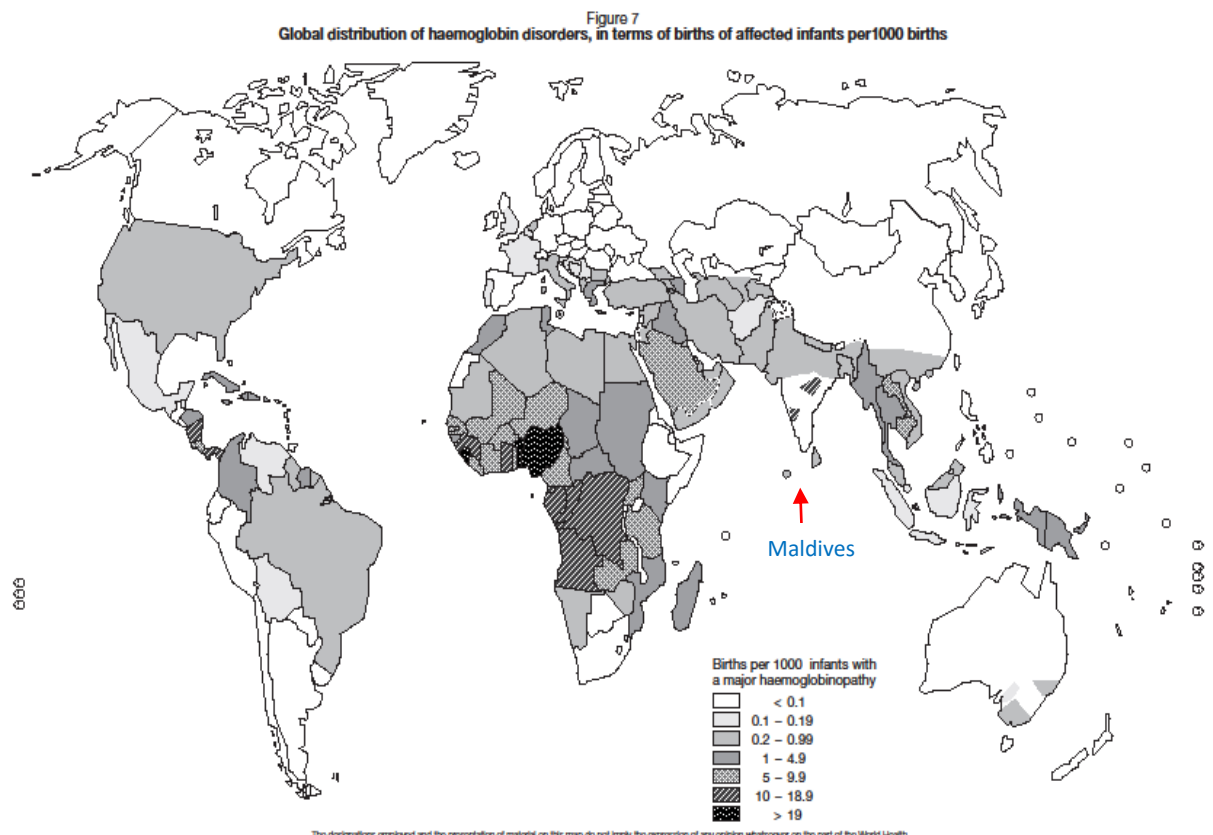


transfusion dependent thalassaemia patients in Maldives.”

**Reference:** Waheed F, Fisher C, Awofeso A, Stanley D. Predictors of Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives: A cross-sectional study. Journal of Quality of Life Research. 2015. (Submitted)

11. **Chapter 11:** General discussion of the findings of the three studies and a holistic outline of the primary, secondary and tertiary prevention interventions in Maldives.

**Figure 1.2: Global distribution of haemoglobin disorders**



Map Taken and adapted from World Health Organization<sup>2</sup>

## Chapter 2: Literature Review

### Introduction to the chapter

Chapter two covers the literature available on the topic of thalassaemia prevention globally. The content of this chapter includes an introduction to thalassaemia, primary prevention measures in different communities, secondary prevention initiatives and success measures in different countries and tertiary prevention based on Health Related Quality of Life (HRQoL) of thalassaemia majors in different countries. The thalassaemia situation of each level of prevention in Maldives is presented following the international literature at primary, secondary and tertiary prevention levels.

### Literature Review

Haemoglobin related disorders are a common phenomenon in most (71%) countries around the world and among 89% of births.<sup>15</sup> It is estimated that 307,900 children are born with severe haemoglobin disorders on an annual basis.<sup>16</sup> According to Modell and Darlison<sup>15</sup>, approximately 75% of the affected haemoglobin disorders take place in endemic areas. About 80% of those occur in low or middle income countries situated on tropical belt covering from Sub-Saharan Africa through to the Mediterranean, Middle east, South Asia and South East Asia.<sup>17</sup> The cause of high haemoglobinopathy in certain groups of countries is not confirmed, but theories suggest its high frequency and patch distribution is mainly due to natural selection and resistance to malaria.<sup>18</sup> In fact, findings from Africa shows that the two factors are closely interlinked.<sup>19</sup> A study conducted in Sri Lanka also showed that high frequency of thalassaemia in certain areas of Sri Lanka coincided with high transmission periods of malaria before the malaria eradication program in that country.<sup>20</sup> Similar findings were observed in Maldives as well.<sup>21</sup> The observations

based on population genetic theory revealed that falling prevalence of thalassaemia carriers in Maldives was consistent with the predicted effect of malaria eradication.<sup>21</sup> Additionally, some believe that consanguineous marriages, founder effects and genetic drift might have played an important role in the high prevalence of haemoglobin disorders in some areas.<sup>20</sup>

Estimates of Modell and Darlison<sup>15</sup> shows that a minimum of 300, 000 children are born with haemoglobin disorders of either sickle cell anaemia, or one of its variants or with a form of thalassaemia each year globally. Weatherall<sup>18</sup> divides the estimates of annual haemoglobin related births into seven major categories. The most significant of those groups are sickle cell anaemia (217,331), sickle cell disease (54,736),  $\beta$ -thalassaemia major (22,989), HbE  $\beta$  thalassaemia (19 128), S  $\beta$  thalassaemia (11,074), HbH disease (9 568) and Hb Bart hydrops (5 183). As can be seen above, sickle cell related disorders are the most common haemoglobinopathy in the world. Estimates suggests that about 85% of sickle cell disorders and 70% of all sickle cell related affected births take place in Africa.<sup>15</sup> The second most common type of haemoglobin disorder in the world is thalassaemia and its variants.

### Thalassaemia

Thalassaemias are described as “Inherited autosomal recessive disorders characterised by reduced rate of haemoglobin synthesis due to a defect in  $\alpha$  or  $\beta$ -globin chain synthesis”.<sup>22(p353)</sup> Namely, the two most common types of thalasseamias are  $\alpha$  and  $\beta$  thalassaemia.

$\alpha$  thalassaemia is one of the most common hemoglobin genetic abnormalities and it is prevalent in tropical and subtropical regions.<sup>23</sup> Four main types of  $\alpha$  thalassaemia conditions are the silent carrier state, the  $\alpha$  thalassaemia trait, the intermediate form of hemoglobin H disease, and the hemoglobin Bart hydrops fetalis

syndrome.<sup>23</sup> The latter type is the most severe form; which is lethal in utero or soon after birth.<sup>23</sup>

The second most common form of thalassaemia is  $\beta$ -thalassaemia. It is most prevalent in Mediterranean, Middle-East, Transcaucasus, Central Asia, the Indian subcontinent, and the Far East.<sup>24</sup> The severity of  $\beta$ -thalassaemia can vary depending on the clinical and hematological variations.<sup>24</sup> Thalassaemia minors or carriers or heterozygosity for beta-thalassaemia is clinically asymptomatic.<sup>24</sup> Thalassaemia intermedias are clinically and genotypically heterogeneous for thalassaemia with severity ranging from symptomatic carrier state to the severe transfusion-dependent type.<sup>24</sup> Webster's New World Medical Dictionary explains a thalassaemia major as the most serious form of  $\beta$ -thalassaemia with underproduction or absence of  $\beta$  chains leading to underproduction of haemoglobin and profound anaemia that requires regular blood transfusion as a treatment (not a cure).<sup>25</sup>

The pathophysiology of thalassaemia majors can be explained in terms of  $\alpha$  and  $\beta$  globin production.<sup>26</sup> In  $\beta$ -thalassaemia majors, the defect in  $\beta$ -globin chain synthesis leads to a reduced  $\beta$  chain output, thus, increased  $\alpha$  chains and imbalance in globin synthesis.<sup>26</sup> The unbound  $\alpha$  chains of thalassaemia majors precipitate in red cell precursors leading to defective erythroid precursor maturation and ineffective erythropoiesis.<sup>26</sup> Hence, the survival of red-cells are shortened leading to severe anaemia and intense proliferative drive in the bone marrow and its expansion.<sup>26</sup> As a result, a variety of other health complications such as skeletal deformities and a number of growth and metabolic abnormalities can be observed from thalassaemia majors.<sup>26</sup> The complications can become worse due to haemodilution caused by forced blood through expanded marrow, splenomegaly caused by abnormal red cells in the spleen and by increased iron absorption and iron

loading.<sup>26</sup> High iron absorption can also cause progressive iron deposition in the tissues, causing organ failure and death in worst cases.<sup>26</sup>

In addition to thalassaemia majors, intermedias and minors (carriers), other forms of thalassaemia are also common in thalassaemia endemic populations. The four most common groups in this category are Hemoglobin E  $\beta$ -Thalassaemia, Hemoglobin H Disease, Hemoglobin S  $\beta$ -Thalassaemia and Hemoglobin C Thalassaemia.<sup>27</sup>

Thalassaemia is an autosomal recessive condition. The term autosomal recessive means a trait or a disorder that occurs due to the presence of two copies of a mutated gene at a particular locus of the 22 pairs of autosomes; the mutation may occur in a homozygous or compound heterozygous state.<sup>28</sup> Therefore, each conception of two carriers of  $\beta$ -thalassaemia has a 25% chance of being affected, a 50% chance of having an asymptomatic carrier child and a 25% chance of having a non-carrier of the condition.<sup>29</sup>

Genetic studies reveal that children born from consanguineous marriages are more prone to thalassaemia due to possible inheritance of autosomal recessive genes from common ancestors.<sup>30</sup> The more closely related the parents are, greater the probability of inheritance of identical copies of recessive genes.<sup>30</sup> In addition, often a high carrier rate of different forms of thalassaemia such as  $\alpha$  and  $\beta$ -thalassaemia can be observed from the same population.<sup>31</sup> For example, it is reported that Sardinia has a  $\beta$ -thalassaemia carrier rate of 10.3% and  $\alpha$ -thalassaemia carrier rate of 25.6%.<sup>32</sup> Hence, it is also possible that individuals to have double heterozygosity for  $\alpha$  and  $\beta$ -thalassaemia.<sup>33</sup> Double heterozygosity means co-inheritance of  $\alpha$  and  $\beta$ -thalassaemia.<sup>34</sup> As a result of double heterozygosity, it is also possible that the offspring might be Hb Bart's hydrops fetalis (homozygous  $\alpha$ -thalassaemia) or severe

$\beta$ -thalassaemia (homozygous  $\beta$ -thalassaemia), or they can have both disorders if the partner is also a carrier of such conditions.<sup>33</sup>

Estimates show that three percent of the world population is heterozygous for  $\beta$ -thalassaemia with more than 200 different mutations.<sup>35</sup> Researchers further estimate that 56,000 thalassaemia affected conceptions or births take place each year.<sup>15</sup> Unfortunately, a large proportion of that estimate (35,000) require regular transfusion to survive and 5,500 die due to severe  $\alpha$  thalassaemia (Hb Bart's hydrops fetalis).<sup>15</sup>  $\beta$ -thalassaemia cases with severe anaemia also do not normally survive beyond three years if untreated.<sup>15</sup> According to Galanello and Origa<sup>29</sup>,  $\beta$ -thalassaemia is mostly found in Mediterranean, Middle East, Central Asia, India, Southern and Eastern China and north coast of Africa and South America.

Treatment of thalassaemia majors is a huge cost in many thalassaemia endemic countries and it is less costly to prevent it than lifelong treatment. Hence, many countries have thalassaemia prevention programs and Cyprus is one of the best examples so far. Cyprus is an island nation with a population of 793,000 people with a  $\beta$  thalassaemia carrier rate as high as one in every seven people.<sup>36</sup> They were able to control the number of new cases and achieve approximately zero new cases within the first 15 years of their prevention program.<sup>36</sup> Their initial thalassaemia prevention program incorporated public awareness, health education and screening.<sup>36</sup> Premarital screening was made compulsory in 1980.<sup>37</sup> As the technology grew, prenatal diagnosis and pre-implantation genetic diagnosis was implemented in Cyprus in the 1980s and 1990s, giving more reproductive options for Cypriots.<sup>36</sup>

Another well-known example is Sardinia in Italy which has a  $\beta$ -thalassaemia carrier population of 12%.<sup>24</sup> The thalassaemia program of Sardinia also contained intense health education and awareness efforts, screening and non-directive genetic

counselling accompanied by prenatal diagnosis.<sup>38</sup> It is believed that their awareness program is one of the best. Literature suggests that the impact of the Sardinian awareness programs was so high because of the small number of populations distributed in small villages, hence, making coverage of the whole population under the awareness efforts easier.<sup>38</sup>

Iran is a middle Eastern country that started its thalassaemia program in 1997, much later than Cyprus and Sardinia.<sup>39</sup> Iran's program was able to prevent up to 80% of the affected births and 53% of at risk marriages.<sup>39</sup> Many middle Eastern countries such as Saudi Arabia, United Arab Emirates (UAE) and Iraq have high thalassaemia carrier rates and Iran is one of the few Middle Eastern countries that achieved a 65% decrease in affected birth rate.<sup>39</sup> Statistics show that since the start of the program, the affected birth rate decreased from 39.38 to 2.68 in 100,000 live births from 2005 to 2010.<sup>40</sup> Similar to Cyprus, the Iranian premarital screening program is mandatory and its mandatory nature might be a reason for the success in both countries.

### **Thalassaemia in Maldives**

Thalassaemia is the most common genetic disorder in Maldives. The evolution of thalassaemia in Maldives is not clear, but there is a study that suggests that high thalassaemia carrier rate of Maldives is due the selective advantage that they confer against Malaria.<sup>21</sup> The earliest diagnosed case of thalassaemia in Maldives was recorded in 1970.<sup>41</sup> During 1970 – 1980, a few more cases were reported and there was a dramatic increase during 1980 -1990.<sup>41</sup> Maldives has a  $\beta$ -thalassaemia prevalence rate of 16-18%, which is one of the highest internationally.<sup>14</sup> The  $\beta$ -thalassaemia carrier prevalence rate ranges from zero to 41% by islands and 8.9% to 27.1% by atolls.<sup>21</sup> Table 2.1 provides population size of

atolls based on 2014 census records<sup>3</sup> and  $\beta$ -thalassaemia carrier rates as estimated by Firdous, Gibbons and Modell.<sup>21</sup>

Other types of thalassaemia in Maldives include  $\alpha$  thalassaemia (2.1%), Haemoglobin E (HbE) (0.9%), Haemoglobin S (HbS) (0.13%) and Haemoglobin D (HbD) (0.43%).<sup>14</sup> Other common haemoglobinopathies such as sickle cell diseases are not commonly found in Maldives. According to the screening records of Maldives Blood Services (MBS) (previously known as National Thalassaemia Centre), only 11 (10 HbS/ beta thalassaemia and one HbS/HbD) cases of sickle cell disease were detected during their screening.<sup>14</sup> Please refer to Appendix 2 for further details of thalassaemia variants in Maldives.

The national thalassaemia program of Maldives was initiated by the non-governmental organization, Society for Health Education (SHE) in 1992.<sup>41</sup> The initial program was basically an awareness program with screening and counselling in the capital Male'.<sup>42</sup> As the program expanded to atolls, the magnitude of the problem was felt and the need for a special care centre was brought to the government's attention in the early 1990s. Hence, the then National Thalassaemia Centre was established in 1994 and registration of patients for treatment was started in that same year.<sup>42</sup> As at August 2014, a cumulative total of 803 thalassaemia patients were registered at MBS and 563 were living.<sup>14</sup> This means about 1.6 persons in every 1000 Maldivians is a thalassaemia major.<sup>14</sup> Furthermore, according to the 2014 report of the Thalassaemia International Federation (TIF), a total of 459 of registered patients were  $\beta$ -thalassaemia majors and the rest include thalassaemia intermedia, HbE/beta thalassaemia, HbS/ beta thalassaemia, sickle cell syndrome, HbS/HbD , HbH disease (alpha thalassaemia) and other haemolytic anaemias.<sup>14</sup> The age distribution of the living patients ranged from zero to 36 years with a median



around 13 years.<sup>14</sup> Approximately 288 thalassaemia majors were living in the capital Male while the other half live in atolls.<sup>14</sup>

**Table 2.1: Population size and  $\beta$ -thalassaemia carrier rates in different atolls of Maldives**

| Atoll         | Population size of the atoll | $\beta$ - thalassaemia carrier percentage |
|---------------|------------------------------|-------------------------------------------|
| Haa Alifu     | 12,939                       | 16.8                                      |
| Haa Dhaalu    | 18,515                       | 20.4                                      |
| Shaviyani     | 12,091                       | 23.6                                      |
| Noonu         | 10,483                       | 25.4                                      |
| Raa           | 14,862                       | 13.7                                      |
| Baa           | 8,878                        | 12.6                                      |
| Lhaviyani     | 7,905                        | 18.2                                      |
| Kaafu         | 12,166                       | 16.2                                      |
| Capital, Male | 129,381                      | 18.8                                      |
| Alifu Alifu   | 5,905                        | 14.5                                      |
| Alifu Dhaalu  | 8,145                        | 16.6                                      |
| Vaavu         | 1,601                        | 8.7                                       |
| Meemu         | 4,705                        | 15.6                                      |
| Faafu         | 4,119                        | 18.7                                      |
| Dhaalu        | 5,305                        | 14.0                                      |
| Thaa          | 8,901                        | 16.2                                      |
| Laamu         | 11,795                       | 22.8                                      |
| Gaafu Alifu   | 8,334                        | 14.0                                      |
| Gaafu Dhaalu  | 11,587                       | 9.0                                       |
| Gnaviyani     | 7,984                        | 17.1                                      |
| Seenu         | 19,319                       | 8.3                                       |

The national program has expanded and many new developments have taken place. Thalassaemia was added to the National secondary school curriculum in 1999 as part of the effort to improve awareness.<sup>41</sup> Another important development was the legalising of prenatal diagnosis and selective termination of pregnancy for thalassaemia on the 1<sup>st</sup> of November 1999.<sup>43</sup> The endorsement of the Thalassaemia Prevention Bill on the 25<sup>th</sup> April of 2012 was another major development.<sup>44</sup> The new

Bill, approved and became a law on the 10<sup>th</sup> of May, 2012,<sup>44</sup> mandates every Maldivian child to be tested for thalassaemia before the age of 18 (earliest age that a person can marry in Maldives).<sup>44</sup>

Additionally, it is mandatory to register every thalassaemia major child with Maldives MBS, so that necessary services can be provided for them.<sup>44</sup> MBS provides blood transfusion and iron chelation free of charge for the thalassaemia patients of Maldives.<sup>18</sup> Access to Bone Marrow Transplant (BMT) is also available overseas for patients who have matching siblings and can afford it at a government subsidised rate. Hence, the thalassaemia program of Maldives has a history of more than 20 years and many developments can be observed at different prevention levels.

Thalassaemia prevention programs are usually built around three main disease stages of pre-disease, latent disease and symptomatic disease as in Leavell and Clark's prevention model.<sup>45</sup> The primary prevention interventions are targeted at pre-disease stage aiming to decrease number of cases who move from pre-disease stage to latent disease stage. Examples of prevention in thalassaemia include awareness, health education, genetic screening and counselling. The secondary prevention interventions are targeted at latent disease stage aiming to decrease the number of cases who move from latent disease stage to symptomatic disease stage (birth of major children). Examples of secondary prevention in thalassaemia include prenatal diagnosis and pre-implantation genetic diagnosis to prevent the birth of thalassaemia major children. The tertiary prevention interventions are targeted at symptomatic disease stage aiming to decrease disability and rehabilitation of the patients of targeted condition/disease. Examples of tertiary prevention interventions in thalassaemia prevention include BMT, blood transfusion treatment and management of disease complications.

## **Primary prevention: Health education, screening and genetic counselling**

Health education, screening and genetic counselling are the core components of primary prevention of thalassaemia around the world, with the three phased components following one after the other in the sequence of health education followed by screening and, finally, counselling for those who are carriers of the condition.

### ***Health Education***

Health education is the starting point of most health related prevention programs. Its aim is to improve awareness and knowledge of the issue of concern among the target population. Health education is conducted to improve or protect health via voluntary behaviour change as an outcome of learning opportunities provided by different mediums.<sup>46</sup> The mediums can be anything from information leaflets, information sessions, radio, television, internet and so forth. Normally, health education is provided before genetic screening or carrier screening initiatives.

Health education is the main means of imparting knowledge and increasing awareness of health issues. Awareness and knowledge play a vital role in a thalassaemia prevention programs' effectiveness and success. Studies show that awareness, knowledge and understanding of the genetic condition of thalassaemia impact the screening decisions in many communities. For example, findings from a focus group study conducted in Malaysia to study the awareness, attitudes, perceptions, and screening reservations towards thalassaemia showed that the public lacked understanding about the difference between  $\alpha$ -thalassaemia major and a carrier and the inheritance patterns.<sup>47</sup> Additionally, the participants in that study did not test though it was a common condition in Malaysia and most were willing to get tested when they were provided with the information.<sup>47</sup>

Prior knowledge of the condition was shown to be helpful in deciding on marriage decisions as well. For example, a study conducted in Saudi Arabia showed that prior knowledge was one of the major factors that influenced couples who cancelled wedding plans.<sup>48</sup> Another study in Saudi Arabia showed that knowledge imparted by counselling and health education sessions also increased the number of marriages being cancelled.<sup>49</sup> A study conducted among the Pakistani population in the United Kingdom (UK) also showed that knowledge deficit was one of the main reasons that UK Pakistanis do not test for thalassaemia and, hence the high birth prevalence of major cases in their community.<sup>50</sup>

In relation to thalassaemia, studies show that knowledge was related to many factors such as education level<sup>51,52</sup>, age, employment status and average household income.<sup>52</sup> Method of counselling and the health education approach were also shown to be important determinants of knowledge in genetic counselling for thalassaemia.<sup>49</sup> Another factor that impacts knowledge is the family members of the carriers. For example, a study conducted by Ahmed, Bekker, Hewison and Kinsey<sup>50</sup> showed that family was the most frequently mentioned source of information on thalassaemia among Pakistanis in the UK. Another study conducted by Ulph, Cullinan, Qureshi and Kai<sup>53</sup> also showed that families play a vital role in screening knowledge, decision and service use of carriers. Their study revealed that families were often the knowledge base of voluntary screening as well as being the main source of support. There is evidence, however, that some family members do withdraw their support and control information.<sup>53</sup> For example, some participants in that study did not disclose information to the family in order to maintain their own control over their health.<sup>53</sup> In addition to family, other sources such as friends, mass media, health carers and schools were also identified as knowledge sources of

thalassaemia in some studies.<sup>47</sup> Knowledge and awareness are important starting points of primary prevention. More importantly, they motivate people to move on to the next stage of prevention; which is screening or testing for the condition.

### *Screening and genetic counselling for thalassaemia*

Screening followed by genetic counselling for carriers is the second stage of primary prevention of thalassaemia. Depending on the need and effectiveness, different screening approaches are used in different communities. Some of those approaches include voluntary screening targeted at different age groups, screening based on ethnic origin, obligatory premarital screening and family-centred or cascade screening.

Genetic screening is described as “Any kind of test performed for the systematic early detection or exclusion of a genetic disease, the genetic predisposition or resistance to a disease, or to determine whether a person carries a gene variant, which may produce disease in offspring.”<sup>54 p.903</sup> Well planned screening programs normally offer comprehensive genetic counselling for carriers following screening. A carrier of a genetic condition is “An individual who possesses in heterozygous state the mutated gene determining an inherited disorder, and who is essentially healthy...”<sup>55p.102</sup> Genetic counselling for thalassaemia carriers is important to achieve the required outcome of screening programs.<sup>56</sup> Screening is essentially a secondary prevention activity, but in the context of thalassaemia, screening of carriers to prevent thalassaemia propagation is a primary prevention activity. Genetic counselling is aimed at informing carriers about issues such as reproductive options, partner selection, birth control and foetal testing.<sup>57</sup> It is advised that comprehensive genetic counselling should cover diagnostic and clinical aspects of the condition explaining inheritance patterns, risk estimations, possible preventive

options and further measures.<sup>55</sup> As a general rule, genetic screening programs are recommended to be voluntary for individuals and for populations as well.<sup>58</sup> However, not all thalassaemia screening programs are voluntary. A comprehensive review that compared thalassaemia screening programs around the world showed that most countries had voluntary programs, but in a number of countries the programs were mandatory.<sup>58</sup> Some countries that had voluntary screening programs were Greece, Sardinia in Italy, Israel and England.<sup>58</sup> Some countries that had mandatory screening programs included Turkey, Saudi Arabia, Gaza Strip in Palestine and Iran.<sup>58</sup> The Cyprus program was quasi-mandatory for Greek Cypriots under the Church and mandatory for Turkish Cypriots under the government.<sup>58</sup>

The most common primary prevention approach used for thalassaemia prevention is premarital screening. Like any other prevention program, premarital screening is also successful only in some communities. There are some studies that show that premarital screening and genetic counselling have not been fully successful in reducing thalassaemia major incidences, especially when provided without secondary prevention opportunities. Cyprus was one of the first countries that started premarital testing and genetic counselling. Their experiences of premarital screening and counselling when provided without prenatal diagnosis was that it was not effective.<sup>59</sup> The initial premarital screening program of Saudi Arabia also showed limited success. For example, research done in Saudi Arabia showed that 98%<sup>60</sup>, 88.2%<sup>48</sup> and 89.9%<sup>49</sup> of at risk couples in three different studies proceeded with marriage even after knowing the risks involved.

Even though premarital screening was not successful in some communities, literature does show that it is a successful measure in many. In fact, obligatory premarital screening programs are shown to be very effective in many communities.

For example, a study that screened 100,000 people preparing for marriage in Isfahan Iran, showed that premarital screening and genetic counselling were effective in preventing thalassaemia in that location<sup>61</sup> with 90% of carrier couples deciding not to marry and no new thalassaemia major child was detected among the screened population. The premarital screening program of South Iran also showed significant decrease in number of thalassaemia major cases since its implementation.<sup>62</sup>

Palestine also adopted obligatory premarital testing for  $\beta$ -thalassaemia in 2000.<sup>63</sup> The study conducted by Tarazi, Al Najjar, Lulu and Sirdah<sup>63</sup> in Gaza Strip, Palestine showed that mandatory premarital testing for  $\beta$ -thalassaemia decreases new incidences of major cases. Their study findings (which was based on five years of obligatory premarital screening) showed that many couples did not proceed to marry carrier partners after knowing the carrier status; indicating that mandatory premarital testing can work in some communities.<sup>63</sup>

Even though the initial findings were negative in Saudi Arabia, long term impact of the premarital screening program showed an improvement in marriage cancellation in Saudi Arabia as well. The evaluation of six years of premarital screening data in Saudi Arabia showed a five-fold increase (9.2% to 51.9%,  $P < .001$ ) in voluntary cancellation of marriage in that country.<sup>64</sup>

Another screening approach used in primary prevention of thalassaemia is screening certain ethnic groups that are more prone to the condition. For example, thalassaemia is common in the Pakistani and Bangladeshi communities in the UK and ethnic origin was used as the basis for selection in their plan for screening for haemoglobinopathies in the UK in 2004.<sup>65</sup> However, this method was shown to have as high as 20% misclassification<sup>65</sup> and other complications related to service provision, social values and ethics. For example, a pilot study conducted to evaluate

the attitude of general practitioners and midwives towards ethnic basis for hemoglobinopathy screening revealed that they have positive attitude towards education, but not towards ethnically targeted screening.<sup>66</sup> Their main reasons against ethnicity based selection were related to social norms and negative peer opinion.<sup>66</sup>

Another screening approach is family-centred screening or cascade screening. As thalassaemia is an autosomal recessive disorder, carriers are normally healthy and unidentifiable from the outside, but they can pass the defective gene to their offspring. Therefore, if a family has an identified carrier or a major, it is very likely that there will be more carriers in that family. Studies show that cascade screening is very effective in large populations such as in India and Pakistan. A study in India that reported on the screening of 691 extended family members identified 151 carriers and they argued that they would not be able to identify as many carriers as they did with any other methods. The authors stated that they would have to screen about 5600 school children or 9500 antenatal women to identify 151 carriers if those two groups were used. Therefore, they concluded that family centred screening was most cost effective and practical in the Indian community.<sup>67</sup> Similar findings were also reported in Pakistan.<sup>68</sup>

Screening and genetic counselling as a primary prevention strategy works well in some communities while it has little impact in others. There are many factors that decrease the effectiveness of screening programs. Timing was one of the major factors that negatively impacted the program outcome in Saudi Arabia.<sup>48,49</sup> Studies show that cultural factors can also have a negative impact on the effectiveness of premarital screening programs. For example, the negative impact of culture was observed in Saudi Arabia<sup>60</sup> and in India.<sup>69</sup> Another major factor that decreased the



impact of screening programs in some countries was wedding plans that could not be cancelled.<sup>48</sup> Fear of stigmatization was also an impediment that was recorded in many communities such as in Saudi Arabia<sup>48</sup>, Indonesia<sup>51</sup> and in India.<sup>48,51,59</sup> Perceived stigma and discrimination attached to being a carrier of thalassaemia was also identified as a major issue in the Malaysian community.<sup>47</sup> The nature of the disease (carriers are normally healthy) and denial were also reasons why some people do not want to be tested voluntarily, hence decreasing the effectiveness of outcomes of primary prevention in thalassaemia.<sup>70</sup> In addition, high cost and difficulty of accessing primary prevention services and lack of integrated prevention programs were also reported as two major factors that negatively impacted premarital screening programs in some communities such as in India.<sup>69</sup> Furthermore, religion was shown to be an important factor in religious communities. Literature shows that religious leaders and faith organizations had the potential to influence haemoglobinopathy related health education and health promotion programs in religious communities.<sup>71</sup> For example, it is viewed that the screening program of Cyprus was successful partly because of the support from the religious authorities.<sup>72</sup>

### *Impact of major children on family*

A thalassaemia major child is sometimes born without parents' knowledge of their carrier status while at times a major child is born to the parents who are aware of their genetic makeup and the risks involved. Either way, the intended outcome of the primary prevention intervention is not achieved when a major child is born. Whichever the case, the birth of a major child is a huge responsibility, and caring for a major child is physically, mentally and financially burdensome for the carers. Many researchers have explored mental, physical and financial aspect of carers of thalassaemia majors in different communities.

A study conducted in Tehran, Iran to evaluate the emotional status of mothers of children with thalassaemia or blood malignancies using Beck Depression Inventory (BDI) showed a significant relationship with the children's condition and mothers BDI scores.<sup>73</sup> A study conducted to analyse the psychosocial burden of caring for thalassaemia major children in Antalya, south Turkey also showed that 82% of the parents in that study experienced anxiety due to the thalassaemia condition of their children.<sup>74</sup> Sapountzi-Krepia, Roupa, Gourni, Mastorakou, Vojiatzi, Kouyioumtzi<sup>75</sup> studied mothers' feelings associated with the news of the diagnosis of their thalassaemia major children in Greece. According to their findings, the news of the diagnosis was shocking for some mothers, some were in denial for some time, some felt anger, some were sorrowful and distressed and some feared stigmatization.<sup>75</sup> The literature about the feelings associated with caring for thalassaemia majors in Greece also showed that mothers felt stressful and avoided children's questions including for example, about death. In addition, the same study showed that mothers experienced anxiety, frustration, and sorrow knowing that child's life will never be normal, and anger and guilt about issues such as not being able to give time for other children and passing the gene to the child.<sup>75</sup> Similar experiences were reported among parents in Antalya, South Turkey as well.<sup>74</sup>

In addition to poor emotional health, many families face financial difficulties as well because thalassaemia treatment, where it is not free, is expensive. Even in those countries where treatment is free, parents felt financial difficulty due to the care needed for thalassaemia majors. For example, one study showed that 47% of the parents of thalassaemia majors in Antalya, South Turkey experienced financial difficulties even though iron chelation and blood transfusion expenses were covered by the state government in Turkey.<sup>74</sup> A study that looked into the financial

difficulties associated with caring for thalassaemia major children in the UK also revealed that most parents (15/20) in that study were in need of financial assistance from the government to care for the child.<sup>76</sup>

Review of literature shows that screening programs have been more effective in some countries in comparison to others. Programs are affected by many factors such as the timing of the screening, wedding plans, method of counselling, health education and prior knowledge, fear of stigmatization, culture, the nature of the disease, personal beliefs such as denial, level of education, age, employment status, income and cost. In addition, the birth and caring for major children is a huge responsibility that affects the emotional and financial wellbeing of affected families.

### **Primary Prevention in Maldives**

Health education and increasing awareness was the first attempt at thalassaemia prevention in Maldives. The high prevalence of Thalassaemia in Maldives motivated the Society for Health Education (SHE), a local NGO to initiate the first awareness program.<sup>41</sup> SHE conducts nationwide health education programs with the aim of empowering the public to make informed decisions.<sup>41</sup> The initial program included distributing leaflets, conducting workshops by mobile teams and awareness programs broadcasted via radio and television.<sup>77</sup> The inclusion of thalassaemia in the school health program was also a part of awareness program.

Currently, the most well-known primary prevention strategy in Maldives is screening and counselling. Screening for thalassaemia carriers was initiated by SHE, in 1992.<sup>41</sup> Their screening program covered all the inhabited islands (200 islands) by 2002<sup>41</sup> and screened 68,986 Maldivians born between 1970 -1990 under that first initiative.<sup>21</sup> At present, screening is available from SHE and MBS; which are both situated in the capital city Male'. The screening services for outreach populations is

still provided by the mobile teams of SHE.<sup>41</sup> However, there are many who travel and visit the two screening centres of Male' at their own expense. The test results are followed and genetic counselling is provided by both centres for those who are identified as carriers of the diseases.<sup>77</sup> Counselling is provided via phone for those who live in the islands and face-to-face for those who comes to the two centres personally to collect their screening result.

The premarital screening program of Maldives certainly has achieved much. The National thalassaemia register of Maldives showed an approximate 60% fall in affected birth prevalence after the establishment of a population screening programme.<sup>21</sup> However, the program itself still needs to be looked at more carefully in order to improve its effectiveness. The cumulative total cases registered as at August, 2014 was 803.<sup>14</sup> The data of Ministry of Health of Maldives (2002-2012) shows that on average, approximately six premature deaths take place annually.<sup>78</sup> Records of Ministry of Health (2001-2012) shows that average number of new cases that were recorded for atolls (approximately 23cases) were much higher compared to Male' (approximately 5 cases) where screening is freely available ( please refer to Appendix 1 for more details).<sup>78</sup> Approximately one third of the Maldivian population lives in capital city Male'. The trend has been the same for most of the past years<sup>78</sup> though the screening program has been operating for more than 20 years.

The poor performance of the screening program in the islands of Maldives is not clear. The main contributing factor might be that testing facilities are available in Male' and until 2012, it was mandatory that couples were tested in order to get their marriage registered in the capital city only. Thalassaemia card or test result (both positive and negative) is considered as a 'must document' by the family court in Male' for marriage registration since 2002 (Ahmed Abdulla, marriage registrar of

family court of Male' Maldives, 2012, June 16). However, that rule was fully implemented in the capital Male' only. Screening for thalassaemia was not mandatory in other islands of the Maldives until 2012, as testing is not available in atoll and island health settings. Still the standard marriage registration form is common for Male' and atolls and it is recommended to be tested even if the intending person lives on another island. Another reason for the difference might be that screening teams are not able to reach the whole population of child bearing age. Moreover, it might be possible that people in the islands marry and have children even after knowing their carrier status. Additionally, though consanguineous marriages with first cousins are not common in Maldives, more distant consanguineous marriages in less populated islands might be a contributing factor to the high number of thalassaemia cases in the atolls.

### **Secondary Prevention: Prenatal Diagnosis and Selective Termination of Pregnancy**

Many believe that it is best to prevent thalassaemia by preventing the birth of thalassaemia major children.<sup>42</sup> The main reason is the cost of the major children for the society and families. Prenatal diagnosis and termination of affected pregnancies is the most common secondary level prevention approach used in thalassaemia prevention. Studies show that the cost of prenatal diagnosis would be less compared to cost of treatment<sup>79</sup> and psychological and social burden<sup>80</sup> incurred to support a thalassaemia major child. Hence, many countries including Greece<sup>81</sup>, Iran<sup>82</sup>, Saudi Arabia<sup>83</sup>, Egypt<sup>84</sup>, India<sup>85</sup>, Italy<sup>86</sup>, Cyprus<sup>37</sup> and many other countries offer prenatal diagnosis and selective termination as a preventive measure for thalassaemia. Those who hold the above view suggest that thalassaemia prevention programs should

include sensitization or awareness of the public, access for screening and provision for genetic counselling followed by parental diagnosis.<sup>42</sup>

Prenatal diagnosis for  $\beta$ -thalassaemia was first accomplished in 1970 by foetal blood obtained at 18-22 weeks.<sup>87</sup> The Sardinian thalassaemia prevention program, which is one of the oldest programs that offered prenatal diagnosis for thalassaemia was started in 1977 using placenta-centesis.<sup>88</sup> Later, they introduced amniocentesis, fetoscopy and cordocentesis in 1982, trans-cervical Chorionic Villus Sampling (CVS) in 1983, cardiocentesis in 1984 and trans-abdominal CVS in 1986.<sup>88</sup> Out of all above mentioned procedures, CVS is the most commonly used technique in most countries. CVS is done by foetal DNA analysis to identify if the foetus is affected by a genetic disorder.<sup>89</sup> It is normally carried out after 10 weeks' gestation either trans-cervically or trans-abdominally.<sup>89</sup> More recently, less invasive methods of pre-implantation genetic diagnosis were introduced giving relief for couples who do not feel comfortable terminating pregnancy after gestation as in prenatal diagnosis.<sup>87</sup> Furthermore, non-invasive prenatal diagnosis for  $\beta$ -thalassaemia by identifying paternal mutation in maternal plasma was also shown to be a hopeful method.<sup>90</sup>

Prenatal diagnosis is important in preventing thalassaemia as studies show that many tend to get married and have children even after knowing their carrier status. It is a reproductive option for at risk couples who want to have unaffected children. Additionally, studies show that cost is less compared to the expenses<sup>79</sup> and psychological and social burden<sup>80</sup> that would incur to support a thalassaemia major patients. In fact, there are studies that show that prenatal diagnosis followed by selective termination is more cost effective compared to treatment for thalassaemia major children. For example, a Hong Kong based study that screened 18, 936

pregnant women showed that providing universal prenatal screening and offering prenatal diagnosis when required is a cost effective method of approaching thalassaemia. In that study, it was more cost effective to terminate thalassaemia affected pregnancies (18/19) than lifelong treatment that would be needed for major patients otherwise.<sup>79</sup> Hence, many countries offer prenatal diagnosis and selective termination as a thalassaemia prevention measure and it is a fast growing approach in many countries.

Prenatal diagnosis programs in different countries show varying degrees of success. There are many countries such as Cyprus that were able to control thalassaemia using this approach. The program in Cyprus was exceptionally successful and it effectively decreased the number of thalassaemia majors.<sup>37</sup> Another country that had implemented a successful prenatal diagnosis program is Greece.<sup>81,91</sup> The national thalassaemia prevention program of Greece which was implemented in 1973 was shown to be effective in preventing major births of thalassaemia and sickle cell disease.<sup>81</sup> The figures of 2002-2006 in Greece showed that their approach of screening followed by counselling and voluntary prenatal diagnosis was able to effectively control the birth of new thalassaemia cases.<sup>81</sup> The prenatal diagnosis program of Southern Iran was also found to be effective.<sup>62</sup> Studies conducted in Hong Kong<sup>79</sup> and Turkey<sup>74</sup> also showed positive results. A study where 112 parents of thalassaemia majors in Antalya, South Turkey were interviewed revealed that most parents (93%) in that study would have chosen to terminate their pregnancy if they knew they were carrying a thalassaemia major child.<sup>74</sup>

On the contrary, it has to be noted that prenatal diagnosis is not supported and it is not a successful thalassaemia control measure in some countries. A Malaysian study that explored public opinion towards thalassaemia and selective

termination showed that the majority of the population in that study (63.4%) were unsupportive of selective termination of pregnancy in case of thalassaemia.<sup>52</sup> A study conducted in Pakistan also showed that 60% of at risk couples who already had a thalassaemia major child did not seek prenatal diagnosis services for their following pregnancy.<sup>92</sup> Additionally, some studies in Egypt also showed that prenatal diagnosis was not acceptable<sup>84</sup>, though differential attitudes can be observed in more recent studies.<sup>93</sup> Furthermore, studies in Ontario, Canada also revealed poor usage of prenatal diagnosis services for thalassaemia.<sup>94</sup>

Literature shows many factors that contribute to the poor utilization of prenatal diagnosis services. One of the main factors is incomplete services. For example, prenatal diagnosis services without the option of corresponding termination services for thalassaemia major foetuses on a timely manner are not cost-effective. Findings from Pakistan (Rawalpindi & Islamabad) showed that lack of awareness, high cost, poor access, mothers' education level, timing and advice against the test contributed to poor utilization of the service.<sup>92</sup> Studies in Iran show that economic burden and cost<sup>40,82</sup>, cultural factors<sup>40,62</sup>, unwanted pregnancies<sup>62</sup>, superstition, faith in a supernatural solution and experience of previous termination of pregnancy<sup>40</sup> were the main reasons that people did not use prenatal diagnosis services for thalassaemia in Iran. Egyptian researchers suggest that the high level of negative attitude towards termination of pregnancy in that country might be due to culture, religious beliefs and a high level of illiteracy.<sup>84</sup> Other factors included timeliness and gestational age, influence of significant others, moral belief and perception of severity of the condition.<sup>95</sup> Additionally, personal belief and consequences of the disease were also found to affect decisions to use or not use prenatal diagnosis services.<sup>96</sup> Religion was identified as one of the strongest factors that influenced the



prenatal diagnosis decisions of the families in Islamic countries such as Iran<sup>40</sup>, Saudi Arabia<sup>83,97</sup> and in Egypt.<sup>93</sup> Similar observations were also made in Malaysia (a predominantly Muslim country).<sup>47</sup>

Religion is one of the most important factors that affected the success of prenatal diagnosis programs in many countries such as above. In fact, literature shows that religious leaders and faith organizations have the potential to influence hemoglobinopathy related health education and health promotion programs in religious communities.<sup>71</sup> The research findings of the studies that looked into the details of religion in relation to prenatal diagnosis and termination of pregnancy for thalassaemia were mixed and contradictory. Some studies show that religion is not the main decisional factor while other studies show that religion is the prime factor in prenatal diagnosis decisions.

In Islam, termination of pregnancy is allowed for thalassaemia major fetuses detected before 120<sup>th</sup> day of the pregnancy. The fourth resolution of the Muslim World League conference of jurists held in Mecca in 1992 states that abortion is forbidden after the 120<sup>th</sup> day of gestation even if the foetus is identified to have a major disability by a medical procedure or a test.<sup>98</sup> However, if a trustworthy team of specialist doctors confirms that the mother's life is in danger due to the foetus, it is permitted to terminate the pregnancy even after 120<sup>th</sup> day of gestation whether the foetus is healthy or not.<sup>98</sup> The *fatwa* of the Muslim World League states that if a trustworthy specialist medical team agrees that an unborn child is grossly malformed and cannot be cured with any medical procedure and if the birth of the child will be a calamity for the child and family, termination of the pregnancy within the first 120 days of gestation with the consent of the two parents is permissible in Islam.<sup>98</sup> This fatwa is developed based on *Quru'an*, *Sunna*, *Hadith* and *Ijtihad* of

Islamic medical ethics experts. Many Islamic countries such as Saudi Arabia, Yemen, Maldives, Iran, Pakistan and Sudan allow termination of pregnancy for medical purposes based on the fatwa of Muslim World League and Islamic *Shari'ah* (Islamic jurisprudence).<sup>99</sup>

There are many studies that show that religion is not the main decisional factor in prenatal diagnosis and termination of pregnancy in thalassaemia. For example, a study conducted in England shows that prenatal diagnosis was more of a personal decision than a religious one.<sup>96</sup> The participants of that study gave equal importance to the consequences of the diseases and religion.<sup>96</sup> The same study also showed that most participants of different faith groups such as Muslims use their religion in a very broad context of individual self, family and other social relationships. Another study that looked into the attitudes towards prenatal diagnosis and termination of pregnancy among the UK residents of Pakistani origin showed that Islam was not the main factor that affected their decision to use prenatal diagnosis or termination.<sup>95</sup> The study conducted by Darr, Small, Ahmad, Atkin, Corry and Benson<sup>100</sup> also revealed that many Pakistani origin Muslims who reside in the UK had a flexible religious perspective towards prenatal diagnosis and termination of pregnancy. Their study showed that some were against termination of pregnancy for thalassaemia while many believed that the ruling on termination of pregnancy in Islam is flexible and allowed.<sup>100</sup>

On the contrary, there are studies that show that religion is a major factor that impact the prenatal diagnosis decisions of couples of faith. For example, a study conducted by Ahmed, Atkin, Hewison and Green<sup>101</sup> reported that parents' decisions would be influenced by faith when it comes to prenatal diagnosis. Most Christian and Muslim participants in that study revealed that their decision would be

influenced by religious belief to some extent.<sup>101</sup> Another study conducted among the Pakistani origin UK population also revealed close opinions with regard to prenatal diagnosis and termination of pregnancy for genetic disorders.<sup>100</sup> Some participants in that study believed that termination of pregnancy is not an option in Islam except unless the mother's life was in danger.<sup>100</sup> Similar findings were also reported in Iran. Even though prenatal diagnosis programs were very successful in Iran, studies had shown that there is a correlation with medical abortion and religious beliefs in Iran.<sup>62,82</sup> The Egyptian experience also showed that religion was a main factor that influenced the decision to continue with the pregnancy<sup>84</sup>, and even when it comes to termination.<sup>36</sup> Research conducted in Saudi Arabia also showed that religion was an important factor that affected prenatal diagnosis decisions of Saudis.<sup>35</sup>

Pre-implantation Genetic Diagnosis (PGD) is a complex procedure that is less invasive and more expensive than prenatal diagnosis. PGD has been used by carrier couples of genetic disorders for more than 20 years.<sup>102</sup> It is an assisted reproductive technique that is used to identify, select and transfer unaffected embryos via in vitro fertilization (IVF); hence termination of affected pregnancies can be avoided.<sup>102</sup> Many carrier couples of monogenetic disorders such as  $\beta$  thalassaemia who are not comfortable with termination of pregnancy prefer PGD over prenatal diagnosis. For example, a study conducted by Alsulaiman and Hewison<sup>103</sup> in Saudi Arabia showed that most couples in their study who already had a thalassaemia major child were interested in PGD and six out of seven couples were interested and willing to use PGD to avoid affected pregnancies in the future.<sup>103</sup>

Based on literature, it can be seen that prenatal diagnosis programs had varying level of success in different communities. The success of the programs were affected by factors including lack of awareness, poor access to services, high cost,

level of education, timing and gestational age, advice against the procedure, culture, unwanted pregnancies, influence of significant others, moral and personal beliefs, perception of the severity of the condition and religious beliefs. Of all the factors, religion is the most debatable factor in most communities. Literature findings related to religion and its impact on prenatal diagnosis were mixed.

### **Secondary prevention in Maldives**

Maldives also felt the need to provide prenatal diagnosis services because screening alone was found not effective in controlling or preventing the number of new incidences of thalassaemia majors. Prenatal diagnosis was legalised in Maldives on the 1<sup>st</sup> of November, 1999 with the ruling of the religious scholars.<sup>43</sup> The Ministry of Health asked for a legal ruling from Supreme Council of Islamic Affairs of Maldives in 1998.<sup>43</sup> Hence, the Fatwa (a consensus edict)<sup>104</sup> that legalized prenatal diagnosis was first broadcast in 1999 and again on August 5<sup>th</sup>, 2012 from National radio.<sup>105</sup> The Fatwa of Supreme Council of Islamic Affairs of Maldives says that prenatal diagnosis and selective abortion is permissible (with conditions) if the foetus is found to be affected by thalassaemia or sickle cell anaemia.<sup>43</sup> The conditions are, disease condition has to be confirmed by a doctor accepted by the government, both parents should approve of it and abortion has to be carried out before the 120<sup>th</sup> day of the pregnancy.<sup>43</sup> The fatwa of Maldives was developed by evaluating the rulings of all four Sunni schools of Islam (Hanefi, Maleki, Shafe'i and Hanbali) and opinions of schools of Thahiri, Ibadhi, Zaidhe and Ah-Sheathul-Imaamiyya.<sup>43</sup> In addition, specific reference was made to the prenatal fatwa of Kuwait and Fatwa given by Sheikh Ali Jad-al Hag, the Grand Mufti of Egypt.<sup>43</sup>

Though termination of pregnancy is allowed under some schools of Islam, it still is one of the most controversial issues in Islamic Sharia. Under four main Sunni

schools, termination of pregnancy is decided based on ensoulment timing; either 40<sup>th</sup>, 90<sup>th</sup> or 120<sup>th</sup> day depending on the school of thought.<sup>106</sup> Hence, differences can be observed among Muslim countries regarding this issue. According to Husseni<sup>106</sup> 13 out of 21 predominantly Muslim Middle East and North African countries do not allow termination of pregnancy unless to save the life of the mother. Prenatal diagnosis is allowed in Maldives, but services are not yet available. At present, couples travel to neighbouring countries to access prenatal diagnosis services.

With the high carrier rate, it is estimated that 54 children would be born with beta thalassaemia syndromes each year in Maldives if prevention measure were not taken into account.<sup>14</sup> The prevention rates were recorded as 31% in 2008, 53% in 2009, 59% in 2010 and 41% in 2011.<sup>14</sup> Please refer to appendix 1 for details of number of new cases recorded between 2001 and 2010. Even though the prenatal diagnosis services are not available in Maldives, the records of SHE shows that approximately 40 Maldivian couples travel to India on an annual basis and on average eight pregnancies are terminated due to foetus being thalassaemia major.<sup>21</sup> The figure is based on prenatal diagnosis appointments sought from Vellore, India via SHE. In addition, it is well known in Maldives that many Maldivians make their trip without consultation to SHE. Therefore, it is fair to say that the average number of termination of pregnancy due to thalassaemia would be higher than eight in a single given year.

As identified in the literature, religion is one of the most controversial factors that influenced prenatal diagnosis decisions. Maldives being a 100% Sunni Muslim country, potential ethical conflicts with Islamic view on termination of pregnancy within the four Sunni schools might be the reasons why Maldivians do not demand service within the country though there is the need for it.

## **Tertiary Prevention: Treatment for Thalassaemia Majors**

### **Thalassaemia Treatment**

Thalassaemia majors are born when primary and secondary prevention efforts are either ineffective or not in place. In the South East Asia region, a total of 20,420 new  $\beta$ -thalassaemia births are recorded each year.<sup>15</sup> A total of 9,983 of those births are estimated as transfusion dependent and unfortunately, only 9.6% are able to start transfusion as required. As a result, 9,021 thalassaemia majors die due to inadequate transfusion in the South East Asia region on an annual basis.<sup>15</sup> Additionally even if many are able to start the transfusion on time, only 19% are estimated to be on adequate iron chelation therapy which is needed for regularly transfused patients and 1,444 deaths are recorded each year in South East Asia due to no, or inadequate, iron chelation therapy.<sup>15</sup>

The only permanent treatment for thalassaemia is Bone Marrow Transplant (BMT), which is extremely expensive and requires a compatible (HLA-identical) donor.<sup>107</sup> Even when BMT is done, it is important that it is done when the major patients are young and free of thalassaemia related complications such as iron overload and other infections such as hepatitis in order to minimise mortality and morbidity.<sup>108</sup> Gene therapy<sup>22,109</sup> is also a promising new treatment for genetic diseases like thalassaemia. However, due to the high cost of those treatments and other limitations, thalassaemia is normally treated by regular blood transfusion. Blood transfusions are normally done on a schedule of four week intervals<sup>22</sup>, sometimes more frequently. It is recommended Hb level of 9g/dl be maintained in thalassaemia management.<sup>110</sup> This method of treatment is time consuming, expensive and often risky due to transmission of infections.<sup>22</sup> Additionally, it leads

to excess iron in the blood, which can damage liver, heart, pancreas and other endocrine organs.<sup>22</sup>

Iron chelation therapy is used to remove excess iron from the body of thalassaemia majors.<sup>22</sup> Conventional iron chelation therapy *Deferoxamine* requires subcutaneous infusion, five to seven nights a week on an 8 -12 hourly basis.<sup>111</sup> With the new pharmacological developments, oral chelators have been developed and have been in use for some time now. The most common oral chelators for iron overload include *Deferiprone* and *Deferasirox*.<sup>111</sup> Like many other lifelong treatments, side effects of iron chelation are common and the treatment requires commitment and compliance with monitoring.<sup>22</sup> According to the Thalassaemia International Federation (TIF), poor adherence to treatment leads to poor growth, facial and other deformities, fragile bones and bone fractures, enlarged liver and spleen and impairment of normal physical activities.<sup>112</sup> Other issues such as physical deformity and growth retardation are also common among thalassaemia patients.<sup>113</sup> In addition, many thalassaemia majors face sexual growth complications such as delayed puberty, arrested puberty and hypogonadism.<sup>114</sup>

In addition, thalassaemia majors have compromised immune systems in many cases.<sup>115</sup> The cause of the immune abnormality is not very well understood, but it is thought that repeated blood transfusion, iron overload, zinc deficiency, presence of abnormal erythrocytes and splenectomy in some thalassaemia patients are some of the many factors that contribute to the abnormality of the immune system.<sup>115</sup> In addition to immune abnormalities, thalassaemia majors are also prone to iron overload and bacterial infections.<sup>115</sup> More worryingly, due to the repeated transfusions, thalassaemia majors are prone to more serious viral infections such as hepatitis C and B.<sup>115</sup>

### **Health Related Quality of Life of Thalassaemia Majors**

Due to the time, cost, and the subsequent complications and side effects, many believe that transfusion and iron chelation therapy is not enough in thalassaemia treatment. Rather, a more holist approach that includes consideration of quality of life of the patients should be implemented. Quality of life is defined as “individual’s perceptions of their position in life in the context of the culture and value system where they live, and in relation to their goals, expectations, standards and concerns”.<sup>116(p17)</sup> In fact, some argue that quality of life should be considered as one of the indexes that determine the effectiveness of the treatment for thalassaemia.<sup>117</sup> Additionally, some suggest that all thalassaemia patients should undergo quality of life assessments, so that treatment can be made more effective by implementing interventions that focus on affected or poor quality of life domains.<sup>118</sup>

Quality of life is based on both subjective and objective measures and they are divided into four different domains.<sup>119</sup> Subjective concepts used in measuring quality of life in health include concepts such as life satisfaction, moods and emotions, pleasant or unpleasant.<sup>119</sup> Objective measures include objective living conditions such as income, housing, neighbourhood quality and other indicators similar to health.<sup>119</sup>

Improving the Health Related Quality of Life (HRQoL) is the main purpose of any tertiary prevention intervention including in thalassaemia. Thus, it is a well researched area in many thalassaemia endemic countries. Most research is undertaken using either Paediatric Quality of Life Inventory for younger age major children and Short Form SF-36 survey for older children and adults.

### ***HRQoL based on Paediatric Quality of Life Inventory***

Research shows that many aspects of HRQoL are much lower for thalassaemia majors compared to the normal population. For example, research done



in Jordan showed that thalassaemia major children in that country had lower HRQoL in all dimensions (Physical Functioning, Emotional Functioning, Social Functioning and School Functioning) in comparison to their non-affected counterparts.<sup>120</sup> The study was conducted using Paediatric Quality of Life Inventory and 128 thalassaemia majors and 83 healthy Jordanian children took part.<sup>120</sup> The scores of thalassaemia majors were much lower in all domains and as a result, a major difference was observed in the total score as well. The mean total scores obtained in that study were 59.15 for thalassaemia majors and 80.73 for normal children with a total difference of 21.22.<sup>120</sup> Research findings on Malaysian thalassaemia majors were similar. One study conducted by Ismail, Campbell, Ibrahim and Jones<sup>121</sup> using Paediatric Quality of Life Inventory showed that Malaysian thalassaemia majors had significantly lower HRQoL in three dimensions (Physical Functioning, Social Functioning and School Functioning) compared to their healthy counterparts. Ismail and her colleagues recruited 78 thalassaemia majors and 235 normal children for their control group.<sup>121</sup> A study conducted in Thailand also showed that children with thalassaemia scored poorly ( $67.89 \pm 15.92$ ) on school functioning subscale of Paediatric Quality of Life Inventory.<sup>122</sup> The Thailand study included 315 thalassaemia majors with a mean age of 10 years.<sup>122</sup> Studies in the UK also showed compromised HRQoL among thalassaemia majors.<sup>76</sup> A study conducted by Clarke, Skinner, Guest, Darbyshire, Cooper, Shah<sup>76</sup> to determine the HRQoL of thalassaemia majors in the UK and impact of caring for them showed that thalassaemia majors had poor HRQoL scores in all dimensions of Paediatric Quality of Life Inventory compared to the population norms.<sup>76</sup> The HRQoL scores of UK thalassaemia majors in that study were physical functioning, 66.52; emotional functioning, 73.54; social functioning, 77.60; school functioning, 60.86; and

psychosocial health summary, 68.33. The total HRQoL score achieved in that study was 69.06. Research undertaken in Italy also showed that both physical and mental health components were worse off for thalassaemia patients compared to the general norms.<sup>123</sup> A broad study conducted by Caocci, Efficace, Ciotti, Roncarolo, Vacca, Piras<sup>124</sup> that examined the HRQoL of thalassaemia majors aged 5-17 years in a mix of Middle Eastern countries (Kurdistan, Palestine, Libya, Iran and Syria) also showed compromised HRQoL in some domains. The study scores in that study were physical functioning, 75; emotional functioning, 85; social functioning, 82.50; school functioning, 75; and psychosocial health summary, 79.15.<sup>124</sup> The mean total HRQoL score for the Middle Eastern children in that study was 77.75.<sup>124</sup>

#### *HRQoL based on SF-36 survey form*

Literature shows similar results for older thalassaemia majors as well. The HRQoL of older thalassaemia majors are mostly measured using SF-36 survey form. The SF-36 scores are based on a scale of zero to 100; zero being the lowest or worst possible and 100 being the highest or best score possible. The domains of the form are Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). Study findings in Athens, Greece showed that thalassaemia majors' HRQoL measured using Short Form-36 (SF-36) was significantly lower compared to patients with short-term injury in Athens.<sup>113</sup> According to Yengil, Acipayam, Kokacya, Kurhan, Oktay and Ozer<sup>125</sup>, thalassaemia majors in Turkey also experienced compromised HRQoL in most domains. The four worst domain scores of their study were RE (41.3), GH (50.12), RP (52.8) and VT (55.5).<sup>125</sup> Three different studies conducted in Iran also showed that thalassaemia majors' HRQoL were not at the excellent state.<sup>126-128</sup> Most domain scores of the three studies were in the range of 65 and 52. A broad study that included participants from Australia,

Belgium, France, Germany, Greece, Italy, Netherlands and the UK also showed that thalassaemia majors in those countries have compromised HRQoL.<sup>129</sup> The results obtained by Porter, Bowden, Economou, Troncy, Ganser, Habr<sup>129</sup> from those eight countries were generally suboptimal and extremely poor for GH (51.31) and VT (59.53). The research findings on Malaysian thalassaemia majors obtained by Ismail and Campbell<sup>130</sup> were also more or less similar. Their study results showed that GH score for Malaysians was 51.9 and VT score was 58.6.

### *HRQoL after BMT*

The only effective treatment for  $\beta$ -thalassaemia majors is hematopoietic stem cell transplantation (HSCT) or more commonly called BMT. There are some studies that evaluated the HRQoL of thalassaemia majors after HSCT. Successful HSCT can eliminate the need for ongoing blood and its adverse effects of iron overload.<sup>131</sup> However, the issues such as retarded growth, cardiovascular problems and liver disease might still occur or continue even after HSCT.<sup>131</sup> Additionally, the clinical complications or adverse effect of the procedure might require repeated hospital admissions.<sup>131</sup> Furthermore, the procedure can be stressful and patients might be faced with psychological problems as well. Hence, HRQoL might not reach to the similar levels as to that of the normal population. There are a few studies that had looked into the HRQoL of thalassaemia majors of those who had undergone HSCT. One such study was conducted by La Nasa, Caocci, Efficace, Dessì, Vacca, Piras<sup>131</sup> in Sardinia. Their study looked into the long term (after 20 years) HRQoL of thalassaemia majors who undertook HSCT in Sardinia.<sup>131</sup> The study recruited 130 patients and results were compared with matched peers from Italian population.<sup>131</sup> The generic HRQoL was measured using SF-36 survey form.<sup>131</sup> The results showed

that only GH domain had a significant difference between the normal and HSCT patients.<sup>131</sup>

### **Factors that Affect HRQoL of Thalassaemia Majors**

Several aspects are explored when measuring the HRQoL of populations. In general, most researches look at physical functioning, emotional wellbeing, social functioning, pain, vitality, role limitation and school functioning in the case of school age population. Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH) are normally observed in the case of older population. When research shows poor performance in overall or in any specific quality of life domains, predictors or associated factors are also explored in many cases.

Many factors are associated with HRQoL of thalassaemia majors. One such factor in the literature is age of start of transfusion. Univariate and multivariate analysis conducted by Caocci, Efficace, Ciotti, Roncarolo, Vacca, Piras<sup>124</sup> showed that delay in the start of iron chelation study had a significant ( $p = 0.046$ ) negative impact on total HRQoL scores in their study that examined HRQoL of Middle Eastern children.

The distance that had to be travelled to access the services was identified as an important factor that has an association with HRQoL of thalassaemia majors in the UK. Study findings based on mothers shows that HRQoL scores were lower for emotional, physical and social functioning scores for children who had to travel more than 30 miles for treatment in the UK compared to those majors who live closer to the service centres.<sup>76</sup>

Thalassaemia treatment is costly in most countries even if the transfusion and iron treatment is freely available. A cross-sectional study conducted in Kolkata,

India revealed that on average, 18.5% of the annual income of the families of thalassaemia majors were spent on their treatment.<sup>132</sup> Financial burden is also shown to have a major impact on the quality of life of thalassaemia majors. Study findings in the UK showed that parents who experienced financial concerns also reported lower total mean HRQoL scores for their major children.<sup>76</sup> Similar findings were reported by other researchers in other countries. For example, a study conducted in Jeddah, Saudi Arabia showed that PF of thalassaemia majors in Jeddah were significantly lower ( $p=0.049$ ) for those who were from lower income families.<sup>133</sup> Study findings in Iran also conformed to the inverse association between financial capability and HRQoL of thalassaemia majors. Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi and Parand<sup>126</sup> reported that lower income was negatively correlated to physical and mental health scores of thalassaemia majors in their Iranian study while Safizadeh, Farahmandinia, Soltani nejad, Pourdamghan and Araste<sup>128</sup> reported that high income had a positive association with HRQoL scores of thalassaemia majors in Kerman, Iran. Research conducted by Ismail, Campbell, Ibrahim and Jones<sup>121</sup> in Kuala Lumpur, Malaysia also showed that household income of the thalassaemia majors was a significant predictor of some of the HRQoL functions (PF, SF and school functioning) of Malaysian thalassaemia majors based on PedsQL 4.0 generic Scale.

The presence of depression has also shown to impact the HRQoL of thalassaemia majors in some studies. For example, a study conducted in Greece by Mikelli and Tsiantis<sup>113</sup> showed that thalassaemia majors in Greece had a higher level of depression measured by the Beck Depression Inventory and a lower level HRQOL measured using the SF- 36 survey when compared to the normal population who did not have any chronic condition. The mean depression scores of that study

were 5.78 (SD 6.93) for thalassaemia majors and 2.50 (SD 4.51) for the control group.<sup>113</sup> The mean total quality of life scores were 638.2 (SD 119.6) for thalassaemia majors and 683.3 (SD 93.6) for normal population.<sup>113</sup> The depression score of thalassaemia major patients in that study had a significant correlation ( $p = 0.01$ ,  $r = 0.6121$ ) with their quality of life scores.<sup>113</sup>

Gender is also an important factor in HRQoL of thalassaemia majors. Findings in Greece shows that female thalassaemia majors had better quality of life when compared to males.<sup>113</sup> Similar findings were reported by Ansari, Baghersalimi, Azarkeivan, Nojomi and Hassanzadeh Rad<sup>134</sup> in Iran. Their study also showed that female Iranian thalassaemia majors had a better HRQoL based on WHOQOL- BREF questionnaire compared to Iranian males.<sup>134</sup> Gender was also a significant predictor of all HRQoL functions except for emotional functioning for Malaysian thalassaemia majors in Kuala Lumpur, Malaysia.<sup>121</sup> The research findings based on thalassaemia majors in Jedda, Saudi Arabia also showed that gender had a significant association with EW function of HRQoL based on SF-36 survey.<sup>135</sup>

However, gender and its association with HRQoL functions is a controversial issue in the literature. There are studies that show that gender does not have any significant association with HRQoL functions. For example, the study conducted by Caocci, Efficace, Ciotti, Roncarolo, Vacca, Piras<sup>124</sup> found no significant association between gender and any of the HRQoL functions of Pediatric Quality of Life Inventory in Middle Eastern children from Kurdistan, Palestine, Libya, Iraq and Syria. Another major study conducted by Trachtenberg, Gerstenberger, Xu, Mednick, Sobota, Ware<sup>136</sup> that included participants from the UK, USA and Canada also showed no significant association between gender and HRQoL domains of SF-36. Similar findings were also observed by Gharaibeh and Gharaibeh<sup>120</sup> in Jordan

and Thavorncharoensap, Torcharus, Nuchprayoon, Riewpaiboon, Indaratna and Ubol<sup>122</sup> in Thailand.

Age is an important factor in thalassaemia majors and their HRQoL research. For example, a longitudinal cohort study that included participants from the UK, the USA and Canada showed a significant negative association between increased age and HRQoL functions of PF, BP, VT and MH or EW.<sup>136</sup> The study by Ismail, Campbell, Ibrahim and Jones<sup>121</sup> in Kuala Lumpur Malaysia also showed that age was a significant predictor of some of HRQoL functions such as physical functioning of school aged thalassaemia majors. However, it has to be noted that differential findings were reported for age in some studies. The two studies conducted by Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi, Parand<sup>126</sup> and Safizadeh, Farahmandinia, Soltani nejad, Pourdamghan and Araste<sup>128</sup> in Iran showed no association between HRQoL domains and age. The study findings of Gharaibeh and Gharaibeh<sup>120</sup> in Jordan also did not show any association with age and HRQoL.

Education level is reported to have a positive association with the HRQoL of thalassaemia majors in some studies. For example, Ayoub, Radi, Azab, Abulaban, Balkhoyor, Bedair<sup>133</sup> reported that SF scores were significantly higher for school educated thalassaemia majors in Saudi Arabia. Two different study findings in Iran also showed that thalassaemia majors with higher levels of education had better HRQoL scores, showing a significant positive correlation between higher education and HRQoL functions.<sup>126,134</sup>

Presence of other medical conditions or co-morbidities is a common issue among thalassaemia majors. For example, findings from a retrospective cohort study conducted in Hamadan province in Iran by Zamani, Khazaei and Rezaeian<sup>137</sup>

showed that 26.3% of the thalassaemia majors had other disease related complications from diseases such as diabetes, heart disease and hepatitis C.<sup>137</sup> Having other co-morbidities is shown to have a significant negative association with HRQoL of thalassaemia majors in many studies. For example, studies undertaken by Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi, Parand<sup>126</sup> in Iran, Trachtenberg, Gerstenberger, Xu, Mednick, Sobota, Ware<sup>136</sup> in the USA, UK and Canada, Gharaibeh and Gharaibeh<sup>120</sup> in Jordan, Boonchooduang, Louthrenoo, Choeypasert and Charoenkwan<sup>138</sup> in Thailand, Salama, Hussein, Al Faisal, Belhool, Hasan Mahdy, El Sawaf<sup>139</sup> in Dubai, UAE and Ansari, Baghersalimi, Azarkeivan, Nojomi and Hassanzadeh Rad<sup>134</sup> in Tehran, Iran showed negative associations between co-morbidities and HRQoL.

Iron chelation therapy is an important part of thalassaemia treatment for majors. Two main types of chelation are subcutaneous and oral chelation. Literature shows that iron chelation therapy plays a vital role in the HRQoL of thalassaemia majors. According to Payne, Rofail, Baladi, Viala, Abetz, Desrosiers<sup>140</sup>, iron treatment had a negative impact on HRQoL scores of transfusion dependent thalassaemia, sickle cell and myelodysplastic syndromes patients in the UK. Similar association between the two aspects was also reported by Payne, Desrosiers, Caro, Baladi, Lordan and Proskorovsky<sup>141</sup> in the USA. More specifically, type of iron treatment; subcutaneous or oral iron chelation therapy was shown to have a major impact on HRQoL of thalassaemia majors. A study that included participants from Australia, Belgium, France, Germany, Greece, Italy, the Netherlands, and the UK showed that treatment with oral chelator deferasirox improved mean HRQoL scores of  $\beta$ -thalassaemia majors participants in all categories of HRQoL in their study.<sup>129</sup> Studies conducted by Ansari, Baghersalimi, Azarkeivan, Nojomi and Hassanzadeh



Rad <sup>134</sup> and Safizadeh, Farahmandinia, Soltani nejad, Pourdamghan and Araste <sup>128</sup> also showed that use of oral chelators had a positive impact on HRQoL domains of Iranian patients. A broad study based on participants from Australia, Belgium, France, Germany, Greece, Italy, the Netherlands, and the UK also showed that oral iron chelation therapy Deferasirox (Exjade) had a positive impact on HRQoL of transfusion dependent patients in those countries.<sup>129</sup>

Compliance to treatment is also an important predictor of HRQoL of thalassaemia majors as it is important for enabling them to stay healthy. According to the findings of Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi and Parand <sup>126</sup>, poor compliance to iron chelation had an inverse correlation with physical health dimensions among thalassaemia majors in Iran. Similar findings were reported by Dahlui, Hishamshah, Rahman and Aljunid <sup>117</sup> in a cross-sectional study conducted in two tertiary hospitals in Kuala Lumpur, Malaysia. Their results revealed that PF scores were significantly higher ( $p = 0.018$ ) for thalassaemia majors who used optimal dosages of desferioxamine iron medication compared to those who used suboptimal dosages of the treatment. However, compliance to iron chelation can be time consuming and painful at times if taken subcutaneously. There are some studies that show a negative association between compliance to chelation and some domains of HRQoL such as SF. One such study was conducted by Trachtenberg, Gerstenberger, Xu, Mednick, Sobota and Ware<sup>136</sup> that included thalassaemia patients from the UK, USA and Canada. Their study showed a decrease in SF and RE scores when an increase was recorded for adherence to chelation therapy.

One last, but an important factor that was frequently explored by researchers was serum ferritin level of thalassaemia majors and its association with HRQoL. A cross-sectional study conducted in Thailand by Boonchooduang, Louthrenoo,

Choeypasert and Charoenkwan<sup>142</sup> showed that high serum ferritin levels had a negative association with total HRQoL of thalassaemia majors in that country.<sup>138</sup> Another study in Iran also showed that lower ferritin level was positively associated with better quality of life scores.<sup>134</sup> Similar findings were reported from a study conducted in Dubai, UAE.<sup>139</sup> However, differential findings were also reported in the literature in regard to serum ferritin level and HRQoL scores. For example, a study that included participants from Kurdistan, Palestine, Libya, Iraq and Syria showed no significant difference in HRQoL when participants were categorised according to ferritin levels.<sup>124</sup>

Another important factor that shows association with HRQoL of thalassaemia majors is the diagnosis. A study that looked into the HRQoL of thalassaemia majors in Dubai, UAE showed that total quality of life was better for thalassaemia intermediates compared to thalassaemia majors in that country.<sup>139</sup> However, differential findings were reported by Pakbaz, Treadwell, Yamashita, Quirolo, Foote, Quill<sup>118</sup> in a study conducted in Oakland, California. Their findings showed that thalassaemia Intermediates suffer from serious impairment in quality of life.

Literature shows many factors that affect HRQoL of thalassaemia majors. Some of the most researched factors include age of transfusion, gender, age, presence of emotional disorders such as depression, educational level, financial cost of the treatment and caring, access (travel) to treatment, presence of other co-morbidities, type of chelation therapy, compliance to chelation therapy, serum ferritin level and diagnosis.

### **Tertiary Prevention in Maldives**

Despite efforts, most countries with thalassaemia trait including Maldives still see children born with the condition. At the end of August 2014, 803

thalassaemia major patients were registered in the National Thalassaemia Centre of Maldives.<sup>14</sup> The records of 2014 shows that 563 (approximately 1.6/1000) patients were living.<sup>14</sup> Of those, 459 were  $\beta$ -thalassaemia majors and 88 (six thalassaemia intermedias and 82 HbE/beta thalassaemia) were non-transfusion dependent cases.<sup>14</sup> In addition, there were 10 HbS cases, one HbS/HbD case, three HbH cases and two cases of haemolytic anaemia.<sup>14</sup> Of the total living, 288 were living in the capital and taking treatment from MBS.<sup>14</sup> In addition, many patients travel to Male' on a regular basis for their treatment and the rest of the patients take treatment from the Regional Hospitals, Atoll Hospitals or Island Health Centres.<sup>14</sup> Furthermore, many patients travel to Male' for necessary medical checkups and tests such as serum ferritin test. The annual cost of treating a thalassaemia child in Maldives is approximately US \$6,000/patient; which is free for all thalassaemia patients in Maldives by law.<sup>44</sup> This amount is incompatible with countries that provide optimal care for thalassaemia majors. According to TIF, it would cost approximately \$40,000 per year to provide optimal care for a thalassaemia major patient.<sup>14</sup>

The thalassaemia treatment services in Maldives are suboptimal. According to TIF, the services in Maldives include haematological diagnosis which is done before start of transfusion.<sup>14</sup> Some of the important procedures such as Leukodepleted blood is done but red cell antigen typing is not done in Maldives.<sup>14</sup> Cross matching is the regular protocol but, screening for antibodies is not done.<sup>14</sup> Additionally, thalassaemia majors and their parents find it difficult to keep a Hb level of 9-10 g/dl due to unavailability of blood on time.<sup>14</sup> Magnetic resonance imaging (MRI) scan and biopsy services are important procedures used to evaluate the liver iron concentration of thalassaemia majors but it is not available for majors in Maldives.<sup>14</sup> Chelation medications (Desferrioxamine, Deferiprone and

Deferasirox) are available in Maldives for free.<sup>14</sup> However, many from atolls have to travel long distances to access the medication.

As it can be seen that treatment (tertiary prevention intervention) is suboptimal in Maldives, and it will definitely impact the quality of life of thalassaemia majors. TIF strongly recommends Maldives to take a holistic approach for treatment and to look into the HRQoL of thalassaemia majors to improve the outcome of the treatment. However, no literature is available on the HRQoL of Maldivian thalassaemia majors. The little data available shows that a number of premature deaths are recorded each year due to thalassaemia. For example, the records of the Ministry of Health show that nine premature deaths occurred in 2002, three in 2004, six in 2006, eight in 2008, five in 2010 and six in 2012.<sup>78</sup> Please refer to Appendix 3 for more details.

## Chapter 3: Methodology

### Introduction to the chapter

This chapter describes the research methodology employed for this study.

This study examined primary, secondary and tertiary thalassaemia prevention interventions in Maldives. Primary and secondary prevention efforts were examined using a qualitative approach. Examination of the tertiary prevention intervention required a quantitative approach and the methodology for that part is described separately from the first and second study.

The research direction of this study was based on Leavell and Clark's prevention model. The primary prevention intervention required examining two aspects of the prevention program. Hence, study one was again divided in to two parts and referred to as study 1a and 1b. Study 1a examined the reasons why Maldivians marry without screening for thalassaemia. Study 1b examined the reasons for Maldivians marrying and having children without any precaution in spite of knowing their carrier status. Examination of secondary prevention (Study 2) explored the experiences of Maldivians who undertook prenatal diagnosis for thalassaemia. Study 3 examined tertiary prevention aspect of HRQoL of thalassaemia majors in Maldives.

The qualitative methodology is explained in terms of study approach and methods. The methods section includes sampling and participant selection, data collection, data analysis and rigour. The quantitative approach is described in terms of research design, instrument used, participants and sampling and data analysis. The final part of this chapter describes the ethical aspects of the study.

## Methodology

### Research Direction

Genetic diseases manifestation, thalassaemia takes place at different levels. Each level is unique and effective prevention requires distinctive approaches appropriate for each level. Disease prevention experts such as Leveall recommended studying each level of disease manifestation and states that, “without such study in the community as a whole, we can have only an incomplete picture of the course a disease follows, and of the various manifestations it may have from the mildest type of disorder on the one hand, to death on the other.”<sup>45p.490</sup> Therefore, prevention models that look into all levels of disease manifestation are important. One such model is the “Disease prevention model”, which was first initiated by Leavell and it was later adapted and referred to as population prevention model in epidemiology and preventive medicine. The five levels of Leavell’s first prevention model included health promotion, specific protection, early diagnosis, limit disability and rehabilitation.<sup>45</sup> The model was later adapted to a four level model that included primordial, primary, secondary and tertiary level preventions.<sup>143</sup> Later still, the same model was adapted to a three level model referred to as Leavell and Clark’s prevention model. The three level prevention model targets primary, secondary and tertiary level interventions.

Primary prevention interventions target the total population or a selected group with a specific causal factor with the aim of reducing or preventing the occurrence of disease by actions such as immunization and genetic screening.<sup>143</sup> At this level, the number of new cases are minimised by reducing the risk of exposure.<sup>144</sup> Secondary interventions are planned to reduce prevalence by targeting individuals with a certain disease or a condition at early stage with actions such as early detection and prompt intervention.<sup>143</sup> Interventions at this level are aimed at

limiting disease progression by early detection and offering appropriate treatment and prognosis.<sup>144</sup> Tertiary interventions are planned to reduce mortality and morbidity by rehabilitation and treatment of patients with the condition or disease and maximise potential years of useful life.<sup>143</sup> They are aimed at slowing down the progression of the disease and preventing further damage and improve quality of life.<sup>144</sup>

Most successful thalassaemia prevention programs such as in Cyprus<sup>36</sup>, Sardinia<sup>24</sup> and Iran<sup>39</sup> have three levels of prevention interventions as described in Leavell and Clark's disease prevention model. The three levels are health education, screening and counselling (primary interventions), prenatal diagnosis (secondary intervention) and treatment (tertiary intervention). As noted in Chapter 1, the aim of my research was to explore and evaluate the effectiveness of thalassaemia prevention interventions in Maldives. Therefore, I followed the three levels of population prevention model to attain a holist picture of thalassaemia prevention interventions in Maldives through an examination of each level separately; three sub studies, each targeting a different intervention level were conducted to examine the whole program as in Figure 3.1.

As noted previously in Chapter 1, the objectives of the first study (primary prevention intervention) were to;

- (1) Explore the reasons for couples marrying without premarital testing for thalassaemia in Maldives; and
- (2) Explore the reasons why carriers of thalassaemia in Maldives marry and have children despite knowing their carrier status.

The objectives of the second study (secondary prevention intervention) were to;

- (3) Explore the reasons that motivate at risk Maldivian couples to go

through prenatal screening and diagnosis for thalassaemia.

- (4) Explore the barriers and facilitators that are faced by Maldivian couples who go through prenatal screening and diagnosis for thalassaemia.
- (5) Explore the potential ethical conflicts with an Islamic view of prenatal diagnosis and selective termination of pregnancy for thalassaemia in Maldives.

The objects of the third study (tertiary prevention intervention) were to;

- (6) Evaluate the Health Related Quality of Life of transfusion-dependent thalassaemia patients who are 14 years and above in Maldives.
- (7) Determine the predictors of Health Related Quality of Life of transfusion-dependent thalassaemia patients who are 14 years and above in Maldives.

This chapter is divided into two sections. Part one (studies 1a, 1b and 2) describes the qualitative approach used to explore the primary and secondary prevention interventions. Part two (study 3) describes the quantitative procedures used to evaluate the tertiary prevention intervention.

### **Study1a, 1b and 2: primary and secondary prevention**

#### **Study Approach**

Qualitative research studies are shaped by historical location, disciplinary orientation and philosophical perspective of the researcher.<sup>145</sup> Qualitative research examines how people interpret their experience, construct their worlds and elucidate the implications of their experiences.<sup>146</sup> As such, it is a common view that qualitative research studies seek to understand a certain phenomenon from the perspectives of the person or group of people who are experiencing it.<sup>147</sup> This study was the first of its kind in Maldives. Views and perspectives related to thalassaemia carriers who are



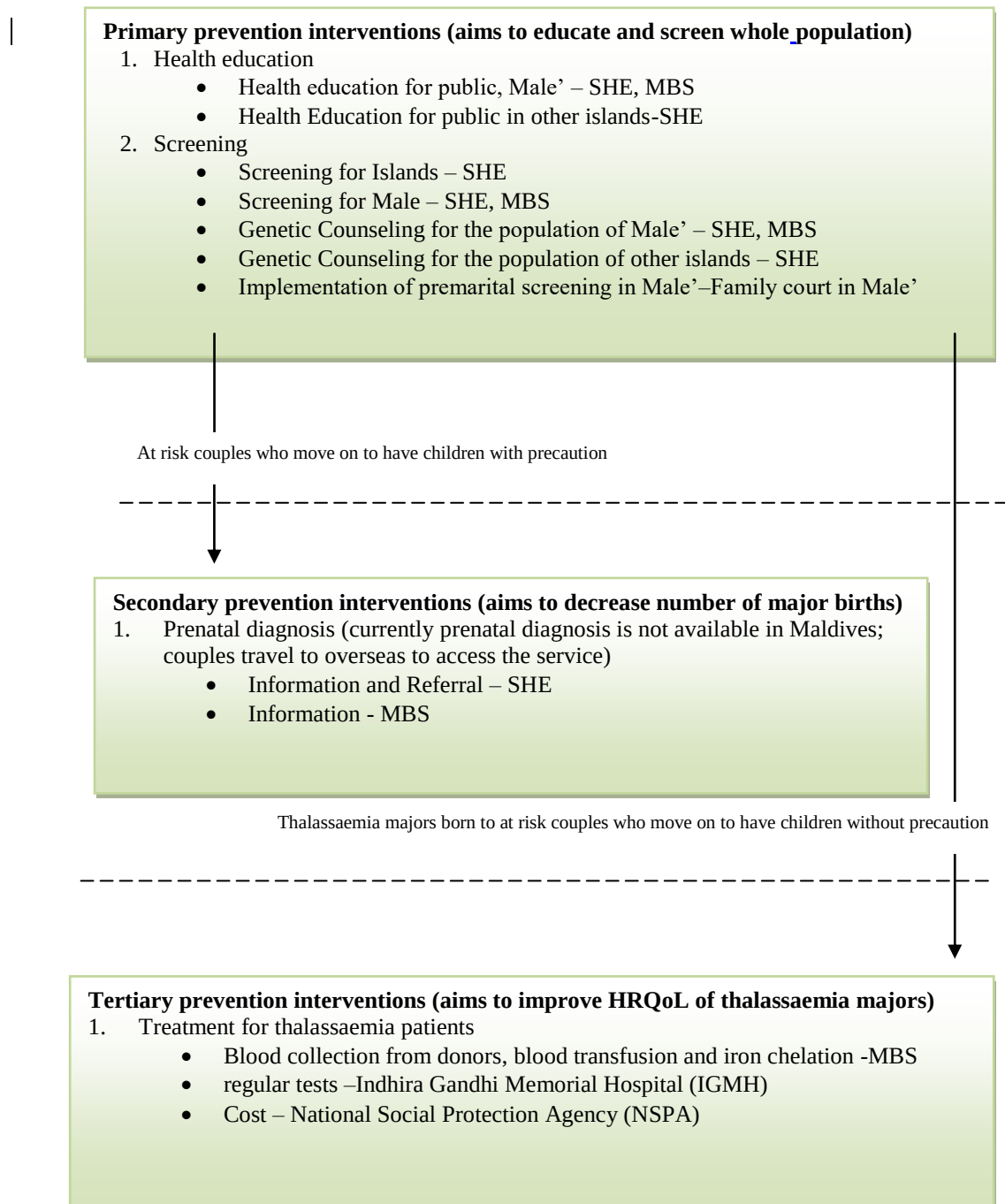
aware/unaware of their carrier status have not previously been researched in the Maldivian context. As in-depth understanding was seen to be important for this field, a qualitative approach was most appropriate for studies one and two.

Many qualitative approaches use similar methods, procedures and techniques at epistemological, aesthetic, ethical and procedural levels.<sup>147</sup> As a result of that overlap between approaches, many encourage a ‘generic’ approach to qualitative research.<sup>147</sup> Due to lack of prior research, and the exploratory nature of researching the issue in a Maldivian context, a flexible qualitative approach was needed for the studies. Hence, a ‘generic’ qualitative approach’ which would provide an emic understanding of the issue <sup>148,149</sup>, and underpinned by a constructivist ontological and epistemological stance was utilized for sub studies 1a, 1b and 2.<sup>149</sup> The objectives 1-5 (described above) were addressed using this generic qualitative approach.

Qualitative research approaches use different paradigms depending on the purpose of the research. Guba and Lincoln <sup>150p.233</sup> describe paradigms as, “axiomatic systems characterized essentially by their differing sets of assumptions about the phenomena into which they are designed to inquire”. A constructivist paradigm assumes multiple realities subjective to individuals or groups. Packer and Goicoechea <sup>151</sup> described ontology as, “consideration of being: what is, what exists, what it means for something-or somebody-to be” <sup>151p.227</sup> and epistemology as “systematic consideration, in philosophy and elsewhere, of knowing: when knowledge is valid, what counts as truth, and so on.” <sup>151p.227</sup> More briefly, Merriam<sup>146</sup> explained ontology as the nature of reality while epistemology as the nature of knowledge. As there was no previous research addressing thalassaemia prevention in the context of Maldives, I required a flexible, but scholarly and

rigorous way of exploring and understanding the experiences of thalassaemia carriers. Therefore, this study was underpinned by a constructivist paradigm with a relativist ontology and transactional and subjectivist epistemology.

**Figure 3.1: Thalassaemia prevention levels and interventions in Maldives**



## Methods

### *Sampling and Participants*

According to Merriam<sup>146</sup>, probabilistic sampling is not justifiable in qualitative studies as statistical generalization is not the purpose of qualitative inquiries. She suggests that sampling methods such as purposive sampling is logical as long as the main target of the study is not to answer questions such as total or frequency, but rather to explore what occurs, implications of occurrences and relationships that links occurrences<sup>146</sup> and in such instances non-probabilistic sampling such as purposive sampling would be most appropriate.<sup>146</sup> My purpose at primary and secondary prevention levels was to explore the experiences of thalassaemia carriers with different circumstances and experiences in Maldives. Hence, purposive sampling<sup>146</sup> was used to select participants who could provide detailed, rich and nuanced information for each area.

According to Bowen<sup>152</sup> an appropriate sample should be a group who could best represent or have the knowledge of the issue on hand. Hence, my target was to recruit at least 20 (10 males and 10 females) participants for each study. Three aspects (objectives 1-5) of this study required participants with three different types of experiences. Maldives does not have a register of parents of children affected by severe thalassaemia. Therefore, the best method to access participants was to visit the main transfusion centre of the Maldives (MBS) to ascertain if parents were interested in participating. Hence, I visited MBS on several occasions and personally approached the parents of thalassaemia major children during the transfusion of their children. Only biological parents were invited to participate in the study. Most thalassaemia majors were accompanied by their parents during their transfusion, irrespective of child's age. During my interactions with parents, contact details of those who showed interest in participating in the study were recorded – their names,

phone numbers and addresses. At that stage, special care was taken to ensure that I recorded the names according to the inclusion criteria for each study (please see below) to ensure that potential participants were not offended by a situation such as inviting participants into the study examining prenatal diagnosis if this procedure had not been undertaken. Later, participants were contacted by phone to cross-check against inclusion criteria and to select informants for each group in the studies. Special care was taken during those interactions to ensure participation from all possible atolls of Maldives to ensure maximum variation.

The main study commenced in February 2013; however, interviews were purposely postponed until April 2013 (school study-break). This allowed access to participants during school break and was a time period when many parents from the islands visited the MBS to consult the doctors and do regular three monthly or six monthly ferritin tests for their thalassaemia-affected children. Through this delay, there was an opportunity to meet many visitors from atolls who normally do their transfusions at island/atoll level health centres and thus, potentially could be included in this study.

#### *Study 1a: participants who did not test for thalassaemia*

To be included in this part of the study, participants were required to be Maldivians who married without knowing their thalassaemia carrier status and have had a thalassaemia major child or children after the year 1992: thalassaemia screening was introduced in Maldives in 1992. The final sample of 16 individuals and three couples comprised of 14 women and 8 men from 13 different atolls. Please see Table 3.1 for a full description of the final sample.

**Table 3.1: General characteristics of participants who did not test prior to marriage**

| No | Gender | Age (years) | Atoll      | Marital status | No of major children | Education    | Employment | related to partner | Testing centre |
|----|--------|-------------|------------|----------------|----------------------|--------------|------------|--------------------|----------------|
| 1  | Female | 37          | G.Dh.      | Married        | 1                    | Grade 5      | No         | No                 | NTC            |
| 2  | Female | 42          | Ha. Alif   | Married        | 2                    | Grade 7      | self       | No                 | SHE            |
| 3  | Female | 37          | Noon       | Married        | 1                    | Grade 5      | Yes        | distant            | NTC            |
| 4  | Female | 30          | Sh.        | Married        | 1                    | Grade 7      | No         | distant            | SHE            |
| 5  | Male   | 41          | Ha.Dhaa I  | Married        | 1                    | Grade 9      | yes        | No                 | NTC            |
| 6  | Male   | 40          | Sh.        | Married        | 1                    | Grade 7      | yes        | distant            | SHE            |
| 7  | Male   | 48          | Male'      | Married        | 2                    | General      | yes        | No                 | Did not test   |
| 8  | Female | 39          | Male'      | Married        | 3                    | O'Level      | No         | No                 | NTC            |
| 9  | Female | 37          | Alif. Alif | Divorced       | 2                    | O' Level     | Self       | second cousins     | NTC            |
| 10 | Female | 48          | Seenu.     | Married        | 1                    | Gr. 7        | No         | distant            | SHE            |
| 11 | Male   | 42          | Tha.       | Divorced       | 2                    | Missing      | yes        | No                 | SHE            |
| 12 | Female | 42          | Kaaf.      | Married        | 1                    | General      | No         | No                 | NTC            |
| 13 | Male   | 45          | Kaaf.      | Married        | 1                    | Gr. 7        | Yes        | No                 | NTC            |
| 14 | Female | 35          | H.Dh.      | Divorced       | 1                    | Gr. 8        | Yes        | No                 | NTC            |
| 15 | Female | 35          | Male'      | Married        | 1                    | Gr. 9        | No         | No                 | NTC            |
| 16 | Female | 40          | H.Dh.      | Widowed        | 1                    | General      | self       | No                 | NTC            |
| 17 | Female | 36          | H. Alif    | Married        | 2                    | Gr. 7        | self       | No                 | Did not test   |
| 18 | Male   | 41          | H. Alif    | Married        | 2                    | Gr. 7        | self       | No                 | Did not test   |
| 19 | Male   | 53          | Faaf       | Married        | 1                    | General      | self       | distant            | Did not test   |
| 20 | Female | 30          | Kaaf       | Divorced       | 1                    | O' Level     | Yes        | No                 | SHE            |
| 21 | Female | 41          | Male'      | Married        | 1                    | Bachelor     | Yes        | No                 | NTC            |
| 22 | Male   | 44          | Lh.        | Married        | 1                    | Postgraduate | Yes        | No                 | NTC            |

*Study1b: participants who tested for thalassaemia, but took no further action and had children in spite of their carrier status.*

To be included in this part of the study, participants were required to be Maldivians who married and had thalassaemia major child/children despite knowing their positive carrier status. A total of 15 individuals and 4 couples from 10 different atolls of Maldives contributed to this study - 13 women and 10 men. Please see Table 3.2 for a full description of the final sample.

**Table 3.2: General characteristics of participants who tested for thalassaemia prior to marriage**

| No | Gender | Age | Test age | Atoll     | Marital status | Total no of children | No of major children | Education | Employment | related to partner | Testing centre |
|----|--------|-----|----------|-----------|----------------|----------------------|----------------------|-----------|------------|--------------------|----------------|
| 1  | Female | 32  | 15       | Raa       | Divorced       | 1                    | 1                    | Diploma   | No         | No                 | SHE            |
| 2  | Male   | 38  | 20       | A.Dhaal   | Married        | 4                    | 2                    | Gr.5      | Yes        | No                 | SHE            |
| 3  | Female | 37  | 25       | Noon      | Married        | 1                    | 1                    | Gr7       | No         | No                 | NTC            |
| 4  | Female | 26  | 16       | Male'     | Divorced       | 2                    | 2                    | O' Level  | No         | No                 | SHE            |
| 5  | Male   | 29  | 14       | Raa       | Married        | 1                    | 1                    | O' Level  | Yes        | distant            | SHE            |
| 6  | Male   | 28  | 20       | Raa       | Married        | 1                    | 1                    | O' Level  | Yes        | No                 | NTC            |
| 7  | Female | 27  | 15       | Baa       | Married        | 1                    | 1                    | O' Level  | No         | No                 | SHE            |
| 8  | Female | 27  | 18       | Alif.Alif | Divorced       | 2                    | 1                    | Gr.7      | No         | Not                | NTC            |
| 9  | Male   | 32  | 24       | Male'     | Divorced       | 2                    | 2                    | O' Level  | Yes        | No                 | SHE            |
| 10 | Female | 40  | 22       | Male'     | Married        | 2                    | 1                    | O' Level  | Yes        | No                 | SHE            |
| 11 | Male   | 35  | 25       | Male'     | Divorced       | 2                    | 1                    | Gr.6      | Yes        | No                 | SHE            |
| 12 | Female | 32  | 13       | Male'     | Divorced       | 1                    | 1                    | O' Level  | No         | No                 | SHE            |
| 13 | Female | 29  | 17       | Seenu     | Divorced       | 2                    | 1                    | A' level  | No         | No                 | SHE            |
| 14 | Female | 33  | 11       | Male'     | Married        | 2                    | 1                    | Gr. 9     | No         | No                 | SHE            |
| 15 | Male   | 33  | 17       | Thaa      | Married        | 2                    | 1                    | Gr. 6     | Yes        | No                 | SHE            |
| 16 | Female | 21  | 15       | Noon      | Married        | 2                    | 1                    | Gr. 7     | No         | Distant            | NTC            |
| 17 | Male   | 29  | 16       | Noon      | Married        | 2                    | 1                    | Gr. 7     | Yes        | Distant            | SHE            |
| 18 | Female | 23  | 14       | Alif.Aif  | Married        | 2                    | 1                    | Gr. 7     | Yes        | No                 | SHE            |
| 19 | Male   | 30  | 16       | Alif.Alif | Married        | 1                    | 1                    | Gr. 7     | No         | No                 | SHE            |
| 20 | Female | 21  | 15       | Lhaviyani | Married        | 1                    | 1                    | Gr. 10    | No         | No                 | SHE            |
| 21 | Male   | 36  | 17       | Male'     | Married        | 3                    | 2                    | Bachelor  | Yes        | No                 | NTC & SHE      |
| 22 | Female | 50  | 20       | Male'     | Married        | 2                    | 2                    | Gr. 7     | No         | No                 | SHE            |
| 23 | Male   | 50  | 25       | Haa.Alif  | Married        | 3                    | 3                    | MPhil     | Yes        | No                 | SHE            |

### *Study 2: participants who undertook prenatal diagnosis due to thalassaemia*

Participants for this part of the study were required to be Maldivians who had undertaken prenatal diagnosis due to thalassaemia. Participants were purposely selected from two broad groups; parents who have a major child and had undertaken prenatal diagnosis in the subsequent pregnancy and participants who did not have a

major child but had undertaken prenatal diagnosis for every pregnancy. The first group was accessed from among the parents of thalassaemia majors using the same recruitment process as in Study 1a and 1b.

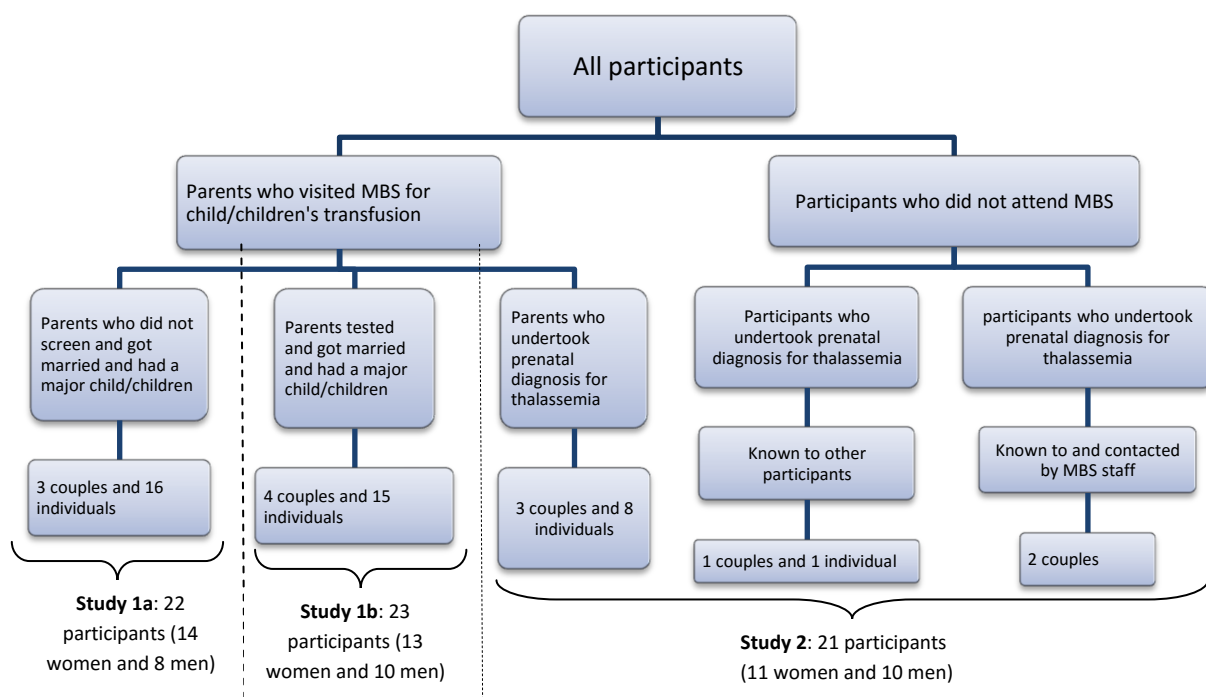
**Table 3.3: General characteristics of participants who undertook prenatal diagnosis**

| No | Gender | Age | Atoll    | Marital status | related to partner | Education     | No of children | No of majors | No of CVS | No of termination | Test centre | Place of termination | Employment |
|----|--------|-----|----------|----------------|--------------------|---------------|----------------|--------------|-----------|-------------------|-------------|----------------------|------------|
| 1  | M      | 39  | Noon     | Married        | No                 | O'Level       | 2              | 1            | 2         | 1                 | Vellore     | Trivandrum           | Yes        |
| 2  | F      | 39  | Seenu    | Married        | No                 | Diploma       | 2              | 0            | 5         | 3                 | Vellore     | Trivandrum           | Yes        |
| 3  | M      | 39  | G.Dhal   | Married        | No                 | Post Graduate | 2              | 0            | 5         | 3                 | Vellore     | Trivandrum           | Yes        |
| 4  | F      | 29  | G. Alifi | Married        | No                 | Post Graduate | 0              | 0            | 1         | 1                 | Delhi       | Bangalore            | Yes        |
| 5  | F      | 36  | Male'    | Married        | No                 | Diploma       | 1              | 0            | 2         | 1                 | Vellore     | Bangalore            | Yes        |
| 6  | M      | 32  | Sh       | Married        | No                 | Diploma       | 1              | 0            | 2         | 1                 | Vellore     | Bangalore            | Yes        |
| 7  | F      | 45  | H.Alif   | Married        | No                 | Gr. 7         | 3              | 1            | 2         | 1                 | Vellore     | Trivandrum           | Yes        |
| 8  | M      | 50  | H.Alif   | Married        | No                 | Gr.7          | 3              | 1            | 2         | 1                 | Vellore     | Trivandrum           | Yes        |
| 9  | M      | 34  | G.Alif   | Married        | No                 | O' Level      | 1              | 0            | 1         | 0                 | Vellore     | N/A                  | Yes        |
| 10 | F      | 45  | Male'    | Married        | No                 | A' Level      | 2              | 1            | 3         | 2                 | Sydney      | Sydney               | No         |
| 11 | F      | 38  | G.Alif   | Married        | No                 | Diploma       | 3              | 1            | 3         | 1                 | Vellore     | Trivandrum           | Yes        |
| 12 | M      | 41  | Sh       | Married        | No                 | Bachelor      | 3              | 1            | 3         | 1                 | Vellore     | Trivandrum           | Yes        |
| 13 | F      | 31  | Thaa     | Married        | No                 | Bachelor      | 1              | 0            | 1         | 0                 | Vellore     | N/A                  | Yes        |
| 14 | M      | 31  | H.Dhaal  | Married        | No                 | Diploma       | 1              | 0            | 1         | 0                 | Vellore     | N/A                  | Yes        |
| 15 | F      | 30  | Shi      | Married        | No                 | O' Level      | 2              | 1            | 1         | 0                 | Vellore     | N/A                  | Yes        |
| 16 | M      | 34  | G. Alif  | Married        | No                 | A' Level      | 2              | 1            | 1         | 0                 | Vellore     | N/A                  | Yes        |
| 17 | F      | 39  | Male'    | Married        | No                 | Bachelor      | 2              | 1            | 2         | 1                 | Vellore     | Vellore              | Yes        |
| 18 | M      | 41  | H.Alif   | Married        | No                 | Gr. 7         | 2              | 1            | 2         | 1                 | Vellore     | Vellore              | Yes        |
| 19 | F      | 37  | Baa      | Married        | No                 | O' Level      | 1              | 0            | 1         | 0                 | Vellore     | N/A                  | Yes        |
| 20 | M      | 30  | Male'    | Married        | No                 | Diploma       | 2              | 0            | 3         | 1                 | Vellore     | Male'                | yes        |
| 21 | F      | 33  | Raa      | Married        | No                 | Gr. 6         | 3              | 1            | 2         | 0                 | Vellore     | N/A                  | No         |

Many who undertook prenatal diagnosis did not have a major child and hence did not have the need to attend MBS. To recruit this second group of participants, two couples from the community who were known to have undertaken prenatal diagnosis for thalassaemia were contacted by nurses and laboratory technicians of MBS. Their contact details were forwarded as they were willing to participate in the study. Additionally, snowball sampling was used and through this very appropriate method, three participants (one couple and a male participant) were recruited to the study. A total of 21 participants (nine individuals and six couples) participated in

this study. Please see Table 3.3 for a full description of the participants of study 2. A summary of the total sample and selection process for the three qualitative studies (1a, 1b and 2) are provided in Figure 3.2.

**Figure 3.2: Number of participants and selection process for qualitative study 1a, 1b and 2.**



## Data Collection

Interviews are appropriate to use when the behaviour or feeling cannot be observed or when we need to explore past events that cannot be replicated.<sup>146</sup> There are three main types of interviews; structured, semi-structured, unstructured.<sup>146</sup> I used semi-structured face-to-face in-depth interviews<sup>153</sup> for data collection. Semi-structured interviews are guided but flexible and use a mix of structured and unstructured questions and issues that need exploration.<sup>146</sup> This type of interview can be used when all questions need flexibility or some parts need flexible administering.<sup>146</sup> However, normally a large part of semi-structured interviews are guided using issues of interest.<sup>146</sup> The interview guide is flexible, allowing the



researcher to respond to the situation at hand, the emerging worldview of the respondent and new ideas that they come across in the conversation.<sup>146</sup> Hence, I was able to move back and forth with the issues and explore new ideas when needed. The issues to be addressed in the interviews were developed using literature beforehand as part of preparing for data collection and familiarizing with the issue. The issues included in the interviews for the three sub-studies (1a, 1b and 2) are presented in Table 3.4.

**Table 3.4: Interview guide used for study 1a, 1b and 2**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>General demographics themes common for all participants</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"> <li>• Name</li> <li>• Residential Island and atoll</li> <li>• Age</li> <li>• Employment and income</li> <li>• No of major children and their names and ages</li> <li>• Education</li> <li>• Marital status</li> </ul>                                                                                                                                                                                                                                                                                                                            |
| <b>Study 1a: Participants who married without testing and had a major child or children</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <ul style="list-style-type: none"> <li>• Marriage decision (when, why, how, who is involved)</li> <li>• Reasons for not testing</li> <li>• When was the carrier status known and its impact</li> <li>• Impact on or from partner and family</li> <li>• Family size</li> <li>• Reaction from Family, other relatives, friends</li> <li>• Effect of counselling</li> <li>• Health education and prior knowledge</li> <li>• Culture</li> <li>• Nature of the disease and denial</li> <li>• Implications of major child</li> <li>• Stigma</li> <li>• Cost.</li> <li>• Coping</li> </ul> |
| <b>Study 1b: Participants who knew carrier status and married and had a major child or children</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• Reasons for testing</li> <li>• Timing of the screening</li> <li>• Health education and prior knowledge</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                          |

- 
- Effect of screening or knowing the carrier status
  - Effect of counselling
  - Reasons for marrying or decision to marry
  - Cultural factors
  - Influential others
  - Wedding Plans
  - Stigmatization
  - Cost
  - Religion
  - Decision to have children
  - Impact of major child or children
  - Coping
  - Impact on marriage
- 

**Study 2: Participants who undertook prenatal diagnosis due to thalassaemia carrier status**

- Time of carrier test
  - Type of Prenatal Diagnosis test performed
  - Country where the test and diagnosis was done
  - Prior knowledge and awareness (condition, consequences and options)
  - access to services
  - Cost
  - Any other difficulty
  - Any facilitators in the family or community
  - Advice about the procedure
  - Culture
  - Influence of significant others
  - Moral and personal beliefs
  - Perception of the severity of the condition
  - Religious factors
    - timing and gestational age
    - religious ruling
    - opinion of religious scholars
    - Maldivian Fatwa
- 

Thalassaemia is a sensitive issue and being a parent of a major child is very sensitive for many parents. Therefore, sensitive issues such as reasons for not testing, contraceptive use and prenatal diagnosis were approached using special interviewing

strategies like “devil’s advocate” and hypothetical questions as advised by Merriam<sup>146</sup> in her guide to deal with sensitive issues in interviews.

All interviews were conducted in Maldivian local language Dhivehi as all participants preferred to speak in local language rather than English. I am a native Dhivehi speaker and I conducted all the interviews in this study. Each interview lasted approximately one hour. The intent was to interview the participants individually because it would provide a greater opportunity for them to express their perspectives more freely. However, a few preferred to be interviewed as couples.

According to Merriam<sup>146</sup>, the most common way of capturing interview data is by recording. The advantage of recording is that it will preserve everything for analysis and allow the researcher to listen and improve consecutive interviews.<sup>146</sup> Thus, digital recording was undertaken for all interviews. Some discomfort was observed at the start from some participants, but it was not apparent after a short time, similar to how it was described by Merriam.<sup>146</sup> Most interviews were conducted in the private room provided by the MBS for this study. However, a few participants preferred to be, and were, interviewed at their own home.

### **Data Analysis**

The qualitative data analysis program NVivo 10 was used for data storage, management, retrieval and interrogation during my analysis. Translated (Dhivehi to English) versions of the data were stored in NVivo10. Data analysis started at the completion of the first interview. Each interview was listened to and notes were made before proceeding to the next interview in each group. Field notes and notes taken from the previous interviews were used to prepare for the next interview. This method helped to explore new ideas and move to and forth in between important issues that were apparent in the previous interview. A diagrammatic view of the data analysis process is provided in Figure 3.3.

As a second stage, I translated all recorded interviews from Dhivehi to English and transcribed concurrently. During translation and transcription, extra care was taken to ensure that contextual, cultural and emotional meaning of Dhivehi language was preserved. A total of 43 (30 individual and 13 couples) interviews were translated to English and transcribed for this study.

After transcription, a thematic analysis as described by Braun and Clarke<sup>154</sup> was used to analyze the data. As such, I followed their six step guideline of thematic data analysis.<sup>154</sup>

### *Step one- familiarizing with data*

For me, the familiarization process started when I wrote field notes to prepare for each subsequent interview. Braun and Clarke<sup>154</sup> suggest transcribing data and reading and re-reading the data, noting down initial ideas in this stage. As previously noted, I personally translated and transcribed all the interviews and in addition to this process, read the transcripts several times as my next step to become familiar with the content. During that process, I noted down broad ideas and concepts to prepare for initial coding.

### *Step two- Generating initial codes*

As a second step, I went through the whole data set for each group and coded potential and interesting characteristics in each group of interviews. Following this, I undertook a close reading and coding of the interviews to collect together data that were relevant to each of those initial codes. Some examples of the initial codes are given below:

- Awareness/knowledge
- Difficulties associated with service
- cost
- Divorce

- Counselling
- Family and friends
- Faith and religion
- Coping

### *Step three- Searching for themes*

As the analysis progressed I searched for potential themes from among the initial codes and gathered all relevant data under these emerging potential themes. During this process I moved back and forth between initial codes and sometimes back to transcripts to confirm my thoughts before all codes were recorded under initial themes. Some examples of initial themes are as follows:

- Knowledge of thalassemia
- Knowledge of availability of screening services
- Difficulties associated with prenatal diagnosis
- Difficulties associated accessing the treatment for the child
- Cost and price of travelling overseas
- Cost of staying in Male'
- Divorce and separation to get a non thalassemia child
- Availability and quality of counselling
- Extended family attitude
- Friend's attitude
- Belief in fatwa
- Belief in Quruan and Allah's words
- Faith in Allah's decree

### *Step four- Reviewing themes*

Under step four, I further reviewed all the themes. During this stage, some potential themes were removed as they did not fit the developing analysis and some

were divided in to two to three themes to better reflect the generated data. Some examples of themes after review are provided below:

- Poor awareness of the condition
- Fear and anxiety related to Prenatal diagnosis procedure and results
- Difficulties associated with accessing prenatal diagnosis services
- Financial cost associated with rentals in Male'
- Financial costs associated with overseas travel for PND
- Divorce due to being a carrier and not wanting to risk another pregnancy with uncertainty.
- Divorce and re-marrying a non carrier to get a non-thalassemia child
- Quality of counselling
- Poor access to counselling
- Stigma associated with the condition in extended family
- Friends' advice to separate to get a normal child.
- Believing the fatwa but not fully accepting it in their heart
- Struggle with accepting fatwa as Quran prohibits harming any sole unjustly.
- Accepting the circumstances as Allah's will as a way of coping

#### *Step five- Defining and naming themes*

At this stage, the themes were refined further and final themes selected and named for reporting in the findings. An example of refined final theme is "*Coping: A Test of Faith in Islam*"

#### *Step six- Producing the report*

As a final step of analysis, most convincing and visible quotes were selected under each theme and they were further analysed using literature in research papers

for each of the objective of the particular study. Two examples of visible quotes under refined final theme “*Coping: A Test of Faith in Islam*” are as follows:

“Having a thalassemia child (pause)... what I would say is what is there in Allah's decree will happen. That’s how I see it”.

“Everything happens according to Allah's Will”.

### **Rigor**

Authenticity in qualitative research deals with criteria of fairness, ontological authenticity, educative authenticity, catalytic authenticity and tactical authenticity.<sup>155</sup> In reference to constructivism, those criteria are placed in order to overcome power imbalances and misrepresentation, false experiences, misunderstandings, impracticality and disempowerment.<sup>155</sup>

Many qualitative researchers have identified definitive checklists of how to ensure rigour in qualitative research. For example, Whittemore, Chase and Mandle<sup>156</sup> have identified 29 techniques that apply to design consideration, data generation, data and analysis and presentation to ensure rigour in your study. Creswell and Miller<sup>157</sup> chose to focus on eight strategies that are frequently used by qualitative researchers and argue that qualitative researchers should engage in at least two of those strategies. Tracy<sup>158</sup> identified eight criteria of quality in qualitative research. Lincoln and Guba<sup>159</sup> are among the many qualitative researchers who believe it is inappropriate to rely on positivists’ concepts of validity and reliability in order to evaluate qualitative research. They identified four alternative concepts that more accurately reflect the assumptions of qualitative research – credibility, dependability and transferability, conformability. These four concepts, which taken together establish the trustworthiness of qualitative findings.

None of the above criterion could strictly be applied to this research. Rather, a mix of many of those aspects was employed to ensure the rigour of this research.

Peer review is one process that can be used to achieve internal validity or credibility and it can be undertaken by a colleague who is familiar or new to the research.

Reliability in quantitative research is the extent to which results can be replicated or it asks if the study is repeated, would it give the same results.<sup>146</sup> Hence, reliability

from a scientific approach is an issue in qualitative research which looks at human behaviour and experience from participants' worldviews.<sup>146</sup> Replication of

qualitative studies will not give same results according to Merriam.<sup>146</sup> Rather, she suggests that it is more important to see "if the results are consistent with the data

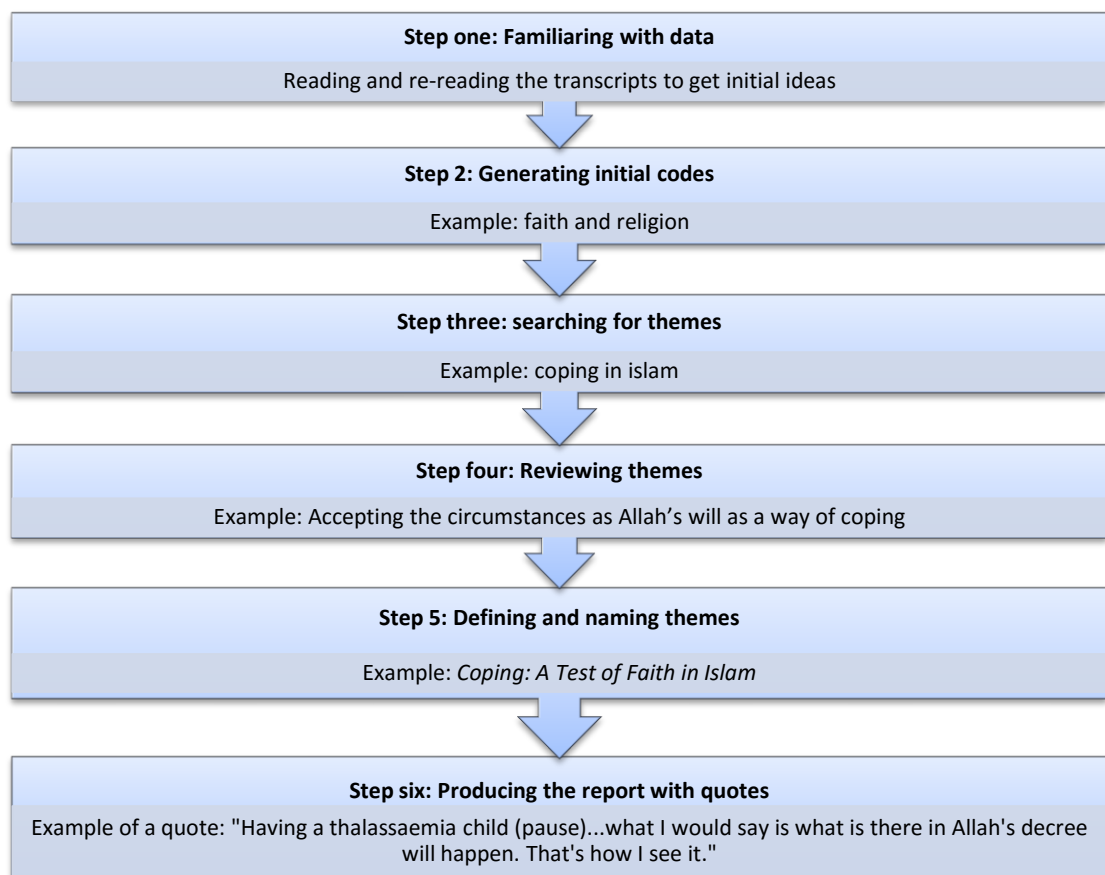
collected".<sup>146p.221</sup> <sup>146</sup> A Maldivian who was fluent in local language (Dhivehi) and English compared the English transcripts with the Dhivehi audio records to check for accuracy and to ensure the cultural context was preserved in the transcripts. As such, random checks of the content were undertaken for six transcripts from group one, four from group two and for all the transcripts in group three. The peer review comments did not identify any inconsistencies or misinterpretations.

Credibility of qualitative research is concerned with accuracy of how a phenomenon is described or portrayed. Normally, credibility is achieved by triangulation, member checking or prolonged engagement in the field work. Member checking was not possible for this study as the interviews were done in Dhivehi Language, but analysis was done using translated English transcripts of the interviews. Hence, the accuracy of descriptions was ensured by engaging in the field for a long period (approximately 5 months). During that time I was able to engage with the participants and access most relevant participants from different backgrounds. I was able to meet the participants in an informal manner for several times before the interviews. That engagement helped to build trust and respect between the participants and me.



In addition to that, rigour of the study was assured by keeping a detailed audit trail throughout the research process. During the research process, all the data generated, the methods used, the data sources and all the analysis decisions were recorded in a research journal in detail. Therefore, if need arises the same process can be followed by another researcher. Additionally, the findings are reported in detail to provide sufficient information for other researchers and readers, so that they can assess the appropriateness of my findings. Furthermore, the categories and themes were discussed with supervisors and reviewed many times to ensure that the meaning of the data were appropriate. Most importantly, special care was taken to ensure the findings and conclusions were not biased due to researcher's position, rather they were made based on the participants' stories and the research condition.

**Figure 3.3: Qualitative data analysis process**



### **Study 3: Tertiary prevention**

#### **Research Design**

A quantitative approach was followed for the study related to tertiary prevention; study 3. Specifically, the study was a cross-sectional survey.<sup>160</sup>

According to Martin<sup>160</sup> cross-sectional studies allow standardized measurement of attributes of interest and can be used to measure the impact of health experiences.

The literature shows that there are many studies that have used the cross-sectional survey method to measure the HRQoL of thalassaemia majors in different communities.<sup>76,117,122,161,162</sup> Hence, a cross-sectional survey was used to evaluate the HRQoL of thalassaemia majors in Maldives.

#### **Research instrument**

RAND 36-Item Short Form Health Survey (SF-36)<sup>163</sup> was used for the study.

It is a generic survey freely available for interested researchers from RAND

Corporation.<sup>164</sup> SF-36 survey measures eight domains of health which are relevant across age, disease and treatment groups.<sup>165</sup> The eight domains include Physical

Functioning (PH), Role limitation due to Physical health (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role limitation due to Emotional health (RE) and Emotional Wellbeing/Mental Health (EW/MH).<sup>165</sup> In summary, PF, RP, BP, VT and GH are physical health domains and RE, SF and EW are mental health domains that are assessable via SF-36.

SF-36 survey form was shown to be reliable, valid and sensitive enough to measure the quality of life of thalassaemia patients when translated to other languages such as Malay<sup>130</sup> and Arabic.<sup>166</sup> A number of studies that have used SF-36 to measure the HRQoL of thalassaemia majors can be found in the literature.<sup>113,117,123,167</sup>

Hence, SF-36 was an appropriate tool to use for the study translated into Maldivian local language (Dhivehi). As directed by RAND website, the SF-36 survey was translated to Dhivehi and back translated <sup>168</sup> before the actual survey. Two Maldivians who were native to Maldives and were fluent in Dhivehi and English language checked the translated version for its consistencies with the original English version.

The survey can be self-administered by people 14 years of age or older, or it can be administered as an interview in person or by telephone. <sup>165</sup> Even though it can be self-administered, I administered all forms as an assisted interview.

In addition to SF-36 survey, another short form was administered to document general characteristics, diseases related complications, type of iron chelation treatment and compliance to iron chelation treatment of individual patients. The additional information form that was administered to thalassaemia major population is provided in Figure 3.3. Additionally, patient records of past six months of all participants were photographed in order to attain the most recent serum ferritin levels and diagnosis of individuals. MBS provided the average haemoglobin level of the participants for the past six months and details of registered patient numbers of all patients who were 14 years and above.

### **Participants and Sampling**

According to the records of MBS, the accumulated registered thalassaemia population of Maldives at the time of this study was 776 (which is different from the figures of TIF). All patients have to be registered in MBS in order to access the blood transfusion and free medication in Maldives. Since the start of registration in 1992 and the time of this study, a total of 168 premature deaths occurred. Hence, 575 patients were living at the time of this study. The study was targeted at patients aged

above 14 years – also the recommended youngest age by the SF-36 survey distributor, RAND.<sup>165</sup> According to records of MBS, there were 194 thalassaemia majors who were 14 years or above and taking treatment when this study was conducted. Two participants declined to participate and a total of 149 participants completed the SF 36 survey form.

However, four participants (three HbE  $\beta$ -Thalassaemia and one Sickle cell  $\beta$ -Thalassaemia) were excluded from the study as they stated that they did not need regular blood transfusions. All four stated that they had a transfusion occasionally (two approximately twice a year, one only when she is pregnant and the sickle cell patient only during a crisis). It is unfortunate that I had to remove four participants during analysis stage, but it was a necessary step to ensure the validity of the results. I personally, approached all the patients who were 14 years and above. At that stage, I did not know who were transfusion dependent or not because I did not want to access their medical records at MBS without their consent. Later when they filled the survey form only, I became aware that they do not require regular transfusion and they are not transfusion dependent. The consent to access patient records at MBS was obtained with the survey form, but by then they had filled the survey. Therefore, they had to be removed from the participant list at the analysis stage. Hence, the final sample represents 74.7% (145) of Maldivian thalassaemia patients who were 14 years and over at the time of the study. Please refer to Figure 10.1 for details of participant selection for study 3.

As can be seen from Figure 10.1, I was able to access 76.8% of the total participant population. After excluding the four participants who did not quite fit the criterion of ‘transfusion dependent’, 74.7% (N=145) of the total eligible population was included in this study. I was able to access that percentage by taking the

advantage of collecting the data during school holidays; a time when parents visit Male' with their major children for routine tests such as serum ferritin test. Hence, my sample is a representative sample of the total participant population. Please refer to Table 3.5 for the details of number of thalassaemia majors who are 14 years and above in each atoll (information provided by MBS) and number of participants participated in this study from each atoll.

**Table 3.5: Total population, Carrier rate, number of majors (14 years or above) and number of participants from each atoll**

| Atoll         | Population size | $\beta$ - thalassaemia carrier (%) | No of majors who are 14 years or above | No of participants |
|---------------|-----------------|------------------------------------|----------------------------------------|--------------------|
| Haa Alifu     | 12,721          | 16.8                               | 10                                     | 9                  |
| Haa Dhaalu    | 18,284          | 20.4                               | 8                                      | 4                  |
| Shaviyani     | 12,135          | 23.6                               | 5                                      | 2                  |
| Noonu         | 10,513          | 25.4                               | 7                                      | 7                  |
| Raa           | 14,865          | 13.7                               | 16                                     | 10                 |
| Baa           | 8,860           | 12.6                               | 6                                      | 6                  |
| Lhaviyani     | 7,905           | 18.2                               | 7                                      | 7                  |
| Kaafu         | 11,315          | 16.2                               | 9                                      | 5                  |
| Capital, Male | 133,019         | 18.8                               | 69                                     | 61                 |
| Alifu Alifu   | 5,556           | 14.5                               | 4                                      | 2                  |
| Alifu Dhaalu  | 8,111           | 16.6                               | 2                                      | 1                  |
| Vaavu         | 1,565           | 8.7                                | 0                                      | 0                  |
| Meemu         | 4,703           | 15.6                               | 2                                      | 0                  |
| Faafu         | 4,044           | 18.7                               | 11                                     | 8                  |
| Dhaalu        | 5,356           | 14.0                               | 3                                      | 2                  |
| Thaa          | 8,945           | 16.2                               | 9                                      | 8                  |
| Laamu         | 11,856          | 22.8                               | 7                                      | 3                  |
| Gaafu Alifu   | 8,427           | 14.0                               | 4                                      | 4                  |
| Gaafu Dhaalu  | 11,663          | 9.0                                | 5                                      | 3                  |
| Gnaviyani     | 8,055           | 17.1                               | 1                                      | 1                  |
| Seenu         | 19,712          | 8.3                                | 9                                      | 2                  |
| <b>Total</b>  |                 |                                    | <b>194</b>                             | <b>145</b>         |

### Data Analysis

All except three survey forms were completed fully. Three survey forms had

one missing response in each. Additionally, some data were missing from demographic forms and the records of MBS.

There is no record of the SF-36 survey form being translated into the Maldivian language and used in the Maldives. Therefore, as a first step, Cronbach's Alpha was calculated to assess the internal consistency and reliability of SF-36 survey components administered in Dhivehi.

The scoring of the survey was carried out in a two step process as advised by RAND health.<sup>169</sup> As such, all scores (the scores of SF-36 survey are based on a scale of 1 to 6) were converted to an aggregate percentage score between zero and 100; the lowest is zero and highest possible is 100. The scores from functional groups are then averaged to calculate the score of each quality of life function; PH, RP, RE, VT, EW/MH, SF, BP and GH.

As a second step, descriptive statistics were calculated to explore the general characteristics of the population - calculated in terms of percentage, mean and standard deviation and frequencies. The scores of the functional categories were later centered using means and descriptive frequencies to identify the percentage proportions that lie below and above the mean scores. Final scores of the functional groups were interpreted in reference to the whole construct of the SF 36 survey.

For the final analysis, Pearson's correlation was used to identify correlations between continuous predictor variables in Table 10.2 and HRQoL scores. Simple linear regression was used to examine the association between HRQoL domains in Table 10.3 and demographic/clinical variables in Tables 10.1 and 10.2. The variables were considered significant at  $p \leq 0.05$ . The variable 'Diagnosis' which has three categories was dummy coded as ' $\beta$ -thalassaemia major' and 'HbE  $\beta$ -thalassaemia or thalassaemia intermedia' in order to run simple linear regression for diagnosis. For

the categorical variable ‘compliance to iron chelation treatment’, participants were considered not compliant if they had missed treatment for more than once in a week in the past four weeks. Data were analysed using IBM SPSS Statistics 23.

**Figure 3.4: Demographic information of Thalassaemia majors**

| <b>Demographic and clinical survey form of patients</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Demographics (14-18 years)</b></p> <ol style="list-style-type: none"> <li>1. Name.....</li> <li>2. Gender.....</li> <li>3. Age.....</li> <li>4. Residential Atoll and Island.....</li> <li>5. Highest education.....</li> <li>6. Enrolled in School: Yes/No</li> <li>7. Household income.....</li> <li>8. Rental status : Yes/No</li> <li>9. Travel by sea for transfusion : Yes/No<br/>If Yes, how long does it take to and from: .....</li> </ol> <p><b>Demographics (18 years and over)</b></p> <ol style="list-style-type: none"> <li>1. Name.....</li> <li>2. Gender.....</li> <li>3. Age.....</li> <li>4. Residential Atoll and Island.....</li> <li>5. Highest education.....</li> <li>6. Employment status: Yes/No</li> <li>7. Personal Income.....</li> <li>8. Household income.....</li> <li>9. Rental status : Yes/No</li> </ol> | <p><b>Questions for all participants</b></p> <ol style="list-style-type: none"> <li>1. Onset of anaemia.....</li> <li>2. Diagnosis.....</li> <li>3. Age of first transfusion.....</li> <li>4. Age of start of iron chelation.....</li> <li>5. Type of iron chelation(choose one or both)               <ol style="list-style-type: none"> <li>a. Oral :<br/>Name.....<br/>Dosage.....</li> <li>b. Subcutaneous:<br/>Name: .....<br/>Dosage.....</li> <li>c. Not applicable</li> </ol> </li> <li>6. Comply fully to iron chelation: Yes/No<br/>If No, how many days do you miss in a typical week?<br/>.....</li> <li>7. Frequency of transfusion.....</li> <li>8. Usual number of units of blood transfused in each transfusion:<br/>.....</li> <li>9. Any other co-morbidities or complications:<br/>.....<br/>.....<br/>.....<br/>.....<br/>.....<br/>.....<br/>.....</li> </ol> |
| <p><b>Information that will be taken from your record books and your records in MBS</b></p> <ol style="list-style-type: none"> <li>1. Average haemoglobin level (MBS records):<br/>.....</li> <li>2. Latest serum feratin level (personal record book photographed):<br/>.....</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

## Ethics

The Human Research Ethics Committee of the University of Western Australia (Ref: RA/4/1/5626) approved this study on the 9<sup>th</sup> of January 2013. It was also approved by the National Health Research Committee of Maldives on the 7<sup>th</sup> of February 2013. All participants provided written consent before participation. In addition to participants, guardians of participants who were under 18 years (a minor under Maldivian Law) of age provided written consent for their children to participate in this study. Written consent was obtained from all participants and parents/guardians of those who are under 18 years of age to access their medical records in MBS.

The issue of thalassemia is a sensitive issue in Maldives. I faced several unexpected ethical issues during the course of the study. One main issue was access to participants who undertook prenatal diagnosis and termination of pregnancy. The initial arrangement was accessing them through SHE (prior arrangements were made via emails) as they have a register of couples who they make appointments from India for prenatal diagnosis in Vellore, India. However, SHE was not able to provide access to the register due to internal issues at the last stage. Therefore, I had to change the participant selection approach to snowball sampling which was difficult because termination of pregnancies is not an openly discussed issue in Maldives. Therefore, I had to take extra precautions when I met that group for interviews. Many participants did not want to be identified as ‘someone who terminated a pregnancy’. Hence, I had to reassure them their participation was confidential and any of their identifiable information will not be used under any circumstance.

Another main issue I faced was meeting participants’ expectations. Many participants were of the opinion that this study might bring some advantage for the



thalassemia community by means of goods or finance. This issue arose mainly due to the fact that many international organizations do small scale opinion surveys and community research for their project implementation purposes (for example WHO). I had to make sure that they understood my position as a researcher, but not a financial provider who has any liaison with any other organization such as WHO.

Another issue I faced was that I needed to recruit among different groups of participants for interviews, but half way through the interviews with some participants I found out that they did not fit into any of the three target groups for Study1 (a and b) or Study 2. Rather they were a group of people who married their carrier partners because they received erroneous results in their carrier screening. About 13 participants belonged to that group. I started those interviews assuming that they knew their carrier status, because in the initial introductions, they stated that they did the screening test for thalassemia carriers before their marriage. However, their situation only surfaced after some time through the interviews and I could not stop the interviews because I felt they might be offended if I asked. Therefore, I continued the interviews and later my supervisors and I decided that we will analyse the data from those participants separately after the completion of the thesis.

### **Types of voices in this study**

The aim of this study was to cover the three levels of prevention of thalassemia in Maldives. Hence, both qualitative and quantitative approaches are used depending on what best fits each level and participant voices of “the important group” was selected for each study at each level. Only the most important group was selected for each level because of time and cost limitations. Unfortunately, that means I was not able to explore many other important voices. Views of other

important stakeholder groups such as policy makers, service providers (doctors, nurses, insurance providers, education providers etc.), friends and families of thalassaemia majors and carriers and general public would add value to the findings of this study. If I was able to include all stakeholder groups, it would provide a more holist picture of the prevention program of Maldives. Hence, it has to be noted that not being able to include the voices of all important stakeholders in each prevention level is a main limitation of this study.

### Introduction to the Chapter

Chapter four is the first paper produced based on the first objective of the study; “Explore the reasons why carriers of thalassaemia marry and have children without screening for thalassaemia in Maldives.” The paper was submitted to the Journal of Community Genetics. The reference is as below.

*Reference:* Waheed F, Fisher C, Awofeso N, Stanley D. Thalassaemia in Maldives: Reasons for not Screening and its Consequences. Journal of Community Genetics. 2015. (Submitted).

The paper included abstract, introduction to the paper, introduction to Maldives and thalassaemia situation in Maldives, study method, results, discussion, conclusion and limitations of the study. The paper is presented as submitted to the journal except with the changes of Figure and Table numbers and reference style. The numbers given for the Figure and Table were 1 in the original paper. The chapter number was added to the original Figure and Table number to assist the flow of the thesis. APA referencing was used in the original article that was submitted to the journal. The referencing was changed from APA to Vancouver system to ensure consistency in referencing throughout the thesis.

**Title: Thalassaemia in Maldives: Reasons for not Screening and its Consequences.**

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## Abstract

The Republic of Maldives (Maldives) is an island nation in the Indian Ocean with a population of 344, 023. Studies show that Maldives has one of the world's highest thalassaemia carrier rates. It is estimated that 16-18% of the Maldivians are  $\beta$  thalassaemia carriers and approximately 28 new major cases are recorded annually. Poor uptake of screening for the condition is one of the main reasons for this high number of new cases. The aim of this study was to explore the reasons for not testing for thalassaemia in Maldives before or after marriage. Findings show that participants did not undergo carrier tests because of poor awareness and not fully knowing the devastating consequences of the condition. The outcomes of not testing were distressing for most participants. Religion played a vital role in all the decisions made by the participants before and after the birth of a major child.

## Keywords

Awareness; Maldives; premarital testing; screening; thalassaemia

## Introduction

Thalassaemias are described as “inherited autosomal recessive disorders characterized by reduced rate of haemoglobin synthesis due to a defect in  $\alpha$  or  $\beta$ -globin chain synthesis”.<sup>22, p.353</sup> According to Webster's New World Medical Dictionary<sup>25</sup>, a major patient of thalassaemia is someone who is transfusion dependent due to severe anaemia caused by underproduction or absence of beta chains and hence, underproduction of haemoglobin. It is one of the most common hereditary disorders reported in the world. Estimates show that 3% of the world population is heterozygous for  $\beta$ -thalassaemia with more than 200 different mutations.<sup>35</sup> Furthermore, it is estimated that each year, more than 300,000 children are born with severe  $\beta$ -globin disorders.<sup>35</sup>

The main primary prevention strategy used in thalassaemia endemic countries is health awareness with genetic screening and counselling. Premarital or carrier screening and genetic counselling as a primary prevention strategy works well in some communities while it has little impact in other communities. The success of such programs depends on the acceptability and uptake of the carrier screening in different communities. People do not undertake carrier screening test for thalassaemia for a variety of reasons. Studies show that lack of awareness was one of the main reasons that carriers bypass or do not undertake screening for thalassaemia before marriage.<sup>170</sup> Gender, education level, age, being single and income were also identified as factors that contribute to unwillingness to participate in premarital screening for hemoglobinopathies.<sup>170</sup> Studies had also shown that carriers sometimes refuse the genetic screening or testing due to cultural reasons.<sup>171</sup> Fear of stigmatization was also reported as an impediment for genetic testing for thalassaemia in a number of studies.<sup>48,51,59</sup> Additionally, the nature of the disease

(carriers are normally healthy) and denial were identified as additional reasons why people do not want to be tested voluntarily for genetic conditions such as thalassaemia.<sup>70</sup> In addition, high cost and difficulty of accessing the services were also reported as factors that prevented people from screening for thalassaemia.<sup>69</sup>

## **Maldives**

Thalassaemia is a common genetic disorder in South Asia, the region encompassing Maldives. Maldives is an archipelago in the Indian Ocean, about 700 km southwest of Sri Lanka. The country is 820 kilometers in length and 130 kilometers in width, with a total area of 90, 000 square kilometres.<sup>6</sup> Maldives has 1192 low lying coral islands divided into 20 atolls for administrative purposes and 194 of those islands are inhabited. Population of the islands ranges from a few hundred to more than 100,000 in the capital Male'.<sup>172</sup> The registered local population of Maldives as of 2014 was 344, 023.<sup>172</sup> The life expectancy of Maldivians is reported as 77 years for men and 79 years for women.<sup>10</sup> The population of Maldives is 100% Sunni Muslim by law<sup>173</sup> and Dhivehi is the local language. Country development indicators show that Maldives has a literacy rate of 98%.<sup>174</sup>

## **Thalassaemia in Maldives**

Thalassaemia is the most common genetic disorder in Maldives. According to Firdous<sup>41</sup>, the earliest case of thalassaemia in Maldives was reported in 1970. It is not clear how thalassaemia evolved in Maldives, but there are few studies that imply that the high  $\beta$ -thalassaemia carrier rate of Maldives is due the selective advantage that thalassaemia carriers confer against Malaria.<sup>21</sup> Maldives has a  $\beta$ -thalassaemia prevalence rate of 16-18%.<sup>14</sup>

The first national thalassaemia program of Maldives was an awareness program with screening and counselling.<sup>42</sup> It was initiated by the non-governmental

organization, Society for Health Education (SHE) in 1992.<sup>41</sup> With the new insight into the problem by SHE, the government of Maldives recognized the magnitude of the problem and established The National Thalassaemia Centre (NTC) of Maldives in 1994. NTC was later merged with National Blood Transfusion Services to form Maldives Blood Services (MBS) in 2012. MBS provides treatment for major patients and carrier testing for the public. As at August 2014, a cumulative total of 803 thalassaemia patients were registered with the Service and a total of 563 were living.<sup>14</sup> At present, screening is available from SHE and MBS; both of those centers are situated in capital city Male'. The screening services for outreach populations are still provided by the mobile teams of SHE.<sup>41</sup> However, there are many who travel and visit the two screening centres in Male' to get screened at their own expense.

Thalassaemia test result has been considered a 'must document' in Male' by the family court for marriage since 2002 (Ahmed Abdulla, marriage registrar of family court of Maldives, personal communication, June 16, 2012). That rule was only fully implemented in the capital Male' because access to testing in atolls is not readily available and is very much dependent on the visits of the mobile teams, which are often infrequent and the schedules for which are often not publicized. In spite of that, the standard marriage registration form is common for the whole of Maldives and it is recommended that all intending couples do premarital testing even if the intending couple lives on an island other than Male'. The Thalassaemia prevention law of Maldives that was enacted in 2012 mandates all Maldivians be tested before the age of 18 and test results are required to be presented by all Maldivians in order to get married.<sup>175</sup> Eighteen years is the earliest age a person can legally get married in Maldives. The mandatory testing under the new law is,



however, a precautionary measure only. Marriages between carriers are still legal in Maldives.

Despite awareness raising efforts and free screening, a number of new cases of thalassaemia are recorded annually. The records of the Ministry of Health of Maldives<sup>78</sup> shows that an average of 28 new cases were registered each year for the past decade, which is a high incidence rate given the population size of Maldives. The constant high number of new cases is a worrying issue for the small population of Maldives. It is very likely that there are issues within the thalassaemia prevention program of Maldives that needs to be changed in order to combat this high level of new incidences. This study was the first part of a larger study that examined primary, secondary and tertiary levels of the thalassaemia prevention program of Maldives. The aim of the broader study was to examine the effectiveness of thalassaemia control measures at the respective levels. The aims of this component of the study were to explore the reasons for couples marrying without premarital testing for thalassaemia in Maldives and to explore the reasons for married couples having children without screening for thalassaemia after the introduction of the screening services in 1992.

## **Method**

A Generic Qualitative Approach<sup>149</sup> using face-to-face in-depth interviews<sup>176</sup> was utilized for this study to enable us to explore the participants' perspectives and reasons for their decisions in relation to the objectives of the study.

### *Participants and Sampling*

We used purposive sampling<sup>146</sup> to select participants who could provide detailed and nuanced information. To be included in the study, participants were required to be Maldivians who married without knowing their thalassaemia carrier

status and have had a thalassaemia major child or children after the year 1992: thalassaemia screening was introduced in Maldives in 1992. Only biological parents were invited for the study. As there was no register of the parents of children affected by severe thalassaemia in Maldives, the first author (FW) visited the main transfusion centre of Maldives (MBS) on several occasions and personally approached the parents of major children during transfusion. Most patients, irrespective of their age, were accompanied by their parents during their transfusion. During those interactions, the contact details of the parents who showed interest in participating in the study were recorded and later cross-checked against inclusion criteria to ensure they were eligible to be included. Special care was taken during final selection to ensure participation from all possible atolls of Maldives.

We commenced the main study in February 2013; however, interviews were purposely postponed until April 2013 (school study-break). This allowed access to participants during school break and was a time period when many parents from the islands visited the MBS to consult the doctors and do regular three monthly or six monthly ferritin tests for their thalassaemia-affected children. Through this delay, there was an opportunity to meet many visitors from atolls who normally do their transfusions in island/atoll level health centres and thus, potentially be included in this study. The final sample of 16 individuals and three couples comprised of 14 women and 8 men from 13 different atolls.

#### *Data collection*

The interviews were conducted by FW in the Maldivian local language Dhivehi, using an interview guide that was developed based on the literature. Each interview lasted approximately one hour and was digitally recorded for analysis purposes. The intent was to interview the participants individually because it would

provide a greater opportunity for the participants to express their perspectives more freely. However, a few preferred to be interviewed as couples. Accordingly, 16 individuals and 3 couples were interviewed for the study. Fourteen individuals and one couple were interviewed in the private room provided by the MBS for this study. Two individuals and two couples preferred to be, and were, interviewed at their own home.

### *Data Analysis*

Data collection and analysis occurred concurrently which enabled moving back and forth between the data and analysis. That process was flexible as suggested in Merriam <sup>146</sup> and enabled the interviewer to guide participants more appropriately in subsequent interviews by incorporating important issues raised in previous interviews. A thematic analysis as described by Braun and Clarke <sup>154</sup> was undertaken by FW in collaboration with the other authors. In the first stage of data analysis FW listened to the interviews, wrote memos and recorded initial impressions about the interviews in a field journal. Recorded interviews were then translated from Dhivehi to English by FW and transcribed concurrently. During translation and transcription, extra care was taken to ensure that contextual, cultural and emotional meaning of Dhivehi language was preserved. As a next step, FW read the transcripts several times in order to become familiar with the data before open coding. This was followed by an open coding process where concepts - significant statements and phrases related to the research aims were identified and openly coded. As a next step, potential themes and relevant data were identified using the broadly coded concepts in the initial stage. In the next stage of analysis, all the potential themes were reviewed again to further refine them. As a final stage of analysis, all the refined themes were examined again to clearly define and name

them before producing the final report based on the data. All the open coding was done by FW as she was a local Maldivian familiar with culture, religion and local language and other three co-authors were not. However, they reviewed and got more involved starting from refining themes. The qualitative data analysis program NVivo 10 was utilized to assist with data storage, management, analysis and interrogation.

## **Results**

Being a carrier and a parent of a thalassaemia major child was a particularly emotional issue for the participants. Their decisions to get married without premarital testing or not doing the test after getting married changed their lives. The birth of a thalassaemia major child and the complex care needed for them adversely affected the everyday life for our study participants. Since all the participants were Sunni Muslims, their decisions and attitudes before and after the birth of the major child were influenced by Islam and its teachings in many ways. We initially report the demographics and participant reasons for getting married followed by their reasons for not testing. This is followed by how participants came to know their carrier status and the consequences of giving birth and having to care for a thalassaemia major child. Figure 4.1 at the end of the results section shows how the findings of this study are linked and are shaped by Islam.

### *Demographics*

The study participants included more women (14) than men (8). Participants resided on islands in the north, south and middle parts of Maldives and their ages ranged from 30 to 53 years. All men were employed while seven of the women were either self-employed or worked in Government. The educational background of the participants varied from basic to postgraduate education and all knew how to read and write in the local language. All participants except five were married to the

mother/father of the major child. Four participants were divorced and living separately at the time of the study. The husband of one participant passed away a few months before this study. Table 4.1 shows more details of the participant characteristics.

**Table 4.1: Participant characteristics**

| Participant Characteristics                           | No of participants |
|-------------------------------------------------------|--------------------|
| <b>Total (16 individuals and 3 couples)</b>           | 22                 |
| No. of Men                                            | 8                  |
| No. of Women                                          | 14                 |
| <b>Participants' residential area</b>                 |                    |
| North of Male'                                        | 10                 |
| Male'                                                 | 7                  |
| South of Male'                                        | 5                  |
| <b>Age of the Participants</b>                        |                    |
| 30 - 40 years                                         | 11                 |
| 41 – above                                            | 11                 |
| <b>Year of marriage</b>                               |                    |
| before 1992                                           | 7                  |
| After 1992                                            | 15                 |
| <b>Marital status</b>                                 |                    |
| Married                                               | 17                 |
| Divorced                                              | 4                  |
| Widowed                                               | 1                  |
| <b>Related to the partner</b>                         |                    |
| Not related at all                                    | 16                 |
| Distant relatives (3 <sup>rd</sup> cousin or further) | 5                  |
| Second cousins                                        | 1                  |
| <b>Employment</b>                                     |                    |
| Employed                                              | 15                 |
| Not employed                                          | 7                  |
| <b>Education level</b>                                |                    |
| Completed basic education                             | 4                  |
| Completed primary education (Grade 5)                 | 2                  |
| Completed Middle school (Grade7)                      | 11                 |
| Completed Secondary school or higher                  | 5                  |
| <b>Testing center</b>                                 |                    |
| Society for Health Education (SHE)                    | 6                  |
| Maldives Blood Services (MBS)                         | 12                 |
| Have not tested yet                                   | 4                  |
| <b>No of major children</b>                           |                    |
| More than one child                                   | 5                  |
| Only one child                                        | 17                 |

### *Reasons for getting married*

Islam is the basis of many culture and societal norms of Maldives. According to our participants, cultural and societal expectation of marriage was shaped by Islam

in many ways. The participants provided a range of reasons for their marriage and they are presented here as cultural and religious, family and personal factors.

Marrying because of cultural and religious factors was dominant in participant interviews. Most participants described finding a partner and dating for some time before marriage as the custom in Maldives, but living together before marriage was described inappropriate in their society. All the participants except three selected their own marriage partners and dated for more than six months before marrying. They described dating and consequent familiarity, closeness and comfort led to a marriage in most cases. For example, one participant stated, “We started dating while very young. Dating continued for about three years and then (we) married.”

Even though Islam does not encourage dating before marriage, many cultural aspects of marriage in this study were closely related to Islamic teachings. Marriage is sacred in Islam. Islamic teachings and marriage advice given by *Ghazis* (a Government employed lawyer to conduct marriage on behalf of government) stress that prospective couples should make the marriage last and they should not divorce unless it is unavoidable. Accordingly, some participants married because they thought they had a good prospective partner for life.

Some participants married because they were advised to do so by their parents in order to ensure that they are ‘safe’ in accordance to Islamic teachings. For example, one man described the decision he and his wife made: “Even parents would push to get married early because children might take a wrong turn or walk on a bad path or something sad might happen.” Another participant thought her mother advised her to get married because according to the Shariah, children are not allowed

out of wedlock: “They [parents] might have thought that I might take a wrong turn. Lot of girls got pregnant out of wedlock even in those days.”

Personal factors such as limited options on the islands including not having an opportunity to continue education was also a reason for marrying for a few of the participants in this study. For example, one participant described her decision as follows, “Just that... we cannot continue the education any further in the island. So I wanted to get married and start a life.”

### *Reasons for not testing*

Carrier testing has been freely available in Male’ since 1992. It was also offered on the islands by the mobile teams of SHE from that year onwards. However, all participants in this study had at least one thalassaemia major child born after 1992, but without them knowing their carrier status. The participants provided a range of reasons for not testing for thalassaemia when the service became available. The main reasons included, poor awareness, insufficient knowledge of the condition, belief that they were not at risk and testing being not mandatory.

Poor awareness and not knowing about the availability of testing services was a main issue that many participants discussed as being a main reason that they did not undergo testing. For example, one participant reflected, “We were not that aware then... I didn’t know that we can test at that time. I knew SHE was there, but I didn’t know much about carriers”. Another participant explained her level of awareness as; “I didn’t think it [testing] was available then. I didn’t even check it... I had no idea that we can get tested for that in Maldives.”

Additionally participants noted that whilst they had some knowledge about thalassaemia, it was insufficient to understand the importance of getting tested. This reasoning was common amongst those who married before 1992 as well as those

who married after 1992. For example, one participant who married before 1992 noted, “I heard about it [thalassaemia] a little, but didn't give much attention.”

Similarly a woman who married after 1992 stated, “I remember hearing about it [thalassaemia], but I wasn't concerned much about it at the time.”

Some participants knew a little more than the above mentioned participants, but did not understand the severity or the possible consequences of the condition. Some of them said they had thalassaemia major relatives and knew that major children needed continuous transfusions. They did not, however, realize its consequences fully because no one really talked about it. For example, a couple who had major relatives on both sides of their family described their situation as “[Our] Awareness was not there... If his sister told us that “this is that big” and “it’s good to do the tests” - we would have known if she [husband’s sister] had said at least something like that.” Another participant added noting, “We knew there is something called thalassaemia, but didn't know that it is this big.” Therefore, poor awareness of possible consequences was also a major factor for many participants in this study not being tested for thalassaemia before marriage or having children.

Additionally, the findings show that some participants had a good knowledge of thalassaemia as a genetic condition, but they did not do the test before or after their marriage because they did not think that they would be carriers and they were confident in that belief. For example, one participant explained her decision not to test, “So I would hear about it [thalassaemia]... But I didn't think that I needed to test. Maybe that’s why that happened. I didn't think that it would happen to us.” Another woman described that it was shocking when she found out that she was a carrier, “Even the island didn’t have any carrier couple who has any children with thalassaemia. So, we wouldn't do the tests, right? I never thought that I would be



one of them [thalassaemia carriers].” A man who thought he would not be a carrier described his confidence and stated, “I knew it [thalassaemia] was hereditary. The thing was I didn't see anyone from my family. I was so sure that I would not be a carrier because no one else in my family is.”

Furthermore, a few of the participants stated that they did not undertake premarital testing despite knowing that it was important because it was not mandatory at the time of their marriage. For example, one participant who married after 1992 in Male’ noted, “Now we can’t get married without testing for it [thalassaemia]. There were no such regulations in those days.”

When asked if they would get married to the father/mother of the child if they knew their carrier status and the risks involved, most of them replied “No”. Two participants said they might, but in that case they said they would seek alternatives when having children. Another two participants replied that they do not know what their decision would be in that situation.

### *Realization of the carrier status*

Participants of this study realized their carrier status in two ways. Most participants came to know their carrier status with their first diagnosed thalassaemia major child while some others found out via ad-hoc screening conducted by the mobile teams of SHE for the islands.

The results show that most participants came to know their carrier status as a result of their child/children being diagnosed with the condition. Current practice in Maldives is for parents to undertake a carrier test before confirming their child’s diagnosis. Hence, many participants who had younger major children found out their carrier status through the carrier test as part of the diagnosis of their child. For example, one of the older couples, who have a major child of less than a year stated,

“Yes, [we came to know about our status] after she was born. They explained that we need to get tested [as part of diagnosis of the child]. When we received the results, we both turned out to be carriers.”

Some participants found out their carrier status as a result of ad-hoc screening conducted by the mobile teams from SHE. For this group in the study, it is important to note that all of them became aware of their carrier status before the child’s diagnosis. They did their carrier test while the woman was pregnant with the child, or when the child was a few months old with no symptoms. For example, one participant said they just took part in random testing because they had the opportunity to do it, “It’s just that we got the opportunity to do it while we were on the island.... The team came to our island, so we thought we should get tested. When we tested, we both were carriers.”

In addition, a few (four) participants accepted their carrier status based on their doctor’s explanation and their child’s condition, without a carrier test. One of them stated, “No, I haven’t [done the carrier test]. Doctors say that children need (to be) transfused because we both are carriers. There’s no point of testing after that point of time, right?... So we didn’t do the test.”

### *Life after the Diagnosis of Thalassaemia Major Child/Children*

Our results show that giving birth to a major child had a significant impact on the participants’ lives in many ways. The main influencing aspects included, difficulties with treatment for the child, having to migrate, impact on family size, change in knowledge and attitude, hardship related to caring for a major child, prejudice felt due to the condition and divorce as a result of the carriers status.

The treatment process for the major children was distressing for most participants in this study. Treatment for thalassaemia major children in Maldives is

blood transfusion and iron chelation. Maldives does not have a suitable blood banking service for the patients who need transfusions. According to the participants, the normal procedure for all thalassaemia majors was for parents/guardians to find donors and then the service provider would do cross-match and transfusion for thalassaemia majors free of charge. All participants went through that process of finding a donor every other week or so. Some of them described the process as quite “all right”.

However, for some others, accessing blood was difficult. Those participants discussed many difficulties including being unable to secure donors at times and the embarrassment of having to ask donors repeatedly. For example, one participant described contacting the donors as uncomfortable and stated, “Most of the times, if they don't answer the phone, I feel uncomfortable to call again.” Another participant described that they become helpless when they cannot find suitable donors and stated, “Once I got very helpless. I left all my dignity and asked people on the road. I approached strangers and asked their blood group and if they can give some blood.” In most cases, participants described the time passed without being able to get a matching donor as worrying and distressing.

Migration as a result of the child's diagnosis was a common scenario for many participants of this study who were from smaller islands. Many participants moved to larger islands, especially to the capital Male' to ease the difficulties of accessing transfusion services for their child/children. One such participant stated that, “We can do the transfusion from the island, but what happens is, it's difficult to get blood from a crowded place like this [Male'] even. So, we cannot get donors from the island to do transfusion every other week.” However, most of the migrated participants described the life in Male' as difficult and expensive even though access

to services was easier.

Most participants expressed the desire to have a larger family due cultural and religious reasons. For example, in Maldivian culture, children look after their elderly parents and a participant in our study reflected on this: “Everyone will grow old one day. We will need their [children’s] help and if I have many children, I will get some help.” Another participant stated she wanted a normal child because she had only one child who is a major. Some even expressed that they wanted a larger family because it is recommended in Islam, “I want another child from that [Islamic] aspect as well. It is like that in Islam, right?”

However, even with the desire and need to have a larger family, all participants used some kind of child-spacing or contraceptive method after the diagnosis of their first major child. Many started contraception because they were afraid that they might not be able care for the major child they already had. For example, one participant stated, “It is more than thalassaemia. We will not be able to give attention to this child if we get another child. If we can’t give good care for this girl [thalassaemia major child], I don't want another child.” Additionally, some participants were afraid of having another thalassaemia major child. For example, one participant stated, “I want another child, but I don’t know what will happen. If I get another thalassaemia major child, it will be an addition to the present child. It will be an additional responsibility. It will be burdensome for us.” Seeing their children pass away due to the condition and witnessing the suffering of their children when undergoing treatment were also reasons for some participants not wanting to have more children. In fact, two couples and 10 individual participants did not have an additional child after their first diagnosed major child.

Diagnosis of their first major child significantly changed the participants' knowledge of thalassaemia and attitude towards marriage between carriers. Following diagnosis, most participants in the study understood the possible consequences of being a carrier couple. All participants knew and accepted the fact that they had a major child because both were carriers of thalassaemia. They also understood that thalassaemia is hereditary and there was a chance that they might have a major child every time they get pregnant. The collective attitude of the participants towards carriers marrying carriers was, "it is not recommended" and most participants expressed strong discouragement towards it. For example, one participant expressed his opinion as follows:

What I want to say is no matter how much you love someone do not marry a carrier. You can get someone else that you love and the other person can be forgotten, but what you have to face by marrying a carrier can never be forgotten. Never get married! A huge risk like that should not be taken in life... You shouldn't get into something that hasn't got any guarantee. I will say, don't do it!

Hardship of caring for a major child was a common issue discussed by most participants in this study. Most participants expressed that having a major child was hard financially and mentally. Participants described that treatment itself was not costly because thalassaemia services were free for registered patients, but indirect costs mostly related to renting and travelling were burdensome for those who were not from Male'. For example, one participant noted, "Rent, food and other things cost about MVR10, 000 [Approximately U\$600] to stay here for about 10 days." That was a large sum of money in her case as she was a self-employed single mother

who earns about \$300 per month. Most participants described the emotional hardship that they go through when caring for a major child as being harder than anything else. For example, a man described his emotions as follows:

Actually, I get very worried. I am most saddened about these children. Their hardship and the anguish they will feel in their heart. That part is most distressing. I get very sad because of that. They were very young and cry a lot during transfusion. It was very tormenting. I cannot even explain what went through my heart at times. Those feelings are too difficult to explain. Even now I think about this girl [major daughter] a lot. Sometimes when I am alone, I think about her to the extent that I cry for myself. The sufferings she goes through and how sad she will be, how joyful others of her age are. Things like that come to my mind a lot.

Despite most participants feeling that they did not face any prejudice due to their carrier status, a few (3) expressed concerns about how the society looked at them. For example, one woman described being labelled because of the condition, “Things like ‘the child got sick because I am a bad person. There is a disease in me that I am hiding from doctors’. I got very sad when they [relatives of her husband] talked like that.” Additionally, some participants talked about their children (both major and non-major) facing prejudice in the community, albeit not in the school system. For example, one participant noted that, “They [public] look at thalassaemia major children very differently, very different than normal children; especially, in less developed islands. There are situations when they even say things at those children.” Also, a few participants felt that their non-major children faced discrimination because of their major siblings. One of them noted:

We cannot say it's [prejudice towards normal siblings] not there in Maldives... It is actually there. Sometimes (pause) for example, I have a normal child, but people restrict girls from talking to him. Like, there are some girls who don't want to get involved with my son because he has major brothers in the family... We don't exactly know the issue. It might be because it would be expensive and it might become a barrier for their future achievements. Maybe they are worried that they might have to spend on those children [thalassaemia major siblings].

Despite most participants suggesting that divorce was not a solution to their problem and they would rather stay together and assume responsibility together, a few faced the devastating consequence of divorce as a result of being a carrier. One man stated that he went for a divorce because he wanted a normal child and did not want to take the risk of another pregnancy with his carrier wife. A single mother described the diagnosis of the child and their screening as devastating and it caused them to separate in the end,

As soon as he came inside [just after the test result], he said 'we cannot live together and we should get separated.' From there...Our relationship became very weak from that day onwards... we ended up with a divorce after 10 years of marriage.

### *Coping: A Test of Faith in Islam*

Despite the hardship, worries, separations and prejudice, all participants still believed that whatever happened, it happened for the best and everything happens according to Allah's decree. For example, one participant stated, "Having a thalassaemia child (pause)... what I would say is what is there in Allah's decree will

happen. That's how I see it". Another participant stated that, "Everything happens according to Allah's Will". Since, most participants' viewed their circumstance as Allah's decree, they naturally believed that they should not complain or regret their situation. For example, one participant stated, "I look at it from a religious point of view. I cannot complain about it. We have to accept and be happy with Allah's decree."

Additionally, many participants viewed their circumstances as a test of faith from Allah and believed that Allah would not place undue burden on a human being that could not be carried out by that person. For example, one participant described his hardship as, "Allah will not burden someone to the extent that it cannot be carried by that person. So, I am being patient in these things and live my life." Moreover, most participants firmly believed that their major children are a trust from Allah given for safe keeping and it should not be neglected under any circumstance. They believed that responsibility of caring for a major child was a test of patience from Allah and it should be endured with courage. For example, one man stated that:

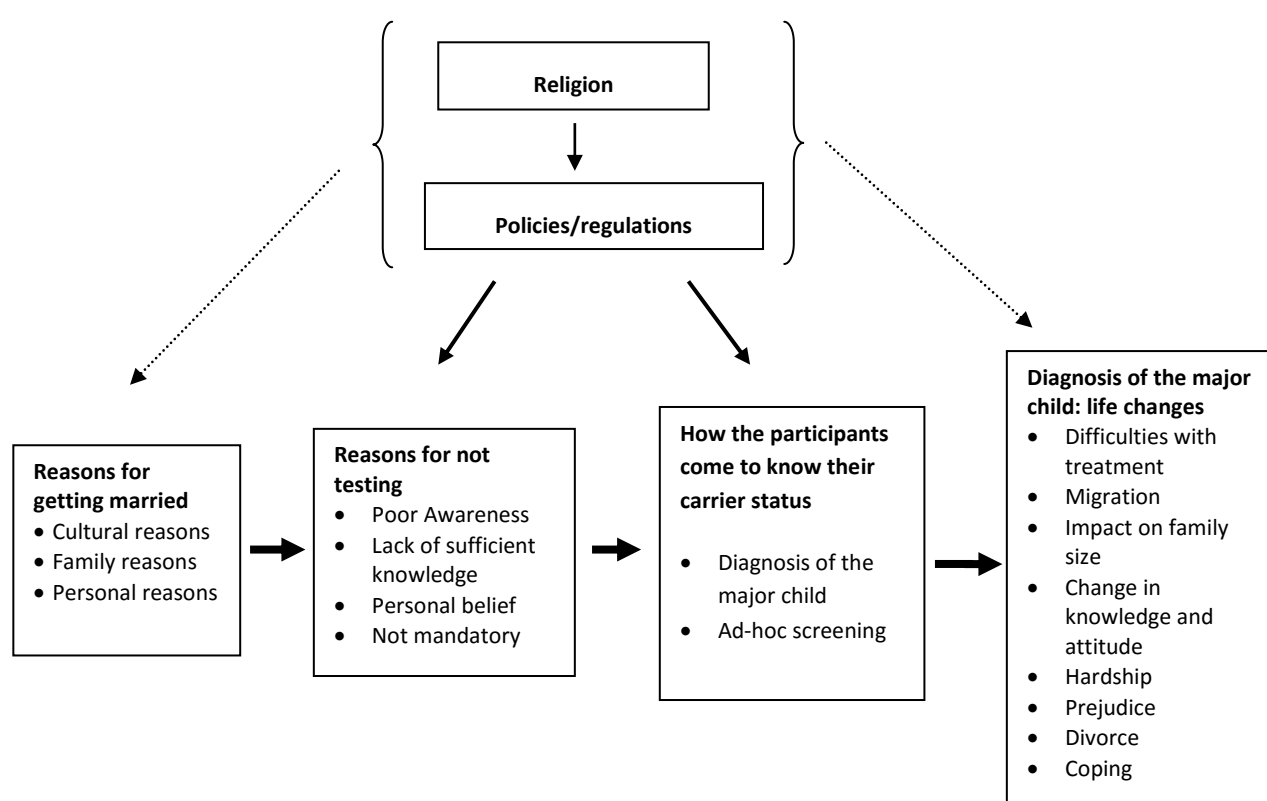
We have to work for it as long as she [major child] lives because it is an *amaanai* (trust given for safe keeping) from Allah, right? I cannot neglect her. I don't want to abandon that '*amaanai*' from Allah... There is no way that I will neglect that responsibility. I will not neglect her while my knees touch this ground (mumbles). It's a difficult responsibility that is being given to us.

Furthermore, some participants believed that they will be rewarded more from Allah for taking care of a major child because Islam says even the simplest of good deeds will be rewarded. For example, one participant stated that, "Islam says



that an affliction of a disease will wipe away sins. From what I hear, we will get more rewards and blessings for looking after a child like this than taking care of a normal child.” Hence, despite most participants described caring for major children as hard and emotionally draining, most of them accepted it as their fate and it should be endured as best as they can.

**Figure 4.1: Reasons for not testing for thalassaemia and its consequences in Maldives**



## Discussion

Findings of this research suggest that there are many reasons that individuals and/or couples do not undertake testing for thalassaemia before or after marriage in Maldives. One of the main reasons for not doing the carrier test in our study was poor awareness and lack of understanding of the possible consequences of having a thalassaemia major child. This finding is similar to the findings of Ahmed, Bekker, Hewison, and Kinsey<sup>177</sup> and Widayanti et al.<sup>51</sup> The research conducted by Ahmed

and her colleagues shows that there was a low level (61%) of intention to test among British Pakistanis and they had poor knowledge about being a carrier and inheritance of the conditions. They concluded that the high prevalence of thalassaemia major births among British Pakistanis was the results of poor knowledge and negative attitude towards carrier testing. The study by Widayanti, Ediati, Tamam, Faradz, Sistermans and Plass<sup>51</sup> was conducted to explore the opinions of Javanese mothers about thalassaemia. Their study was based on a sample of 180 Javanese mothers of whom 74 had a major child. Their findings showed that, many (43%) of their study participants had never heard of thalassaemia and only 18% of their study participants were aware of carrier testing for thalassaemia. However, most of their study participants were keen to get information and carrier testing, implying that lack of awareness played a vital role in the low levels of carrier testing among their study participants.

Awareness related findings of this study are in accordance with Health Belief Model.<sup>178</sup> Our findings show that most of our participants did not do the carrier test because they did not have the full knowledge of the condition. Hence, many of them did not perceive their susceptibility to the condition prior to the diagnosis of their first major child. That is how most of our participants became aware of their carrier status. As a result, our participants neither perceived the severity of the condition nor the benefit of testing well in time to take any precaution. Perhaps, changing the approach of health education, screening and genetic counselling provided by SHE and MBS might improve the use of the services at an earlier stage. That in return might help Maldivian population to understand the condition and its consequences better and it might help in reproductive decision making of carrier couples beforehand. In addition, this finding in Maldives suggests that awareness programs

are not achieving the targeted outcome from the whole population. At present, the awareness programs are centered in the capital Male' and populations in the islands have limited access to those services. Making it more local to the island populations and making the information more freely available to everyone in Maldives (via schools, health centres, hospitals and clinics) might be helpful in changing the situation for better.

Poor awareness in our study might be due to participants not receiving the many messages that were conveyed by the awareness programs at the time of their marriage. According to Firdous<sup>41</sup>, printed materials on thalassaemia were distributed and made available for the public via island health centres from the start of the Thalassaemia Awareness Program of SHE in 1992. In addition, the same program included extensive public education and awareness via school health education programs. Furthermore, thalassaemia was included in secondary school curricula and training courses of teachers and health personnel in 1996 as part of advocacy building among national stakeholders.<sup>41</sup> Maldives has one of the highest school attendance and literacy rates in South Asia and even the smallest populated islands have health posts with a family health worker or a community health worker. Therefore, the gap between the awareness level that programs could deliver and the real awareness level of the public needs much attention. Perhaps, it is possible that health promotion activities were well planned, but not well delivered throughout the country.

Most participants in our study stated that they would not marry if they knew their carrier status and the risks involved. This view is similar to the findings related to cancellation of marriages by participants after premarital testing in countries like Saudi Arabia<sup>64</sup> and Gaza Strip.<sup>63</sup> Memish and Saeedi found that 51.9% of those who

were tested and found to be carriers chose not to proceed with the marriage in their evaluation of outcome of national premarital screening and genetic counselling program in Saudi Arabia. The study undertaken in the Gaza Strip, Palestine by Tarazi, Al Najjar, Lulu and Sirdah <sup>63</sup> showed that as high as 73.7% of the carriers in their study did not proceed with the marriage to their carrier partners. Hence, the negative attitude towards carriers marrying carriers among our participants provides a point of intervention for more effective strategies in the thalassaemia program.

Timing is an important factor that needs further attention in Maldives. Premarital screening undertaken just prior to marriage like in many other Muslim countries (see for example the study conducted by Memish and Saeedi <sup>64</sup> in Saudi Arabia) might not work in Maldives. It might be ‘too late’ to not proceed with marriage due to the cultural differences. Dating and seeing the other person as a compatible life partner was one of the major factors that contributed for most participants’ decision to proceed to marriage in our study. Hence, premarital testing just before marriage might not be effective as dating for a long period would make the relationship public on most islands and it might be difficult for intending couples not to proceed with the marriage even if testing confirms their positive carrier status. Difficulties experienced with cancelling wedding plans and stigmatization were common reasons for proceeding with the marriage in other countries as well. For example, studies conducted in Saudi Arabia showed that many Saudi couples proceeded with marriage even though they were advised about their carrier status because of issues like cost of cancelling wedding plans and stigmatization.<sup>48,49,179</sup> Additionally, studies conducted in Southern Iran also showed similar findings because cancelling wedding plans once they become public was not an option for many in Southern Iran.<sup>62</sup> Therefore, the marriage culture of ‘dating and marrying’

suggests that timing of the screening is an important factor that might influence the choice of prospective marriage partners in Maldives.

A few participants in our study indicated that compulsory premarital testing would have prevented them getting married without testing. They indicated that they knew about thalassaemia, but did not do the test because it was not compulsory at the time of their marriage. This finding is similar to the findings of Bozkurt<sup>37</sup> in Cyprus and screening related findings in primary health care centres of Oman.<sup>170</sup> According to Bozkurt's study<sup>37</sup>, only 42% of the participants in Cyprus volunteered for the screening test while 58% undertook the screening because it was compulsory. Likewise, Al-Farsi and his colleagues<sup>170</sup> found that 84.5% of their study participants in Oman thought that premarital screening was important and 49.5% participants believed that it should be made compulsory. The new thalassaemia law of Maldives mandates every child is screened before 18 years of age. Therefore, the future uptake of screening might be different from the findings of this study.

Not screening for thalassaemia before or after marriage had devastating consequences for our study participants. The most difficult and distressing consequence was the emotional trauma that they experienced as a result of the suffering of their child/children. This finding provides qualitative insight into the high prevalence of depression observed among the mothers of thalassaemia and blood malignancies children in Iran<sup>73</sup> and high parental anxiety that was apparent among the parents of thalassaemia major children in Turkey.<sup>74</sup> The Iranian study was conducted using the Beck Depression Inventory. The mothers in that study had a depression score of 2.17 (95% CI = 1.16–4.0, P = 0.015). The study conducted in Turkey by Sharghi and his colleagues<sup>73</sup> reported that 82% of the parents of their study had high levels of anxiety. Maldives has a large thalassaemia major

population, but there are no support services (formal) for parents of thalassaemia majors Maldives. This finding shows the importance of support service for the mental wellbeing of the parents of thalassaemia majors.

Thalassaemia treatment is free of charge in Maldives, however, many participants, especially those who were from the islands described indirect costs such as rentals and travelling to access the services was burdensome for them. This phenomenon was observed among the parents of thalassaemia patients in other countries as well. For example, a study conducted in Turkey by Canatan, Ratip, Kaptan and Cosan<sup>74</sup> revealed that almost half (47%) of the families that were included in their study had financial difficulties because of thalassaemia major children and related issues despite the treatment itself being free of charge in Turkey. This finding reveals the need for the government based extra financial assistance for thalassaemia majors and their families who were experiencing financial difficulties due to the indirect factors such as travel.

Many participants in our study wanted larger families, but all started some kind of child spacing or contraception after the diagnosis of their first major child in order to prevent further pregnancies. The main reason for that was the fear that they might not be able to take care of the present major child and the uncertainty around the status of the child from any subsequent pregnancies. Hence, trying to compensate for the genetically affected child was not a common phenomenon among this group of participants. These findings are different to the findings that were observed among the parents of thalassaemia majors in Fars province, Iran.<sup>180</sup> The findings in Fars province showed that regardless of the number of affected children with thalassaemia in a family, parents in that area had a similar average number of unaffected children as parents without that disorder. The difference in our study

might be due to the fact that participants were not aware of their carrier status when they started the family and were more concerned about wellbeing of the major child than trying to compensate for the loss. Which is different from findings in other countries and it would be a good area for further research.

The consequences of having a major child were extremely hard for most of our participants, but none of them regretted giving birth to their major child. Most participants believed their circumstances were, “Allah’s Will”. Additionally, many believed that the major child was a test from Allah and they will be rewarded for caring them. Furthermore, many believed that their major children were an ‘*amaanai*’ (trust for safe keeping) from Allah and they should not neglect that responsibility under any circumstance. Similar findings were observed by Shaw and Hurst<sup>181</sup> and Rozario.<sup>182</sup> Shaw and Hurst’s<sup>181</sup> study showed that their participants (mainly British Pakistani Muslims) believed the genetic condition that they faced was God’s decision and most of them believed their condition or that of their children was a test from God and they should endure it. Findings from the study undertaken by Rozario<sup>182</sup> also showed that strong faith and being content with Allah’s decision was important for the Bangladeshi couples in their study. Hence, faith played an important role in the lives of our study participants’ and how they dealt with issues related to their carrier status and the birth of their major child/children.

### **Limitations**

The study was conducted in the capital city Male’ and by doing that we were not able to access all the cases in Maldives. This was the main limitation of the study. We were, however, able to access participants from 10 different atolls out of the 20

atolls. Therefore, potential of the study is still strong in terms of access to participants.

## **Conclusion**

Thalassaemia is a common genetic disorder across Maldives. The population wide carrier testing program for thalassaemia was introduced in 1992, free of charge. The findings of this study revealed that there are many reasons why Maldivians do not undertake premarital testing or testing after marriage. Most common reasons included poor awareness of the availability of the service, poor knowledge about the condition and the consequences of it and the non-compulsory nature of the test at the time of their marriage. The consequences of giving birth to a thalassaemia major child were challenging and life changing for most participants in this study. Most challenges were related to caring for major child and the concomitant emotional hardship they experienced. In addition, having a thalassaemia major child was inevitably life-changing with parents moving to the larger population centre Male' to obtain services and having to control their family size. Religion appeared to inform every decision at every stage of their life, however, which is considered positive.

It is apparent from our findings that the thalassaemia awareness program of Maldives needs to be strengthened. Maldives has a culture of selecting own partners and dating before proceeding to a marriage. Therefore, even if the population receives the awareness messages, cancellation of marriages based on premarital test results might be less effective compared to many other Muslim countries where marriages are mostly arranged. Therefore, in order to improve outcomes, the prevention program needs to incorporate more reproductive options such as prenatal diagnosis and pre-implantation diagnosis.



### **Acknowledgement**

We would like to thank all the participants who took part in this study and all the staff of MBS for all the help they provided during data collection.

### **Conflict of Interest**

Fazeela Waheed, Colleen Fisher, Niyi Awofeso and David Stanley declare that they have no conflict of interest.

### **Compliance with Ethics Guidelines**

This study was approved by the ethics committee of the University of Western Australia (Ref: RA/4/1/5626) in accordance with the requirements of the National Statement on Ethical Conduct in Human Research (National Statement) and the policies and procedures of The University of Western Australia. In Addition, the study was approved by the National Health Research Committee of Maldives on 7<sup>th</sup> of February, 2013. All procedures of this study were carried out in accordance to the laws and regulations of Australia and Maldives. All participants provided written consent prior to study.

## Chapter 5: Paper Two

### Introduction to the Chapter

Chapter five is the second paper produced based on the second objective of the first study, “Explore the reasons why carriers of thalassaemia in Maldives marry and have children despite knowing their carrier status.” The paper was submitted to the Journal of Community Genetics and the reference is as follows:

*Reference:* Waheed F, Fisher C, Awofeso N, Stanley D. Why do Maldivians marry and have children in spite of positive thalassaemia carrier status. Journal of Community Genetics. 2015. (Submitted).

The paper included abstract, introduction to thalassaemia and thalassaemia prevention, introduction to Maldives and thalassaemia prevention in Maldives, study method, results, discussion, conclusion and limitations of the study. The paper is presented as submitted to the journal except with the changes of Figure and Table number and reference style. The numbers given for the Figure and Table were 1 in the original paper. The chapter number ‘5’ was added to the original Figure and Table number to assist the flow of the thesis. APA referencing was used in the original article that was submitted to the journal. The referencing was changed from APA to Vancouver system to ensure consistency in referencing throughout the thesis.

**Title: Why do Maldivians marry and have children in spite of positive thalassaemia carrier status.**

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## Abstract

Thalassaemia is one of the most common genetic disorders globally. The Republic of Maldives (Maldives) has one of the world's highest carrier rates with 16-18% of Maldivians being  $\beta$ -thalassaemia carriers. Carrier screening services were established in Maldives in 1992. However, 28 new major cases are recorded, on average each year. The aim of this study was to explore the reasons why thalassaemia carriers in Maldives marry and have children despite knowing their carrier status. The study was conducted using qualitative methods. Our findings show that most participants were tested in their early teens. They claimed that their marriage was their choice and genetic make-up was not a barrier to marriage. Despite this, most participants regretted their decision to have children without preventive measures such as prenatal diagnosis. Hence, it is evident that many Maldivians are aware of the importance of testing for thalassaemia, but there are significant differences in motivations for screening, marriage and having children.

## Keywords

Maldives; thalassaemia; carrier testing/screening; premarital testing; major children

## Thalassaemia

Thalassaemias are described as “a group of autosomal-recessive conditions comprising of abnormalities in  $\alpha$ - and  $\beta$ -globin synthesis”.<sup>183, p.558</sup> They are among the most commonly found genetic disorders in the world. Population estimates show that 3% of the world population is heterozygous for  $\beta$ -thalassaemia.<sup>35</sup> According to Birgens and Ljung<sup>35</sup>, more than 300,000 children are born with severe  $\beta$ -globin disorders each year. A ‘thalassaemia major’ is described as someone who has severe transfusion-dependent anemia due to homozygous or compound heterozygous for two  $\beta^0$ -thalassaemia alleles.<sup>35</sup> Beta-thalassaemia cases with severe anaemia do not normally survive beyond three years if untreated.<sup>15</sup> At present, bone marrow transplant from a fully compatible donor is the only cure for  $\beta$  thalassaemia majors. However, it is an extremely expensive and difficult procedure due to non-availability of suitable donors and the risks involved in the procedure. Hence, the main treatment used for thalassaemia major children is regular blood transfusion representing a major health care cost for thalassaemia endemic countries. Thus, most thalassaemia prevalent countries have prevention strategies to minimize the number of new cases.

## Thalassaemia Prevention

Screening with genetic counselling are the main primary prevention strategies used in thalassaemia prevention programs. Genetic screening programs are developed and implemented differently in different communities depending on the need. There are screening programs that target school age students to inform them of their carrier status at an early stage (see for example,<sup>184</sup>). Some communities have more targeted ethnic or family-centered screening<sup>100</sup>, for example, targeting certain ethnic groups that have high thalassaemia carrier rates and people who have a

familial history of the condition.<sup>185</sup> In addition, it is sometimes done in early antenatal checkups<sup>186</sup> or as part of early clinical screening for newborns such as in United Kingdom (UK).<sup>187</sup> A commonly practiced approach however, is premarital testing with genetic counselling targeting couples who are planning to get married. Many countries such as Iran<sup>188</sup>, Saudi Arabia<sup>64</sup>, Greece<sup>91</sup>, Cyprus<sup>37</sup> and Dubai in the United Arab Emirates<sup>189</sup> have premarital screening programs in place for thalassaemia. According to Alswaidi and O'Brien<sup>190</sup>, the aim of premarital screening programs in such countries is to identify carriers of hemoglobin disorders and assess the risks of having children with severe forms of those disorder. For the purpose of this paper, we define premarital testing as being screened for thalassaemia just prior to marriage, for the purpose of getting married and later to start a family.

### **Republic of Maldives**

Republic of Maldives (Maldives) is an island nation in the Indian Ocean, South West of Sri Lanka. It comprises 1192 coral islands divided into 20 atolls for administrative purposes. According to the census of 2014, Maldives has a local population of 344, 023 and about one third (129,381) of the Maldivian population lives in the capital Male'.<sup>172</sup> Islam is the state religion and all Maldivians are Sunni Muslim by law.<sup>173</sup> Maldives has a literacy rate of 98%<sup>174</sup> and Dhivehi is the local language.

### **Thalassaemia and Screening in Maldives**

$\beta$ -thalassaemia is one of the most common genetic disorders in Maldives with the country having one of the highest  $\beta$ -thalassaemia carrier rates (16-18%) in the world.<sup>14</sup> The carrier prevalence rate of individual islands ranges up to 41% and

between 8.9% and 27.1% by atolls.<sup>21</sup> As a result, Maldives has a comparatively large thalassaemia major population in relation to its total population size; a cumulative total of 803 thalassaemia patients were registered for treatment as at August 2014.<sup>14</sup> Hence, the burden from this disorder is quite high for Maldives and a number of preventive measures are in place to minimize new major cases.

Screening for thalassaemia in Maldives was first initiated by the non-governmental organization, Society for Health Education (SHE) in 1992.<sup>41</sup> Its screening program offered testing in Male' in its facility and testing in islands by its mobile teams. The National Thalassaemia Centre (NTC), now part of Maldives Blood Services (MBS), was established with screening, patient registration and treatment facilities in 1994.<sup>42</sup> At present, screening is available from SHE and MBS, both of which are situated in capital city Male'. The screening services for outreach populations is still provided by the mobile teams of SHE<sup>41</sup>, however, there are many who travel and visit the two screening centres in Male' at their own expense. According to the program guidelines, trained counsellors provide genetic counselling in both centres.<sup>191</sup> Under SHE's screening program, one-to-one genetic counselling is provided to carriers who live in Male' and at-risk couples in outer atolls are followed up by return telephone calls when their results are issued.<sup>41</sup>

According to Firdous, Gibbons and Modell<sup>21</sup>, the national thalassaemia register of Maldives shows an approximate 60% fall in affected birth prevalence after the establishment of the population screening program. However, after this fall in the initial stage, the number of new cases has remained more or less constant in the last decade. Data from the Ministry of Health<sup>78</sup> for the period of 2001 to 2012 shows that, on average 28 new cases are registered annually. Which is a quite high incident rate compared to the success achieved by many other countries that have

mandatory premarital testing for thalassaemia such as Cyprus<sup>37</sup>, Iran<sup>188</sup>, Gaza Strip and Palestine.<sup>63</sup> The cause of this ongoing high incident rate in Maldives, however, has not previously been researched.

Until recently, premarital testing for thalassaemia was a recommendation in all parts of Maldives except in the capital city Male', where it has been mandatory since 2002 (Ahmed Abdulla, marriage registrar of family court of Male', Maldives, personal communication, June 16, 2012). Under the current thalassaemia law (approved 10<sup>th</sup> May 2012), it is mandatory for all Maldivian children to be screened for thalassaemia before the age of 18, which is the earliest legal age that a person can marry in Maldives.<sup>175</sup> The common rule is that premarital testing was and is not necessary if the intending couples had tested for thalassaemia before and if they can provide their test results. Even though screening was not mandatory in most parts of Maldives prior to the thalassaemia law, a large population was screened by SHE on voluntary basis. The screening program of SHE reached all inhabited islands (200 island) of Maldives by 2002<sup>41</sup> and over 65% of the reproductive aged population were screened by 2007.<sup>21</sup>

Hence, the high incidence of new thalassaemia major cases might be a result of many Maldivians marrying and having children despite knowing the carrier status. Research into this issue is required to improve the outcomes of thalassaemia screening measures used in Maldives. This study was a part of a larger study, the aim of which was to explore thalassaemia control measures at Primary, Secondary and Tertiary level in Maldives. The objective of this particular study was to explore the reasons why carriers of thalassaemia in Maldives marry and have children despite knowing their carrier status.



## Method

Views and perspectives related to thalassaemia carriers who are aware of their carrier status and had major children have not previously been researched in the Maldivian context. Most studies that have explored the perspectives of carriers and the effectiveness of thalassaemia screening programs have been quantitative by design<sup>48,51,60,62,161</sup> with limited studies using qualitative approaches.<sup>50,192</sup> Due to its exploratory nature and the need for an in-depth understanding of the issue, a qualitative approach which would provide an emic understanding of the issue<sup>148</sup> was chosen for this study and, as such, would be an important contribution to the literature. Therefore, a generic qualitative approach<sup>149</sup> was utilized, underpinned by a constructivist ontological and epistemological stance.

### *Recruitment and Sample*

Participants were purposively selected to ensure a broad coverage of atolls. To facilitate this we arranged data collection to coincide with school study-break - a time when many parents from the atolls visit the MBS (the main transfusion centre of Maldives) to consult doctors and to undertake regular tests of their major children.

To be included in the study, participants were required to be Maldivians who married and had major child/children despite knowing their positive carrier status. To access the participants, the first author (FW) visited MBS on several occasions and approached the parents of major children during transfusion. Culturally, it is the norm that most patients, irrespective of their age are accompanied by their parents during their transfusion. The contact details of the parents who showed interest in participating in the study were noted during the first few interactions before inviting them to participate in the interviews. Later, potential participants were contacted to

arrange a mutually convenient time and a place for the interview.

### *Data Collection*

We used Face-to-face in-depth interviews<sup>153</sup> to collect the data for this study. An interview guide based on literature was developed prior to data collection. Using the guide, FW conducted all the interviews in Maldivian local language Dhivehi. Each interview lasted for about an hour and was digitally recorded for analysis purposes. Our aim was to interview individual women and men because individuals may be more willing to share information that they may not disclose in front of their partners.<sup>193</sup> However, four individuals preferred to participate in the interviews with their partner. Twelve individual interviews were conducted in the private room provided for this study by the centre with three individuals and four couples preferring to be interviewed in their own home.

### *Data Analysis*

Preliminary data analysis commenced following the first interview and continued concurrently with data collection by FW in collaboration with CF. Initially, FW listened to audio recordings, wrote memos in a field journal about the perspectives of the participants and recorded first impressions for each interview. This immersion in the data was an opportunity for the interviewer to guide the participants more appropriately in subsequent interviews through bringing important issues raised in previous interviews into the discussion.<sup>194</sup>

A thematic analysis as described by Braun and Clarke<sup>154</sup> was used to analyse the data. Following the completion of the interviews, all were translated from Dhivehi to English, transcribed concurrently and read to become familiar with the data. This was followed by a close line-by-line reading and open coding of data

through identification of significant concepts that were relevant to the research objectives. The concepts were then clustered together to form potential themes. All the potential themes were further developed and refined in the next stage through interrogation of each theme individually. As a final stage of analysis, all the refined themes were again reviewed to clearly define and name them for reporting. We used qualitative data analysis program NVivo 10 for data storage, management, retrieval and interrogation.

## **Results**

Data from the interviews provided an in-depth understanding of the reasons why Maldivians marry and have children despite knowing their thalassaemia carrier status. We initially describe participant characteristics and participants' reasons for undergoing screening for thalassaemia followed by an exploration of participants' access to genetic counselling. We then report our findings regarding their decision to marry and have children as three themes; 'Carriers also can marry', 'Marriage is our choice' and 'Life after marriage'. A conceptual map of the findings is provided in Figure 5.1.

### *Participant Characteristics*

Details of the demographic characteristics of participants are outlined in Table 5.1. A total of 15 individuals and 4 couples from 10 different atolls of Maldives contributed to this study - 13 women and 10 men. The testing age of the participants in this study ranged from 11 to 25 years. Most (22/23) participants found out their carrier status in their teens - long before they married or started dating. All except four participants were not in a relationship at the time of their test. Hence, it suggests that there was no premarital couple screening as such; rather individuals undertook screening in their preferred time or occasion.

Table 5.1: Characteristics of Participants

| Characteristics                                       | No of participants |
|-------------------------------------------------------|--------------------|
| <b>Total (23)</b>                                     |                    |
| No. of Men                                            | 10                 |
| No. of Women                                          | 13                 |
| <b>Participants' residential area</b>                 |                    |
| North of Male'                                        | 10                 |
| Male' (capital city)                                  | 8                  |
| South of Male                                         | 5                  |
| <b>Age of the Participants</b>                        |                    |
| 21 - 30 years                                         | 10                 |
| 30 – 40 years                                         | 13                 |
| <b>Testing age</b>                                    |                    |
| 11- 17 years                                          | 15                 |
| 18 -25 years                                          | 8                  |
| <b>Age of marriage</b>                                |                    |
| 18-25 years                                           | 14                 |
| 26-35 years                                           | 9                  |
| <b>Marital status</b>                                 |                    |
| Married                                               | 16                 |
| Divorced                                              | 7                  |
| <b>Related to the partner</b>                         |                    |
| Not related at all                                    | 21                 |
| Distant relatives (3 <sup>rd</sup> cousin or further) | 2                  |
| <b>Employment</b>                                     |                    |
| Employed                                              | 11                 |
| Not employed                                          | 12                 |
| <b>Education level</b>                                |                    |
| Completed primary education (Grade 5)                 | 3                  |
| Completed Middle school (Grade7)                      | 7                  |
| Completed Secondary school or higher                  | 13                 |
| <b>Testing center</b>                                 |                    |
| SHE                                                   | 15                 |
| Thalassaemia center                                   | 4                  |
| Both SHE and thalassaemia center                      | 4                  |
| <b>Genetic counseling</b>                             |                    |
| Received                                              | 9                  |
| Did not receive                                       | 14                 |

### *Reasons for Screening*

Participants in this study were screened and checked their thalassaemia carrier status for various reasons. Most participants stated that they did the screening test because they heard about its importance via different information sources such as radio, television, schools, friends, family members and other community

members. Some participants undertook the test because they said testing was ‘encouraged’ among young adults and they followed their close friends and family when they were getting screened for the condition. A few participants screened because they had thalassaemia major siblings or cousins in their families. In addition, availability of screening through mobile teams of SHE was another reason for some who came from outer atolls to be tested. Only one participant did the carrier test to get married (premarital test). She stated that she and her intended husband had to undertake premarital screening for thalassaemia because she had not done the test before and they had to provide the test result when lodging their marriage form in Male’.

#### *Test related counselling*

Most of our study participants (15) did their carrier test from SHE with four participants testing through NTC in our study. Four more participants tested through SHE and later repeated the test through NTC to obtain further confirmation. Nine participants received genetic counselling with their positive test result and 14 participants stated that they did not receive any counselling or information in any form when they received their test results.

Participants who received counselling perceived the counselling session to be brief with the main subject being the chance of conceiving a major child if they married another carrier. Receiving a positive test result or providing information during subsequent test related counselling did not appear to impact greatly on participants’ marriage plans and decisions. Both those who received counselling and those who did not expressed the same kind of views and thoughts in regard to their marriage decision. For example, one participant who did not receive counselling with the result stated that “No, it [test result] didn't change my thinking [about

marriage] as such.” Another participant who received counselling with the positive test result stated, “I didn't think like that [dating a non-carrier]... I didn't give much thought even though they gave counselling.” In fact, most participants who did not receive counselling thought that their decision to marry their carrier partner would probably not change even if counselling was received. However, some participants from both groups stated that they sought more information when they received the positive test result with most seeking information related to reproductive health options/procedures for carrier couples, the cost of those procedures and where they were available. The most commonly sought information was prenatal diagnosis related information.

In the following sections we report our findings related to participants' reasons to marry their carrier partners and have children despite knowing their carrier status.

#### *Carriers also can Marry*

Being a thalassaemia carrier is a common phenomenon in the islands of Maldives. Carrier testing at an early age and having the knowledge of their genetic condition, did not deter our participants from marrying other carriers, that is, they considered ‘carriers also can marry’. Most participants were aware that thalassaemia is hereditary and what the outcome would be if two carriers started a family. In addition, most participants were aware of the possible reproductive options available for carrier couples. Hence, most participants did not consider genetic make-up as a reason for them to not to marry carriers. For example, one participant described his thoughts as, “My justification is just being a carrier does not mean that we shouldn't [get married].”

Most participants in this study understood that any of their children might be thalassaemia major with only two stating that they had trouble understanding that the probability of having a major child in every pregnancy was 25%. One of them explained his understanding as: “I didn’t think my second child might be a major as well (pause) because my first child is a major”. It appears that he understood the probability of a one in four chance as being one from four children, rather than a one in four chance in every pregnancy.

Despite most participants’ understanding of the possibility of having a major child, most of them did not appear to perceive or comprehend the severity and hardship of the condition when they made the decision to marry. For example, one man reflected: “I didn’t think about that [the consequences] too much at that time...what it [having a major child] really meant.” Another man noted that, “I didn’t feel it [thalassaemia] much then. I didn’t realize what it [thalassaemia] is...I didn’t know what it would be like to have a major child. I didn’t feel the suffering involved in it [thalassaemia].” The participant who did premarital testing noted that:

Transfusion dependent children or thalassaemia majors were not important topics for me then. I didn’t have time to worry about those things. I just asked what it [test] was for. When I asked them [people in the marriage court] they gave their answer. So, I said, “what’s the big deal about it? What’s the problem even if we get a major child”. What I knew at the time was that there were major children. I didn’t know the difficulties involved in it or the damage it would have on a child.

### *Marriage is our choice*

Since the participants in this study did not consider their genetic make-up as a barrier to marriage, their decision was to get married. There were three main

factors impacting on their pre-marriage views that ‘marriage is our choice’: their religious faith, their intent to undertake prenatal diagnosis and a declaration that they would address any situation together when or if it arose.

Most participants stated that they and their partners hoped for a normal child but even if they had a major child ‘it is Allah’s will’. For example, one man stated that, “I believe that Allah will not burden us with something that cannot be carried out by us.” Another man stated that, “Getting or not getting a child [a major child] is not in our hand.” Another participant responded to the question of their thoughts when they decided to get married as “We left it for Allah. Whatever happens is for good.”

In addition to trust in Allah, most participants made the decision to marry their carrier partner because they had planned to undertake prenatal diagnosis once they had conceived. As such one man noted:

When we got married we thought there were so many options. We thought we could also do PND [prenatal diagnosis] and option to terminate was also there. That’s what we thought. We actually considered that [prenatal diagnosis] when we got married.

Additionally, some participants were very much aware of the possibilities of having a major child, but they made their choice hoping to ‘face it together’ if they birthed a major child. For example, one man explained, “We got married even though we are carriers. We did it because we were prepared to face it even if we get a major child.” Another man reflected that, “We knew how much effort we have to put in [if their child is a major] and how patient we have to be in the worst case scenario” but considered they were prepared to face that challenge together. One of



the women noted that, “We decided that we will face all that [if they get a major child] together and we got married on that understanding.”

### *Life after Marriage*

The choice or decision to marry their carrier partner was easy for most participants in this study, but life after the marriage was not as smooth as most of them expected. Many factors affected the participants’ marriage with their carrier partners including pregnancy, the stress involved in the pregnancy, impact on their family size and regret.

As noted previously, most participants married after their decision to undertake prenatal diagnosis once they conceived. Many of them, however, ended up not using that service for variety of reasons including that the reality of contemplating this procedure, once they had conceived, was very different to contemplating it at some time in the future. For example, one woman explained that she was not prepared to face the pregnancy because it was unexpected and stated that, “I wasn't ready when I got pregnant... We didn't have the intention of getting a child as soon as we get married”. Another participant explained, “It [pregnancy] was an accident. We didn't know that she was pregnant. We came to know about it when her period got delayed and when she got very sick....it was passed four months”

Financial difficulties and the cost of the procedure was another major reason that some participants in this study did not proceed with prenatal diagnosis. Prenatal diagnosis services were not available in Maldives which meant that participants would have had to travel overseas to access the service resulting in a high cost that they could not afford at the time. For example, one participant stated that, “It [prenatal diagnosis] cannot be done from here and we have to travel overseas. They

[SHE] provided all the information like, where we have to go, the cost and the time it will take. But we couldn't afford it at that time.”

In addition to preparedness and cost, some participants who thought they would use prenatal diagnosis in their pregnancies later changed their mind because they might have to terminate the pregnancy if the foetus was diagnosed as a major child. Most participants stated that the diagnosis part of the procedure was not an issue for them. However, for some participants, terminating a pregnancy in case of a major child was a significant factor that changed the thinking about going through with prenatal diagnosis. For example, one woman who had undertaken prenatal diagnosis twice before and terminated her first pregnancy stated that, “We both had the intention of doing prenatal [prenatal diagnosis] when we have children. We did it [prenatal diagnosis] for the second baby as well...but I couldn't go through it for a third time...abortion was too traumatic for me.”

Additionally, a few participants in the study stated that they did not undergo prenatal diagnosis because they hung on to the hope that they would have a normal child. For example, one woman stated that, “I didn't think it would happen to me. I was thinking that it will be good with Allah's will. People get normal children, right? So, I didn't look for any more information or anything like that [tests or precautions].” Another woman whose first child was a major child and was five months pregnant at the time of the interview described her thoughts as:

I didn't even think about it [that child might be a major child] when I was pregnant. I didn't think that the child might be a major. I always hoped that she [her first child] would be normal. This time is also like that. I am not too worried even this time. I am hoping that this child will be normal. I pray that this child will be a normal child.

Knowing their carrier status and being pregnant but not knowing the thalassaemia status of their unborn child was stressful and worrisome for most participants. For example, one participant reflected: “I was worried all the time thinking about what kind of a child it would be.” Another participant noted: “They [doctors in the reproductive health centre] advised us to do the test. Then it started to trigger in my mind. Then I started worrying and I was very unhappy the whole time.”

As stated previously, most participants did not realize the consequences of the condition until they had their major child. All participants started some kind of family planning after the diagnosis of their first major child through fear of conceiving another. In fact, most participants restricted their family size after their first major child and some did not want another child. For example, a woman whose first child was diagnosed as a thalassaemia major described her decision about a second child as follows:

I didn't want to try and get a normal child while we have one child. I didn't want get a child with that intention. I didn't want to try and get a normal child because she is a major child... My husband said we should get one more child. But I told him that I don't want another child based on the fact that she is a major child. Also, I kept on thinking that she might think that we got another child to get a normal child. That's why I didn't want another child.

More commonly, participants used child spacing and had a long gap before the next child. For example, one woman stated that she waited for 10 years contemplating whether she should have a second child. Additionally, some had

fewer children than they really wanted because they would have had to undergo prenatal diagnosis for each pregnancy to ensure they did not birth another major child. For example, one participant stated that, “We thought we had to do all the tests [prenatal diagnosis] even if we go for a third child. So, two is Ok for us. That’s why, I didn’t think of a third child.”

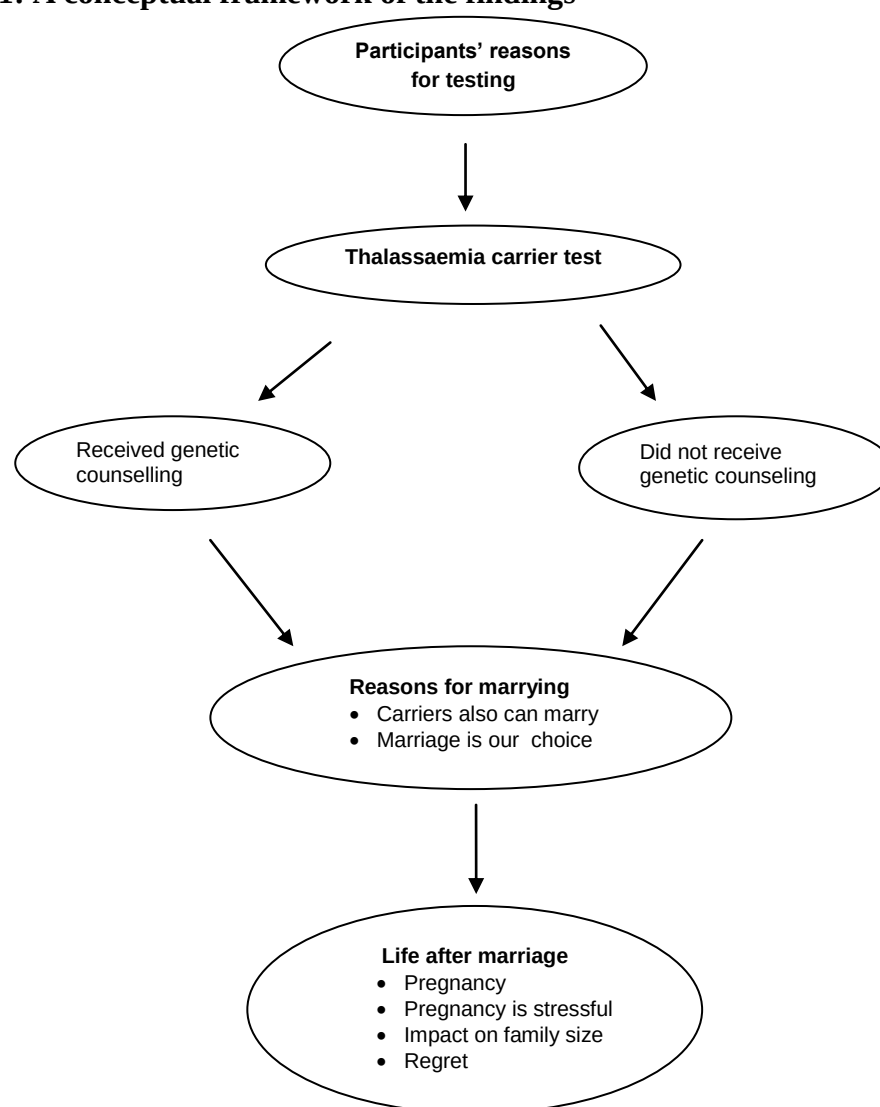
In addition, some participants had a second or an additional child after a long gap because the doctors advised them to have a sibling to secure a donor and enable a bone marrow transplant for the major child – a so called ‘saviour child’. For example, one woman stated that, “We wanted to do bone marrow [Bone Marrow Transplant]. When we talked to doctors, all of them advised us to go for a second child. So, that’s why we got a second child.” Five of those who tried for a ‘savior child’, had that next child after prenatal diagnosis. Further, eight participants stated that they want and might try for a savior child for their major child in the future, but, in that case, will go for prenatal diagnosis.

Despite all the difficulties, only a few participants regretted their decision to get married. One such woman noted that: “I feel very guilty when I have to say that I knew it [both are carriers] and got married. I feel that I got married because I am very selfish. I feel like that a lot.” Another participant who regretted her marriage decision said, “At that moment [when the child got diagnosed] I even thought that it would have been better if we hadn’t got married.”

Some participants, however, regretted not doing prenatal diagnosis even though they were content with their major child. For example, one woman described her thoughts as “Later, when I got my daughter and when I saw her suffering, I thought our decision [to not to do prenatal diagnosis] was not right.” Another participant who wished that she had done prenatal diagnosis expressed her regret as:

Now I get very upset because I was so careless at that time. I should have thought about it [the suffering of the major children]. We have one in our family and we see everything right next to us. I didn't think about it [the suffering] at all at that time.

**Figure 5.1: A conceptual framework of the findings**



## Discussion

Most participants in this study found out their carrier status during their early teens which is long before marrying age in Maldives. This suggests that reach of the screening program is such that premarital testing is not a major component of prevention efforts around thalassaemia in Maldives. Rather early school age

screening is more common. However, early knowledge of their carrier status did not deter our participants from marrying other carriers and having children. This finding contradicts with the outcome of the scholastic universal screening offered for school age students in Latium, Italy.<sup>184</sup> The Latium program was targeted at school age students of 13 to 14 years and young adults.<sup>184</sup> The Latium program was initiated in 1975 and no new incidents were reported since 1993.<sup>184</sup> The authors suggest that they were able to prevent new incidences because the early identification of thalassaemia carrier status and provision of information might have helped in choosing appropriate reproductive options.<sup>184</sup> According to our study findings, awareness and uptake of screening at an early age was evident in Maldives, but the intended outcome of screening – prevention of birth of major children – does not appear to be being met in many instances. Hence, attention needs to be paid to the early carrier testing offered in Maldives as it has the potential to be made more effective as reported from the program in Latium, Italy. Change in areas such as the information provided or genetic counselling might help to improve the situation in Maldives. Information provided and counselling should be made readily available and accessible for the public, especially for carrier couples. Additionally, counselling should be relevant, comprehensive and in languages and terms that are understandable for couples from different backgrounds.

Our findings show that less than half of our study participants received any test related genetic counselling or information when they received their positive carrier test results irrespective of where they were tested. This is contradictory to the observation of Firdous<sup>41</sup> in her review of the thalassaemia prevention efforts in Maldives. According to Firdous<sup>41</sup>, one-to-one genetic counselling was offered to carriers who live in Male' and at-risk couples in outer atolls were followed up by

return telephone calls when their results were issued. However, our finding suggests that access to thalassaemia related genetic counselling was poor and it needs to be improved in Maldives. Rather than trying to follow up with return phone calls, arrangements with health entities can be made to provide face to face genetic counselling. Usually, all health centres have trained health promotion staff and use of that human resource for genetic counselling could be negotiated with the health ministry. If the genetic counselling could be arranged through island and atoll health facilities, referral to further genetic counselling for more complicated cases can also be arranged through the system.

Those participants who did receive genetic counselling, reflected that it was very brief, which may have led to misconceptions about the ‘probability of having a major child in every pregnancy’ among a few participants in our study. Similar findings were reported by Cousens, Gaff, Metcalfe and Delatycki <sup>192</sup>, who found that some of their study participants also received insufficient information leading to such misconceptions and confusions including that all their children would die if their partner was also a carrier. This highlights the importance of ensuring that carriers are well informed when their results are issued to them.

Additionally, we found that most of our study participants sought further information related to reproductive health options potentially indicating that counselling sessions did not cover all the information that they needed. Similar issues were highlighted by Ngim, Lai and Ibrahim <sup>195</sup> in their study about attitudes towards prenatal diagnosis and abortion in Malaysia. Their study aim was to assess health care workers’ attitude towards discussing prenatal diagnosis and termination in genetic counselling sessions for thalassaemia. The findings of that study showed that most health care workers were in favour of discussing prenatal diagnosis but not

about termination of pregnancy because many of them felt the condition was not serious enough to suggest termination as an option, as well as religious (mostly Muslim) and legal reasons. Accordingly, Ngim and her colleagues<sup>195</sup> found that Malaysians who were screened for thalassaemia received counselling, but did not receive comprehensive information about prenatal diagnosis and termination options. Like the findings in Malaysia, the genetic counsellors of Maldives might have avoided talking about reproductive options such as prenatal diagnosis and termination of pregnancy for thalassaemia due to religious reasons as Maldives is a 100% Muslim country. This issue needs further clarification in order to improve the genetic counselling offered in Maldives. At the moment, there are no guidelines for genetic counselling; hence it is difficult to say whether the counsellors provide the information about reproductive options for thalassaemia carrier couples. Therefore, this area needs to be studied further in order to develop guidelines for genetic counselling for thalassaemia in the Maldives.

When comparing those who received counselling and those who did not, no real difference was observed regarding decisions to marry, suggesting that the brevity of the counselling sessions may impact on participant understanding of the consequences of thalassaemia carriers having children and knowledge of reproductive health options such as prenatal diagnosis. Thus, inadequate genetic counselling might be a factor in many of our study participants' decision to proceed to a marriage with their carrier partner and having children without any prevention measure. This finding is similar to that of a quantitative study undertaken by Alswaidi and his colleagues<sup>196</sup> in Saudi Arabia. Results of that study did not show any significant difference between those who received genetic counselling and those who did not with regard to marriage decisions. However, contrary to that, there are



studies that show that premarital testing with genetic counselling does in fact lead to cancellation of marriages in many thalassaemia carrier cases. For example, a study conducted to evaluate the obligatory premarital screening in Gaza Strip, Palestine revealed that most at risk couples in that study decided to separate after screening and genetic counselling.<sup>63</sup> Like Maldives, the above two countries are predominantly Sunni Muslim, but shows different results. The difference in different countries might be due to cultural factors. Maldives, though a 100% Muslim country has a very different marriage culture from above mentioned countries. For example, it is the norm in Maldives that young adults date before selecting their partner for marriage. In addition, marriages are rarely arranged by the families and consanguinity marriages are discouraged in Maldives unlike in Saudi Arabia<sup>197</sup> and Gaza Strip, Palestine.<sup>198</sup> Hence, the influence of culture on genetic counselling needs to be further studied to conclude its effect on the carriers in Maldives. For example, advice on separation and finding new partners would be odd in Maldivian culture where dating many people might lead to stigmatization in the communities. Therefore, it is important to study and clarify the cultural aspects that govern genetic counselling in Maldives. That being said, we would argue that accessibility to and the comprehensiveness of genetic counselling for thalassaemia carriers needs much attention in Maldives.

The majority of our participants felt that their carrier status or their genetic make-up was not a barrier to marriage and hence married their carrier partners. This finding is similar to the findings in many parts of Iran, Saudi Arabia and Iraq. The evaluation of the Iranian National thalassaemia program shows that about one half of the population who screened positive proceeded to marriage.<sup>188</sup> The findings from Saudi Arabia also show high levels of marriage despite knowledge of positive carrier

status. For example, 98%<sup>60</sup>, 88.2%<sup>196</sup> and 89.9%<sup>49</sup> of at risk couples in three different studies proceed with marriage even after knowing the risks involved. A study in North-East Iraq that evaluated the effectiveness of their thalassaemia prevention program also showed that about 98% of at risk couples proceeded with marriage.<sup>199</sup> Therefore, it is possible that many Maldivians may also go ahead with marriage with carriers similar to other countries. Carrier status might not have much of an influence on marriage decisions; rather they may have more of an impact on subsequent decisions such as having children.

However, the above argument does not necessarily mean that adequate counselling would not have an impact on marriage decision. Many of our participants described that they did not fully understand the realities of having a major child. Therefore, comprehensive genetic counselling that cover diagnostic and clinical aspects of the condition explaining inheritance patterns, risk estimations, possible preventive options and further measures<sup>55</sup> might change the attitudes towards marriage between carriers. Improving the service provision for genetic counselling might minimize the number of marriages between carriers as in the findings from Gaza Strip, Palestine.<sup>63</sup>

Most of our participants were happy to undergo prenatal diagnosis for thalassaemia, but were not comfortable with termination of pregnancy as a preventive measure for major children. Similar opinions were revealed in a survey conducted in Malaysia to study the attitudes towards prenatal diagnosis and abortion among parents of thalassaemia children.<sup>200</sup> The results of that survey showed that 71.6% of their participants agreed to prenatal diagnosis, but only 28.4% agreed on termination following prenatal diagnosis.<sup>200</sup> Religion (Malaysia is a majority Sunni Muslim country) was a significant factor for the participants who declined

termination in that study. It might be the case for our Maldivian participants in this study as well because all our participants were Sunni Muslim (Note: differential findings were observed in another study conducted by same authors that included Maldivian who undertook prenatal diagnosis and termination for thalassaemia). Medical termination of pregnancies is allowed for thalassaemia in Maldives by a *fatwa* (consensus of religious scholars)<sup>43</sup>, but still it is a controversial issue among many Muslim Scholars. Therefore, in addition to prenatal diagnosis and termination, providing information regarding alternative reproductive options such as pre-implantation genetic diagnosis in genetic counselling might help to decrease the prevalence of new major cases each year.

Since all participants of this study were Sunni Muslims, Islam and belief in “Allah’s Will” was a major factor that influenced participants’ decision to marry and have children. Many participants in this study believed that having or not having a major child was Allah’s Will and even if they birthed a major child they would be able to endure it because Muslims believe that Allah would not burden a soul with something that cannot be endured. Additionally, many participants believed that whatever happens, it is for the best. These findings are similar to the findings of Ahmed, Green and Hewison<sup>95</sup> in England. Their findings on Pakistani women’s attitudes towards thalassaemia and prenatal diagnosis in the north of England revealed that Islam was one of the most important factors for their thalassaemia carrier participants in their decision to have children. That study revealed that participants believed that having or not having a major child was Allah’s Will for them and Allah’s will is best for them<sup>95</sup>. Therefore, it is apparent that religion may play a vital role in the thalassaemia carriers’ decisions on marriage and having

children in Maldives. Thus, it is important that necessary religious aspects are incorporated into all thalassaemia screening and counselling services in Maldives.

### **Limitations**

The main limitation of this study was that we were only able to access participants from the atolls who attended MBS in Male. Those who do not, or are unable to make the trip to Male may have different perspectives. Our accessing of 10 of the 20 atolls of Maldives, however, does provide diversity in terms of geographical representation.

### **Conclusions**

The study results show that premarital testing was not common in Maldives; rather people tended to screen for thalassaemia in their teenage years. Knowing about carrier status did prepare the participants to some extent for the possible consequences of birthing a thalassaemia major child including how they would deal with pregnancies and children. However, the intended outcome of screening, which is preventing major births, was not achieved among our study participants. Hence, it is evident that there is a gap between the intent of screening, and subsequent marriage and having children in Maldives.

Genetic counselling, where it was offered, appears to be too brief and needs much improvement. Additionally, it appears that most participants did not have an issue with using a prenatal diagnosis service, but termination of pregnancy in case of major children was an issue for them. It is important to note that prenatal diagnosis services were not available within Maldives and therefore access issues such as cost was a major barrier for participants. The number of new major cases might decrease in Maldives if religious beliefs are considered and comprehensive genetic counseling

is offered with the option of prenatal diagnosis. Furthermore, other reproductive options such as pre-implantation genetic diagnosis might be of help for those who are financially capable, but are not comfortable with prenatal diagnosis and termination.

### **Acknowledgement**

We would like to thank all the participants who took part in this study and all the staff of MBS for all the help they provided during data collection.

### **Conflict of Interest**

Fazeela Waheed, Colleen Fisher, Niyi Awofeso and David Stanley declare that they have no conflict of interest.

### **Compliance with Ethics Guidelines**

This study was approved by the ethics committee of the University of Western Australia (Ref: RA/4/1/5626) in accordance with the requirements of the National Statement on Ethical Conduct in Human Research (National Statement) and the policies and procedures of The University of Western Australia. In Addition, the study was approved by the National Health Research Committee of Maldives on 7<sup>th</sup> of February, 2013. All procedures of this study were carried out in accordance to the laws and regulations of Australia and Maldives. All participants provided written consent prior to study.

### Introduction to the Chapter

Chapter six (paper three) is based on the first objective of the second study, “Explore the reasons that motivate at risk Maldivian couples to undertake prenatal screening and diagnosis for thalassaemia.” The paper was submitted to the Journal of Prenatal Diagnosis and the reference is as follows:

*Reference:* Waheed F, Fisher C, Awofeso N, Stanley E. Reasons for undertaking prenatal diagnosis for thalassaemia in Maldives. Journal of Prenatal Diagnosis. 2015. (Submitted)

The paper is divided into abstract, introduction to the procedure prenatal diagnosis and its use in Maldives, study method, results, discussion, conclusion and limitations of the study. The paper is presented as submitted to the journal.

## **Title: Reasons for undertaking prenatal diagnosis for thalassaemia in Maldives**

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### **Conflict of interest:**

No conflict of interest is known.

### **What is already known about this topic?**

Reasons for undertaking prenatal diagnosis and termination of pregnancy for thalassaemia is a well researched topic.

### **What does this study add?**

Reasons for undertaking prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives is a new area that has not been studied yet. This paper explores the reasons from the views of Maldivians who had undertaken prenatal diagnosis for thalassaemia. Hence, the findings of this paper will add to the literature.

**Word count:** 3,474

## Abstract

**Objective:** The objective of this study was to explore the reasons why Maldivians undertake prenatal diagnosis for thalassaemia.

**Method:** A generic qualitative approach utilizing face-to-face in-depth interviews was used for this study. Participants were Maldivians who had undertaken prenatal diagnosis due to thalassaemia. Purposive sampling was used to select the participants. All interviews were conducted in Maldivian local language and later transcribed to English for analysis. A thematic analysis was carried out to analyse the data.

**Results:** A number of reasons motivated the study participants to undertake prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives. The main reasons (themes) included ‘I desire the joy of pregnancy’, ‘Our wish is not a choice’, ‘If I didn’t, others would blame me’, ‘It is the ethical decision’, ‘Encouragement and recommendation’, ‘Experience with majors’, ‘Religion allows it’ and ‘We want a ‘Savior Child’.

**Conclusion:** Prenatal diagnosis and termination of pregnancy is acceptable for Maldivian in this study. The procedure is legalized by a *fatwa*, but service is not available in Maldives. Given its legal and religious status, it may well represent an important intervention point for prevention of thalassaemia in Maldives.



## Introduction

Thalassaemia is one of the most common genetic disorders globally. Many believe that the best prevention strategy for thalassaemia is preventing the birth of thalassaemia major children<sup>42</sup> suggesting that thalassaemia prevention programs should include genetic screening followed by parental diagnosis and selective termination of pregnancy if needed.<sup>42</sup> Prenatal diagnosis for  $\beta$  thalassaemia is commonly done by Chorionic Villus Sampling (CVS), amniocentesis or cordocentesis.<sup>112</sup> Those methods were shown to be reliable and successful in identifying affected children for genetic conditions like thalassaemia.<sup>86</sup>

Therefore, many countries offer prenatal diagnosis and termination of pregnancy services with varying degrees of success. Countries, such as Cyprus<sup>37</sup> and Greece<sup>81,91</sup> have been able to control thalassaemia using this approach. Also, southern Iran was able to significantly reduce the new thalassaemia major cases via prenatal diagnosis.<sup>62</sup> Studies conducted in Hong Kong<sup>79</sup> and Egypt<sup>93</sup> also showed positive results.

Republic of Maldives (Maldives) has one of the world's highest  $\beta$ -thalassaemia carrier rates (16-18%)<sup>14</sup> ranging from 0 to 41% by islands and 8.9% to 27.1% by atolls.<sup>21</sup> Maldives is a 100% Sunni Muslim country by law and prenatal diagnosis and selective termination of pregnancy was legalized based on a *fatwa* (a consensus of religious scholars) on 1<sup>st</sup> November 1999.<sup>43</sup> Though prenatal diagnosis and selective termination of pregnancy is legal, the service is not available in Maldives and most Maldivians travel to India to access the service. It is estimated that at least 40 at-risk Maldivian couples make the trip to India to access prenatal diagnosis annually.<sup>21</sup> The experiences of Maldivians who undergo prenatal diagnosis have not previously been studied, but are important to understand if prenatal

diagnosis services are to be established in Maldives. This study is a part of a larger study, the aim of which was to explore different levels of thalassaemia prevention in Maldives. The objective of this specific part of the study was to explore the reasons why Maldivians undertake prenatal diagnosis for thalassaemia.

## Methods

As reasons for undertaking prenatal diagnosis is an unexplored area in the Maldivian context, a generic qualitative approach<sup>149</sup> utilizing face-to-face in-depth interviews<sup>153</sup> was used. Interviews were conducted using a guide based on literature. All the interviews were conducted in Dhivehi (local language of Maldives) by FW and were audio recorded for analysis.

Participants were required to be Maldivians who had undertaken prenatal diagnosis due to thalassaemia and were purposively selected from parents who visited Maldives Blood Services (MBS) for blood transfusion of their major children, from broader community members who are known to have undertaken prenatal diagnosis for thalassaemia and through snowball sampling. To access participants, the first author (FW) visited MBS on several occasions and approached the parents of major children during transfusion. Participants who were selected from the community were known and contacted by FW, nurses and laboratory technicians of MBS. Additionally, some participants contacted others in their thalassaemia circle and forwarded several contacts of people who were interested in participating.

Data were thematically analysed as described by Braun and Clark.<sup>154</sup> Initial data analysis of listening to each interview and making field notes, enabled a back and forth process between data collection and analysis.<sup>194</sup> Later, all the interviews were translated from Dhivehi to English and transcribed concurrently. As a second step, transcripts were read several times to ensure familiarity with their content and

important concepts were identified through close line-by-line reading. Like concepts were then categorized together and abstracted to potential themes. Those themes were then refined and interrogated to clearly define content and names for reporting. The qualitative data analysis package QSR NVivo10 was used to store and manage, interrogate and facilitate analysis of data.

## **Results**

Our findings show that participants expressed a number of reasons that motivated them to undertake prenatal diagnosis and termination of pregnancy for thalassaemia. First we report participant characteristics followed by the main findings presented as reasons for undertaking prenatal diagnosis: ‘I desire the joy of pregnancy’, ‘Our wish is not a choice’, ‘If I didn’t, others would blame me’, ‘It is the ethical decision’, ‘Encouragement and recommendation’, ‘Experience with majors’, ‘Religion allows it’ and ‘We want a ‘Savior Child’.

### **Participant characteristics**

A total of 21 participants (9 individuals and 6 couples) from 11 different atolls of Maldives, ranging in age from 29 – 50 years participated in this study. All had completed primary education with most having secondary education or higher. All women undertook CVS as the prenatal diagnosis test for  $\beta$  thalassaemia and all except one travelled to Vellore, India to access the service. Most participants terminated at least one pregnancy based on prenatal diagnosis.

### **Reasons for undertaking prenatal diagnosis**

#### ***I desire the joy of pregnancy***

Many participants stated that they wanted to undertake prenatal diagnosis because they wanted to know the status of their unborn child. Culturally and religious-wise, a pregnancy is mostly a happy occasion among Maldivians. People

celebrate and send good wishes as children are considered a blessing from *Allah*. However, the unknown possibility of a major child was of concern for all participants and most stated that they felt anxious when they conceived. For example, one participant described her feelings when she found out that she was pregnant as, “I was feeling suffocation. I was thinking about what will happen if the child turned out to be a major. The moment I get pregnant, I start to worry about what type of child it would be.” Most participants stated that their anxiety and worries would not go away unless they undertake a prenatal diagnosis to find out their unborn child’s genetic condition. For example, one woman described her reasons for undertaking prenatal diagnosis as, “All of it [pregnancy and testing] is a big test on the nerves. There is so much going through the head. The joy of pregnancy is not there, until all of it is done and over with.”

#### *Our wish is not a choice*

All participants wanted children and wished and hoped for a healthy family. Hence, they considered that they had no choice but to undertake prenatal diagnosis. For example, one couple expressed their opinion as, “So yes, there wasn't much to gain by worrying about it. That (pause), there was no choice.” Another man who experienced his wife going through prenatal diagnosis and termination for their first pregnancy stated that, “It was our child. It was our first baby, but still we did not have much choice.”

#### *If I didn't, others would blame me*

Some participants were worried that society would judge them as selfish or cruel if they birthed a major child while knowing their carrier status and when prevention options such as prenatal diagnosis were available. In other words, they felt pressure to undertake prenatal diagnosis because otherwise society would

negatively label them for putting their own desire before the child's suffering. For example, when asked whether he and his wife would go for prenatal diagnosis and termination for a second time, one man stated:

We have to test, right? If not (pause)... It's a difficult thing to decide. Even the world will mock us if we blindly had a child, isn't it? Yes, those thoughts [thoughts of termination of previous pregnancy] still haunts me. But people will point fingers if we had a major child without testing. It bothers me. I know people will say such things.

### *It is the ethical decision*

Many participants reflected on their views as to whether it is right or wrong to bring a thalassaemia major child into the world and concluded that it was morally wrong and unethical to birth a major child knowingly. It was apparent from their narratives that many of them rationalized their decision to go ahead with prenatal diagnosis based on those moral values. For example, one couple expressed their opinion as follows:

I don't have an issue with that [prenatal diagnosis and termination]. For me, I think I consider the hardship the child would go through when we birth them. That's what I think about. We might not be able to provide what is needed and eventually that would lead to a premature death. I think its negligence. I think it's better to let the child go without that hardship before the child is born.

Other women similarly described their decision to undergo prenatal diagnosis and termination of pregnancy:

“So after thinking thoroughly, we thought that this is the only way. It would be an injustice if we continued this time. It was a major child. So we had an abortion... I believe it would be cruel to have the child”

“(I did prenatal diagnosis because) I felt that it was injustice to bring a major child

to the world. I don't think continuous blood transfusion and desferral and other things will be an easy process even if a child can get used to it over time. The child will have to bear more discomfort and pain than we as their parents.”

### *Encouragement and recommendation*

Encouragement from family and friends appeared to be very influential in decisions around prenatal diagnosis. For example one couple described their family support and encouragement as: “My mother encouraged me. My Family is very supportive, basically, everyone in this house, sister, brother-in-law.” A man who had experienced prenatal diagnosis three times and one termination stated that, “My parents already had major children and they knew how hard it is. So my father encouraged us to do it [prenatal diagnosis].” A woman described how her friend encouraged her and stated, “I talked to my friend. She is very considerate and explained it to me. She said it is allowed to test and go for a termination in our case.”

### *Experience with majors*

Most participants who already had a major child or had the experience of major children were very firm about their decision to undertake prenatal diagnosis. One couple whose first child was a major child and had gone through prenatal diagnosis three times and one termination reflected: “We have to be mindful, right. Once there is one major child in a family, I don't think it will be repeated again in that family.” A woman who had a thalassaemia major nephew described her thoughts as, “The baby [her nephew] turned out to be a major. It was like a nightmare, really! It is the main reason why I decided so firmly to go with prenatal diagnosis. I saw what it's [to have major child] like.”

### *Religion allows it*

Most participants in our study were well aware of the Maldivian *Fatwa* on prenatal diagnosis and termination. They understood that it was a unanimous decision of

religious scholars, and it was one main factor that motivated them to undertake the test. Most participants who had to go for a termination stated that they made their decision because it is allowed in the *fatwa*. The following quote is typical of many others: “At that time there was the *fatwa* from the Ministry. It was easier to accept it [prenatal diagnosis and termination] after reading it [*fatwa*].” Most participants believed that scholars would know the Islamic ruling better and they should accept the scholars’ rulings. For example, a woman affirmed: “Yes. I can believe it [*fatwa*]. I can. They [scholars who gave the *fatwa*] would know it better than me. So we have to follow them.”

Reflective of the importance of religion in their lives, many participants also discussed their situation with local and international scholars before making their decision about prenatal diagnosis because they might have to terminate the pregnancy. They indicated that most scholars (both local and international) were of the opinion that, whilst it is not encouraged, it is not ‘*haraam*’ (forbidden) to terminate a pregnancy for a cause like thalassaemia in a prescribed time period. Hence, the opinions of the scholars on the issue provided comfort and assisted many participants to decide on prenatal diagnosis and termination. As a woman noted: “Earlier I was, yes very wary of that [termination] as a sin. But later with the awareness and all from religious perspective... the *Sheikhs* (Islamic scholars) were of the view that it is permissible if we know it is harmful for the child.”

### *We want a ‘Savoir Child’*

A few participants who already had an older major child believed they could cure that child if they birthed another healthy child, possibly a matching sibling. Hence, they were motivated to undertake prenatal diagnosis to birth a healthy child who might be able to save their thalassaemia major child if turned out to be a match for bone marrow transplant (note: none of the participants terminated any non major

child whether it matched or not with the major child). For example, one participant indicated that, “We wanted one because my other child [thalassaemia major child] asks from time to time whether there isn't anyone who matches with his bone marrow.... So that was on my mind. That's why we wanted to do prenatal diagnosis and have another child.” A couple who underwent prenatal diagnosis for their second child described their decision to undertake prenatal diagnosis and stated, “The hope of a bone marrow match with him [major child]. Thoughts like that made us go through the test.”

## Discussion

One of the main findings of our study is that couples can and do become anxious and worry not knowing the genetic status of their unborn child. For them, undertaking prenatal diagnosis would end that uncertainty so they could enjoy their pregnancy. Similar findings were reported by Ahmed, Green and Hewison<sup>95</sup> in one of their studies that explored the attitudes of British Pakistani Muslim women towards prenatal diagnosis for  $\beta$  thalassaemia. Their findings showed women's reasoning for undertaking the test included wanting to know the status of their baby, so that they can stop worrying about it or prepares themselves for a major child. However these finding contrast with the findings of Liamputtong, Halliday, Warren, Watson and Bell.<sup>201</sup> Their findings showed that many women in their study did not want to undertake prenatal diagnosis test as the new knowledge of the test might lead to emotional distress and further difficult decisions.

Islamic *fatwa* of the Maldives on prenatal diagnosis and termination of pregnancy for thalassaemia was a comfort for most participants in this study. Fatwa (termination is allowed for thalassaemia) and other scholars' opinions (termination is not encouraged, but it is not forbidden) helped our participants' to make the decision



to undertake the test. In other words, religious stance was important for the study participants. Religious stance on the issue was found to be important in other Muslim communities as well. For example, Ahmed, Green and Hewison<sup>95</sup> found that religious ruling was important for Muslim Pakistani women in the North of England. Many participants of that study were concerned about religious position on prenatal diagnosis and they had the desire to know more about Islamic stance on the issue. Likewise, studies conducted in Egypt where the population is predominantly Sunni Muslim showed that most Egyptians accept prenatal diagnosis when religious points of views were clearly explained in counselling sessions.<sup>93</sup>

However, differential findings were observed in by same authors in another study that involved Maldivian thalassaemia carriers who married and had children despite knowing their carrier status. In that study many Maldivians did not want to undertake a pregnancy termination due to thalassaemia. Similar attitudes towards termination of pregnancy were observed from Muslims in Malaysia<sup>161,200</sup> and among migrant Muslim women in Australia.<sup>202</sup> Findings from a study undertaken in Southern Iran also showed that religion was the main reason for not accepting medical abortion for thalassaemia.<sup>82</sup> Hence, explaining the religious stance on prenatal diagnosis and termination of pregnancies in counselling sessions may be extremely important in Maldives.

Decisions appear to become easier to make if the parents had a major child or had experiences with them. Findings of our study revealed that, in these circumstances, participants were more positive about their decision to undertake prenatal diagnosis and termination. Similar findings were reported from Malaysia where parents of major children were more positive towards prenatal diagnosis and termination compared to Malaysians who do not have a major child.<sup>203</sup> Hence, close

experience plays a vital role the decision making of prenatal diagnosis and termination.

Encouragement from family and friends was a major reason or motivator for undertaking prenatal diagnosis for our participants. This finding has precedence in the literature. Family support was a major factor that helped the women to make the decision to undertake prenatal diagnosis and termination in the study conducted by Ahmed, Green and Hewison<sup>95</sup> with Pakistani women in England. This suggests that interventions aimed at changing family attitudes could be productive.

Perceived severity of thalassaemia was also a factor that motivated our participants to undertake prenatal diagnosis and termination. Their view about the severity of the condition appeared to be persuasive in their belief that children should not be made to experience such a condition. These findings are similar to the views of Pakistani women in England<sup>95</sup> and the majority of women in the study undertaken in Malaysia by Ngim et al.<sup>200</sup> When examining the influencing factors on prenatal decisions around thalassaemia in a different study, Ahmed et al<sup>101</sup> found that severity of the condition was in fact the most important factor for their participants when making decisions around prenatal diagnosis and termination. Atkin, Ahmed, Hewison and Green<sup>204</sup> also reported that severity of the condition and religious beliefs were given same level of importance when it comes to prenatal diagnosis among faith groups (including Muslims) in England. These findings, however, are not without dissent. For example, the study findings of Ngim, Lai, Ibrahim and Ratnasingam<sup>200</sup> shows that 28.4% of their study participants declined the antenatal test and termination and 14.3% of those who accepted the antenatal test but declined termination did so because they did not view thalassaemia as severe enough to

terminate a pregnancy. These attitudes are also apparent in the Malaysian general population.<sup>200</sup> Hence, severity of the condition thalassaemia is a subjective issue.

Bone Marrow Transplant from a compatible donor (normally a sibling) is the only cure for thalassaemia major children. Many participants of our study who already had a major child were motivated to undergo prenatal diagnosis to birth a 'savior child'. This phenomenon was found to be quite common among thalassaemia parents in China where parents opt for prenatal diagnosis and often terminate pregnancies that were not necessarily majors but also if the child was not a compatible match.<sup>80</sup> Participants in our study did not terminate any healthy pregnancy unlike among Chinese parents, but birthing a healthy child (possible saviour child) was often a motivator to undertake prenatal diagnosis among our participants. The Maldivian fatwa allows termination of only major children; therefore they abided by the religious fatwa and were only willing to terminate the effected pregnancies. This finding is more similar to attitudes of thalassaemia parents in Egypt.<sup>93</sup>

## **Conclusions**

As in many other Muslim countries, the issue of prenatal diagnosis and termination of pregnancy is acceptable for Maldivian participants of this study. Religion stance on the issue was an important factor that helped the participants to make their decision to undertake prenatal diagnosis. More than that, the severity of the condition, having experienced the condition up close and moral values influenced their decision in a positive manner. Additionally, participants were drawn to undertake prenatal diagnosis because they felt that it was the only choice and if they did not, they will be blamed for it. The procedure is legalized based on a religious fatwa in Maldives. The service itself, however, is not available in Maldives but given its legal and religious status, it may well represent an important intervention

point for prevention efforts for thalassaemia in Maldives. As such consideration should be given to make the procedure available locally.

### Introduction to the Chapter

Chapter seven (fourth paper) is based on the on the second objective of the second study, “Explore the barriers and facilitators that are faced by the Maldivian couples who undertake prenatal diagnosis for thalassaemia.” The objective was to explore barriers and facilitators. However, during the data analysis, when the themes were formed, all the facilitators the participants talked about fits better with the first objective of this study: ‘Explore the reasons that motivate at risk Maldivian couples to go through prenatal screening and diagnosis for thalassaemia.’ The facilitators the participants described were their reasons and motivators of their decisions. Therefore, the ‘facilitators’ were presented in the first paper as motivators and reason for undertaking prenatal diagnosis for thalassaemia in Maldives in chapter six (paper 3) and this paper is solely on barrier faced by Maldivians when undertaking prenatal diagnosis for thalassaemia.

The paper was submitted to the Journal of Prenatal Diagnosis. The reference is as follows:

*Reference:* Waheed F, Fisher C, Awofeso N, Stanly A. Socio-cultural barriers faced by Maldivians who undertake prenatal diagnosis for Thalassaemia. Journal of Prenatal Diagnosis. 2015. (Submitted)

The paper was divided into abstract, introduction to the procedure prenatal diagnosis and its use in Maldives, study method, results, discussion, conclusion and limitations of the study. The paper is presented as submitted to the journal.

**Title: Socio-economic and Cultural Barriers faced by Maldivians who  
Undertake Prenatal Diagnosis for Thalassaemia in Maldives.**

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**Conflict of interest:**

No conflict of interest is known.

**What is already known about this topic?**

Socio-economic and cultural barriers faced by couples who undertake prenatal  
diagnosis and termination of pregnancy for thalassaemia in different communities.

**What does this study add? (70 words max)**

Socio-economic and cultural barriers faced Maldivians who undertake prenatal  
diagnosis and termination for thalassaemia is a new area that has not been studied  
yet. This study presents the findings that explain the socio-cultural barriers faced by  
Maldivians who undertake prenatal diagnosis and termination of pregnancy for  
thalassaemia.

**Word count:** 3,250 words

## Abstract

**Objective:** The aim of this study was to explore the barriers faced by Maldivians in undertaking prenatal diagnosis for thalassaemia.

**Method:** A generic qualitative approach using face-to-face in-depth interviews was used for this study. Participants of this study were required to be Maldivians and had undertaken prenatal diagnosis for thalassaemia. Purposive sampling was used to select the best informants. All interviews were conducted in Maldivian local language and later translated and transcribed to English for analysis. Thematic analysis was used to analyse the data.

**Results:** Two major types of barriers were apparent from this study; personal and emotional barriers and procedure related barriers. Personal and emotional barriers included perceived fear and distress and hope and wishful thinking. Procedural related barriers included barriers related to prenatal diagnosis procedure, travel cost, technical difficulties and difficulties associated with termination of pregnancy.

**Conclusion:** Prenatal diagnosis is not available in Maldives. Hence, a range of systemic and access related barriers were reported. Hence, in-country service provision is an area of importance in Maldives. However, when and if prenatal diagnosis made available in Maldives, the religious fatwa needs to be taken into account, particularly in respect of the timeframe that it permits termination.

## Introduction

Many countries offer prenatal diagnosis and termination of affected pregnancies as an option for couples who are at-risk of birthing children with genetic disorders such as thalassaemia. There are three main types of prenatal diagnosis; non-invasive techniques (Ultrasound and MRI), minimally invasive techniques (Cell free fetal DNA and Pre-implantation genetic diagnosis) and invasive techniques (Chorionic villus sampling, Amniocentesis and Cordocentesis).<sup>89</sup>

When would-be parents are known to be carriers of a hereditary genetic disorder such as thalassaemia, Chorionic Villus Sampling (CVS) is offered via fetal DNA analysis to identify if the fetus is a major child of that genetic disorder.<sup>89</sup> The CVS procedure is normally carried out after 10 weeks' gestation either transcervically or transabdominally.<sup>89</sup> Studies show that cost of prenatal diagnosis would be less compared to cost of treatment<sup>79</sup> and psychological and social burden<sup>80</sup> incurred to support a thalassaemia major child. Hence, many countries including Iran<sup>82</sup>, Saudi Arabia<sup>83</sup>, Egypt<sup>84</sup>, India<sup>85</sup>, Italy<sup>86</sup> and Cyprus<sup>37</sup> and many more countries offer prenatal diagnosis and selective termination as a preventive measure for thalassaemia.

Despite this, studies indicate that prenatal diagnosis is not supported or effective in some communities for many reasons. For example, a Malaysian study that explored public opinion towards thalassaemia and selective abortion showed that majority of the population (63.4%) were not supportive of selective termination of pregnancy for thalassaemia.<sup>52</sup> Similar results were reported in studies undertaken in Pakistan<sup>92</sup> Egypt<sup>84</sup> and in Ontario, Canada.<sup>94</sup>



## Thalassaemia and Prenatal diagnosis in Maldives

Republic of Maldives (Maldives) is a group of islands in the Indian Ocean, South-west of Sri Lanka. Maldives had a population of 341, 256 as at 2014<sup>205</sup> and it is estimated that 18.1% of the total population is heterozygous for  $\beta$ -thalassaemia.<sup>41</sup> Hence, thalassaemia prevention is important for Maldives with prenatal diagnosis and termination of affected pregnancies allowed since 1998.<sup>43</sup> As the Maldivian population is 100% Sunni Muslim by law,<sup>206</sup> prenatal diagnosis and termination is allowed based on a Fatwa (a consensus of the religious scholars) of the Supreme Council of Islamic Affairs of Maldives<sup>43</sup>; which is in accordance with the abortion-related fatwa of the Muslim World League.<sup>98</sup> Despite a range of prevention strategies in place in Maldives, including prenatal diagnosis and termination, many new major cases of thalassaemia are registered every year - 28 new cases on average annually for the period 2001 to 2012<sup>78</sup> - indicating low uptake of prenatal diagnosis.

Whilst there are potentially many barriers that prevent at-risk couples from undertaking prenatal diagnosis, this had not been researched in a Maldivian context. This study was a part of a larger study conducted with the aim of exploring thalassaemia prevention measures in Maldives. The aim of this specific study was to explore the barriers faced by Maldivians in undergoing prenatal diagnosis for thalassaemia.

## Method

Most studies that examined attitudes towards prenatal diagnosis for thalassaemia were quantitative.<sup>82,92,161,207, 95</sup> Hence, to add depth to understanding, we utilized a generic qualitative approach<sup>149</sup> using face-to-face in-depth interviews.<sup>153</sup> The interviews were conducted in Maldivian local language (Dhivehi) by FW and were recorded digitally for analysis.

To be included in the study, participants were required to be Maldivians and had undertaken prenatal diagnosis for thalassaemia. Participants were purposively selected from parents who visited Maldives Blood Services (MBS, previously known as National Thalassaemia Centre), and through snowball sampling. To access participants, the first author (FW) visited MBS on several occasions and approached parents of major children. Additionally, nurses and laboratory technicians of MBS contacted some participants who had contact with them and the centre due to their carrier condition. Additionally, some participants contacted others who they knew through their thalassaemia circle and forwarded details of those interested in participating to FW.

A thematic analysis as described by Braun and Clarke<sup>154</sup> was used to analyse the data. Interviews were first translated from Dhivehi to English and transcribed concurrently. As a second step, transcripts were read for several times and openly coded as study objective-related concepts. All like concepts were then clustered together to form potential themes. As a final step, themes were refined and interrogated individually and across the data set to ensure they reflect the data and to clearly define names for reporting. Data were managed using qualitative data analysis software program QSR NVivo 10.

## **Results**

A total of 21 participants (nine individuals and six couples) participated in this study. All participants undertook a CVS procedure for prenatal diagnosis of the fetus and all except two accessed services from Christian Medical College (CMC) of Vellore, India.

Our study results show that there were a number of barriers that disheartened Maldivians when undertaking prenatal diagnosis and termination of pregnancy for thalassaemia. We first report the personal and emotional barriers followed by

procedure related barriers.

### **Personal and Emotional Barriers**

Our study findings show that a number of factors disheartened our participants in regard to prenatal diagnosis and termination for thalassaemia. All the personal and emotional factors could be grouped into two; perceived fear and distress and hope and wishful thinking.

#### ***Perceived Fear and Distress***

Most participants feared what was involved in the procedure, the consequences of receiving a positive diagnosis and found the wait for results distressing. A major source of participant fear was the possibility of the procedure harming the foetus. For example, one female participant described this fear as, “If by chance the needle pricks any other parts other than the placenta, it might require an abortion. It was a scary thought.”

Participants were also fearful of learning their unborn child was a major and having to face a termination. One woman who waited for 10 years without wanting to conceive because of the fear of a possible termination described her apprehension as:

...it was the thought about my baby...My husband wants to have a child. But I didn't want to risk it. He says that there are options of testing and that we might have a healthy baby. But I kept saying what happens if the baby is a major?! I kept telling him that I cannot go through an abortion.

For those who had experienced a previous termination, their fear was elevated and many certainly did not want to face it again. Some even questioned whether it is worth conceiving if they had to undertake prenatal diagnosis and potential termination.

It [termination] was distressing, and I was all confused. To start with, aborting an

innocent tiny baby was an issue for me...I could not sleep for days and felt remorseful and those days I cry very easily... It is something that leaves one very sick emotionally. It impacts the whole life...I kept questioning why should I get pregnant because I kept throwing away my babies.

Some participants stated that they were hesitant to undertake prenatal diagnosis because they feared being negatively judged or stigmatized by friends, family and community because of it. Some found it so difficult to explain or share their decision with others that they kept it hidden from everyone around them. For example, one man stated that he did not share their decision with anyone else because, "It [the decision to terminate the pregnancy] might change other's view about us...So we didn't tell and I'm sure nobody knows. No one would know. Not even our parents or office mates." A woman who had prenatal diagnosis three times and termination twice stated that she had never shared that information with anyone except her family because she feared that people would talk about it: "People will make stories out of things like that in Male'. So I didn't talk about it...not even with my husband's family."

Understandably, the waiting time for the result was a major distressing factor for all participants in this study. A couple described their feeling as, "It was a sad situation...The wait after the investigation is agonizing. That's the hardest time. Waiting for results – for three days! It was like not able to breathe (pause). No appetite. Time was so long. No mood to sleep either."

### *Hope and wishful thinking*

Hope and wishful thinking are often considered positive as they can provide strength to go on and help coping with negative situations. A few participants in this study, however, stressed that they were actually barriers for them as they were

contemplating prenatal diagnosis because they clung to the hope that their foetus would not be thalassaemia major. For example, one couple who had a normal child at first and then a major child stated that they undertook prenatal diagnosis for the first child, but not for the second child because:

At the time we assumed we will not get a major. We just had wishful thinking that we will get a normal child. The doctor advised us to go and test. But I told him I don't want to. I was hoping it would work out. I just had hope. I had hope. And at that moment I just did not want to go. So we decided not to go for the test. But after sometime when we got time to think I thought we should test. But then again was thinking I should have faith...We were hoping for the 75% window.

### **Procedure related Barriers**

Our analysis showed a large number of Procedural related barriers that are faced by Maldivians who wanted to undertake prenatal diagnosis and termination for thalassaemia. Most of those barriers are related to prenatal diagnosis procedure, travel cost, technical difficulties and difficulties associated with termination of pregnancy.

### ***Prenatal Diagnosis Procedure***

Prenatal diagnosis services were not available in Maldives at the time of the study and all but two travelled to Vellore, India to access the service at CMC. CVS was the method used at CMC to perform prenatal diagnosis. Most participants described the procedure as extremely 'invasive', 'uncomfortable' and/or 'painful'. The following quotes exemplify each of these:

“It was painful, but I was reassuring myself that I just have to do it once and I have to do it for the sake of the baby.”

“They do it via our private area. So it was very invasive and uncomfortable and we have to stay very still, but I did wriggle without wanting to. They even

indicated that legs to be tied together lest I moved.”

“It felt as if the tube went in shredding my muscles...I felt difficult to breathe... It was difficult. I can't really explain it all.”

### *Travel and Cost*

Most described the trip to Vellore as tiring and difficult, especially because it had to be undertaken in the first trimester of pregnancy. Typical of experiences was that of one woman, “It [the trip] was very uncomfortable. I was vomiting. I was just very unwell. I did faint on the road one day... Yes, I vomited so much and as a result fainted.”

Additionally, there were costs involved in undertaking the procedure. Although participants did not consider the prenatal diagnosis procedure itself expensive (the cost of all the investigations and the procedure varied between US\$300 and US\$500), with travel costs, accommodation and food, the total was approximately US\$2000. Hence, even though the medical procedure was relatively inexpensive, participants perceived that the enabling effects of this could be diminished, particularly if not planned well because of the cost of related expenses. For example, one participant reflected his experience, “No, it's [cost] not that much, if things are planned. It's not something that cannot be done. Saving prior to pregnancy and all would make it work, but if unplanned it will be a huge cost.”

Despite the difficulties involved both personally and financially, for many participants, the benefits from the procedure were seen to outweigh the cost and the burden of potentially birthing a major child. As one participant noted, “It never crossed my mind that it [cost of the trip and procedure] was too expensive, compared to the dilemma we were in.”

### *Access to Services*

Many of our participants described a number of difficulties they encounter in the process of access to services. Many of the issues were related to appointments, access pathways and the lack of available on-site termination services. A number of participants stated that they were able to book an appointment for the procedure before travelling from Maldives, mainly through Society for Health Education (SHE). For many, having an available appointment at the time of their visit ensured a smooth transition into the clinical setting. However, a few participants stated that their appointments were not valid when they tried to access the service. One couple experienced that scenario more than once: “we went to Vellore after making an appointment through SHE, but we found that there was no appointment when we reached. Same thing happened both times.” Another participant described how he had to make a new appointment despite having an appointment letter from SHE because the hospital administration staff told him that the letter was of no use:

From this end - last time we made appointment through SHE...But they did not look at it at all. I mean SHE booked for us through them. But still they will not even look at any of it... Even when we show the appointment letter and all, they say it is of no use and asked us to follow their procedures. Just have to barge in like the rest of them.

Most participants described the service access pathway as difficult, particularly on a first visit because it was not clearly described nor was it self-explanatory. One man described his experience as, “The first time was difficult...Long queue and no systematic arrangement and they don't issue any tokens or anything like that... We have to barge in every now and then. There was such a crowd of people.” A couple described their frustration as, “The place is just too big. They didn't give much information and things weren't clear. We didn't know what

was going on.”

One of the main service access related difficulty that participants highlighted was the non availability of medical termination of pregnancy services. Most participants who had to terminate their pregnancy based on prenatal diagnosis were not happy with the fact that it was not available from the same hospital, with all but one having to travel to other states nearby to access pregnancy termination services. Typical of experiences were those of a couple who had gone through three terminations:

They [CMC hospital] said they can't do it [surgical abortion]. It's a Christian hospital, and according to them they don't do surgical abortion - but have to be delivered - no matter how small the fetus is. They advised that we can do abortion in Trivandrum and that it would not take long.

## **Discussion**

Prenatal diagnosis is a component of prevention efforts for thalassaemia by the government of Maldives, but the service is not available in the country, nor is the procedure covered under the social health insurance scheme of Maldives. This is something that requires governmental attention as participants in this study explained that whilst the cost of the procedure was not a major issue, the total cost required saving and, as such they needed to prepare their finances in advance if they are to be able to access it. Essentially, the cost of the procedure was affordable but the total cost was expensive because it can only be accessed from overseas. The situation for Maldivians is not unique. Cost related issues are similarly reported in other studies. It was reported as one of the main reasons for would-be parents not using prenatal diagnosis services in studies conducted in Pakistan<sup>92,207</sup> and in Iran.<sup>82</sup> As it is legal in the Maldives, consideration could be given to having the procedure



covered under the social health insurance scheme, enabling more Maldivians to access the service. Additionally, the intake might be more if prenatal diagnosis services are available locally.

Fear of the procedure was a major concern for the participants of this study. Participants described that they were hesitant about the CVS procedure because of what it involves and the fear that it might harm the foetus. Similar findings were reported from studies conducted among Pakistani women in Pakistan<sup>207</sup> and in England<sup>95</sup> as well as in a qualitative study conducted in Australia.<sup>201</sup> The Australian women's reason for declining prenatal screening and/or prenatal diagnosis included a high level of belief that it is unsafe for the baby.<sup>201</sup> Therefore counselling and psychological support might help women who want to undertake prenatal diagnosis.

The timeframe for termination of pregnancy under the Maldivian Fatwa is 120 days. All participants wanted to abide by the Fatwa, but it was a major hurdle for them. They wanted to ensure they undertook the CVS procedure well in advance, so that, they could undertake a timely termination if required. The perspectives of participants in our study are reflected in a study conducted in England to explore the attitudes of Pakistani women towards prenatal diagnosis and termination for thalassaemia. Gestational age and the timing of the test were found to be important factors for the women in that study.<sup>95</sup> Hence, arrangements that allow early and timely termination when and if need is an important factor for Maldivians.

Our study participants described transcervical CVS as extremely invasive, uncomfortable and painful. Similar findings were reported by Liamputtong, Halliday, Warren, Watson and Bell<sup>201</sup>. Their findings in relation to Australian women showed that CVS was often declined because the test was too painful or too uncomfortable.<sup>201</sup> Conversely, trans-abdominal CVS done in week 12-16 was

accepted among Pakistani thalassaemia carriers (mostly Muslims).<sup>208</sup> Therefore, if made available, trans-abdominal CVS might be more acceptable to Maldivian women. However, more research is needed into this area as some of our participants wanted the procedure done as early as possible because of the limited timeframe available for termination under the Islamic fatwa.

## **Conclusion**

A number of barriers to prenatal diagnosis were reported in this study. Some of the barriers such as fear and hope are subjective and unique to individuals. However, a range of systemic and access related barriers were mostly felt by participants because they had to travel to a foreign country to access the service. Hence, in-country service provision is an area that needs attention in Maldives. However, when and if prenatal diagnosis made available in Maldives, the religious fatwa needs to be taken into account, particularly in respect of the timeframe that it permits for termination.

### Introduction to the Chapter

Chapter eight (paper five) is based on the third objective of the second study, “Explore the potential ethical conflicts with the Islamic view of prenatal diagnosis and selective termination of pregnancy for thalassaemia in Maldives.” The paper was submitted to the Journal of Prenatal Diagnosis. The reference is as follows

*Reference:* Waheed F, Fisher C, Awofeso N, Stanly A. Ethical conflicts and Islamic fatwa on prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives. Journal of Prenatal Diagnosis. 2015. (Submitted)

The paper included abstract, introduction Maldives and the Islamic Fatwa that permits prenatal diagnosis and its use in Maldives, study method, results, discussion, conclusion and limitations of the study. The paper is presented as submitted to the journal.

**Title: Ethical conflicts and Islamic fatwa on prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives**

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**Conflict of interest:**

No conflict of interest is known.

**What is already known about this topic?**

Ethical conflicts faced by religious communities when they are faced with medical choice of prenatal diagnosis and termination of pregnancy.

**What does this study add?**

Ethical conflicts faced by Maldivians when they have to undertake prenatal diagnosis and termination of pregnancy for thalassaemia is a new area of study. The issue is examined from a religious point of view as all Maldivians are Sunni Muslims.

**Word count:** 3,395

## Abstract

**Objective:** The objective of this study is to explore the ethical conflicts with Islamic view of prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives.

**Method:** A generic qualitative approach was used for this study. Face-to-face in-depth interviews were used to explore participants' perspectives on the fatwa and their decision to undertake prenatal diagnosis and termination. The inclusion criterion was Maldivians who had undertaken prenatal diagnosis for thalassaemia. Purposive sampling was used to select the best informants. A thematic analysis was used to analyze interview data.

**Results:** This study shows that participants heavily relied on the fatwa and scholars' advice when they made their decisions on prenatal diagnosis and termination. Findings show that participants believed fatwa and scholars' advice, but had difficulty accepting the actions that follows. Hence, even though they believed fatwa, many felt guilty of their actions.

**Conclusion:** Study shows that Islamic fatwa on prenatal diagnosis and termination of pregnancy is important in Maldives. All the participants used fatwa as the main basis for their action. However, the conflict between accepting and doing what is allowed (termination of pregnancy) in the fatwa put them in a position of guilt and uncertainly.

## Introduction

Republic of Maldives (Maldives) is a group of islands in the Indian Ocean with a population of 344, 023<sup>3</sup> that is 100% Sunni Muslim by law.<sup>9</sup> Article 10 of Chapter Two of the Constitution of Maldives states that the religion of Maldives is Islam and Islam shall be the basis of all its laws.<sup>9</sup> Additionally, the same article states that ‘No law contrary to any tenet of Islam shall be enacted in Maldives’<sup>9(p2)</sup> reflecting the many laws that are in accordance with *Shari’ah* (Islamic jurisprudence). Maldives has many laws that are specific to crimes, family and justice which specifically talk about harm, justice and rights of the Maldivians under its constitution. However, no law clearly defines the status of medical termination of pregnancy in Maldives.

Termination of pregnancy was first raised as a national issue due to the high prevalence rate of the genetic disorder thalassaemia among Maldivians. Maldives has one of the highest  $\beta$  thalassaemia carrier rates (16-18%)<sup>14</sup> with prevalence rate ranging from 0 to 41% by islands.<sup>21</sup> Screening for thalassaemia was established in 1992. However, screening alone was found to be not successful in reducing the prevalence of thalassaemia as marriage between carriers was common. Like Iran<sup>82</sup>, Saudi Arabia<sup>106</sup>, Egypt<sup>93</sup>, Greece<sup>91</sup>, India<sup>209</sup> and Cyprus<sup>37</sup>, officials in Maldives also felt the need to incorporate prenatal diagnosis and selective termination as an intervention to prevent thalassaemia.

The *Quran, Hadith or Sunna* does not explicitly define the ruling on termination of pregnancy in Islam.<sup>210</sup> Maldives being a 100% Muslim country by law, prenatal diagnosis and termination of pregnancy could not be offered without a religious consensus. Therefore, the Ministry of Health of Maldives asked for a legal ruling on it from the Supreme Council of Islamic Affairs of Maldives in 1998<sup>43</sup> bringing the issue to national attention for the first time.<sup>43</sup> When an issue is not

clearly defined in Qur'an, Hadith or Sunna, Shari'ah uses *Qiyaas* (reasoning by analogy)<sup>211</sup> or *Ijthihad* (deductive logic)<sup>104</sup> in order to reach a collective consensus opinion of scholars called *Ijmau*.<sup>211</sup> A consensus edict of scholars on an issue is known as a *fatwa* in Muslim communities. The Supreme Council of Islamic Affairs of Maldives passed a *fatwa* that legalized medical termination of pregnancy on 1<sup>st</sup> November 1999.<sup>43</sup>

The Maldivian *fatwa* outlines two main situations when pregnancies can be terminated and thalassaemia major is one of the two reasons.<sup>43</sup> The preconditions that need to be met before prenatal diagnosis and selective termination are it has to occur within the first 120 days of the pregnancy, consent of both parents and confirmation from a 'trustworthy' doctor.<sup>43</sup> [Note: Trustworthiness is a subject measure; however, no criterion was given as who is a trustworthy doctor]

Many studies that have examined attitudes on prenatal diagnosis and termination of pregnancies in Muslim communities show that there is a strong relationship between faith and prenatal diagnosis and termination of pregnancy (see for example, Ahmed, Atkin, Hewison and Green<sup>101</sup>, Karimi, Johari and Cohan<sup>82</sup> and El-Beshlawy, El-Shekha, Momtaz, Said, Hamdy, Osman<sup>93</sup>). Despite the pronouncement of the *fatwa* that legalized, prenatal diagnosis and termination of pregnancy in Maldives having been in place for over a decade, no research has been carried out to date exploring its impact on thalassaemia carriers' reproductive decisions. This study is a sub-study of a larger study, the aim of which was to explore the different levels of thalassaemia prevention efforts in Maldives. The objective of this study is to explore the ethical conflicts with Islamic view of prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives.

## Method

A generic qualitative approach<sup>149</sup> was used for the study due to its exploratory nature. Face-to-face in-depth interviews<sup>153</sup> were used to explore participants' perspectives. All interviews were conducted in Maldivian local language (Dhivehi) by FW and audio recorded for analysis.

Participants of this study were required to be Maldivians who had undertaken prenatal diagnosis due to thalassaemia. Participants were purposely selected from two broad groups; parents who have a major child and had undertaken prenatal diagnosis in the subsequent pregnancy and participants who did not have a major child but had undertaken prenatal diagnosis for every pregnancy. To access the first group, the first author (FW) visited Maldives Blood Services (MBS) on several occasions and approached the parents of major children during transfusion. Participants who did not have a major child were recruited from the community by FW, nurses and laboratory technicians of MBS. Additionally, some participants referred others in their thalassaemia circle who expressed an interest in participating.

A thematic analysis as described by Braun and Clarke<sup>154</sup> was used to analyze interview data. Initial data analysis started with the onset of data collection as FW listened to each interview and made field notes before moving to subsequent interviews. All interviews were translated from Dhivehi to English and transcribed concurrently. Transcripts were then read several times line by lines, in order to identify broad concepts. The like concepts were then grouped together under broad themes. As a final step, those themes were examined individually and refined to clearly define the themes for reporting. Qualitative data analysis package NVivo was used to manage the data of this study.



## Results

A total of 21 participants (11 women and 10 men) were interviewed for this study. The age of the participants varied from 30-50 years. All participants undertook prenatal diagnosis test at least once and 14 participants terminated at least one pregnancy due to thalassaemia. From the findings of this study it was clear that Islam and its ruling on prenatal diagnosis and selective termination of pregnancies was an important issue among thalassaemia carriers in Maldives. Participants relied heavily on the *fatwa* and advice of their trusted Islamic scholars when they made their decisions on prenatal diagnosis and termination. We present our findings as themes ‘we believe the fatwa’, ‘religious scholars’ advice’, ‘fatwa is right, but my heart is not content’ and ‘I’m guilty of sinning’.

### *We believe the Fatwa*

All the participants agreed on the importance of thalassaemia related fatwa in Maldives and all except one accepted it and relied on it when they made the decision to undertake prenatal diagnosis and termination. Though most participants accepted the fatwa, their reasoning for acceptance varied with the most common being their belief that the informed scholars of Islam would know the Islamic ruling on the issue better than they themselves would. The following response was typical: “...But still, the scholars have a better understanding than us, so there is no reason why we should not believe it.” Hence, this finding suggests that participants trusted the scholars’ understanding of the issue and their collective consensus decision (*fatwa*).

Fatwa alone, however, was not convincing enough for some participants. Hence some undertook their own research on the ruling of the fatwa. They then compared their understanding from Qur’an with the *fatwa* before accepting the fatwa. For example, one participant noted that, “I did check Quran and realized that

in the process of the creation of human, there is a stage where the blood clot is not human. And based on the religious fatwa I believe that it is justifiable.”

Other participants took a broader view of Islam and its underlying values as a basis to justify their belief in the fatwa. For example, some participants examined the Islamic value that encourages people not to make religion a burden as their basis for accepting fatwa. Hence, they believed that things that are defined and not defined in Islam have benefits for humankind and that having to rely on a *fatwa* based on *Ijmau* (consensus) in the case of termination of pregnancy for illnesses must have underlying benefits and people should not doubt those *fatwas*. For example, one participant suggested that Muslims have to accept scholars’ *fatwas* and he reasoned as follows:

But still (pause) we have to accept the fatwa; our religion is not a harsh one. I wouldn't say it is ‘*haram*’ (forbidden), when the Fatwa is based on Hadith and Quran and Ijmau. Things prescribed in our religion have underlying benefits for the human race.

### *Religious scholars’ advice*

In addition to the knowledge of *fatwa*, most participants sought individual scholars’ opinions in order to understand better and to confirm the ruling of the *fatwa*. According to the participants, the scholars’ opinions were divided into two groups. One group fully supported prenatal diagnosis and termination of pregnancy for thalassaemia. For example, one couple stated that the religious scholar who they consulted advised them by saying, “It [termination] is not a problem if it is done in the first 120 days - that abortion is permissible if we know life for the child is going to be agonizing.” According to another couple, a scholar advised them to terminate the pregnancy and stated “It is permissible and that it is a good decision to undergo abortion, as otherwise the child will also be going through a lot of hardship in the

world.”

The second group of scholars were of the opinion that termination is not forbidden in Islam for thalassaemia, but did not specifically recommend it. For example, one woman reflected: “They [religious scholars she consulted] also said that it's a hardship that we are giving to the child. They [religious scholars] never said we should abort...They [religious scholars] said before that date it [termination] is permissible.” A man described the advice he received as: “They [religious scholars] don't encourage going for abortion. He [religious scholar the participant consulted] said that some scholars believe it is permissible based on the undue hardship on the child after birth and also the emotional pain for the parents.”

#### *Fatwa is right, but my heart is not content*

Despite all participants considering that prenatal diagnosis and termination is important for Maldives, and believed and accepted religious scholars' advice and the fatwa, at a personal level only a few were fully content with it. In its entirety as a prevention measure: prenatal diagnosis was not of concern, but at the time of their test, most were worried from a religious perspective that they might have to undertake termination if the foetus was diagnosed as a major. For example, one participant suggested: “I am not comfortable even if the fatwa allows it [termination]. Even when we went there, I had the fear and I was praying it would be a normal baby.”

Those participants, who had terminated one or more pregnancy following prenatal test, expressed much regret. For example, a man who experienced his wife going through their first termination after a positive prenatal diagnosis reflected: “I cannot do that [accept termination of pregnancy] whole heartedly. That's why I was having doubts. And I was scared of the eventuality of an abortion. I wasn't able to

believe it [*fatwa*] whole heartedly... I believe it [termination of pregnancy] should be avoided.” One couple described similar regret from their experience:

Even that day [day of prenatal diagnosis] we were unable to eat. It was a difficult feeling. Even if religious scholars say that [termination of pregnancy is allowed], it was difficult to accept it (pause)...Yes, it was difficult. Even now I have some regrets... We did it with trust in Allah. It wasn't the easiest.

A woman who underwent prenatal diagnoses five times and three terminations described her uncertainty towards the fatwa as follows:

But still even if we know that [the rulings of fatwa], the dissatisfaction and uncertainty was there every single time. The fear was there in my heart every single time. The fear that it is not allowed in the religion is always there even if someone says it is ok. Truly believing it in our heart is a different thing, right? I can't totally accept that it is allowed. That scares me.

Some participants who considered the fatwa was religiously correct and believed it, did not however, consider it morally right. For example, a woman who went through two prenatal diagnoses and one termination expressed her thoughts as, “I believe the scholars’ fatwa, but I am unable to convince my heart on a moral level that it [termination of pregnancy] is right.”

### *Guilty of sinning*

Since it was difficult to accept the thalassaemia related fatwa wholeheartedly, most participants who terminated one or more pregnancy faced an enormous challenge. The consequence of not being able to accept the fatwa unconditionally was the ‘feeling of sinning’ and regret. For example, one woman described her fear of sinning as, “The fear is there even if no matter how many scholars say that [termination of pregnancy is allowed in Islam]. The fear is there in my heart... Yes, I feel that abortion is a sin.” A woman who had a termination three months before this

study described her feeling as follows:

Fatwa was there. So after thinking thoroughly, we thought that this is the only way... So I had an abortion. At that moment [time of termination], I started having doubts. I was thinking may Allah have mercy on me. I was thinking that it was not worth doing.

The emotional turmoil that many participants who had to terminate their pregnancy endured did not fully go away with time, they carried the guilt with them. For example, one participant expressed her guilt as, “I can't believe it [*fatwa*] whole heartedly. I am not saying it is wrong. I just have some doubt about it. It [termination] is something that I do not want to do. The guilt that it is a sin is on my mind all the time.” A man who experienced his wife’s termination described his guilt as:

It was a frightening feeling, I felt guilty, and sad. I felt that I have sinned. At that very instant I felt I should not have done it. That I should have taken the responsibility of blood transfusion and all that came with having a major child... I can't accept it...I feel that I killed a child.

## Discussion

All participants of this study undertook prenatal diagnosis for thalassaemia, based on the fatwa, at least once, knowing and accepting that they might have to terminate their pregnancy. Despite related research indicating that many Maldivians do not use prenatal diagnosis services for a variety of reasons (Waheed, Fisher, Awofeso and Stanley, 2015). Our findings suggest that the *fatwa* on prenatal diagnosis and termination of pregnancy in Maldives was the most influential factors in the decisions of participants to undertake prenatal diagnosis and potential termination for thalassaemia. This finding is in line with studies that have examined

prenatal diagnosis in other Muslim communities. For example, a study conducted in Egypt exploring the impact of Islamic fatwa on the attitudes of at-risk couples for thalassaemia found that religion was the main factor that influenced decisions to continue with or terminate a pregnancy.<sup>93</sup> The findings of that study also revealed that incorporation of fatwa in genetic counselling improved the uptake of prenatal diagnosis significantly.<sup>93</sup> A qualitative study that explored the impact of religious fatwa-related education on the attitude of families that are affected by hemoglobinopathy in Saudi Arabia showed that knowledge of fatwa significantly (81.3% uptake) improved parents' attitudes towards prenatal diagnosis and termination of pregnancies.<sup>83</sup>

Similar findings were reported in Muslim communities in non-Muslim countries. For example, British subjects in a study conducted by Ahmed, Atkin, Hewison and Green<sup>101</sup> reported that their decision around prenatal diagnosis would be affected by faith and religious beliefs. In addition to the influence of the national fatwa, most participants in our study explored their trusted religious scholars' opinions towards prenatal diagnosis and termination of pregnancies as a way of confirming their own understanding.

However, our findings also indicate that making decisions around termination of pregnancy was much more complex and participants were conflicted when making such decisions: accepting the fatwa did not necessarily mean that they accepted it wholeheartedly. They believe the fatwa but at the same time disagree with all the actions that it allows.

A possible explanation for this could relate to community norms being mostly based on religious values in Maldives. Islam teaches that killing is wrong and life is sacred, so it should be protected at all times. Islam respects the human embryo

from the onset of fertilization because, according to its teachings, viability of life starts at implantation.<sup>212</sup> For example, according to *Shariah*, an estate cannot be decided until the fetus is born and in the case when a pregnant women is assailed, the assailant is held responsible for any damage caused to the fetus as a result of the assault.<sup>212</sup> Furthermore, sanctity of human life is stressed in many verses of *Quru'an*.<sup>210</sup> For example, *Surah Al-Isra'* (17: 31) is translated as “And do not kill your children for fear of poverty. We provide for them and for you. Indeed, their killing is ever a great sin.” The 32<sup>nd</sup> Verse of *Surah Al-Ma'ida* equates killing one soul (except for a soul or for corruption done on the land) to slaying the entire human race. *Surathul Isra'* 17:70 describes the honor of human race as “And we have certainly honored the children of Adam...and preferred them over much of what we have created, with [definite] preference.” Hence, the obligation to respect human life from the onset of fertilization is a must in Islam and it is clearly defined in Qur'an. Qur'an, Hadith or Sunna does not explicitly define the status of abortion in Islam.<sup>210</sup> Hence, participants of this study had trouble putting aside what is so firmly obligated in Qur'an (Allah's words) and accepting a fatwa (Ijmau or consensus of religious scholars) that was derived using logic and analogy by humans.

Many of our participants reflected on feeling of fear and guilt that they carried with them as a result of previous termination or terminations of pregnancies based on prenatal diagnosis for thalassaemia. According to some, they carried the guilt with them all the time and it never totally went away. Distress and feeling of guilt are common aspects reported in literature in relation to prenatal diagnosis and termination of pregnancies. For example, a study conducted in Norway revealed that women who had terminated a pregnancy had higher anxiety level than the normal population even after a vast period of five years when assessed using Hospital

Anxiety and Depression Scale.<sup>213</sup> A qualitative study conducted in Brazil also showed termination of pregnancies caused sadness, despair and guilt for the women.<sup>214</sup> Hence, psychological and bereavement support for carriers who undergo prenatal diagnosis and termination is an important area that needs attention Maldives.

## **Conclusion**

The findings of this study revealed that Islamic fatwa on prenatal diagnosis and termination of pregnancy was important in the 100% Muslim community of Maldives. Participants in this study based their prenatal diagnosis decision on the religious fatwa and scholars' opinions. However, even though the participants believed the fatwa, most could not accept the fatwa wholeheartedly. As a result, the decision of prenatal diagnosis put them in a position of guilt and uncertainty. The concurrence of wanting to believe the fatwa, but having the doubt if their decision based on the fatwa is right made our participants feel guilty of sinning. Many participants questioned themselves if their decision is truly the right thing to do and they feared that they might be ultimately accountable for their decision. Hence, religious fatwa is important for prevention of thalassaemia in Muslim communities and its incorporation into prevention programs is vital, but policy makers must bear in mind that it may not be accepted universally.



### Introduction to the Chapter

Chapter nine (paper six) is based on the first objective of the third study, “Evaluate the Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives.” The paper was submitted to Journal of Quality of Life Research. The reference is as below:

*Reference:* Waheed F, Fisher C, Awofeso N, Stanley D. Health Related Quality of Life of Maldivians who are living with transfusion-dependent thalassaemia. Journal of Quality of Life Research. 2015. (Submitted)

The paper included abstract, introduction thalassaemia, introduction to Maldives and thalassaemia situation in Maldives, research design/methodology, results, discussion, conclusion and limitations of the study. The paper is presented as submitted to the journal except with the changes of Figure and Table number and reference style. The chapter number was added to the original Figure and Table number to assist the flow of the thesis. Numbered referencing was used in the original article that was submitted to the journal. The referencing was changed from number system to Vancouver system to ensure consistency in referencing throughout the thesis.

**Title: Health Related Quality of Life of thalassaemia majors in Maldives: A cross-sectional study.**

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## **Abstract**

### *Purpose*

The purpose of this study was to evaluate the Health Related Quality of Life (HRQoL) of transfusion dependent thalassaemia patients in Maldives.

### *Methods*

A cross-sectional approach using SF-36 survey was used for this study. The study was targeted at thalassaemia major Maldivians who were 14 years and over. Over 74.7% of the targeted population took part in this study. The SF-36 survey measure eight different domains of health; Physical Functioning (PH), Role limitation due to Physical health (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role limitation due to Emotional health (RE) and Emotional Wellbeing/Mental Health (EW/MH). In addition, patient records and patient registration records of the MBS were collected. The HRQoL scores were calculated as advised in Research And Development (RAND) website.

### *Results*

A total of 145 participants (81 females and 64 males) took part in this study. A hundred and twenty seven participants were  $\beta$ -thalassaemia majors, 15 were HbE  $\beta$ -thalassaemia majors and 3 were thalassaemia intermedias. The maximum age of the participants was 33 years. The mean HRQoL scores from highest to lowest were 87.3 (SF), 83.7 (PF), 77.5 (EW), 75.0 (RP), 71.5 (RE), 68.8 (BP), 64.4 (VT) and 62.3 (GH).

### *Conclusion*

The HRQoL scores were not worse off for thalassaemia majors of Maldives in comparison to other countries. The treatment services should look into, GH and VT domains to improve the total HRQoL further.

### *Keywords*

Thalassaemia major, Health Related Quality of Life (HRQoL), Maldives

## Introduction

The Thalassaemias are described as “inherited autosomal recessive disorders characterised by reduced rate of haemoglobin synthesis due to a defect in  $\alpha$  or  $\beta$ -globin chain synthesis”.<sup>22, p.353</sup> It is one of the most common hereditary disorders reported in the world. It is estimated that 3% of the world population are heterozygous for  $\beta$ -thalassaemia with more than 200 different mutations.<sup>35</sup> Each year, more than 300,000 children are born with severe  $\beta$ -globin disorders in the world<sup>35</sup> and 70, 000 of them are estimated as  $\beta$ -thalassaemia.<sup>58</sup>

The only permanent treatment for transfusion-dependent thalassaemia (thalassaemia major) is Bone Marrow Transplant, which is extremely expensive and requires a compatible (HLA-identical) donor.<sup>107</sup> Pre-implantation genetic diagnosis<sup>215</sup> is also a possible treatment and gene therapy<sup>22,109</sup> is a promising new treatment that may be available in the future. However, due to the high cost of these treatments and other limitations, thalassaemia is normally treated by regular blood transfusions which are done on a schedule of once every four weeks<sup>22</sup>, and sometimes more frequently than that. This method of treatment is time consuming, expensive and often risky (in some countries) due to transmission of infections.<sup>22</sup> In addition to the cost, time and risk of infection involved, it leads to excess iron in the blood which can damage the patient’s liver, heart, pancreas and other endocrine organs.<sup>22</sup>

Like many other lifelong treatments, blood transfusion and iron chelation treatment requires commitment and appropriate compliance, along with regular monitoring. According to the International Thalassaemia Federation<sup>112</sup>, poor adherence to treatment might lead to poor growth, facial and other deformities, fragile bones and bone fractures, enlarged liver and spleen and impairment of normal

physical activities. Other symptoms such as physical deformity, growth retardation and delayed puberty are also common among thalassaemia patients.<sup>113</sup>

Due to the time, cost, the consequent complications and side effects, researchers of thalassaemia consider that transfusion and iron chelation therapy is not enough for the thalassaemia treatment. Rather, a more holistic approach that looks into quality of life of the patients should be implemented. In fact, many researchers of thalassaemia argue that quality of life should be considered as one of the indexes that determine the effectiveness of the treatment for thalassaemia.<sup>117</sup> Moreover, some suggest that all thalassaemia patients should undergo quality of life assessments, so that treatment can be made more effective by implementing interventions that focus on affected domains.<sup>118</sup> Quality of life is described as “individual’s perceptions of their position in life in the context of the culture and value system where they live, and in relation to their goals, expectations, standards and concerns”.<sup>116 p.17</sup>

### **Thalassaemia in Maldives**

The Republic of Maldives (Maldives) is a group of coral islands in the Indian ocean with a population of 341, 256<sup>3</sup>. It has one of the world’s highest  $\beta$ -thalassaemia carrier rates (18.1%).<sup>41</sup> As a result, Maldives has a comparatively large transfusion-dependent thalassaemia population. According the records of Maldives Blood Services (MBS), 776 thalassaemia major cases were registered for treatment and 168 premature deaths were recorded from the start of the program in 1992 to 2013. At present, a total of 608 patients of different ages are taking treatment for thalassaemia in Maldives.<sup>216</sup> The annual cost of treating a thalassaemia child in the Maldives is approximately US \$6, 000 per patient; under Maldivian law the treatment is free for all thalassaemia patients.<sup>44</sup>

The treatment service has been in Maldives for more than two decades. However, the intended outcome of the treatment - which is to improve the Health

Related Quality of Life (HRQoL) of patients - is not known. To date, no research has been carried out on the HRQoL of thalassaemia majors in Maldives. Therefore, this is an area that needs to be studied in the Maldivian context to facilitate and improve the treatment aspect of the thalassaemia program. This study is a part of a larger study that aims to examine the different levels of prevention of thalassaemia in Maldives.

### **Research Design/Methodology**

The objective of this study is to evaluate the HRQoL of transfusion-dependent thalassaemia majors in Maldives. A quantitative approach was followed for the study. Specifically, the study was a cross-sectional survey.<sup>160</sup> According to Martin<sup>160</sup> cross-sectional studies allow standardized measurement of attributes of interest and it can be used to measure the impact of health experiences. The literature<sup>76,117,122,161,162</sup> also shows there are many studies that have used the cross-sectional survey method to measure the quality of life of thalassaemia patients in different communities. Hence, a cross-sectional survey was again used to evaluate the quality of life of transfusion-dependent thalassaemia major Maldivians.

### **Research instrument**

RAND 36-Item Short Form Health Survey (SF-36)<sup>163</sup> was used for the study. It is a generic survey freely available for interested researchers from RAND Corporation.<sup>164</sup> SF-36 survey measures eight domains of health which are relevant across age, disease and treatment groups<sup>165</sup>. The eight domains include physical functioning, role limitation (due to physical health problems), bodily pain, general health, vitality, social functioning, role limitation (due to emotional problems) and mental health.<sup>165</sup>

SF-36 has shown to be reliable, valid and sensitive enough to measure the quality of life of thalassaemia patients when translated to other languages such as

Malay<sup>130</sup> and Arabic.<sup>166</sup> A number of studies that have used SF-36 to measure the quality of life of thalassaemia patients can be found in the literature.<sup>113,117,123,167</sup>

Therefore, it was an appropriate tool to use for this study.

Before data collection the SF-36 survey form was translated to the Maldivian local language “Dhivehi” and then translated back, as directed in the RAND website<sup>168</sup>, to ensure that meanings were not lost in translation. The survey can be self administered by people 14 years of age or older, or it can be administered as an interview in person or by telephone.<sup>165</sup> Even though it can be self-administered, this form was administered as an assisted interview. In addition to the SF-36 survey, another short form was administered to record general demographics and main clinical characteristics of individual patients.

### *Participants and Sampling*

According to the records of MBS, the accumulated registered thalassaemia population of the Maldives at the time of this study was 776. All patients have to be registered with MBS in order to access blood transfusions and free medications within Maldives. The study was targeted at patients aged above 14 years as it was the recommended youngest age. According to records of MBS, there were 195 transfusion dependent patients who were 14 years or above when this study was conducted. A total of 151 thalassaemia patients (14 years and above) visited MBS for transfusion during this study. All 151 were invited to participate, but two participants declined to participate, hence a total of 149 (64 males and 85 females) participants completed the SF 36 survey form. This means that 76.8% of the total Maldivian thalassaemia population aged 14 years and above took part in this study.

However, four participants (three HbE  $\beta$ -Thalassaemia and one Sickle cell  $\beta$ -Thalassaemia) were excluded from the study as they stated that they do not need regular blood transfusions. All four of them stated that they have the transfusion

occasionally (two have them approximately twice a year, one only when she is pregnant and the sickle cell patient said she has transfusion only during a crisis). Hence, 74.7% (145) of the Maldivian thalassaemia patients who were 14 years and over were included in the study.

### *Data Analysis*

There is no record of the SF 36 survey form being translated into the Maldivian language and used in the Maldives. Therefore, as a first step, Cronbach's Alpha was calculated to see the internal consistency and reliability of SF 36 survey components administered in Dhivehi. The scoring of the survey was carried out in a two steps process as advised by RAND health <sup>169</sup>. As such, all scores (the scores of SF-36 survey are based on a scale of 1 to 6) were converted to an aggregate percentage score between zero and 100; the lowest is zero and highest possible is 100. The scores from functional groups are then averaged to calculate the score of each quality of life function; physical functioning (PH), role limitation due to physical health (RP), role limitation due to emotional health (RE), vitality (VT), emotional well-being (EW), social functioning (SF), bodily pain (BP) and general health (GH).

Descriptive statistics were computed to explore the general characteristics of the population. Population characteristics were calculated in terms of percentage, mean, standard deviation and frequencies. The scores of the functional categories were later centered using means and descriptive frequencies were computed to identify the percentage proportions that lie below and above the mean scores. Final scores of the functional groups were interpreted in reference to the whole construct of the SF 36 survey. Data was analyzed using IBM SPSS Statistics 23.



## Results

The SF-36 survey form was translated to Dhivehi and administered in the Maldives for the first time for the purpose of this study. Therefore, internal consistency and reliability of the survey domains were important aspects to look at before the descriptive and survey scores. The Cronbach's Alpha composite score for the 36 questions of the survey form was 0.865 and for the eight sub categories of Quality of Life scores was 0.764. The participant characteristics and reliability scores of the survey are presented in next section followed by HRQoL scores. HRQoL scores are presented in terms of mean, standard deviation, minimum, maximum value and percentages above and below the mean score of each category.

A total of 145 participants (81 females and 64 males) were included in the study. Patient records indicate that 127 participants were  $\beta$ -Thalassaemia Major, 15 were HbE  $\beta$ -Thalassaemia and 3 were Thalassaemia Intermedia. Fifty four participants were between 14 and 17 years of age and 91 participants were between 18 and 33 years of age. None of the participants were over 33 years of age. Most participants (71%) attended secondary schools or higher while 29% completed primary school and did not study any further. Over one third of the participants (36.4%) in this study were from low income families, 32.9% were from middle income families and 30.8% of participants belonged to high income families. Frequency analysis showed that the lowest income was MRF 1500 and the highest was MRF 200,000 per month. More than half (57.9%) of the participants were from islands other than Male'. Some of them were living in Male' temporarily due to their thalassaemia condition and others regularly or often travelled to Male' for transfusion. Male' is the capital of Maldives and it is where MBS is located. Table 9.1 shows more details of participants and total numbers and percentages.

**Table 9.1: Participant characteristics**

| Characteristic                              | Total | Percentage |
|---------------------------------------------|-------|------------|
| <b>Diagnosis (145)</b>                      |       |            |
| β Thalassaemia Major                        | 127   | 87.6       |
| HbE β Thalassaemia                          | 15    | 10.3       |
| Thalassaemia Intermedia                     | 3     | 2.1        |
| <b>Gender (145)</b>                         |       |            |
| Male                                        | 64    | 43.4       |
| Female                                      | 81    | 56.6       |
| <b>Age (145)</b>                            |       |            |
| 14 to 17 years <sup>a</sup>                 | 54    | 37.2       |
| 18 to 33years                               | 91    | 67.8       |
| <b>Education (145)</b>                      |       |            |
| Attended Primary education only             | 42    | 29.0       |
| Attended Secondary Education or Higher      | 103   | 71.0       |
| <b>Household Income/month (143)</b>         |       |            |
| Low (below MVR <sup>b</sup> 10,000)         | 52    | 36.4       |
| Middle (between MVR11,000-20,000)           | 47    | 32.9       |
| High (above MVR 21,000)                     | 44    | 30.8       |
| <b>Residential Island (145)</b>             |       |            |
| Male'                                       | 61    | 42.1       |
| Other islands                               | 84    | 57.9       |
| <b>Chelation medication (144)</b>           |       |            |
| deferoxamine only                           | 29    | 20.3       |
| deferoxamine with oral medication           | 71    | 49.7       |
| deferiprone or Deferasirox                  | 39    | 27.2       |
| Not taking any iron chelation at the moment | 4     | 2.8        |
| <b>Travel for transfusion (144)</b>         |       |            |
| Yes                                         | 25    | 82.6       |
| No                                          | 119   | 17.4       |

<sup>a</sup> all are enrolled in high school and are minors by law

<sup>b</sup> MVR-Maldivian currency (Maldivian Rufiya); 15.50 MVR is approximately US\$1

Descriptive statistics and frequencies of SF-36 are presented in Table 2.

Mean scores of the eight functional domains of Health Related Quality of Life

(HRQoL) of thalassaemia majors who are 14 years and above in the Maldives ranged from 87.3 for SF to 62.3 for GH with a standard deviation of 19.7 and 21.40 respectively. The second highest mean score (83.7) was for PF. The third highest score was 77.5 for EW. The score for RP was 75.50 and for RE was 71.5. The score for BP (68.8) was slightly higher than the GH score, but lower than all other scores. The highest Standard deviation or dispersion of the individual scores were observed for RP (SD =  $\pm 29.8$ ) and BP (SD =  $\pm 29.7$ ). The lowest dispersion of individual scores were observed for PF (SD =  $\pm 16.2$ ) and EW (SD =  $\pm 16.4$ ) domains.

Three categories (RP, RE and BP) had minimum scores of zero, which means one or more participants scored zero for questions 13, 14, 15, 16, 17, 18, 19, 21 and 22. Further analysis of those nine measures of the survey revealed that quite a large percentage scored zero for some measures. Frequency analysis for those nine measures revealed that 21.4%, 29.7%, 30.3% and 18.6% of the participants scored zero for questions 13, 14, 15 and 16 in RP domain. Frequency analysis of RE scores revealed that 13.1%, 23.4% and 49% gave zero for question 17, 18 and 19 respectively. In addition, BP function had zero for minimum because a large portion of the participants (15.2%) stated that ‘they experienced very severe bodily pain in the last four weeks’ scoring zero for question 21. Another 9.7% scored zero for question 22 in BP domain.

The scores of the functional categories were centered using the mean to explore the percentage that fall above and below mean scores. Frequency analysis of centered scores showed that more than 50% of the participants scored higher than the mean in seven of the HRQoL domains. A large number of participants (60.7%) scored lower than mean in the RE domain as many participants scored the lowest possible score (zero) for question 17 (13.1%), 18 (23.4%) and 19 (49%) respectively.

Table 9.2 shows the percentages that were above and below mean scores for all domains.

**Table 9.2: Quality of Life scores of all participants**

| SF -36 dimensions         | Mean (Total) | Std Deviation | Min  | Max   | Percent $\geq$ mean | Percent $<$ mean |
|---------------------------|--------------|---------------|------|-------|---------------------|------------------|
| Physical Functioning (PF) | 83.7         | $\pm 16.2$    | 10.0 | 100.0 | 64.8                | 35.2             |
| Role physical (RP)        | 75.0         | $\pm 29.8$    | 0.0  | 100.0 | 72.4                | 27.6             |
| Role emotional (RE)       | 71.5         | $\pm 28.3$    | 0.0  | 100.0 | 39.3                | 60.7             |
| Vitality (VT)             | 64.4         | $\pm 17.2$    | 20.0 | 100.0 | 51.0                | 49.0             |
| Emotional Well-being (EW) | 77.5         | $\pm 16.4$    | 8.0  | 100.0 | 55.9                | 44.1             |
| Social Functioning (SF)   | 87.3         | $\pm 19.7$    | 12.5 | 100.0 | 72.4                | 27.6             |
| Bodily Pain (BP)          | 68.8         | $\pm 29.7$    | 0.00 | 100.0 | 62.8                | 37.2             |
| General Health (GH)       | 62.3         | $\pm 21.4$    | 10.0 | 100.0 | 51.7                | 48.3             |

## Discussion

Cronbach's Alpha for the 36 questions of the survey was 0.865 and for the eight domains of Quality of Life scores was 0.764. The two figures were above 0.7 and hence, the survey attributes are consistent and reliable when translated and administered in Dhivehi.

Our findings show that HRQoL of Maldivian thalassaemia major patients who are 14 years and over scored comparatively well in all eight functional categories of HRQoL. Table 3 shows functional scores for HRQoL of thalassaemia patients in other countries based on the SF-36 survey form.

Our PF score (83.7) is similar to scores attained in Italy (82.8) by Scalone, Mantovani, Krol, Rofail, Ravera, Grazia Bisconte<sup>123</sup> and in North America (Boston, Oakland, Philadelphia, Toronto, and Vancouver) (82.3) by Klaassen, Barrowman, Merelles-Pulcini, Vichinsky, Sweeters, Kirby-Allen<sup>217</sup>. Our mean PF score is higher than the scores attained in studies conducted in Iran<sup>127,128</sup>, Turkey<sup>125</sup>, Malaysia<sup>130</sup>,

the US <sup>141</sup> and Saudi Arabia.<sup>135</sup> It is also higher than one diverse international study conducted by Porter, Bowden, Economou, Troncy, Ganser, Habr <sup>129</sup> that included participants from Australia, Belgium, France, Germany, Greece, Italy, Netherlands and UK. However, a more recent study conducted in Iran <sup>126</sup> gave a better score of 86.9 for PF function, which is slightly higher than the Iranian norm.<sup>218</sup> Hence, this gives hope that the PF function of Thalassaemia majors can be further improved in Maldives.

The mean RP score of our study (75.0) was very similar to the mean RP score attained by Klaassen, Barrowman, Merelles-Pulcini, Vichinsky, Sweeters, Kirby-Allen <sup>217</sup> in North America. Their study included participants from Boston, Oakland, Philadelphia, Toronto, and Vancouver and achieved a mean score of 75.4 for RP domain. The mean RP score of Maldivian thalassaemia majors is better than many other countries that have studied HRQoL of thalassaemia majors.<sup>123,125-127,129,130</sup> Hence, Maldivian thalassaemia majors' role is not limited due to physical health compared to thalassaemia majors in many other countries. However, there is still scope for improvement.

The mean RE score (71.5) of our study was similar to the score attained by thalassaemia major patients in Italy (71.7).<sup>125</sup> It is comparatively closely similar to the mean scores attained by thalassaemia majors in the study conducted by Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi, Parand <sup>126</sup> in Iran (70.8) and Ismail and Campbell <sup>130</sup> in Malaysia (69.7), but lower than the mean score obtained in the US (84.9) <sup>141</sup> and in North American (77.1).<sup>217</sup> Also, our participants scored lower than the mean RE score (75.99) attained in the international study by Porter, Bowden, Economou, Troncy, Ganser, Habr <sup>129</sup>. However, the participants of this study scored higher than the mean scores obtained

in some of the studies in Iran <sup>127,128</sup> and Turkey.<sup>125</sup> Therefore, a score of 71.5 means there is still the prospect of improvement.

The mean VT score of our study (64.4) was the second lowest score in all eight domains in our study. It is similar to that of patients in Italy (64.5).<sup>123</sup> In contrast, our mean score is higher than mean scores attained in Iran <sup>126-128</sup>, Turkey <sup>125</sup>, Malaysia <sup>130</sup>, North America <sup>217</sup>, the US <sup>141</sup> and Saudi Arabia.<sup>135</sup> Vitality is one area that most countries scored poorly in other studies, as shown in the literature summary table (Table 9.3). Hence, the Vitality score is acceptable in comparison to other studies, but it has much space for improvement compared to other domain scores in our study.

The mean BP score (68.8) we attained in our study was higher than the mean scores attained in the studies conducted in Iran.<sup>126-128</sup> It was similar to the mean scores of the studies conducted by Payne, Desrosiers, Caro, Baladi, Lordan, Proskorovsky <sup>141</sup> in the US (68.2), Scalone, Mantovani, Krol, Rofail, Ravera, Grazia Bisconte <sup>123</sup> in Italy (69.4) and Amoudi, Balkhoyor, Abulaban, Azab, Radi, Ayoub <sup>135</sup> in Saudi Arabia (69.4), but are much lower than mean scores attained in studies conducted in Turkey (78.7) <sup>125</sup> and Malaysia (77.2).<sup>130</sup> The lower score for this category might be due to the high number of participants who were taking *deferroxamine* subcutaneously as their only treatment for iron chelation or as part of their mixed iron chelation therapy as shown in Table 9.1. Hence, the satisfaction and burden of subcutaneous iron chelation needs to be explored further in order to improve the HRQoL of thalassaemia majors in Maldives.

The mean SF (87.3) and EW (77.5) scores of our participants were higher than all the countries in the literature summary, presented in Table 9.3. Those mean scores are quite high and it would be interesting to research those functions further

and see the cause of the difference in Maldives compared to most other recent studies in other countries.

As shown in Table 9. 3, our participants scored well (62.3) in GH function in comparison to thalassaemia population related findings in Iran <sup>127</sup>, Turkey <sup>125</sup>, Italy <sup>123</sup>, North America <sup>217</sup>, Malaysia <sup>130</sup>, Saudi Arabia <sup>135</sup> and the US. <sup>140</sup> Our score is closely related to the mean score of 62.5 obtained by Haghpanah et al <sup>126</sup> in Iran. However, the GH domain is the lowest scored function in our study. Therefore, there is much room for improvement of GH.

**Table 9.3: Summary of HRQoL scores of recent studies that used SF-36**

| Author, country of study, and instrument used to measure HRQoL                                                                                                        | PF          | RP               | RE               | VT          | BP          | SF          | EW          | GH          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------|------------------|-------------|-------------|-------------|-------------|-------------|
| Haghpanah et al <sup>126</sup> , Iran, SF-36                                                                                                                          | 86.9        | 65.4             | 70.8             | 62.5        | 63.7        | 69.5        | 60.9        | 62.5        |
| Khani et al <sup>127</sup> , Iran, SF-36                                                                                                                              | 73.6        | 59.1             | 53.6             | 52.8        | 64.4        | 69.1        | 52.9        | 57.9        |
| Yengil, Acipayam, Kokacya, Kurhan, Oktay and Ozer <sup>125</sup> , Turkey, SF-36                                                                                      | 66.5        | 52.8             | 41.3             | 55.5        | 78.7        | 84.65       | 59.8        | 50.12       |
| Scalone, Mantovani, Krol, Rofail, Ravera, Grazia Bisconte <sup>123</sup> , Italy, SF-36                                                                               | 82.8        | 68.2             | 71.7             | 64.5        | 69.4        | 74.1        | 70.0        | 52.6        |
| Klaassen, Barrowman, Merelles-Pulcini, Vichinsky, Sweeters, Kirby-Allen <sup>217</sup> , North America (Boston, Oakland, Philadelphia, Toronto, and Vancouver), SF-36 | 82.3        | 75.4             | 77.1             | 52.3        | 67.1        | 79.0        | 69.0        | 52.2        |
| Safizadeh, Farahmandinia, Soltani nejad, Pourdamghan and Araste <sup>128</sup> , Iran, SF-36                                                                          | 68.0        | 53.2             | 55.1             | 55.0        | 55.5        | 60.1        | 57.0        | 53.1        |
| Ismail and Campbell <sup>130</sup> , Malaysia                                                                                                                         | 71.9        | 66.8             | 69.7             | 58.6        | 77.2        | 81.1        | 73.9        | 51.9        |
| Amoudi, Balkhoyor, Abulaban, Azab, Radi, Ayoub <sup>135</sup> , Saudi Arabia, SF-36                                                                                   | 61.4        | N/A <sup>a</sup> | N/A <sup>a</sup> | 49.3        | 69.4        | 75.0        | 69.7        | 54.3        |
| Porter, Bowden, Economou, Troncy, Ganser, Habr <sup>129</sup> , Australia, Belgium, France, Germany, Greece, Italy, Netherlands and UK, SF-36                         | 77.99       | 71.03            | 75.99            | 59.53       | 70.53       | 75.29       | 68.53       | 51.31       |
| Payne, Desrosiers, Caro, Baladi, Lordan, Proskorovsky <sup>141</sup> , USA, SF-36 <sup>b</sup>                                                                        | 81.14       | 76.14            | 84.85            | 57.05       | 68.2        | 80.68       | 73.09       | 53.14       |
| <b>Scores of this study</b>                                                                                                                                           | <b>83.7</b> | <b>75.0</b>      | <b>71.5</b>      | <b>64.4</b> | <b>68.8</b> | <b>87.3</b> | <b>77.5</b> | <b>62.3</b> |

<sup>a</sup> Score was not available in the article patients.

<sup>b</sup> The USA study included both sickle cell and Thalassaemia (82%)

### **Conclusion:**

Overall, transfusion-dependent Maldivian thalassaemia patients scored well in HRQoL domains compared to thalassaemia major patients in other studies. The SF and EW scores that we attained were much higher than the scores attained in most recent studies in other countries. Hence, we can conclude that SF and EW are good among Maldivian thalassaemia majors. However, it is difficult to say if the scores were normal, satisfactory or poor in comparison to the general Maldivian population as these norms were not available.

In providing treatment, the functional domains of GH, VT and BP should be further explored to improve the HRQoL of thalassaemia majors in Maldives.

### **Strengths and Limitations**

Summary scores for Physical and Emotional health were not possible as population norms for HRQoL was not available for Maldivian population. Non availability of population norms was a limitation of this study and comparisons could not be made with the HRQoL scores of the general population. Another limitation was that the sample was a convenient sample. Nevertheless, we were able to access 74.4% of the patient population and the participants were well divided between Male' and other islands. Therefore, the findings can be generalized to the transfusion-dependent thalassaemia major Maldivians who are 14 years and over.

### **Compliance with Ethical standards**

The Human Research Ethics Committee of the University (HREC) of Western Australia (Ref: RA/4/1/5626) approved this study on the 9<sup>th</sup> of January 2013. It was also approved by the National Health Research Committee of Maldives on the 7<sup>th</sup> of February 2013. All participants provided written consent before



participation. In addition to participants; guardians of participants who were under 18 years [a minor under Maldivian Law] of age provided written consent for their children to participate in this study. Informed consent was obtained from all individual participants included in the study.

## Chapter 10: Paper seven

### Introduction to the Chapter

Chapter 10 (paper seven) is based on the second objective of the third study, “Determine the predictors of Health Related Quality of Life of transfusion dependent thalassaemia majors who are 14 years and above in Maldives”. The paper was submitted to Journal of Quality of Life Research. The reference is as below:

*Reference:* Waheed F, Fisher C, Awofeso N, Stanley D. Predictors of Health Related Quality of Life of transfusion-dependent thalassaemia major patients in Maldives. Journal of Quality of Life Research. 2015. (Submitted)

The paper included abstract, introduction thalassaemia, introduction to Maldives and thalassaemia situation in Maldives, research design/methodology, results, discussion, conclusion and limitations of the study. The paper is presented as submitted to the journal except with the changes of Figure and Table number and reference style. The chapter number was added to the original Figure and Table number to assist the flow of the thesis. Numbered referencing was used in the original article that was submitted to the journal. The referencing was changed from number system to Vancouver system to ensure consistency in referencing throughout the thesis.

**Title: Predictors of Health Related Quality of Life of transfusion dependent thalassaemia patients in Maldives: A cross-sectional study**

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No conflict of interest is known.

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## **Abstract**

### *Purpose*

The purpose of this study is to evaluate the predictors of Health Related Quality of Life (HRQoL) of transfusion dependent thalassaemia majors in Maldives

### *Methods*

The study was a cross-sectional study conducted using SF-36 survey in the Maldives Blood Services (MBS). SF- 36 measures eight different domains of HRQoL. In addition to the SF-36 survey, clinical and demographic characteristics (predictor variables) were collected during survey. Simple linear regression was computed for all eight HRQoL domains using the predefined predictor variables.

### *Results*

The mean HRQoL scores varied from 62.3 for GH to 87.3 for SF domain. Education, gender, marital status, number of transfusions, presence of co-morbidities, age of first transfusion, compliance to iron chelation therapy, type of iron chelation therapy, average haemoglobin level, transport and residential island showed a significant association with HRQoL domains. Age, household income, serum ferritin level, onset of anaemia, accommodation type, employment, frequency of transfusion and iron chelation therapy type did not show any significant association with the HRQoL scores.

### *Conclusion*

Education, gender, marital status, number of transfusions, co-morbidities, age of first transfusion, compliance to iron chelation therapy, iron chelation medication, average haemoglobin level, transport and residential island showed a significant association with HRQoL domains of thalassaemia majors who were 14 years and above in Maldives.

### *Keywords*

Thalassaemia major, Health Related Quality of Life (HRQoL), Maldives

## Introduction

Thalassaemia is described as “hereditary anemias characterized by reduced synthesis of one or more of the globins that form the hemoglobin tetramer”.<sup>219p.353</sup> Like many other lifelong health conditions, treatment for thalassaemia requires good commitment and compliance with monitoring.<sup>22</sup> According to International Thalassaemia Federation, poor adherence to treatment might lead to poor growth, facial and other deformities, fragile bones and bone fractures, enlarged liver and spleen and impairment of normal physical activities.<sup>112</sup> Other symptoms such as physical deformity, growth retardation and delayed puberty are also common among thalassaemia patients.<sup>113</sup>

Thalassaemia majors are normally treated by regular blood transfusion on a schedule of every three –five weeks intervals.<sup>220</sup> This method of treatment is time consuming, expensive and often risky due to the possibility of transmission of infections.<sup>22</sup> In addition to transfusion, thalassaemia majors require iron chelation therapy to remove excess iron that result from continued blood transfusion.<sup>22</sup> Iron chelation therapy is usually given subcutaneously (*deferoxamine*), five to seven nights a week on an 8- 12 hourly basis or as oral chelators (mostly *deferiprone* or *Deferasirox*).<sup>111</sup>

Similar to any other planned long term treatment, the main purpose of thalassaemia treatment is to ensure that thalassaemia majors can have a normal quality of life. However, as a result of the complications and difficulties involved in the treatment of thalassaemia, many studies show that Health Related Quality of Life (HRQoL) of thalassaemia majors becomes compromised in many circumstances.<sup>76,120,122,123,125,126,129,130,135,162,217</sup>

Maldives is a group of coral islands in the Indian Ocean. It has one of the

world's highest  $\beta$  thalassaemia carrier rate (16-18%).<sup>14</sup> As at August 2014, a cumulative total of 803 thalassaemia major patients were registered at MBS.<sup>14</sup> Furthermore, according to the 2014 report of Thalassaemia International Federation (TIF), a total of 563 were living and 459 of them were  $\beta$ -thalassaemia majors.<sup>14</sup>

The intended outcome of the registration and free services is to improve the HRQoL. However, thus far there is no research on HRQoL or predictors of HRQoL of thalassaemia majors in Maldives. This study is a part of a larger study that aimed at exploring the different levels of prevention of thalassaemia in Maldives. The purpose of this paper is to report the predictors of HRQoL of thalassaemia majors of age 14 years and above in Maldives.

### **Research Design/Methodology**

The study was a cross-sectional survey<sup>160</sup> conducted in MBS treatment centre, from February to June 2013. A cross sectional survey was used because literature shows that many other studies have used cross-sectional approach and it is an appropriate method to measure the HRQoL in different communities.<sup>76,117,122,161,162</sup>

### **Research instrument**

RAND 36-Item Short Form Health Survey (SF-36 survey)<sup>163</sup> was used for the study. It is a generic survey available free of charge for interested researchers from RAND Corporation.<sup>164</sup> SF-36 survey measures HRQoL by providing aggregated scores for eight functional domains; PF, RP, BP, GH, VT, SF, RE and MH/EW.<sup>165</sup>

SF-36 was shown to be reliable, valid and sensitive in measuring HRQoL of thalassaemia majors when translated to other languages such as Malay<sup>130</sup> and Persian.<sup>166</sup> A number of studies that had used SF-36 to measure the HRQoL of

thalassaemia patients can be found from literature.<sup>113,117,123,129,167</sup> Hence, it was an appropriate tool to use for the study and to translated into Maldivian local language (Dhivehi). As such, SF-36 survey was translated to Dhivehi and translated back as directed in RAND website<sup>168</sup> before the actual survey. The administering guideline advises that it can be self administered by people 14 years of age or older.<sup>165</sup> All the survey forms were administered as an assisted interview in order to ensure that participants understood and provided all required information.

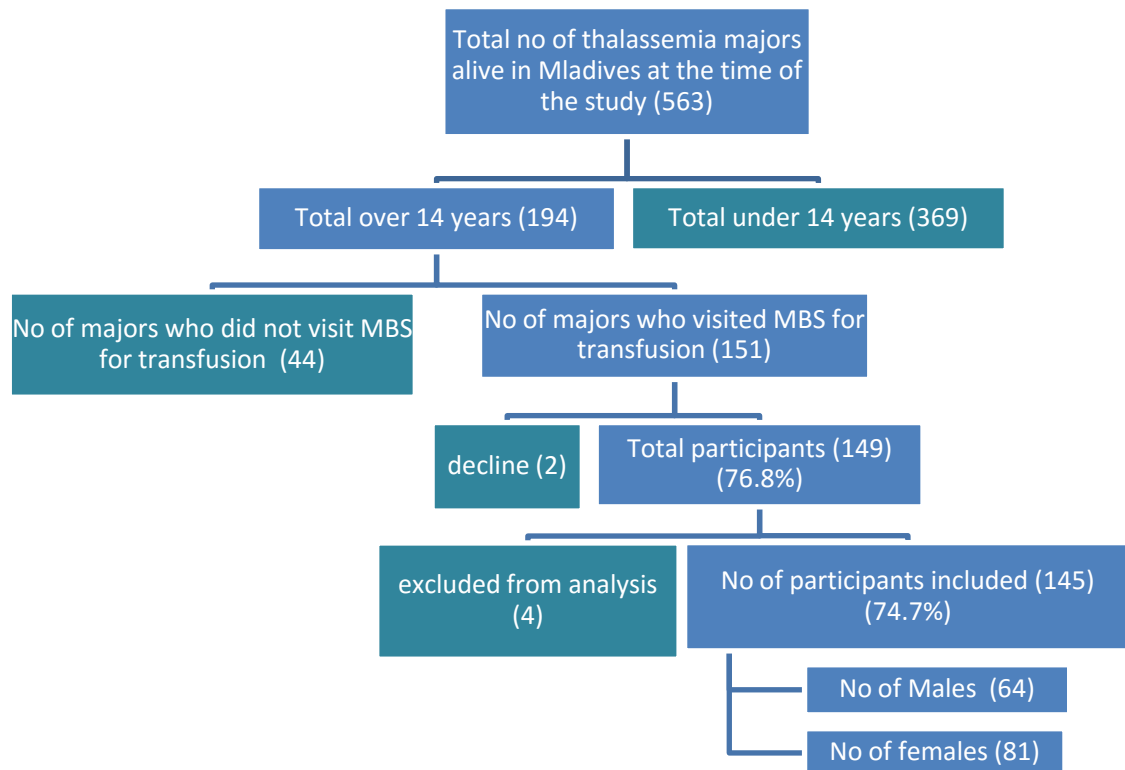
In addition to SF-36 survey, another short form was administered to document general characteristics, diseases related complications, type of iron chelation treatment and compliance to iron chelation treatment of individual patients. Additionally, patient records of the past six months of all participants were accessed in order to attain most recent serum ferritin levels and diagnosis of individuals and MBS provided average hemoglobin levels of all participants for the past six months.

### *Participants and Sampling*

The study was targeted to 14 years and above as it was the recommended youngest age by the SF-36 survey distributor, RAND.<sup>165</sup> The records of MBS shows that there were 195 thalassaemia majors Maldivians who were 14 years or above at the time of this study.<sup>216</sup> Please refer to Figure10.1 for details of participant selection.

Four participants (three HbE  $\beta$ -Thalassaemia and one Sickle cell  $\beta$ -Thalassaemia) were excluded from the study at the analysis stage as they were not transfusion dependent. Therefore, as a final figure, 74.7% (145) of the Maldivian thalassaemia majors who were 14 years and over were included in the study.

**Figure 10.1: Participant selection process for HRQoL study**



### **Data Analysis**

All except three survey forms were completed fully. Three survey forms had one missing response in each. Some data was missing from demographic forms and the records of MBS as well.

Scoring of the survey was done according to RAND health guideline for scoring SF-36 survey.<sup>169</sup> The scores of SF-36 survey that were based on scales of one to six were converted to aggregate percentage scores between zero and 100. Higher scores indicate better HRQoL. The scores of functional domains were then averaged (excluding missing scores list wise) to calculate the final score of each HRQoL domain.



Descriptive statistics were computed to explore the general characteristics of the population and Cronbach's Alpha was calculated to check the reliability and internal consistency of the translated version of SF-36 survey. Population characteristics were calculated in terms of numbers, frequencies, percentages, means and standard deviations. Pearson's correlation was used to assess if any correlations exist between continuous predictor variables in Table 10.2 and HRQoL outcomes domains of SF-36 in Table 10.3. Simple linear regression was used to examine the association between HRQoL domains in Table 10.3 and demographic/clinical variables in Table 10.1 and 10.2. The variables were considered significant at  $p \leq 0.05$ . The variable 'Diagnosis' which has three categories was dummy coded as 'β-thalassaemia major' and 'HbE β-thalassaemia or thalassaemia intermedia' in order to run simple linear regression for diagnosis. For the categorical variable compliance to iron chelation treatment, participants were considered not compliant if they had missed treatment more than once in a week in the past four weeks. Data was analyzed using IBM SPSS Statistics 23.

## Results

Results are presented as summary tables. Categorical predictor variables are presented with total numbers, frequencies and percentages. The three continuous predictor variables are presented as mean, standard deviation, minimum and maximum values. The HRQoL scores are presented in terms of mean, standard deviation and skewness of the distribution. The regression results are presented in terms of Beta coefficients (B), coefficients of determination ( $R^2$ ) and significance (p-value).

**Table 10.1: Participant Characteristics (Independent categorical variables)**

| <b>Variable (total)</b>                                  | <b>Frequency</b> | <b>Percentage</b> |
|----------------------------------------------------------|------------------|-------------------|
| <b>Diagnosis (145)</b>                                   |                  |                   |
| β Thalassaemia Major                                     | 127              | 87.6              |
| HbE β Thalassaemia                                       | 15               | 10.3              |
| Thalassaemia Intermedia                                  | 3                | 2.1               |
| <b>Gender (145)</b>                                      |                  |                   |
| Male                                                     | 64               | 43.4              |
| Female                                                   | 81               | 56.6              |
| <b>Education (145)</b>                                   |                  |                   |
| Attended Primary education only                          | 42               | 29.0              |
| Attended Secondary Education or Higher                   | 103              | 71.0              |
| <b>Marital status (145)</b>                              |                  |                   |
| Married                                                  | 13               | 9.0               |
| Not Married                                              | 132              | 91.0              |
| <b>Residential Island (145)</b>                          |                  |                   |
| Male <sup>a</sup>                                        | 61               | 42.1              |
| Not Male <sup>a</sup>                                    | 84               | 57.9              |
| <b>Accommodation (144)</b>                               |                  |                   |
| Lives in own house                                       | 86               | 59.3              |
| Lives in rental property                                 | 58               | 40.0              |
| <b>Travel for transfusion (144)</b>                      |                  |                   |
| No                                                       | 119              | 82.6              |
| Yes                                                      | 25               | 17.4              |
| <b>Employment (145)</b>                                  |                  |                   |
| Yes                                                      | 54               | 37.2              |
| No                                                       | 91               | 62.8              |
| <b>Frequency of Transfusion (144)</b>                    |                  |                   |
| Every two weeks or less                                  | 82               | 56.6              |
| Every three weeks or more                                | 62               | 42.8              |
| <b>Number of Unis transfused each time (143)</b>         |                  |                   |
| One unit                                                 | 79               | 54.5              |
| Two units                                                | 64               | 44.1              |
| <b>Other Health complications (145)</b>                  |                  |                   |
| No                                                       | 42               | 29.0              |
| Yes                                                      | 103              | 71.0              |
| <b>Iron Cheletion therapy type (140)</b>                 |                  |                   |
| Single                                                   | 71               | 49.0              |
| Mixed                                                    | 69               | 47.6              |
| <b>Iron chelation medication(143)</b>                    |                  |                   |
| Deferoxamin with oral chelators or oral chelators only   | 114              | 79.7              |
| Deferoxamine only                                        | 29               | 20.3              |
| <b>Compliance with iron chelation (134)</b>              |                  |                   |
| No                                                       | 79               | 54.5              |
| Yes                                                      | 55               | 37.9              |
| <b>Onset of anaemia (139)</b>                            |                  |                   |
| During first six months of age                           | 90               | 62.1              |
| After first six months of age                            | 49               | 33.8              |
| <b>Age of first transfusion (138)</b>                    |                  |                   |
| During first six months of age                           | 74               | 51.0              |
| After first six months of age                            | 64               | 44.1              |
| <b>Average Pre-transfusional Haemoglobin level (141)</b> |                  |                   |
| Below 8                                                  | 48               | 34.0              |
| Above 8                                                  | 93               | 66.0              |

<sup>a</sup> Male<sup>a</sup> is the capital of Maldives and it is where MBS is located

**Table 10.2: Participant Characteristics (Independent Continuous variables)**

|                                               | Mean    | Std Deviation | Lowest | Highest |
|-----------------------------------------------|---------|---------------|--------|---------|
| Age (years)                                   | 19.66   | ±4.4          | 14     | 33      |
| Household Income<br>(Maldivian Rufiyaa/month) | 22,730. | ±29,079.9     | 1500   | 200,000 |
| Serum Ferritin <sup>b</sup> (ng/mL)           | 3,813.3 | ±2,534.5      | 444    | 16,100  |

Table 10.3 provides the details of descriptive statistics of HRQoL scores and their distribution patterns. The scores of seven of the functional domains (PF, RP, RE, BP, SF, EW and GH) were negatively skewed while VT domain was positively skewed. Hence, none of the functional domain had a normal distribution. However, all domains had equal variance of residuals when residuals were plotted for regression analysis. Thus, they all met the assumption of homoscedasticity, which was necessary for simple linear regression analysis when the distribution is not normal for an outcome variable.

**Table 10.3: SF- 36 based HRQoL scores (outcome variables)**

| SF -36 dimensions            | Mean | Std Deviation | Skewness |
|------------------------------|------|---------------|----------|
| Physical Functioning (PF)    | 83.7 | ±16.2         | -1.568   |
| Role physical (RP)           | 75.0 | ±29.8         | -1.002   |
| Role emotional (RE)          | 71.5 | ±28.3         | -.765    |
| Bodily Pain (BP)             | 68.8 | ±29.7         | -.960    |
| Vitality (VT)                | 64.4 | ±17.2         | .099     |
| Emotional Well-being (EW/MH) | 77.5 | ±16.4         | -1.459   |
| Social Functioning (SF)      | 87.3 | ±19.7         | -1.842   |
| General Health (GH)          | 62.3 | ±21.4         | -.237    |

Simple linear regression was computed for all outcome variables in Table 10.3 using all predictor variables in Table 10.1 and 10.2. All three continuous variables were tested for correlation with HRQoL scores before computing them in

regression analysis. Only the significant results are reported in this paper as reporting all 160 (20x8) test scores is not in the capacity of this paper. Table 10.4 outlines the B,  $R^2$  and p-values of the significant predictors of HRQoL of thalassaemia majors who were 14 years and above in Maldives.

The Beta (B) values show a quite large difference for some predictor variables. For example, the married participants performed 19.39 ( $p=0.018$ ) times less in RE domain compared to participants who were not married. The RP scores of  $\beta$ -thalassaemia major participants were 15.86 ( $p=0.034$ ) times better than the other two groups (HbE  $\beta$ -thalassaemia and thalassaemia intermedia) combined. The GH scores of the participants who transfused two units of blood in each transfusion session were 15.21 ( $p=0.000$ ) times better compared to participants who transfused one unit of blood in each transfusion session. Overall, the Beta values were quite large and significance levels were quite high for many predictor variables, but the  $R^2$  or the percentage variances explained by most predictor variables were quite low. The highest value for  $R^2$  was 0.41 (41% variance) for other health complications in predicting PF and 0.27 (27% variance) for education in predicting PF.

The Pearson correlation and simple linear regression analysis computed for eight HRQoL domains in Table 10.3 using the three continuous predictor variables (age, household income and serum ferritin level) in Table 10.2 did not show any significant association. In addition, none of the predictor variables in Table 10.1 showed any significant association with SF and MH/EW scores. Furthermore, onset of anemia, accommodation type, employment status, frequency of transfusion and iron chelation therapy type did not show any significant association with any of HRQoL scores.

**Table 10.4: Simple Linear Regression with HRQoL scores**

| <b>Outcome Variable</b> | <b>Predictor Variable</b>                                                             | <b>B</b> | <b>R<sup>2</sup></b> | <b>p-value</b> |
|-------------------------|---------------------------------------------------------------------------------------|----------|----------------------|----------------|
| Physical Functioning    | <b>Education</b><br>Attended primary education(Reference)                             |          |                      |                |
|                         | Attended Secondary Education or Higher                                                | 5.825    | 0.27                 | 0.050          |
|                         | <b>Marital Status</b><br>Not married (Reference)                                      |          |                      |                |
|                         | Married                                                                               | -9.417   | 0.028                | 0.046          |
|                         | <b>Gender</b><br>Male (Reference)                                                     |          |                      |                |
|                         | Female                                                                                | -5.682   | 0.030                | 0.036          |
|                         | <b>Number of units transfused each time</b><br>One unit (Reference)                   |          |                      |                |
|                         | Two unit                                                                              | 8.197    | 0.062                | 0.003          |
|                         | <b>Have other health complications</b><br>No (Reference)                              |          |                      |                |
|                         | Yes                                                                                   | -7.191   | 0.41                 | 0.015          |
|                         | <b>Travel to Male' for transfusion</b><br>No (Reference)                              |          |                      |                |
|                         | Yes                                                                                   | -10.918  | 0.065                | 0.002          |
|                         | <b>Average Hb</b><br>Below 8 (Reference)                                              |          |                      |                |
|                         | Above 8                                                                               | 7.244    | 0.044                | 0.012          |
| Vitality                | <b>Education</b><br>Attended Primary education (Reference)                            |          |                      |                |
|                         | Attended Secondary Education or Higher                                                | 9.589    | 0.064                | 0.002          |
| Bodily Pain             | <b>Age of first transfusion</b><br>During first six months (Reference)                |          |                      |                |
|                         | After first six months                                                                | -11.305  | 0.035                | 0.028          |
|                         | <b>Gender</b><br>Male (Reference)                                                     |          |                      |                |
|                         | Female                                                                                | -12.370  | 0.043                | 0.012          |
|                         | <b>Have other health complications</b><br>No (Reference)                              |          |                      |                |
|                         | Yes                                                                                   | -12.006  | 0.034                | 0.027          |
| Role Physical           | <b>Age of first transfusion</b><br>During first six months (Reference)                |          |                      |                |
|                         | After first six months                                                                | -12.774  | 0.045                | 0.013          |
|                         | <b>Have other health complications</b><br>No (Reference)                              |          |                      |                |
|                         | Yes                                                                                   | -12.569  | 0.037                | 0.021          |
|                         | <b>Diagnosis</b><br>Thalassaemia Intermedia or HbE $\beta$ -thalassaemia (Reference)  |          |                      |                |
|                         | $\beta$ - Thalassaemia Major                                                          | 15.857   | 0.031                | 0.034          |
| Role emotional          | <b>Marital Status</b><br>Not Married (Reference)                                      |          |                      |                |
|                         | Married                                                                               | -19.386  | 0.039                | 0.018          |
|                         | <b>Gender</b><br>Male (Reference)                                                     |          |                      |                |
|                         | Female                                                                                | -11.111  | 0.038                | 0.019          |
|                         | <b>Diagnosis</b><br>Thalassaemia Intermedia or HbE $\beta$ - thalassaemia (Reference) |          |                      |                |
|                         | $\beta$ -Thalassaemia Major                                                           | 13.969   | 0.027                | 0.050          |
|                         | <b>Travel to Male' for transfusion</b><br>No (Reference)                              |          |                      |                |

|                |                                                                   |         |       |       |
|----------------|-------------------------------------------------------------------|---------|-------|-------|
| General Health | Yes                                                               | -13.632 | 0.058 | 0.003 |
|                | <b>Education</b>                                                  |         |       |       |
|                | Attended Primary education (Reference)                            |         |       |       |
|                | Attended Secondary Education or Higher                            | 10.005  | 0.045 | 0.010 |
|                | <b>Residential Island</b>                                         |         |       |       |
|                | Other islands (Reference)                                         |         |       |       |
|                | Male'                                                             | 7.979   | 0.034 | 0.026 |
|                | <b>Number of units transfused each time</b>                       |         |       |       |
|                | One unit (Reference)                                              |         |       |       |
|                | Two units                                                         | 15.212  | 0.126 | 0.000 |
|                | <b>Have other health complications</b>                            |         |       |       |
|                | No (Reference)                                                    |         |       |       |
|                | Yes                                                               | -12.788 | 0.74  | 0.001 |
|                | <b>Compliance with cheletion therapy</b>                          |         |       |       |
|                | No (Reference)                                                    |         |       |       |
|                | Yes                                                               | 8.867   | 0.042 | 0.017 |
|                | <b>Average Hb</b>                                                 |         |       |       |
|                | Below 8 (Reference)                                               |         |       |       |
|                | Above 8                                                           | 8.878   | 0.039 | 0.019 |
|                | <b>Iron chelation medication</b>                                  |         |       |       |
|                | Deferoxamin with oral chelators or oral cheators only (Reference) |         |       |       |
|                | Deferoxamin only                                                  | -13.019 | 0.60  | 0.003 |

## Discussion

These findings show that several variables were significantly associated with the HRQoL scores of thalassaemia majors. The following discussion outlines the HRQoL scores and predictor variables in relation to current literature. The variables are discussed in the order of age, gender, number of transfusion, household income, education, co-morbidities, age of first transfusion, compliance to iron chelation therapy, type of iron chelation therapy, serum ferratin level, marital status and transport.

The study findings show no significant association between age and any of the eight domains of HRQoL. This finding is similar to the findings of Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi, Parand<sup>126</sup> in Iran and Gharaibeh and Gharaibeh<sup>120</sup> in Jordon. Their study findings also did not show any association between age and HRQoL domains. However, there are studies that show significant association between age and certain domains of HRQoL. For example, the study

conducted by Ismail, Campbell, Ibrahim and Jones <sup>121</sup> in Kuala Lumpur, Malaysia showed that age was a significant predictor of physical functioning of thalassaemia majors in Kuala Lumpur. A longitudinal cohort of thalassaemia patients from the UK, USA and Canada also showed a significant negative association with increase in age and HRQoL domains of PF, BP, VT, SF and MH.<sup>136</sup> Therefore, HRQoL scores alone is not enough to make a conclusion on age and its impact on the survival of thalassaemia majors in Maldives, but definitely it is an important area to study further.

Gender was a significant predictor of PF, BP and RE in the study. Linear regression analysis conducted using male as the reference shows that female participants in the study performed poorly in PF (-5.682, p=0.036), BP (-12.370, p=0.012) and RE (-11.111, p=0.019) domains. This finding is similar to the findings of Ismail, Campbell, Ibrahim and Jones <sup>121</sup> in Kuala Lumpur, Malaysia. Their study showed that gender was a significant predictor of all domains of HRQoL except emotional functioning. Similar findings were observed in Jeddah, Saudi Arabia too.<sup>135</sup> However, findings of gender and HRQoL of thalassaemia majors is a divisive issue. There are studies that show gender does not have a significant association with any HRQoL functions of thalassaemia majors at all. For example, the cohort study of Trachtenberg, Gerstenberger, Xu, Mednick, Sobota, Ware <sup>136</sup> that was conducted with participants from the UK, USA and Canada showed no significant association between gender and HRQoL domains of SF-36. Similar findings were reported for gender by Gharaibeh and Gharaibeh <sup>120</sup> in Jordan and Thavorncharoensap, Torcharus, Nuchprayoon, Riewpaiboon, Indaratna and Ubol <sup>122</sup> in Thailand as well. In addition, there are findings that suggest that female thalassaemia majors have better HRQoL. For example, an Iranian study conducted to examine the quality of

life of thalassaemia majors in Iran using WHOQOL- BREF questionnaire reported that Iranian females had better quality of life compared to Iranian males.<sup>134</sup>

Number of units transfused at each transfusion was a significant predictor in this study. Findings show that PF scores were significantly higher (8.197,  $p=0.003$ ) for those who transfused two units at each of their transfusions compared to those who transfused one unit of blood at each transfusion. These findings are different from the results of the cohort study of Trachtenberg, Gerstenberger, Xu, Mednick, Sobota and Ware.<sup>136</sup> Their study showed no significant association between number of transfusions and HRQoL scores of thalassaemia majors in the UK, USA and Canada. In addition, the findings of this study showed no significant association with frequency of transfusion and any of the HRQoL domains of thalassaemia majors. These findings are similar to the findings of Thavorncharoensap, Torcharus, Nuchprayoon, Riewpaiboon, Indaratna and Ubol<sup>122</sup> in Thailand.

The findings showed no significant association between household income and any of the HRQoL domains. This finding contradicts with many of the recent research findings. For example, the study conducted by Ismail, Campbell, Ibrahim and Jones<sup>121</sup> in Kuala Lumpur, Malaysia showed that household income was a significant predictor of PF, SF and school functioning of Malaysian thalassaemia children. Another study conducted by Ayoub, Radi, Azab, Abulaban, Balkhoyor, Bedair<sup>133</sup> in Jeddah, Saudi Arabia also showed that PF scores were significantly lower ( $p=0.049$ ) for  $\beta$ -thalassaemia major children who were from lower income families. Also, similar findings were reported by Clarke, Skinner, Guest, Darbyshire, Cooper, Shah<sup>76</sup> in the UK. Additionally, Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi and Parand<sup>126</sup> also reported that lower income was negatively correlated to physical and mental health scores of thalassaemia majors in their



Iranian study.

Education level was an important predictor of PF, VT and GH in this study. All three functions had a positive association with higher education level. Some similar findings were reported for thalassaemia majors in Saudi Arabia by Ayoub, Radi, Azab, Abulaban, Balkhoyor, Bedair<sup>133</sup> According to Ayoub, Radi, Azab, Abulaban, Balkhoyor, Bedair<sup>133</sup>, SF scores were significantly higher for school educated thalassaemia children in Saudi Arabia. Two studies conducted among Iranian thalassaemia majors also showed that higher education had a significant positive correlation with SF-36 domains.<sup>126,134</sup>

Other health related co-morbidities such as heart conditions, enlarged spleen and retarded growth etc had a significant negative association with PF (-7.191, p=0.015), BP (-12.006, p=0.027) and GH (-12.788, p=0.001) domains in this study. Co-morbidities are shown to be a predictor of poorer HRQoL of thalassaemia majors in many other studies as well. For example, studies conducted Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi and Parand<sup>126</sup> in Iran, Trachtenberg, Gerstenberger, Xu, Mednick, Sobota, Ware<sup>136</sup> in the USA, UK and Canada, Gharaibeh and Gharaibeh<sup>120</sup> in Jordan, Boonchooduang, Louthrenoo, Choeypasert and Charoenkwan<sup>138</sup> in Thailand and Ansari, Baghersalimi, Azarkeivan, Nojomi and Hassanzadeh Rad<sup>134</sup> in Tehran, Iran also showed that co-morbidities or other health complications had a negative association with HRQoL of thalassaemia majors.

Findings of this study showed that age of first transfusion or age when the transfusion was started had a significant association with BP and RP domains. The BP scores were significantly less (-11.305, p=0.028) for those who started transfusion after the first six months of age. Additionally, those who had to start the transfusions after the first six months scored 12.774 (p=0.013) times less in RP

domain as well. Not many studies reported on age of start of transfusion in thalassaemia majors and its association with HRQoL. One of the few studies that reported on that issue was conducted by Thavorncharoensap, Torcharus, Nuchprayoon, Riewpaiboon, Indaratna and Ubol <sup>122</sup> Their study also showed that age of first transfusion had a significant negative effect on HRQoL in the school functioning subscale.<sup>122</sup> However, differential findings were reported by Caocci, Efficace, Ciotti, Roncarolo, Vacca, Piras <sup>124</sup>. Their study showed no significant association between HRQoL and age of first transfusion among Middle Eastern thalassaemia majors.

Regular transfusion leads to iron overload in thalassaemia majors and iron chelation therapy is required to remove the excess iron from the body. Type of iron chelation medication is an important predictor of HRQoL in many studies. For example, Payne, Rofail, Baladi, Viala, Abetz, Desrosiers <sup>140</sup> showed that iron chelation treatment had a negative impact on HRQoL scores of thalassaemia patients in the UK. Similar findings were reported by Payne, Desrosiers, Caro, Baladi, Lordan, Proskorovsky <sup>141</sup> in the USA as well. More specifically, subcutaneous iron chelation therapy was shown to have a negative impact on HRQoL of thalassaemia majors.<sup>129</sup> Findings of this study also show that participants who were on 'Deferoxamine only' scored 13.019 times less compared to those who were on 'oral chelators or on a mix of Deferoxamine and oral chelators'. Similar findings were reported in Greece as well. According to the findings of Goulas, Kourakli-Symeonidis and Camoutsis <sup>221</sup>, HRQoL of  $\beta$ -thalassaemia major patients depended on the type of iron treatment.<sup>221</sup> Their study concluded that transfusion-dependent beta-thalassaemia majors in Greece receiving Deferoxamine had lower PH scores compared to those who were on Deferasirox or Deferoxamine in

combination with Deferiprone.<sup>221</sup> A major study conducted by Porter, Bowden, Economou, Troncy, Ganser, Habr<sup>129</sup> also showed that oral iron chelation therapy Deferasirox (Exjade) had a positive impact on HRQoL of transfusion dependent patients.<sup>129</sup>

Compliance to iron chelation therapy was an important predictor of HRQoL of thalassaemia majors in this study. This study showed that compliance to iron chelation was a significant predictor of higher GH (8.867,  $p=0.017$ ) scores. This finding is similar to the findings of many other studies in literature. For example, poor compliance to iron chelation had an inverse correlation with physical health dimensions among the thalassaemia majors of Iran.<sup>126</sup> Studies conducted in Malaysia also showed that PF scores were significantly higher ( $p = 0.018$ ) for thalassaemia majors who used optimal dosage of desferioxamine iron medication compared to those who used suboptimal dosages of the treatment.<sup>117</sup> Compliance to iron chelation can be time consuming and painful at times. Hence, there are some studies that show a negative association between compliance to chelation and some domains of HRQoL. For example, a decrease in SF and RE scores were reported when there was an increase in adherence to chelation therapy in the cohort study of Trachtenberg, Gerstenberger, Xu, Mednick, Sobota, Ware<sup>136</sup> that included thalassaemia patients from the UK, USA and Canada.

Iron overload and high serum ferritin level can lead to other health complications like heart and liver problems in thalassaemia majors. Many studies show that serum ferritin level is closely related to HRQoL of thalassaemia majors.<sup>134,138</sup> However, the findings of this study did not show any significant association between ferritin level and HRQoL scores. These findings are more similar to the findings of Middle Eastern (i.e. Kurdistan, Palestine, Libya, Iraq and

Syria) children with beta-thalassaemia.<sup>124</sup>

Marriage and its association with HRQoL is a concern as not many participants were married and those who were married performed extremely low in RE domain (-19.386,  $p=0.018$ ) in this study. Not a great deal can be found in the literature in regard to marital status and HRQoL of thalassaemia majors. One study that reported about marital status and its association with HRQoL was by Haghpanah, Nasirabadi, Ghaffarpasand, Karami, Mahmoodi, Parand<sup>126</sup> in Iran. They did not observe any significant relationships between any SF-36 domains and marital status.

Maldives is a group of islands divided by sea and sea transport often becomes difficult in rough seasons. Having to travel by sea for treatment was negatively associated with PF and GH domains in this study. There are no studies that specifically report on travelling by sea to access treatment and its impact on HRQoL. One study that reported on long distance travel by land and its impact on HRQoL was by Clarke, Skinner, Guest, Darbyshire, Cooper, Shah<sup>76</sup> Their findings revealed that UK families who had to travel more than 30 miles for treatment reported significantly lower scores for emotional and child psychological functions based on Paediatric Quality of Life Inventory.

The diagnosis was an important predictor of the RP and RE domains in this study.  $\beta$ -thalassaemia majors in the study scored 15.857 ( $p=0.034$ ) times better in the RP domain and 13.967 ( $p=0.050$ ) times better in RE domain compared to the thalassaemia Intermedias and HbE  $\beta$ -thalassaemia majors grouped as one group. Similar results were reported by Musallam, Khoury, Abi-Habib, Bazzi, Succar, Halawi<sup>222</sup> in Lebanon.

The Haemoglobin level of the participants was a significant predictor of PF

and GH domains of HRQoL in this study. These results show that participants who had an average pre-transfusional haemoglobin level higher than eight g/dL in the last six months performed better in PF (7.244,  $p=0.012$ ) and GH (8.878,  $p=0.019$ ) domains compared to those who had pre-transfusional haemoglobin levels lower than 8g/dL. This finding contradicts with the findings of Safizadeh, Farahmandinia, Soltani nejad, Pourdamghan and Araste<sup>128</sup>. They conducted Pearson's correlation test and results did not show any significant correlation between mean haemoglobin level and any of the HRQoL domains.

The residential island was a significant predictor of GH in this study. The geography of Maldives is unique from most other study settings in this area. Hence, no literature could be found in regard to this finding in similar settings. Other islands (any island other than capital, Male') was used as the reference in the regression for this variable. The results showed that those who were from Male' scored 7.979 ( $p=0.026$ ) times better in GH compared to participants who were from other islands. At first, it was thought that difference in the score might be due to factors such as cost of living in Male'. In the normal circumstances, people who are from other islands live in rental properties in Male' and rental and other expenses are extremely high in Male'. However, the accommodation type (living in own house or in rental property) did not show any significant association with any HRQoL scores. Hence, this variable needs to be further evaluated in relation to issues such as moving from house to house in many cases, time taken to move and settle in Male' and travel between their home island and Male'.

## Conclusion

Several variables of this study had a significant association with HRQoL of thalassaemia majors. Predictor variables, education, gender, marital status, number

of transfusions, co-morbidities, age of first transfusion, compliance to iron chelation therapy, type of iron chelation therapy, average haemoglobin level, transport and residential island were associated with HRQoL domains of thalassaemia majors who were 14 years and above in Maldives. These predictors should be a focus for more attention in order to improve the treatment outcomes of thalassaemia majors in Maldives. Specially, long distance travel to access treatment and impact of residential island on HRQoL should be looked in detail as other alternatives such as same level of care from regional hospitals or atoll hospitals could be a better option in the future. Also, Maximum age is a concerning issue among thalassaemia majors in Maldives and further attention should be given to age related changes in order to improve the survival of thalassaemia majors.

### **Strengths and Limitations**

One of the main limitations of this study is that we were not able to recruit a control group for the study. However, MBS is the main transfusion centre of Maldives and many from other islands visit MBS on a regular basis. We invited all who visited MBS for treatment during the data collection and we were able to access 74.4% of the targeted age group. It is a good proportion, hence, the findings can be generalised to that age group of Maldives.

### **Compliance with ethical standards**

This study was approved by the ethics committee of the University of Western Australia (Ref: RA/4/1/5626) on 9<sup>th</sup> of January 2013 and by the National Health Research Committee of Maldives on 7<sup>th</sup> of February, 2013. Informed consent was obtained from all individual participants included in the study.

## Chapter 11: General Discussion

### Introduction to the Chapter

This chapter is based on general findings from the three prevention levels and their implications. The first part is a general discussion of the specific findings of the three studies. The second part of this chapter discusses the general implications, based on the findings, for the Maldives Thalassaemia Control program as a whole.

### Primary prevention: Health education, screening and counselling

Heterozygous thalassaemia carriers are normally symptom free and live a normal life. Thalassaemia carrier status becomes an issue when the partner is also a carrier of the condition and when the condition is passed to the children from both parents. In that case, a thalassaemia major child is born. Alpha thalassaemia majors (Barts Hydrops) do not survive and  $\beta$ -thalassaemia majors require life-long treatment in the form of blood transfusion and iron chelation unless BMT is performed. Both treatments are expensive and they compromise the HRQoL of major children. Hence, most countries that have high thalassaemia carrier rates have primary and secondary prevention interventions in place to minimise the birth of major cases that would require treatment.

Under the primary prevention intervention, I explored the aspects of health education, genetic screening and counselling. The first question that I tried to answer was why do Maldivians marry and have children without screening for thalassaemia. The literature shows that screening has been available in Maldives since 1992 and a large population of 68,986 Maldivians born between 1970 -1990 were screened for thalassaemia in first screening initiative of SHE.<sup>41</sup> The screening has continued since then. Therefore, the second aspect that I explored under primary prevention was why do Maldivians marry and have children in spite of knowing their carrier status.

The research findings show that most participants did not do the carrier test because they did not have knowledge of the condition. Additionally, many participants expressed that they heard about it, but poor awareness was the main reason for them to proceed with a marriage without testing. In fact, most participants in this group were of the opinion that they would not have married if they had known their carrier status and the risks involved.

Poor awareness in this study might be due to participants not receiving the many messages that are conveyed by the awareness programs. Firdous<sup>41</sup> studied the screening program of Maldives and reported important insights into screening efforts. According to Firdous<sup>41</sup>, printed materials on thalassaemia were distributed to the public, extensive health education programs were conducted for the public and thalassaemia was included in secondary school curricula and training courses of teachers and health personnel. However, findings of this study indicate that many Maldivians who married without being tested for thalassaemia did not receive the awareness message at all or they did not fully comprehend the importance of the messages received. As a result, as in Health Belief Model<sup>223</sup>, many did not understand that they were susceptible to the condition when they married and had children. Participants neither understood the seriousness or the severity of the condition nor the benefit of testing in time to take any precautions. Therefore, the question of testing for thalassaemia did not arise when they married.

In addition, a few participants in this study stated that compulsory premarital testing would have prevented them marrying without testing, indicating that they knew about thalassaemia, but did not do the test because it was not compulsory at the time of their marriage. This indicates the importance of the role and responsibility of the governing bodies towards the behaviour change needs of the



public, indicating that implementation of laws also could help in the cause of prevention of thalassaemia in Maldives. Mandatory premarital testing law worked well and contributed to the fall of thalassaemia incidences in Palestine<sup>63</sup> and Saudi Arabia.<sup>64</sup> Perhaps, family courts around the country can play a more active role in implementing the present law on thalassaemia as, by law, every Maldivian child has to be screened for thalassaemia by 18 years of age which is the youngest age for consenting for a marriage.

Though some marry without knowing their carrier status, screening for thalassaemia was a common phenomenon in Maldives. The second objective of my first study was to explore the reasons why Maldivians marry and have children in spite of knowing their thalassaemia carrier status. Many participants who were interviewed were tested for thalassaemia in their early teens which is long before marrying age in Maldives. This suggests that the reach of the screening program is such that premarital testing is not a major component of prevention efforts around thalassaemia in Maldives. Rather, early school age screening is more common. Early knowledge is considered as a strength in many thalassaemia endemic countries<sup>184</sup>, but it did not quite have the intended positive outcome in Maldives. The findings based on carriers who married and had children in spite of knowing their carrier status (study 1b) showed that early knowledge of carrier status did not deter participants from marrying other carriers and having children.

The counselling services were a major weakness at the primary prevention level in Maldives. Findings of this study show that less than half of study participants received some form of test related genetic counselling or information when they received their test results. This suggests that counselling was not a major follow up component in the screening program, or if counselling was available,

access was poor. Counselling was also seen to be of poor quality. Those participants who received genetic counselling reflected that it was “short and brief”. The information on the service page of the MBS indicates that this might still be the case.<sup>224</sup> MBS offers testing for 50 people each day.<sup>224</sup> The results are given out within the last two working hours and counselling services are open in that two hours only.<sup>224</sup>

Our findings revealed no real difference in marriage decision making between those who received counselling and those who did not. This further supports the finding that counselling sessions are brief. It also suggests that the brevity of the counselling sessions may impact on participant understanding of the consequences of thalassaemia carriers having children and knowledge of reproductive health options such as prenatal diagnosis.

Belief plays a vital role in how people make decisions or behave.<sup>223</sup> The majority of our participants felt their carrier status or their genetic make-up was not a barrier to marriage and hence married their carrier partners. These behaviours conform to the ‘Health Belief Model’.<sup>223</sup> As participants did not perceive their genetic make-up a serious threat to marriage and having children, they did not perceive the need to take any further precautions. This may also have religious underpinnings – “Allah’s Will”, therefore, they should accept it. This finding suggests that, it is possible that carrier status might not have much of an influence on marriage decisions in Maldives; rather it may have more of an impact on subsequent decisions such as family planning and having children.

Marriage decision for carriers was not so difficult, but pregnancy was traumatic and extremely emotional for those knew their carrier status and married and had children. Many of them explained pregnancy was a continuous struggle

because they worried not knowing the genetic condition of their unborn child. Some stated that they could not undertake prenatal diagnosis because they were not prepared financially for the situation. The larger proportion of participants in this group stated that they did not undertake prenatal diagnosis because they did not believe that termination was allowed in Islam and they could not accept the Maldivian fatwa on termination of pregnancy for thalassaemia. [Note: differential views were observed from the participants who undertook prenatal diagnosis and termination for thalassaemia; which is the second study]. This indicates that religious views were extremely important for the majority of participants in their reproductive health decisions, to the extent that they would give birth to a thalassaemia major child rather than terminate a pregnancy. Similar findings were reported from other Muslim communities such as Malaysia<sup>200</sup> and Egypt.<sup>84</sup> This finding indicates that Maldives needs to look at alternative reproductive measures in thalassaemia prevention. As Pre-Implantation Genetic Diagnosis for thalassaemia was acceptable among the Muslims in Saudi Arabia<sup>225</sup>, this appears an option that needs further exploration in Maldives. Pre-Implantation Genetic Diagnosis is an expensive procedure, but some who are against prenatal diagnosis might accept it and be willing to budget for and undertake it in a similar manner as couples plan for prenatal diagnosis.

Not screening for thalassaemia before or after marriage and bearing major children had devastating consequences for our study participants. The couples who married and had children in spite of knowing their carrier status also faced similar consequences with the emotional trauma they experienced due to the suffering of their child/children. Additionally, a few participants in both groups experienced divorce as a result of their carrier status because they or their partner or both did not

want to take the risk of birthing another major child. Despite this, both groups of participants did not regret giving birth to their major child. Most believed their circumstances are, “Allah’s Will” and many believed that the major child was a test and an ‘amaanai’ (a trust for safe keeping) from Allah. Hence, faith played an important role in the lives of the participants and how they dealt with issues related to their carrier status and the birth of their major child/children. In spite of the trauma and emotional burden these couples and children carried, religion provided a coping mechanism for participants with major children.

As parents, both groups of participants experienced difficulties related to treatment for their major children. Specially, finding and contacting a donor every two weeks or so was a continuous issue because the blood banking system of Maldives was not efficient and effective. The work parents have to do to find a donor, manage their own donor group and arrange transfusion was physically and mentally tiring for them. Additionally, not having the access to blood on time was mentally exhausting for many participants. Therefore, the blood transfusion services and how it operates needs to be changed in Maldives.

### **Secondary prevention: Prenatal Diagnosis and termination of pregnancy**

The main secondary prevention intervention used to prevent thalassaemia in most countries is prenatal diagnosis and termination of pregnancy. More advanced and less invasive procedures such as pre-implantation genetic diagnosis is also available in more advanced health care settings. The latter is more expensive and sophisticated; hence it is not as easily available as prenatal diagnosis.

The secondary prevention intervention for thalassaemia in Maldives is Prenatal Diagnosis and selective termination of pregnancies. It was legalised in Maldives by a fatwa on the 1<sup>st</sup> of November 1999.<sup>43</sup> Prenatal diagnosis is allowed

in Maldives, but actual services are not available. At present, couples travel to neighbouring countries, especially to Vellore, India to access prenatal diagnosis services.<sup>21</sup> Under secondary prevention intervention, I explored the reason for undertaking prenatal diagnosis and socioeconomic barriers faced by couples who undertake prenatal diagnosis and termination for thalassaemia as well as the ethical and religious aspects of prenatal diagnosis and termination of pregnancy for thalassaemia.

That Islamic fatwa that allows prenatal diagnosis and termination of pregnancy for thalassaemia in Maldives was a comfort and strength for most participants who undertook prenatal diagnosis for thalassaemia. Fatwa and scholars' advice helped participants make the decision to undertake the prenatal diagnosis test. In other words, religious stance was a strength for study participants. These findings are similar to the findings in other Muslim communities such as in Egypt.<sup>93</sup> However, differential findings were observed from other participants (please refer to the second last paragraph of this section).

Other encouraging factors or reasons for doing prenatal diagnosis included encouragement from family and friends. Many participants in the prenatal diagnosis group explained that their family and friends encouraged them to undertake the prenatal diagnosis. Another factor that helped the decision to undertake prenatal diagnosis was some participants' belief that it was the right thing to do. Having lived with or experience of being around thalassaemia majors in family or among friends was also a factor that helped the participants in this study decide to undertake prenatal diagnosis. In addition, many believed that prenatal diagnosis and termination in case of thalassaemia was the only choice: not doing prenatal diagnosis was only a wish but not a choice for carrier couples. Additionally, many thought that

they should do prenatal diagnosis because otherwise the community would judge them as cruel parents if they birthed a major child for the sake of their own happiness.

Study participants, however, described many socio-economic and cultural barriers they faced when undertaking prenatal diagnosis and termination. One of the main barriers was the unavailability of the service in Maldives. As a result, participants had to travel overseas to access the service. Despite the cost of the procedure itself being considered affordable, the total financial burden incurred was sizeable by virtue of the costs associated with overseas travel and accommodation.

The timeframe for termination of pregnancy under the Maldivian Fatwa is 120 days. All participants wanted to abide by the Fatwa, but it was a major hurdle because of the necessity of overseas travel and the need to undertake the CVS procedure well in advance so that they could undertake a timely termination if required.

These appear to be all good reasons to establish prenatal diagnosis in Maldives if the government is going to abide by the fatwa in thalassaemia prevention. However, if prenatal diagnosis services are offered within Maldives, selective termination of pregnancy should be incorporated in those services. It would be unethical to provide any one service without the other and it would raise ethical issues such as in many Latin American countries, where prenatal diagnosis services are provided, but termination is not allowed by law.<sup>226</sup> If the services were made available locally, it would be less costly and less time consuming. Additionally, carriers would not have to experience the difficulty and anxiety of travelling overseas and navigating a foreign health system in order to access the services.

All participants in study 2 undertook prenatal diagnosis for thalassaemia,

based on the Fatwa, at least once, knowing and accepting that they might have to terminate their pregnancy. Despite the findings from my first study which suggested that many Maldivians do not use prenatal diagnosis services for a variety of reasons - with religious beliefs prominent amongst them - the findings from this group are different. Findings from participants who underwent a prenatal diagnosis suggest that Fatwa on prenatal diagnosis that allows termination of pregnancy in Maldives was one of the main strengths that helped them to undertake the procedure and potential termination.

Findings also indicate that making decisions around termination of pregnancy was very complex and confusing for participants and were conflicted when making them: accepting the Fatwa did not necessarily mean that they accepted it wholeheartedly. All participants who had undergone prenatal diagnosis believed the Fatwa but at the same time some disagreed with all the actions that it allows. A possible explanation for this could relate to community norms being mostly based on religious (Islam) values in Maldives. Islam teaches that killing is wrong and life is sacred, so it should be protected at all times. Therefore, the Fatwa had a positive impact on their decision, but many were devastated when it came to termination as it presented 'killing an innocent' and they saw this as strictly prohibited in Islam.

### **The tertiary prevention: Treatment for thalassaemia major**

Currently, the only permanent treatment for thalassaemia is BMT, which is extremely expensive and requires a compatible donor. In addition, Cord Blood Stem Cells<sup>227</sup> and gene therapy<sup>228</sup> are promising medical procedures that might become available in the future. Due to the high cost of those treatments and other limitations, thalassaemia is normally treated by regular blood transfusion. Blood transfusions are done on a schedule of every two to four week intervals<sup>22</sup>, sometimes more

frequently. This method of treatment is time consuming, expensive and often risky due to transmission of infections and iron overload.<sup>22</sup> Iron chelation therapy is used to remove excess iron from the body of patients with thalassaemia.<sup>22</sup> Iron chelation is usually given subcutaneously, five to six nights a week on an 8-12 hourly basis.<sup>22</sup> Like many other lifelong treatments, side effects of continuous transfusion lead to compromised HRQoL.

The third level of prevention, tertiary intervention in the thalassaemia program of Maldives is treatment for thalassaemia majors. Thalassaemia majors are normally treated by regular blood transfusion. To evaluate the tertiary prevention intervention efforts, I evaluated the Health Related Quality of Life (HRQoL) of thalassaemia majors who were 14 years and above in Maldives. All who were 14 years or above and visited MBS for transfusion during the study period were invited to be involved.

A total of 145 participants took part in this study. The mean HRQoL scores from highest to lowest were 87.3 (SF), 83.7 (PF), 77.5 (EW), 75.0 (RP), 71.5 (RE), 68.8 (BP), 64.4 (VT) and 62.3 (GH). The mean HRQoL scores were good among thalassaemia majors in Maldives in comparison to other countries in the literature.<sup>123,125,126,129,130,135,141,217</sup>

Several variables used in this study had a significant association with HRQoL of thalassaemia majors. Predictor variables, education, gender, number of transfusions, co-morbidities, age of first transfusion, compliance to iron chelation therapy, type of iron chelation therapy, marital status, average haemoglobin level, transport and residential island showed a significant association with the mean HRQoL scores of participants. Age, household income, serum ferritin level, onset of anaemia, accommodation type, employment, frequency of transfusion and iron



chelation therapy type did not show any significant association with the HRQoL scores.

Even though age did not show a significant association with HRQoL, the maximum age of the participants, however - 33 years - was a major concern in Maldives. According to the most recent thalassaemia report of TIF (2014), the oldest living thalassaemia major patient of the Maldives is 36 years old.<sup>14</sup> That age is well below the life expectancy of both males and females in Maldives. The normal Life expectancy of Maldivians are identified as 77 years for males and 79 years for females.<sup>10</sup> The young age of the thalassaemia major participants indicate that thalassaemia majors do not live close to the life expectancy of the normal population of Maldives. There are no studies that explain the low life expectancy of thalassaemia patients in the Maldives. Therefore, this area needs to be studied further.

HRQoL is just one aspect of the quality of the treatment and their survival. It is possible that life expectancy of thalassaemia majors in Maldives are compromised by disease related other complications and how they are managed. Studies in other countries have shown that thalassaemia majors experience a number of other co-morbidities due to heavy transfusion and iron overload. For example, a study conducted in France showed that cardiac failure, diabetes, hypothyroidism, and hypogonadism were common among the study sample of thalassaemia majors.<sup>229</sup> Another study conducted in Italy showed that a large proportion of the thalassaemia majors faced complications such as heart failure, arrhythmia, hypogonadism, hypothyroidism, diabetes, HIV infection, and thrombosis.<sup>219</sup> The authors of the Italian study further evaluated the survival of the thalassaemia majors since birth and complications appearance. Their results showed that 67% of the deaths were due to

heart diseases. The results of this study in Maldives showed that 71% (N=103) of the participants had other health complications. Therefore, prevalence of disease related complications and their management is a major concern in Maldives.

### **Implications of the findings**

When all three levels of prevention are taken together, it is apparent that there are many strengths in the program as well as major weaknesses. The program has been operating for more than 20 years and several activities such as health education in schools and mass media messages have been used to improve knowledge and awareness of the general public on thalassaemia. However, my findings from the primary prevention level (study 1a and 1b) indicate that there is a major gap in knowledge. Somehow, the messages of the awareness program did not reach participants who married without testing for thalassaemia or some issues prevented them from comprehending the messages. According to Valente <sup>230</sup>, at programmatic level, a program should reach its intended audience in order to have its full impact. Knowledge is the first step to changing behaviour or in this case doing the carrier test and taking appropriate precautions. According to the findings, many married without testing because they did not know about it or did not have full knowledge of it. Hence, the intended outcome of ‘being aware’ was not observed from all participants in this study.

The second major issue is related to knowledge-attitude-behaviour. Many participants who knew their carrier status, but married and had children had the knowledge that testing is important and therefore were tested, but they did not take any further action to prevent the birth of new thalassaemia major cases. The issue here is that a change in knowledge does not necessarily mean that it would be translated to a change in attitude and, eventually, a change in behaviour. Knowledge

alone was not a strong enough motivation to change behaviour. In health, behaviour change is referred to as “the explicit intention to shift behaviours in a more ‘desirable’ direction, away from health damaging towards more health enhancing forms. Change might be directed at behaviours towards health services (for example, taking up an invitation for screening)...”<sup>144 p.12</sup> According to Bettinghaus<sup>231</sup>, it is a common belief that many health promotion programs assume that if facts are provided, people will act accordingly and behaviour will be changed. That was what I observed in the second study group (the participants who married and had children in spite of knowing their carrier status), but it is apparent, that more incentives are required for some people to change their behaviour. In fact, the format of risk information and how it is presented affects the understanding of the information by the target population.<sup>232</sup> More tailored messages are viewed as more relevant and, hence, better understood by the target population in health education.

Knowledge is important, but it is well known that simple knowledge building health education programs have limited success. This does not mean knowledge is unimportant, but rather knowledge alone is not enough to change the health related complex behaviour. In addition to knowledge and attitude, some believe that other confounding factors such as social factors should be incorporated in behaviour change initiatives.<sup>233</sup> Change in behaviour depends on inhibiting the resisting behaviours and facilitating enabling factors.<sup>233</sup> Some factors that influence or inhibit behaviour include socioeconomic issues, norms, religion, demographic characteristics, attitudes, gender, age, marital status and educational level.<sup>170,230</sup> Religion may be a particularly important consideration in Maldives. It, along with the importance of marriage and having children may have deterred participants from looking at issues such as their genetic makeup and possible consequences of having

a major child. Health education programs should evaluate the outcomes to ensure that both attitudinal and behavioural objectives are met.<sup>233</sup> Hence, the Maldivian thalassaemia program should examine societal values, norms and religious aspects in order to improve outcomes.

Values and norms in a society are important factors that can either hinder or facilitate health behaviour. According to Grube, Mayton Ii and Ball-Rokeach<sup>234</sup>, attitudes and behaviours are determined by values and self-conceptions. The religious and moral values of the individual participants showed a strong intervention point in my research. The participants in the second study (secondary prevention intervention) acted on the understanding of religious values and self-conceptions. They undertook prenatal diagnosis based on Fatwa and the advice from religious scholars while many of the participants in my second group (participants who married and had children in spite of knowing their carrier status) of the first study (1b) did not want to undertake prenatal diagnosis based on religious objections, and hence gave birth to thalassaemia major children. Therefore, Maldives being a 100% Muslim country, the declarations by religious scholars and religious values should be clearly communicated, so that the public will be able to make fully informed decisions.

When religion is incorporated into service provision, it is important to understand the social context of the individuals and how they practice religion in their world context. Similar to the study of Atkin, Ahmed, Hewison and Green<sup>204</sup>, religion and religious fatwa was barely prescriptive for the participants in this study. Rather, most of them (specially, participants of study 2) used religion and Islamic fatwa as a framework to legitimise their extremely multifaceted prenatal diagnosis and termination decisions. Several factors including personal beliefs and

interpretation of religion, religious Fatwas, religious scholars' advice, moral values, family and friends' attitudes, severity of the condition, previous experience, financial capacity and access and availability of the services on time are some of the decisive factors in this study. The lived or practiced faith in regard to prenatal diagnosis and termination of pregnancy seemed to be mediated based on those factors for a large group in this study.

However, though this group is large in this study, there are some who (some participants who knew carrier status and married had a major child/children) viewed religion from a more prescriptive perspective. For them, termination of a pregnancy was equal to killing; hence that aspect of religion governed their termination decisions and all other factors mattered less. These findings show that religion is negotiated and practised in a very broad social context among the participants in this study similar to the findings of Atkin, Ahmed, Hewison and Green <sup>204</sup>. This finding suggests that religion is one of the most important aspect of the prenatal decision making process of carriers in Maldives. It is a resource that needs to be firmly incorporated in the related policies and service provision guidelines.

At present, the thalassaemia prevention services at different levels in Maldives are shaped by medical needs. The focus of the program as we can see is prevention from a medical perspective similar to Medical model of disability that focuses on prevention and cure.<sup>235</sup> The prevention efforts under a medical model goes to the extent of selective termination of potentially disabled fetuses to prevent the abnormalities.<sup>235</sup> In the case of thalassemia, prenatal diagnosis and termination of affected pregnancies as in this study is a good examples of such prevention efforts.

The medical approach is a way of looking at people with thalassemia as 'eugenic' and less worthy in the society. This study highlighted some issues that

arise due to the stress on prevention from a medical perspective and looking at people with thalassemia as not equal well individuals. For example, prejudice, labelling and stigma faced by families who have children with thalassemia. The medical model is important in the thalassaemia prevention effort, but at the same time, incorporating a social model of disability<sup>236</sup> might be of great value to the program. A social model of disability is about identifying and eradicating the disabling barriers within a society in regard to a disability.<sup>236</sup> This study is limited in identifying the disabling barriers and it is an area that warrants further research in Maldives.

An ‘ecological approach’<sup>237</sup> together with knowledge-attitude-behaviour approach, a medical model of disability and a social model of disability might be better able to achieve the required outcomes. Ecological approaches look beyond education and incorporate the influence of other factors such as social norms, building community infrastructures, providing skills and resources, and bringing changes to the physical, economic, legal, political, and cultural environment.<sup>237</sup> However, this will require intersectional collaboration with many stakeholders across the public and private sectors and civil society.”<sup>116</sup>

My research shows that, currently thalassaemia prevention services exist in Maldives, but most stand alone in an ad-hoc manner. Limited collaboration was observed among the different services. In addition, similar services (i.e. health education, screening and counselling) were provided by two major thalassaemia related organizations; SHE and MBS. Please refer to Figure 3.1 for an outline of the thalassaemia services and organizations at the three prevention levels in Maldives at present.

It is apparent that many services stand alone with no real connection between

stakeholders. In fact, some major services are repeated in different entities. For example, screening and counselling is offered in MBS and SHE. Some awareness programs are conducted by SHE, MBS and Thalassaemia Society. This demonstrates that objectives and responsibilities are not clearly planned and defined in a distinct manner. However, if responsibilities were well defined, time and resources from the program could be saved and the diversity in background and skills among the various entities and stakeholders could support program sustainability.<sup>238</sup> The current fragmentation between the entities and stakeholders, however decreases the effectiveness of the program outcome as a whole.<sup>239</sup> To mitigate against this, all stakeholders should examine the potential to restructure the program in a way that resources are best used without much repetition.

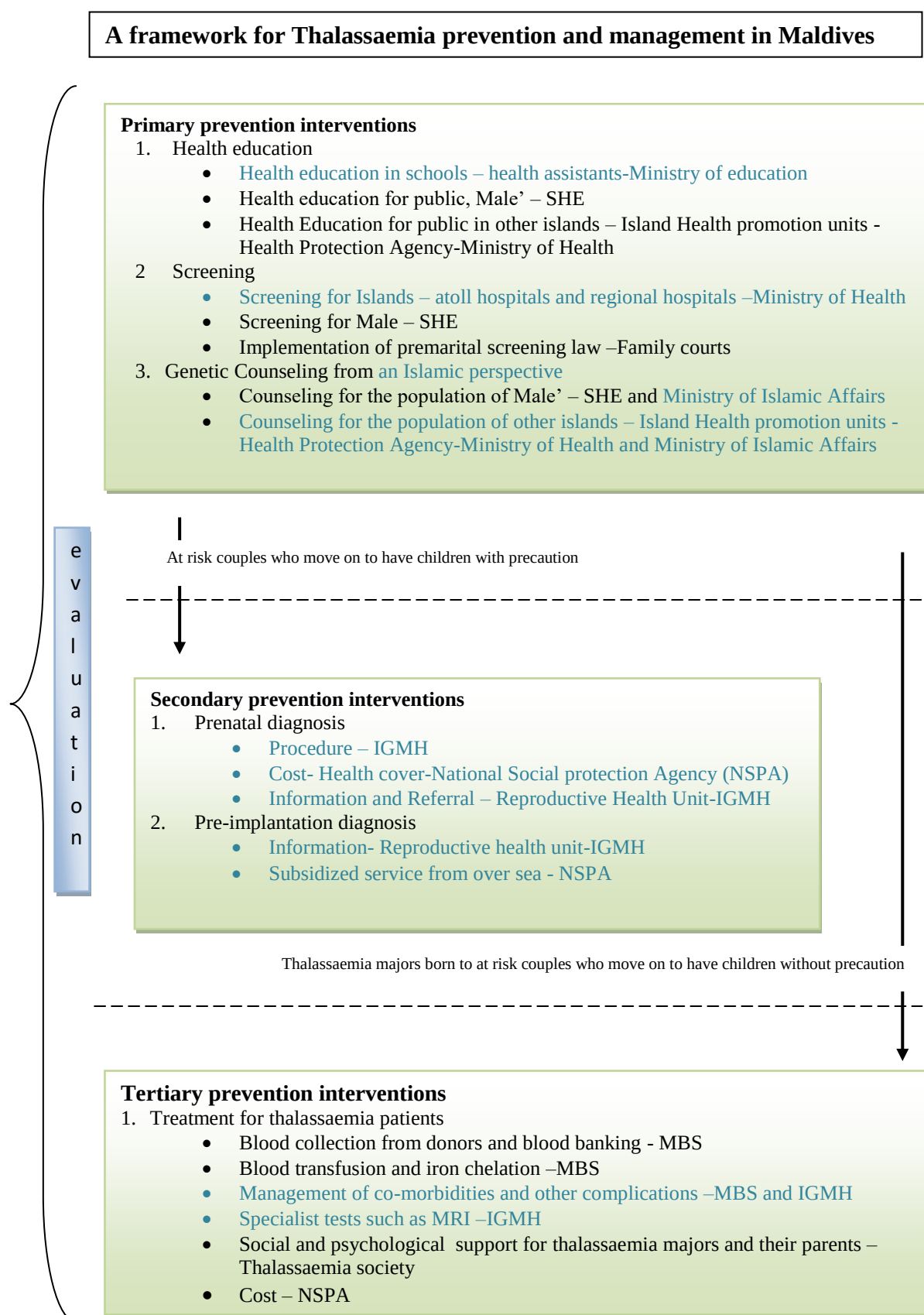
Additionally, stakeholders should examine the potential to involve more specialized entities in order to provide services such as genetic counselling and prenatal diagnosis. Providing those services locally and ensuring that genetic counselling was comprehensive would improve the outcome as the participants indicated that they need those services in a local setting. Additionally, access to blood was a major hurdle described by most participants who had major children. The blood donation service is under the MBS, but despite this, major patients face difficulties in accessing blood when they need it. As a result, many parents end up trying to set up and manage their own donor group; which is extremely inefficient. Some parents explained that days pass without them being able, in some circumstance, to get a matching donor which might be a reason why so many patients had low pre-transfusional hemoglobin level in the tertiary prevention level study.

HRQoL of thalassaemia patients in treatment was good, but more needs be done to improve the outcome of treatment. One main concern was the maximum age of the participants. My study was targeted at all patients who were 14 years and above. The maximum age of the participants was 33 years; which is well below the life expectancy of Maldivians. Hence more research is needed in the survival of thalassaemia majors in Maldives. Further studies on significant predictors of HRQoL might provide a more comprehensive picture of the situation. The health research committee of the Ministry of Health may be ideally placed to advance research in this area. In addition, it is important that Maldives follows the most recent thalassaemia management recommendations that were provided by TIF for the Maldives.<sup>14</sup> Those recommendations can be implemented through the main tertiary hospital of the Maldives (Indhira Gandhi Memorial Hospital, known as IGMH) and their specialist services.

The thalassaemia program must be evaluated just like any other health program.<sup>230</sup> The stakeholders should look at how they can achieve integration, co-operation, collaboration and co-ordination between different entities in order to improve program outcomes.<sup>239</sup> Perhaps services can be separated and one responsible body could be allocated for each broad service. If the services needed to be repeated in two more organizations, how and why should be explained clearly to ensure resources are used most efficiently. Additionally, all relationships have to be clearly defined. Potentially the program will deliver better outcomes if the services are clearly separated and defined at three prevention level as described in Leavell and Clark's prevention model. Figure 11.1 shows how present organizations could take ownership of different services at different levels and what other stakeholders are needed to be involved.



Figure 11.1: A framework for thalassaemia prevention and management in Maldives



The blue colour highlights stakeholders that are not in the network at present, but should be involved. The present School Health Policy<sup>240</sup> and Reproductive Health Policy<sup>241</sup> do not have any strategies to deal with thalassaemia in any way. Additionally IGMH should play a more direct role in thalassaemia prevention. It is the most specialised hospital in Maldives, and its services should include prenatal diagnosis if the government wants to incorporate the religious Fatwa well into prevention efforts. The present method of couples taking the initiative and making appointments via SHE and travelling to India is not effective as it is costly and difficult in many aspects as outlined by participants in studies one and two.

In addition to the stakeholders identified in the framework, the Ministry of Health and the Thalassaemia Society should play a more vital role at all three levels. The Ministry of Health should be the evaluation and quality assurance body while the Thalassaemia Society could be the advocacy body for majors, parents and carriers.

The interventions and responsible bodies that are not highlighted in blue are the services that were present at the time of this study. However, even though some are well established, gaps and inconsistencies remain in service provision at all three levels. For example, screening and counselling is offered from SHE and MBS. The target population is not separate for both. As a result, the services are mainly used by those who can afford to visit the two centres. However, if resources from two centres are targeted to different populations (islands and Male' separately as above), the coverage and outcomes might be better. Additionally, the family court requires thalassaemia test results, but they do not hold any records of it for the future. Many more similar issues potentially exist and the Ministry of Health (the governing body of the program) should undertake a comprehensive evaluation of the program to minimise those inefficiencies.

## Conclusion

Overall, thalassaemia prevention program of the Maldives has many positive aspects such as early screening (early teens) and Islamic fatwa allows prenatal diagnosis and termination and free treatment for the transfusion dependent majors. Conversely, however, the program also has many gaps and weaknesses. A comprehensive evaluation of the program is warranted, new services need be introduced, and inter-sectoral collaboration and stakeholder integration should be developed and strengthened.

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**Appendix 1: Total number of thalassaemia cases registered at MBS between 2001-2012.**

| Year        | Total<br>Thalassaemia<br>cases registered * | NEW CASES |       |        |
|-------------|---------------------------------------------|-----------|-------|--------|
|             |                                             | Republic  | Male' | Atolls |
| <b>2001</b> | 469                                         | 38        | 4     | 34     |
| <b>2002</b> | 501                                         | 32        | 5     | 27     |
| <b>2003</b> | 525                                         | 24        | 5     | 19     |
| <b>2004</b> | 553                                         | 28        | 3     | 25     |
| <b>2005</b> | 579                                         | 26        | 9     | 17     |
| <b>2006</b> | 604                                         | 25        | 2     | 23     |
| <b>2007</b> | 632                                         | 28        | 8     | 20     |
| <b>2008</b> | 669                                         | 37        | 7     | 30     |
| <b>2009</b> | 694                                         | 25        | 4     | 21     |
| <b>2010</b> | 716                                         | 22        | 3     | 19     |
| <b>2011</b> | 747                                         | 31        | 3     | 28     |
| <b>2012</b> | 769                                         | 22        | 6     | 16     |

## Appendix 2: Percentage of Thalassaemia cases by classification, 2004-2012

| Classification                     | 2004        | 2005        | 2006        | 2007        | 2008        | 2009        | 2010        | 2011        | 2012        |
|------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| <i>B- Thalassaemia Major</i>       | 0.37        | 0.45        | 0.60        | 1.12        | 0.38        | 0.16        | 0.08        | 0.10        | 0.04        |
| <i>B- Thalassaemia Non-carrier</i> | 52.73       | 40.91       | 37.46       | 41.61       | 35.65       | 51.07       | 52.96       | 37.57       | 40.40       |
| <i>B- Thalassaemia carrier</i>     | 18.98       | 18.46       | 19.18       | 15.74       | 17.53       | 16.66       | 16.03       | 16.65       | 16.34       |
| <i>A- Thalassaemia carrier</i>     | 0.54        | 3.09        | 4.85        | 2.03        | 5.77        | 1.4         | 0           | 0.00        | 0.00        |
| <i>Hb-E B Thalassaemia</i>         | 0.12        | 0.04        | 0.20        | 0.20        | 0.03        | 0.11        | 0.04        | 0.06        | 0.02        |
| <i>E- Homozygous</i>               | 0           | 0           | 0           | 0           | 0           | 0           | 0.04        | 0.02        | 0.02        |
| <i>Homozygous - D</i>              | *           | *           | *           | *           | *           | *           | *           | 0.02        | 0.04        |
| <i>Hb-E Trait</i>                  | 1           | 1.21        | 0.75        | 0.88        | 0.91        | 0.75        | 0.36        | 0.62        | 0.84        |
| <i>Hb-D Trait</i>                  | 0.54        | 0.36        | 0.75        | 0.32        | 0.44        | 0.46        | 0.16        | 0.40        | 0.40        |
| <i>Hb Sickle B- Thalassaemia</i>   | 0           | 0.04        | 0           | 0           | 0           | 0           | 0           | 0.00        | 0.00        |
| <i>Hb S Trait</i>                  | 0.25        | 0.36        | 1.15        | 0.12        | 0.06        | 0.16        | 0.08        | 0.10        | 0.17        |
| <i>Iron Deficiency</i>             | 2.29        | 4.66        | 3.70        | 2.87        | 2.48        | 3.52        | 0.12        | 0.02        | 1.53        |
| <i>Inconclusive</i>                | 9.40        | 12.86       | 10.44       | 3.51        | 8.09        | 15.1        | 24.64       | 35.54       | 31.95       |
| <i>Total screened</i>              | <b>2403</b> | <b>2232</b> | <b>2002</b> | <b>2509</b> | <b>3189</b> | <b>3722</b> | <b>2496</b> | <b>4972</b> | <b>5220</b> |

Taken from Ministry of Health Maldives<sup>78</sup>

### Appendix 3: Deaths by age group for Thalassaemia, 2002-2012

| Year        | 6-11 months | 1 – 4 years | 5-9 years | 10-14 years | 15-19 years | 20 and above | Total    |
|-------------|-------------|-------------|-----------|-------------|-------------|--------------|----------|
| <b>2002</b> | 0           | 4           | 0         | 2           | 3           | 0            | <b>9</b> |
| <b>2003</b> | 0           | 1           | 1         | 1           | 0           | 0            | <b>3</b> |
| <b>2004</b> | 0           | 0           | 2         | 0           | 1           | 0            | <b>3</b> |
| <b>2005</b> | 0           | 0           | 0         | 1           | 0           | 0            | <b>1</b> |
| <b>2006</b> | 0           | 0           | 0         | 2           | 4           | 0            | <b>6</b> |
| <b>2007</b> | 0           | 0           | 0         | 3           | 5           | 0            | <b>8</b> |
| <b>2008</b> | 0           | 1           | 1         | 2           | 4           | 0            | <b>8</b> |
| <b>2009</b> | 0           | 0           | 1         | 2           | 2           | 0            | <b>5</b> |
| <b>2010</b> | 0           | 0           | 1         | 1           | 3           | 0            | <b>5</b> |
| <b>2011</b> | 1           | 0           | 0         | 2           | 4           | 0            | <b>7</b> |
| <b>2012</b> | 0           | 1           | 0         | 1           | 2           | 2            | <b>6</b> |

Taken from Ministry of Health Maldives<sup>78</sup>