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# Uncertain Existence: The reproductive decision-making of women with Mitochondrial Disease.

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## Abstract

The aim of this thesis was to understand the process of reproductive decision-making in women with maternally inherited mitochondrial disease. It demonstrates the uncertainty fundamental to the experiences of women with mitochondrial DNA mutations (a subsection of women with mitochondrial disease). This uncertainty manifests in the personal accounts of their condition, as well as in relation to their reproductive decision-making.

Twenty semi-structured qualitative interviews were conducted with eighteen women with mitochondrial DNA mutations, sampled via their connection to a mitochondrial disease specialist service in North East England. Retrospective, prospective and hypothetical questions were utilised in data collection. The data generated from the study, which was informed by constructivist grounded theory, can be organised into two central areas, both of which can be related back to uncertainty. The first area relates to how women harbour the desire for a healthy biologically related child. The second area features decision-making, which within the context of maternally inherited mitochondrial disease, is essentially the process by which women consolidate their desires for healthy children, and how they negotiate risk. The women's accounts highlight social aspects of uncertainty that features in their reproductive decision-making, in contrast to the current literature that focuses on more clinical aspects of uncertainty. In addition, they also demonstrate how educational and employment institutions struggle to manage the uncertainty inherent in mitochondrial disease.

An important outcome of this thesis, therefore, has been the adaptation of a sociological conceptual model to address this inconsistency. The model can be utilised by clinicians in discussions with women to comprehensively explore the process of decision-making in the face of uncertainty. This thesis demonstrates how the decision-making process is necessarily social, and highlights the importance of sociological understanding of uncertainty in the mitochondrial disease reproductive advice clinic.

## **Dedication**

This thesis is dedicated to my husband Dan, my parents Lilian and Gary and my little study companion Toby.

## Acknowledgements

I would like to first thank the women and their partners who took part in this study. I am not only grateful for their time to sit with me but for sharing their experiences and viewpoints that have made this research possible.

This research and its outcomes would not have been imaginable had Prof Sir Doug Turnbull not gifted me this opportunity to study alongside my professional role within the mitochondrial team. I would like to thank him for the support with the design, implementation and supervision of this study, along with providing generous resources that have allowed me to engage and participate in the national academic community. I would like to thank Dr Jane Stewart for providing invaluable expertise in the design of the study and helping me to understand the varied experiences of women on their reproductive journeys. I would like to express my gratitude to my progression panel Prof Robert McFarland, Prof Rita Horvath and Dr Judy Richards for their continued words of support and positivity during the lifetime of this project. Thanks are also due to Dr Gráinne Gorman as an inspiration and trusted mentor throughout my time in the group.

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## Chapter 1. Introduction

This thesis explores the experiences of women with mitochondrial DNA (mtDNA) mutations. Findings from the study are structured across this thesis in a broadly chronological order, reflecting the women's accounts of their journey to diagnosis, their experiences of being diagnosed and the impact of that diagnosis. This structure allows for the exploration of the embodied, clinical and social experiences women have of their condition and enables the development of a reproductive decision-making conceptual model.

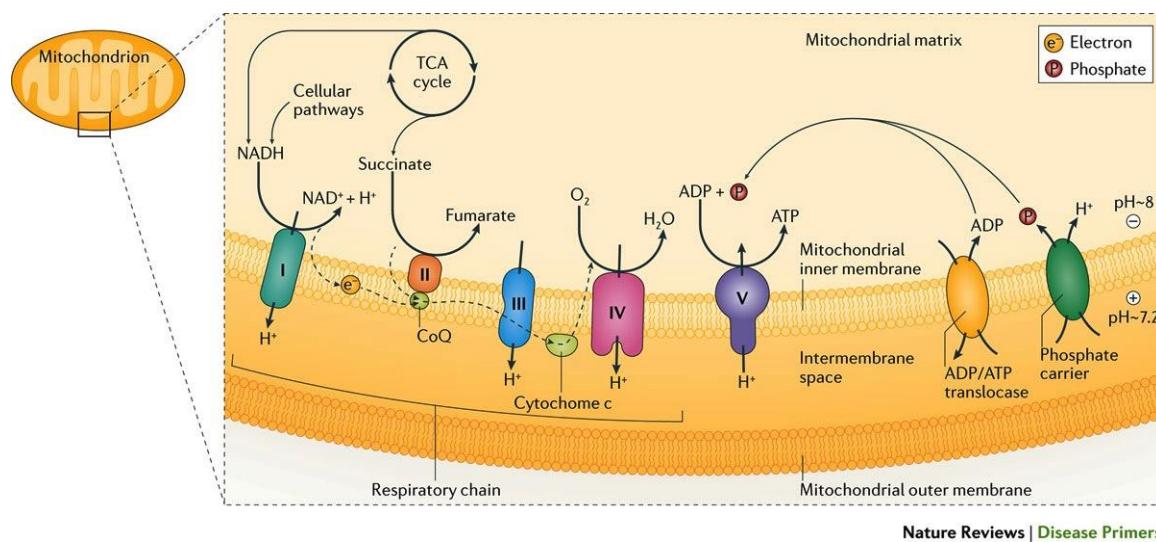
In particular, this thesis illuminates how uncertainty underpins women's experiences of mtDNA mutations. In doing so, it illustrates how the biomedical model of illness struggles to incorporate the full scope of this uncertainty, as do important social institutions relating to education and employment. This thesis advocates taking a more sociological approach to uncertainty in mitochondrial disease, by demonstrating how the reproductive decision-making process is necessarily social and extends beyond the scope of more clinical conceptions of uncertainty.

This chapter presents an overview of current understandings of mtDNA mutations as a rare disorder that has no curative treatment pathway and, in terms of family planning, has an extensive but finite set of reproductive options. It also outlines elements of the social, emotional and financial consequences of experiencing a rare disorder. The research aims and main research questions are followed by a short statement reflecting on the originality and potential impact of the conceptual model developed in the process of conducting this research. This chapter concludes with a summary of each of the remaining chapters.

### 1.1 Mitochondria, Mitochondrial Function

Mitochondria are double membrane structures found in all nucleated cells and their principal function is the production of adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), or more simply termed, the production of cellular energy. Mitochondria are a cell organelle and comprise of an outer membrane, inner membrane, inter-membrane space, cristae space and the

matrix in which many cellular processes occur (Taylor & Turnbull, 2005). During the process of OXPHOS a series of chemical reactions take place within the inner membrane where electrons are transferred across a number of complexes that result in the transformation of adenosine diphosphate (ADP) to ATP and  $H_2O$  (water) generation (Gorman et al., 2016) (Figure 1.1). To compare ATP generation from the mitochondrial respiratory chain to that of glucose metabolism, the mitochondrial respiratory chain produces 38 molecules of ATP to the 2 molecules produced via glycolysis (Berg et al., 2002). In addition to OXPHOS, mitochondria play a fundamental role in normal cellular function; hence dysfunctional mitochondria can have devastating consequences (Schapira, 2006). The density of mitochondria found within a cell denotes its energy requirements, with more mitochondria in high energy demanding tissues such as the heart, brain and skeletal muscle (Schapira, 2006).



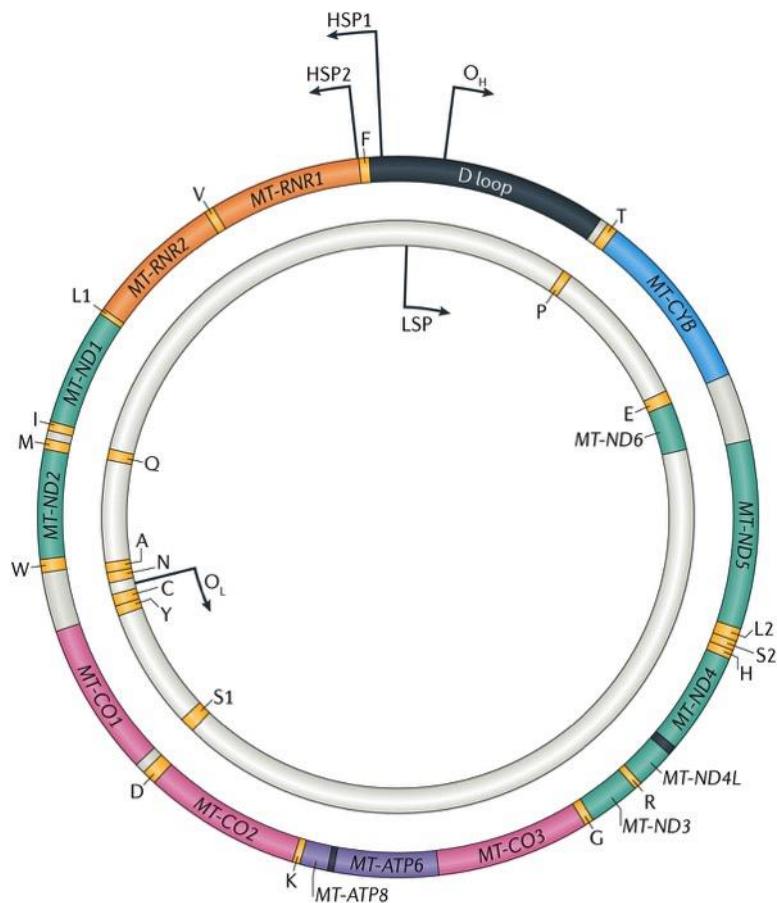
**Figure 1.1** Schematic representation of oxidative phosphorylation showing complex I-IV of the respiratory chain and complex V and ATP synthase (Gorman et al., 2016) Used with permissions.

## 1.2 Mitochondrial Genetics

Mitochondria are the only other source of extra-chromosomal deoxyribonucleic acid (DNA) in a cell (with the exception of plant chloroplasts) and are under dual genetic control, that is controlled by their own DNA (mtDNA) and DNA from the nucleus (nDNA) (Taylor & Turnbull, 2005). Mitochondrial genetics is unlike Mendelian patterns of inheritance, exhibiting uniparental inheritance with mtDNA being inherited from mothers only, leading to the term maternally inherited mitochondrial disorders that I will use throughout this thesis. The predominant and accepted theory is of maternal inheritance only, although there has been a single case report of paternal inheritance of mitochondria in an affected individual (Schwartz & Vissing, 2002) which has never been duplicated.

### 1.2.1 Mitochondrial Genome

Human mtDNA is a double stranded circular DNA composed of ~16.6-kb (16,569 kilo-bases) with a total of 37 genes. This is in comparison to the nucleus, which has 3.3 billion base pairs and codes for between 20,000 and 30,000 genes (Taylor & Turnbull, 2005). Mitochondrial DNA encodes for 13 essential polypeptides for the OXPHOS system, 2 ribosomal RNA's and 22 transfer RNAs (Gorman et al., 2016; Taylor & Turnbull, 2005) (Figure 1.2).



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**Figure 1.2** Human mitochondrial genome. Comprising of ~16.6-kb circular double stranded DNA molecule including annotated coding regions (Gorman et al., 2016) Used with permissions.

### 1.2.2 Heteroplasmy

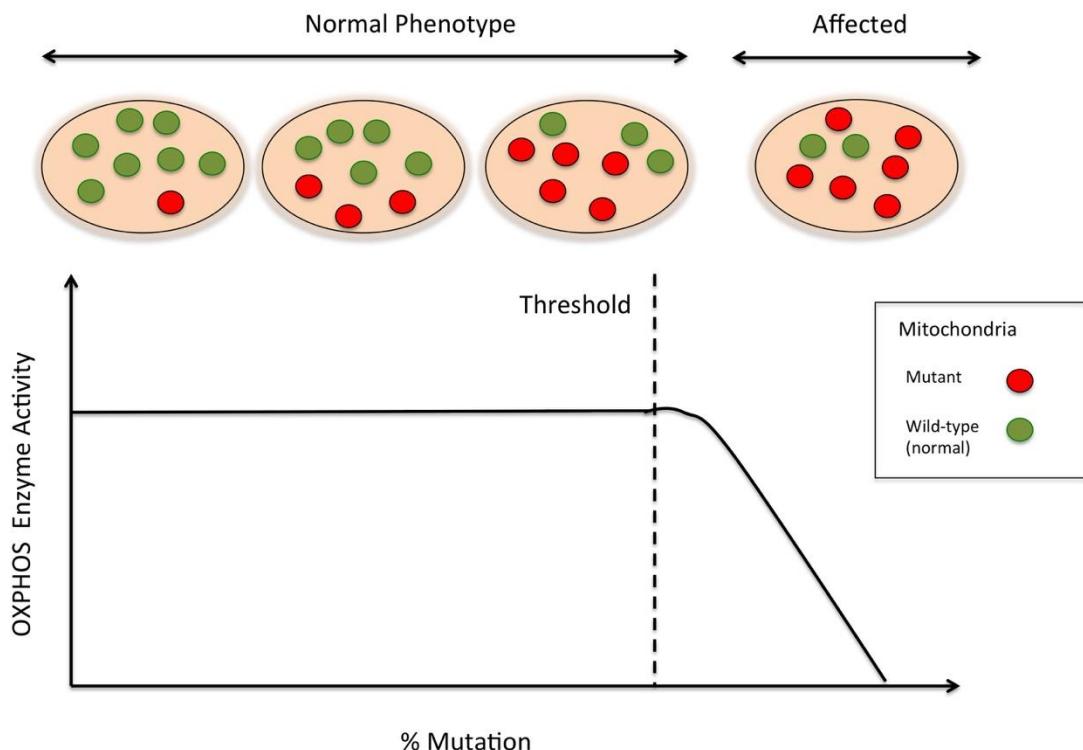
Given the variation in the number of mitochondria present in a single cell, there can be thousands of copies of mtDNA. The mtDNA copy number in mature human oocytes is reported to be between 15,000 (Wai et al., 2010) and 1,600,000 (Greggains et al., 2014). Homoplasmy is the term given when all copies of the mitochondrial genome are identical. Heteroplasmy is the term used to denote the mixture of mutated and wild-type mtDNA, this percentage can determine whether or not the cell functions correctly (Gorman et al., 2016). Some mitochondrial mutations can be homoplasmic, in that they affect all copies of the mitochondrial genome whereas others are heteroplasmic, in that the mutation only affects a proportion of copies (Taylor & Turnbull, 2005). The higher the heteroplasmy level or percentage the higher the number of mutated mtDNA in a

cell, the lower the percentage of heteroplasmy, the higher the wild-type or 'normal' mtDNA. Women who carry a homoplasmic mutation will therefore pass their mutation onto their child at a similarly high level, whilst those women with a heteroplasmic mutation face greater uncertainty with regards to inheritance (Taylor & Turnbull, 2005). This is further complicated by the concept of 'threshold effect', that determines both the clinical phenotype and biochemical defect expression and is typically in the range of 60-90% mutant to wild type mitochondrial mtDNA (see section 1.2.3).

Mitochondrial function or disturbances in function are also linked with numerous other illnesses including cancer and neurodegenerative disorders including Parkinson's and Alzheimer's diseases. Variations in mtDNA mutation copy number have been observed in human malignancies although the exact mechanisms involved are not yet fully understood (Yu, 2011). Links to neurodegenerative conditions are complex and thought to be related to mitochondrial dynamics (which relates to mitochondria size, shape, movement alongside others) as well as the role of mitochondria in aging and the net production of reactive oxygen species (ROS) (Reeve et al., 2012; Lin & Beal, 2006).

### ***1.2.3 Threshold Effect***

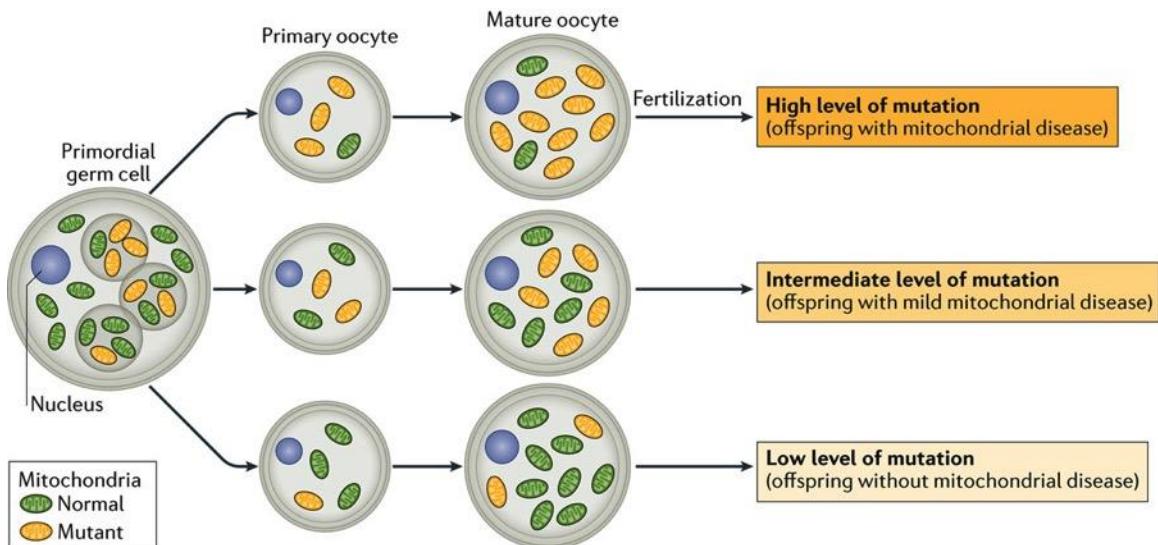
There is a general rule that the more mutated mtDNA present the more severe the resultant symptoms. However this is complicated by the concept of 'threshold effect', which shows that not all tissues are affected in the same way by the same level/type of mutation. The threshold effect is observed when a certain percentage of heteroplasmy is required for both the presence of clinical and biochemical expression of disease (Figure 1.3). The threshold effect can range from mutation percentages of 60% to 90% depending on the type of mutation and the tissue (Alston et al., 2010; Rossignol et al., 2003; Sciacco., 1994; Tuppen., 2010)



**Figure 1.3** Mitochondrial DNA (mtDNA) heteroplasmy and the threshold effect. The percentage of mutant mitochondria determines the heteroplasmy level of a cell. Wild-type (green circles) maintain normal cellular function until the number of mutant mitochondria (red circles) compromises this. This number is the individual cell threshold level and is determined by the type of mutation.

#### 1.2.4 Genetic Bottleneck

The phenomenon of the 'mitochondrial genetic bottleneck' accounts for the rapid alterations in the heteroplasmy levels in one generation. The prevailing theory is that this occurs in early embryonic development where rapid amplification of mtDNA during oocyte maturation results in mature oocytes with differing levels of mutations (Gorman et al., 2016) (Figure 1.4).



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**Figure 1.4** Mitochondrial genetic bottleneck showing how varied levels of mutant and wild-type (normal) mitochondria occur between mature oocytes during oocyte maturation and the potential outcomes relating to affectedness of offspring (Gorman et al., 2016). Used with permissions.

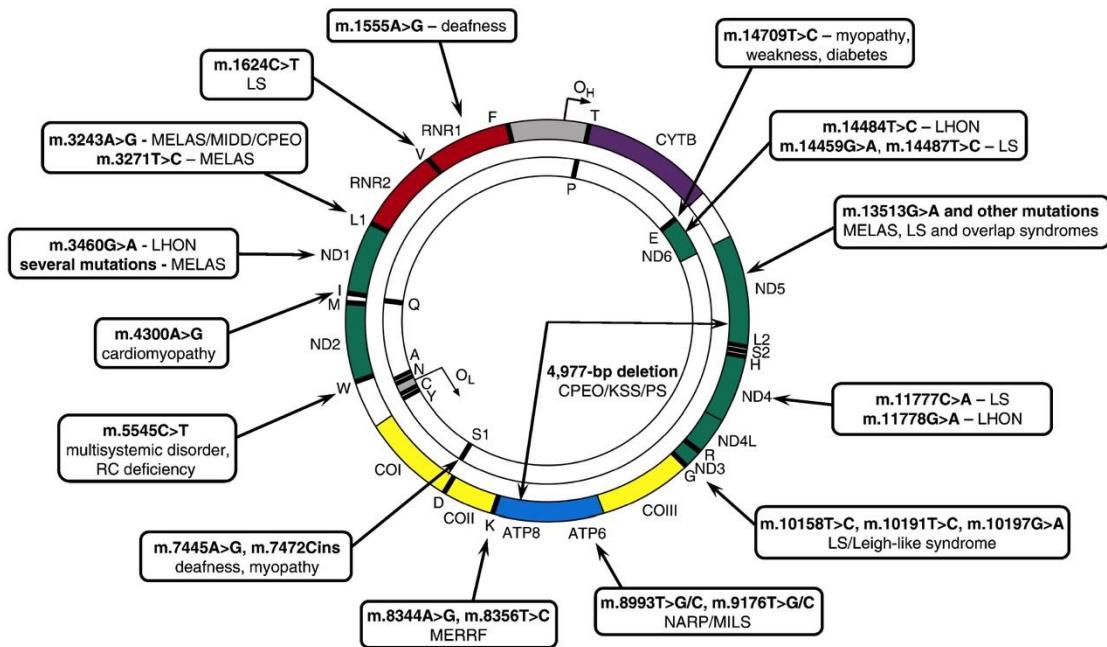
In relation to this thesis, it is important to understand that both the threshold effect and the genetic bottleneck of mtDNA mutations mean that counselling women with a known mtDNA mutation is especially complex. The level of uncertainty around the, almost impossible, predication of an offspring's mutation load and affectedness is a predominant issue for women interviewed in this study. I will now move onto describe how pathogenic mtDNA mutations manifest clinically.

### 1.3 Medical Implications of Mitochondrial Disease

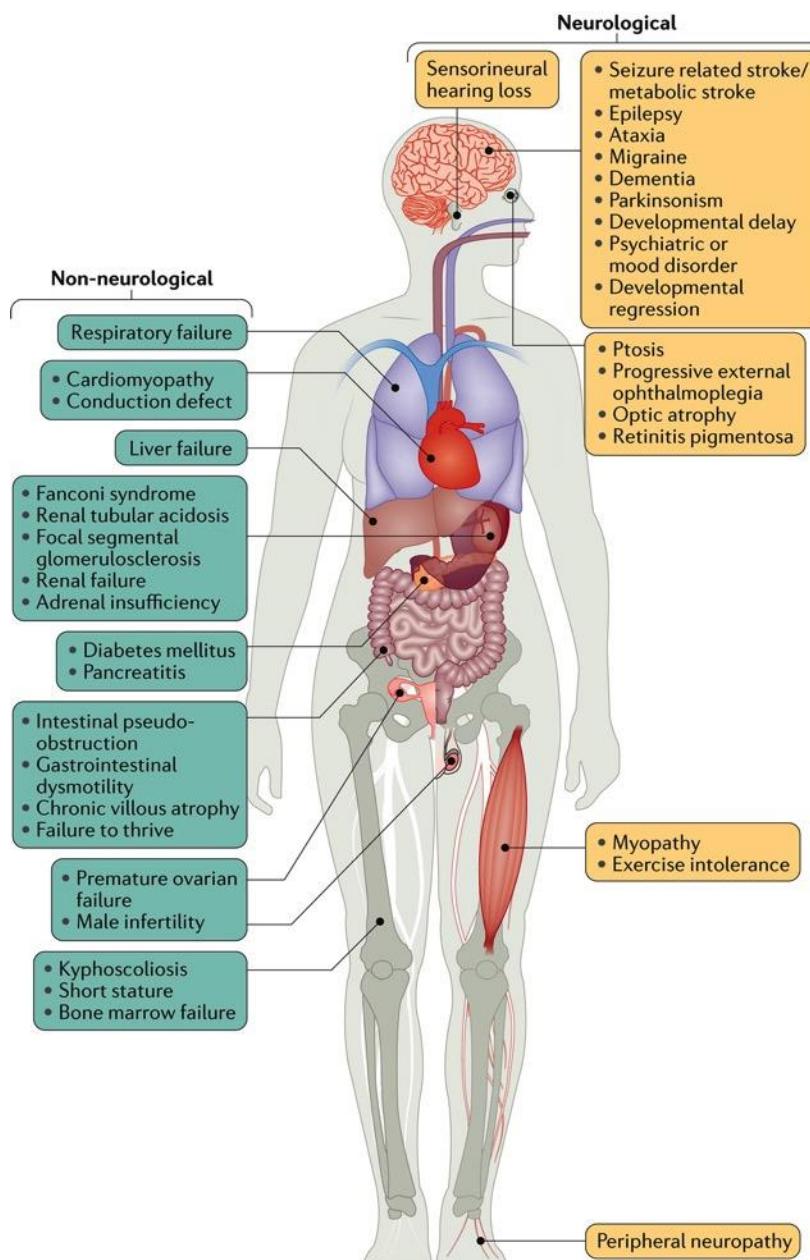
Mitochondrial disease is a group of disorders that are clinically heterogeneous and are caused by defects in mtDNA or in the nuclear DNA (nDNA) of a cell that affects mitochondrial maintenance (Gorman et al., 2016; Smits et al., 2010; Taylor & Turnbull, 2005). They are a clinically and genetically diverse group of disorders that are progressive and can be fatal in some circumstances. They are essentially the result of insufficient OXPHOS or put more simply, 'defective batteries' within a cell. I will dedicate the majority of this section to mtDNA mutations, but for the clarity understanding of mitochondrial disease as a whole I included a summary of nDNA mutations and their clinical presentations.

### **1.3.1 Mitochondrial Mutations**

The incidence of adults with mitochondrial disease due to a pathogenic mtDNA mutation is estimated at 9.6 cases per 10,000 with another 10.8 individuals thought to be at risk of developing mitochondrial disease (Gorman et al., 2015). mtDNA mutations can cause varying phenotypes amongst individuals and their family members. We will come to see within this thesis (discussed in Chapter 7 and 8) how the variation in affectedness impacts upon women and their lived experiences of mitochondrial disease and how this coupled with uncertainty regarding affectedness of children or future children, impacts upon reproductive decision making. I will outline briefly the most common mtDNA mutations as they also encompass the sample included in this study. I have chosen not to link women included in the study to their mtDNA mutation or self-described syndrome to protect their anonymity. Also, where not relevant to the context of the particular argument, I have chosen not to disclose their individual symptoms or symptoms of their relatives. We will also see how the variation in presentation of mtDNA mutations results in complex diagnostic pathways for a proportion of participants and their relatives (discussed in Chapter 5). The diverse phenotypes and clinical presentations resulting from mtDNA mutations are shown in Figures 1.5 and Figure 1.6.



**Figure 1.5** Human mitochondrial genome showing common mtDNA mutations and related clinical symptoms (Tuppen et al., 2010). Used with permissions.



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**Figure 1.6** Common clinical presentations of mtDNA mutations divided into neurological and non- neurological origins (Gorman et al, 2016). Used with permissions.

### **a. Point Mutation m.3243 A>G**

A mutation arising from the nucleotide change A to G at position 3243 in the *MT-TL1* gene is one of the most common mtDNA mutations in the patient population and this is reflected in the sample of women who took part in this study (11 of the 18 women). This point mutation is heteroplasmic and maternally inherited. The phenotype of m.3243 A>G is extremely varied although a number of symptoms and combined syndromes have been recorded. Clinical syndromes linked to the m.3243 A>G mutation include 'MELAS' (mitochondrial encephalopathy with lactic acidosis and stroke like episodes), 'MIDD' (maternally inherited diabetes and deafness) and 'PEO' (progressive external ophthalmoplegia) (Mancuso et al., 2013). However not all patients experience symptoms as severe as these syndromes, making these definitions troublesome to patients (see Chapter 5 for further information). Other clinical symptoms associated with m.3243 A>G mutations include gastro-intestinal dysmotility, cognitive impairment, ataxia, migraine, seizures and cardiomyopathy with links to sudden adult death syndrome; muscle weakness and pain, exercise intolerance and neuropathy (Chapman et al., 2014; Finsterer & Frank, 2017; Mancuso et al., 2015; Nesbitt et al., 2013; Ng et al., 2016a; Ng et al., 2016b).

### **b. Point Mutation m.8344 A>G**

A mutation arising from the nucleotide change A to G at position 8344 in the *MT-TK* gene is referred to as m.8344A>G- related mitochondrial disease and associated with the clinical phenotype 'MERRF' (myoclonic epilepsy with ragged red fibres), although it is important to note that pathogenic variants on other genes are also attributed to this phenotype (Gorman et al., 2016; Taylor & Turnbull, 2005). This point mutation is heteroplasmic like m.3243 A>G. The MERRF phenotype includes primarily epilepsy, ataxia, weakness and dementia but has been linked with myoclonus (brief involuntary twitching), muscle weakness, pain and muscle wasting, hearing loss, cognitive impairment, multiple lipomatosis, neuropathy, migraines, exercise intolerance, optic atrophy, short stature and cardiomyopathy (Shoffner et al., 1990; Mancuso et al., 2013).

### **c. Point Mutation m.11778 G>A and m.3460 G>A**

Both point mutations m.11778 G>A and m.3460G>A are linked to the clinical phenotype of optic neuropathy and the clinical syndrome of 'LHON' (Leber's

Hereditary Optic Neuropathy). These mutations are found on two separate genes, with m.11778 G>A located on the *MT-ND4* gene whereas the m.3460 G>A is located on the *MT-ND1* gene. LHON has also been associated with a third mutation on *MT-ND6* gene, m.14484 T>G. All three mutations are considered both homoplasmic and heteroplasmic. (Gorman et al., 2016; Taylor & Turnbull, 2005). As noted above, children of women with a homoplasmic mutation are guaranteed to pass their mutation onto their child, although this transmission does not denote the affectedness of a child at the same high level, with males being considered to be at greater risk of visual loss than females (50 % in males versus 10 % in females) (Yu-Wai-Man et al., 2009). Symptoms associated with these mutations may also include bilateral painless vision loss, dystonia, cardiac pre-excitation syndromes and multiple sclerosis- like syndrome (Harding Syndrome) (Gorman et al., 2016; Pfeffer et al., 2013; Yu-Wai-Man et al., 2008).

#### **d. Single Large Scale Deletions**

Single large scale mtDNA deletions are commonly referred to as 'single deletions' and are often described as sporadic in their nature with the risk of maternal inheritance thought to be the lowest of any other mitochondrial mutation, with the risk to children of affected mothers recorded as 4.11 % (Chinnery et al., 2004). These deletions are just that, in that a proportion of the mitochondrial genome is deleted or rearranged and can result in varied phenotypes, including clinical syndromes 'Person Syndrome' in children and 'Kearns-Sayer Syndrome (KSS)' in adults (Gorman et al., 2016). Symptoms linked to single deletions include progressive external ophthalmoplegia (PEO), pigmentary retinopathy (progressive visual impairment), increased cerebrospinal fluid protein levels, cerebellar ataxia, cardiac conduction abnormalities, myopathy, diabetes, deafness, bulbar weakness (due to impaired function of cranial nerves) and dementia in adults with additional symptoms (Gorman et al., 2016; Holt et al., 1989; Kearns & Sayer, 1958). Symptoms observed in children include sideroblastic anaemia (related to impaired bone marrow function to produce 'normal' red blood cells) that is associated pancreatic dysfunction, pantocytopenia (reduced blood cell count of red, white and platelet cells) and renal tubulopathy (impaired renal tubule function in the kidneys) (Gorman et al., 2016; Rotig et al., 1989; Rötig et al., 1995).

### **1.3.2 Nuclear Mutations**

Mutations and clinical symptoms arising from nDNA mutations are not the focus of this study. However to enable a more complete view of mitochondrial disease I provide a brief overview. The difference between the aetiology of mutations is naturally very important to treating clinicians although we will come to see that upon initial diagnosis and information seeking activities patients often confuse their mutations origin (discussed further in Chapter 5).

Identification of nDNA mutations had been especially difficult up until the introduction of next-generation sequencing, which allowed for proteins that were previously thought not to be involved in mitochondrial function to be linked with disease (Lightowlers et al., 2015). These disorders, which are also referred to as Mendelian mitochondrial disorders, include but are not limited to; mutations that affected structure and assembly of the protein complexes involved in OXPHOS, mtDNA maintenance genes, mitochondrial translation, lipid metabolism, mitochondrial homeostasis, apoptosis, and mitochondrial metabolism (Lightowlers et al., 2015). Additional information on genotype and phenotype of nDNA disorders can be found in Gorman et al., 2016.

### **1.3.3 Pregnancy in Mitochondrial Disease**

There is limited data available on pregnancy and mitochondrial disease, but a summary has shown that the most common complications are threatened preterm labour and preeclampsia (a condition that includes high blood pressure, high levels of protein in urine and swelling of the hands, feet and legs) (Say et al., 2011). Alongside these, Say and colleagues reported that women experienced variation in pregnancy experiences, ranging from asymptomatic, mild symptoms that resolved once the child was born and severe symptoms that included issues surrounding cardiac conduction (Wolff-Parkinson-White syndrome), persistent paraesthesia (a persistent sensation of tickling, tingling, numbness or burning of the skin) and focal segmental glomerulosclerosis (a condition that affects the kidneys' filtering units- glomueruli- resulting in cortical scarring) (Say et al., 2011). More recently the risk of both threatened preterm labour and preeclampsia have also been supported in a patient case study by Nakamura and colleagues (Nakamura et al., 2016). The incidence of pregnancy complications were asked of women in this study, although these were not notable experiences for the

women and appeared to influence decision making only in exceptional circumstances (discussed further in Chapter 8 section 8.6).

#### ***1.3.4 Treatments in Mitochondrial Disease***

Due to the complexity of mitochondrial disease aetiology and clinical variations, pharmacological treatments are still in early research phases. Mitochondrial disease therapeutic strategies face common challenges associated with rare disease drug development including funding barriers, insufficient homogenous patient population to power studies and the development of robust assessments to measure clinically meaningful outcomes. Treatments for mitochondrial patients are predominantly symptom management approaches.

Treatments targeting specific complications and research treatments are summarised by Gorman and colleagues (2016) and include the use of compounds that 'scavenge' toxins, allogeneic haematopoietic stem cell transplantation as well as enzyme replacement and gene therapies.

There are a number of surgical options available to sub-sets of patients that include organ transplantation (although this may be prohibited by the multi-system presentation of disease but may be beneficial in particular mutations/organs), the placement of vagus nerve stimulators to help reduce seizure activity in children who are non-responsive to antiepileptic drugs, cochlear implants in those patients with hearing impairment and the positioning of cardiac pacemakers and defibrillators (Parikh et al., 2009).

High doses of dietary supplements are often routinely provided to patients, who collectively refer to them as 'mito cocktails' (mitoACTION, 2008). These include supplements that play multiple roles in energy production within a cell such as Coenzyme Q10 (CoQ10 or ubiquinone), Riboflavin (B<sub>2</sub> vitamin), creatinine, L-Arginine, L- Carnitine and Folic acid (El-Hattab et al., 2017; Goldstein & Wolfe, 2013; Parikh et al., 2009). In most cases their efficacy has not been tested in a clinical trials with mitochondrial disease patients (with exception of small studies of creatinine and L Arginine), with optimal dose regimes remaining unknown (Parikh et al., 2009).

Advances in understanding the natural history of specific mutations can allow counselling of patients in relation to their lifestyle such as diet and exercise.

Increased understanding of gut dysmotility can lead to patient specific dietary advice as well as the use of pharmacological treatments of constipation for example, although dietary interventions requires further investigation in the human setting (Gorman et al., 2016).

Despite the above approaches and on-going research into specific treatments many patients remain frustrated with the lack of specific treatment available to them; the uncertainty surrounding the availability of future targeted treatments is highlighted by one woman in particular in this study (discussed further in Chapter 6 section 6.2.1). Such uncertainty, as well as that faced by patients in relation to how their disease burden may alter in the future, underpins their experience of mitochondrial disease. Concerns relating to women's ability to parent in the future also feature in their reproductive decision-making. I will now move on to discuss the social implications of mitochondrial disease.

## **1.4 Social Implications of Mitochondrial Disease**

Very little is found in the literature in relation to the experiences of those living with a mitochondrial disorder and its impact. Although the primary focus of this study was to examining the impact of mtDNA disease on reproductive decision-making, data highlighted that the uncertainty posed by the disorder influenced other areas of women's lives (discussed further in Chapter 6).

### ***1.4.1 Work and Education***

Explicit investigation into the impact of mitochondrial disease on work and education is not present in the literature. Challenges facing those with mitochondrial disease are the variations in symptom type and severity. Some people experience symptoms that can have major impact upon their ability to complete every day tasks meaning that they require devices such as wheelchairs and hearing aids, which clearly mark them as having some form of illness or disability. Others may have symptoms that are less obvious or 'invisible' to others as well as those that are mildly affected and describe marginal or no impact on daily living. For those managing symptoms such as severe fatigue, hearing loss, ataxia, syncope, visual disturbances and diabetes this study highlights their

disruptive nature and how they have impacted upon work and education. The impact of illness both acute and chronic has been shown to affect key life trajectories such as education, with the notion of 'lives interrupted' at key transition points such as school exams (Grinyer, 2007). Disability, poor physical and mental health have also been shown to correlate with financial stress (Jeon et al., 2009). With rare disease and chronic illness said to have a significant negative impact on a sufferer's finances (Barlow et al., 2007). Drawing on sociological theories of the impact of chronic illness on an individual (see Bury (1991) and Williams (2000) for review of key concepts), women's experiences of mitochondrial disease can be viewed as a biographical disruption, which is discussed further Chapter 6.

#### ***1.4.2 Family Relationships***

The predominant evaluations of the impact of mitochondrial disease on families has been conducted via quantitative or clinical descriptive assessment of parents, in particular mothers, around caregiving to affected children (Kim et al., 2010; Read & Calnan, 2000; Senger et al., 2016). In one study, mothers of children affected by mitochondrial disease were compared with those with intractable epilepsy; it was found mothers of children with mitochondrial disease had significantly higher caregiver burden, a poorer quality of life, and higher levels of depression and anxiety than those with intractable epilepsy (Kim et al., 2010). It is postulated that this may result from the maternal inheritance of the disorder, with calls for accurate information to be provided to caregivers to help combat anxiety (Kim et al., 2010). Investigation into the impact of caring for a child affected by a mitochondrial disorder (aetiology not specified) has also been conducted by Senger et al (2016) through an online survey of parents, where respondents were 95% mothers and 5% fathers. Respondents to the survey reported that children had multi-organ involvement, visited several specialists and were subjected to periods of hospitalisation resulting in increased stress indicators in parents attempting to manage their child's disease outweighing those levels seen in other chronic childhood illnesses. The authors suggest that stress experienced by parents may result from the uncertainty involved in the prolonged diagnostic pathways from symptom onset to diagnosis (Senger et al., 2016). The impact of uncertainty and its link to emotional distress, anxiety and depression is

discussed further in Chapter 2 section 2.3. Identifying specific stressors for parents may assist clinicians in supporting families with an affected child and provide care to the entire family unit (Senger et al., 2016).

#### **1.4.3 Social Relationships**

Empirical research examining the impact of mitochondrial disease on social relationships, such as friendships has not been discussed in the literature to date. Lack of high quality relationships has been associated with both physical and psychological ill health (Landsford et al., 2005). The impact of illness on friendships networks has been shown to leave those affected feeling isolated as peers continue with life as normal, whereas the affected person may struggle to maintain social contact (Grinyer, 2007). Although this study did not set out to explore the impact of mitochondrial disease on these relationships, accounts of women's relationships outside their immediate family were negatively affected due to the uncertainty of their disease burden (Chapter 6).

### **1.5 Reproductive Options in Maternally Inherited Mitochondrial Disease**

Thorburn and Dhal (2001) argue that the 'ultimate' reproductive choice made by couples with a known mtDNA mutation will 'depend on the attitudes of the couple influenced by cultural and religious traditions' (p105). There are a number of reproductive options available to women with maternally inherited mitochondrial disease, which are discussed in detail in Chapter 3. Options include genetic counselling, conception without medical intervention, voluntary childlessness, adoption, ovum (egg) donation, surrogacy (both partial and complete), prenatal testing, pre-implantation genetic diagnosis (PGD) and newly licenced mitochondrial donation. An aim of this study was to provide an in-depth exploration of the ideas and preferences of women with whom these reproductive options are available, in contrast to the professional discourse that dominates existing literature.

## **1.6 Research Aims**

### ***1.6.1 Primary Objective***

The main objective of this qualitative study was to interview women with maternally inherited mitochondrial disease and investigate their experiences of reproductive decision-making.

This study sought to specifically explore the following:

- Women's experiences of living with a diagnosis of maternally inherited mitochondrial disease
- Women's knowledge about the risk of transmission to their children, genetic testing and reproductive techniques.
- The impact of health professionals, family and other information sources on reproductive decision-making
- Women's information needs

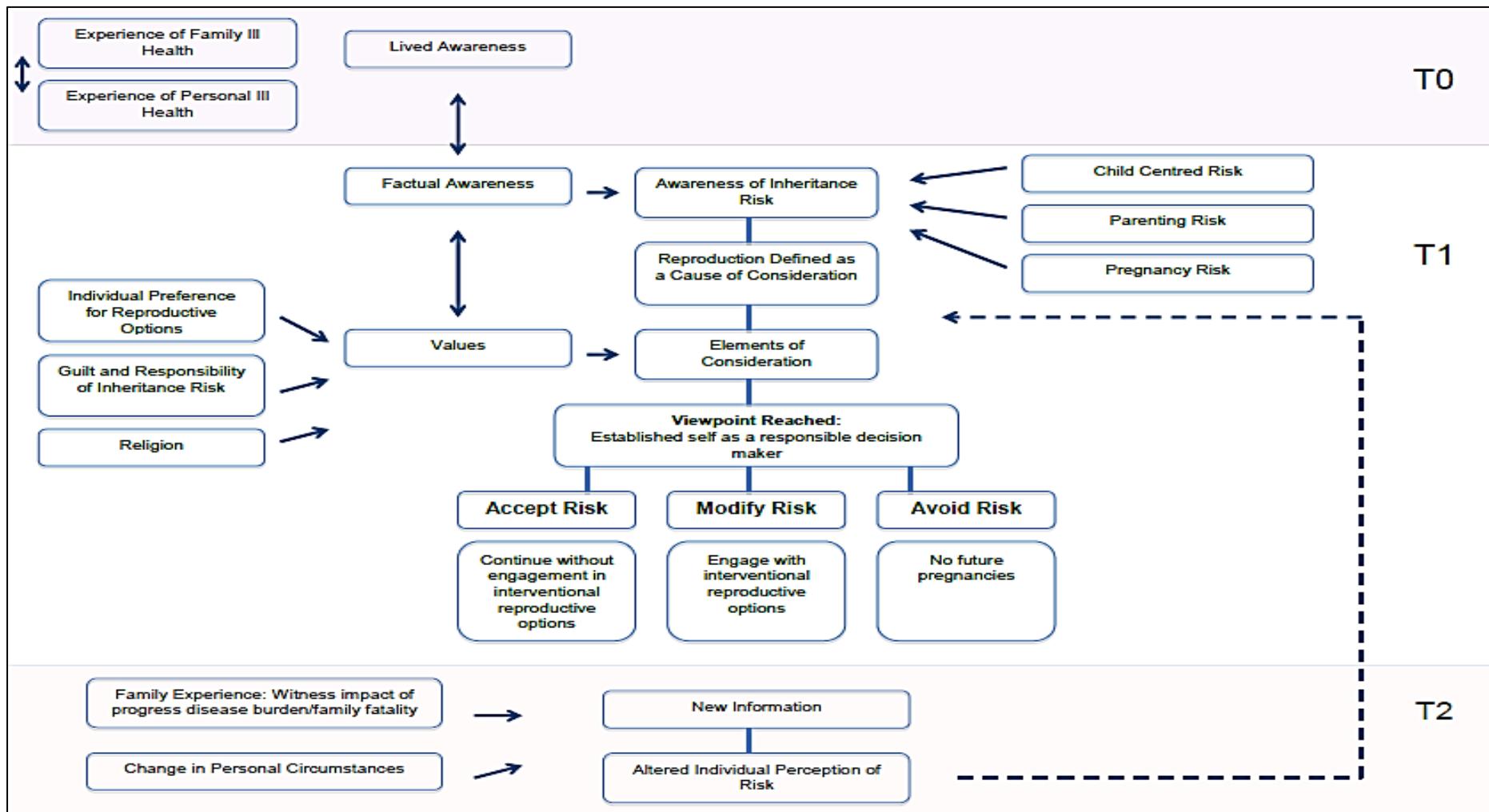
### ***1.6.2 Primary Outcome***

The primary outcome of this study was to inform the development of a patient pathway and provide a conceptual model of decision-making (Figure 1.7) to support discussions of reproduction with women who have maternally inherited mitochondrial disease. The conceptual model may also be helpful in the discussion with couples with known nuclear mitochondrial disorders.

## **1.7 Contribution of Study**

As outlined above there is limited data on patient experiences of living with mitochondrial disease and scarce empirical data on the views of women with maternally inherited mitochondrial disease regarding available reproductive options. In exploring women's ideas and preferences of these options and the development of a conceptual model of reproductive decision-making it became evident that women's social, everyday, experiences of mitochondrial disease were fundamentally important to their decision-making. This thesis offers insight into women's diagnostic journeys and their complex nature from a woman's perspective as well as offering an understanding of the impact of mitochondrial disease on their lives. This provides important context to women's lives, which in turn contributes to reproductive decision-making. This work has allowed for the

adaptation of an existing sociological model of decision-making (Downing, 2005). The adapted model shows how risk is made sense of and negotiated by women with a known pathological mtDNA mutation. The attribution of risk into three domains - acceptance, modification and avoidance - determines how women proceed in their reproductive decision-making. Those women who choose to accept their individual risk continue with conceiving a child without engaging in interventional options, those who wish to modify risk have a preference to engage in interventional options, where as those who are risk averse choose not to have a child or have further children.



**Figure 1.7** Conceptual Model of Reproductive Decision Making In Maternally Inherited Mitochondrial Disease (adapted from Downing (2005))

## **1.8 Chapter Summaries**

This thesis is centred on uncertainty as fundamental to the experiences of women with maternally inherited mitochondrial disease. Uncertainty occurs in relation to their own or their family members' experience of the disease and in their own reproductive decision-making. The introduction has provided an overview of mitochondria, their functions and their genetics that result in the (biomedical) uncertainty of predicting inheritance risk. I have discussed the known medical implications of mitochondrial disease and highlighted the gaps in knowledge surrounding the social implications of mitochondrial disease. I have also outlined the research aims and the primary unique contribution of this thesis a conceptual model of reproductive decision-making in maternally inherited mitochondrial disease.

### ***Chapter 2 Literature Review***

In this chapter I present an overview of the key issues that this thesis interacts with. These include decision-making in the clinic, understandings of risk and uncertainty in reproduction, reproductive decision making in the context of a known genetic disorder, notions of kinship, parenthood and genetic relatedness and the implication that assisted reproductive technologies are purposed to have on these.

### ***Chapter 3 Reproductive Options***

In this chapter I present each of the available reproductive options, providing where relevant, the clinical technique involved as well a summary of the key legal and social considerations of each option. This chapter highlights how there is limited empirical research on the views and preferences of women with a known pathological mitochondrial mutation regarding each option and their subsequent reproductive decision-making.

### ***Chapter 4 Methodology and Methods***

In this chapter I outline the methodology used within this study, as well as the practical approach to conducting the study. I explore the ethical issues that presented prior to and during the course of study and how these were addressed and managed. I introduce the women who took part in the study, how purposive sampling was employed within the study and the practicalities of study interviews.

I describe my approach to maintaining the anonymisation of women, their family members and the health professionals they encountered. A key strength of this study is that 20 semi-structured interviews were collected over a period of three years, in which the political and regulatory landscape changed in regards to mitochondrial donation as an option for women with maternally inherited mitochondrial disease. I discuss how data was collected, analysed and interpreted using aspects of grounded theory and show a step-by-step process of how data was organised into codes and categories. I also reflect on my position as a researcher and how my personal and research backgrounds have shaped elements of the collection and analysis of data. Finally I show the developmental process that led to the proposed conceptual model of reproductive decision-making (Figure 1.7) specific to women with maternally inherited mitochondrial disease, showing early versions of the model and how these were super imposed into Downing's (2005) existing model of responsibility in reproductive decision-making in Huntington's disease.

### ***Chapter 5 Diagnostic Pathways: Women's Practical Experiences***

In this chapter I show the complex and varied diagnostic pathways experienced by women. These pathways were experienced directly by women presenting with symptoms that resulted in them seeking medical assistance, where as others were diagnosed via an affected family member. I show that experiences of mitochondrial disease can pre-exist diagnosis for women and their family members, with symptoms often manifesting from childhood as well as being multi-generational. I discuss that delays in diagnosis prevent women who have had symptoms from the legitimisation that the 'sick role' (Parsons, 1951) affords them and how women experience a sense of relief upon receiving a diagnosis. I present the experiences of mothers whose children are affected by mitochondrial disease and how their child's diagnosis led to their own as well as highlighting that not all women experienced symptoms prior to diagnosis. Throughout the chapter I discuss the relevance of Andersen's model of total patient delay (Andersen et al., 1995) and how it can be applied to the aspects of diagnosis delay in mitochondrial disease but that it cannot address the complexities experienced by all women.

### ***Chapter 6 Social Implications of Diagnosis***

In this chapter I discuss the short and long-term social impacts that receiving a diagnosis has on women. I first discuss the initial response to receiving a diagnosis and how for some women the uncertainty posed by limited information about their prognosis can lead to the fear that they or their family member have a life-limiting condition. I examine women's information seeking activities and how they disclose (or choose not to disclose) their diagnosis. Following this I describe the long-term impact of their diagnosis on social relationships, emotional support, education and work. I conclude with how receiving a diagnosis affects the nature of some women's relationships with health care professionals.

### ***Chapter 7 Reproductive Options: Searching for the Healthy and Biologically Authentic Child***

In this chapter I discuss the core preference for most, but not all women is for 'my healthy child'. This results in mitochondrial donation being the most favourable reproductive option for many women. Mitochondrial donation enables biological parenthood for both parents whilst combating uncertainty related to the child – centred risks, the potential affectedness of a future child. Other reproductive options were either not considered or considered as an interim or last option, with ideas of social and biological kinship and parenthood key issues in women's ideas and preferences for reproductive options. This chapter highlights that reproductive decision-making for these women sits in a wider framework, in which values and preferences are one of a number of influential factors.

### ***Chapter 8 Reproductive Decision Making in Maternally Inherited Mitochondrial Disease: Conceptual Model***

In this chapter I consolidate the findings from this study, organising them into influential factors and elements that make up the proposed conceptual model. These factors include women's awareness of inheritance risk, made up of their lived experience, factual awareness and women's assessment of risk, most notably child-centred risk as well as risks relating to parenting ability and pregnancy complications. Additional elements of consideration include women's preferences towards reproductive options, their thoughts surrounding feelings of guilt and responsibility in the context of the maternal inheritance of mtDNA mutations and for some their religious beliefs. This chapter discusses how

consideration of these enables women to establish themselves as responsible decision makers, which in turn impacts upon their reproductive decisions.

### ***Chapter 9 Discussion, Recommendations and Conclusion***

This final chapter begins with a summary of the main findings presented in this thesis and discusses the implications for women with mtDNA mutations.

Implications are divided between those relating to reproductive decision-making and wider social implications in reference to existing literature. Within this chapter I critically assess the strengths and limitations of the study whilst discussing areas of interest that merit future research, in both reproductive decision-making and the broader experience of living with mitochondrial disease. Finally I make recommendations to clinical practice and commissioning policy as a result of these findings.

## Chapter 2. Literature Review

### 2.1 Introduction

This chapter presents an overview of the literature that surrounds key issues pertinent to this thesis. At the core of this thesis is the impact of uncertainty on women with mtDNA mutations, both in living with the disorder and in relation to their reproductive decision-making. Uncertainty surrounding predicting the affectedness of children conceived by mothers with a known mtDNA mutation means that women are faced with making reproductive decisions with limited clinical information; therefore decision-making is largely informed by social elements. In the first section of this chapter I outline the principals of decision-making in the clinic and how risk and uncertainty is defined and understood in reproduction and decision-making. I discuss reproductive decision-making in the context of genetic disorders, drawing on comparisons in the literature surrounding Mendelian genetic disease. In the final section I review kinship, parenthood and genetic relatedness and how assisted reproductive technologies (ART) have been said to impact upon these.

### 2.2 Perspectives of Decision Making in the Clinic

Over the last 300 years, relationships between a doctor and patient were considered to be paternalistic, rooted in the belief that doctors are best placed to make decisions for their patient and dates back to Hippocratic traditions (Miles, 2009; Truog, 2012). This doctor–patient relationship has been compared to that of a parent and child and by upholding this perspective it enabled doctors to retain their social status as indispensable (Chin, 2002). Chin (2002) notes that although the transition was slow in medicine, movement away from this perspective can be attributed to the rise in Western libertarianism, whereby many areas of society began to denounce decision-making made by those in a position of authority such as religious and political institutions. The paternalistic belief that a doctor has overriding authority in the treatment of their patient is evident in Chin's (2002) comparison between physicians' code of ethics documents from

1847 and 1990, which showed that the prompt and implicit obedience of a patient was later replaced with a patients right to make a decision and their right to refuse or accept treatment.

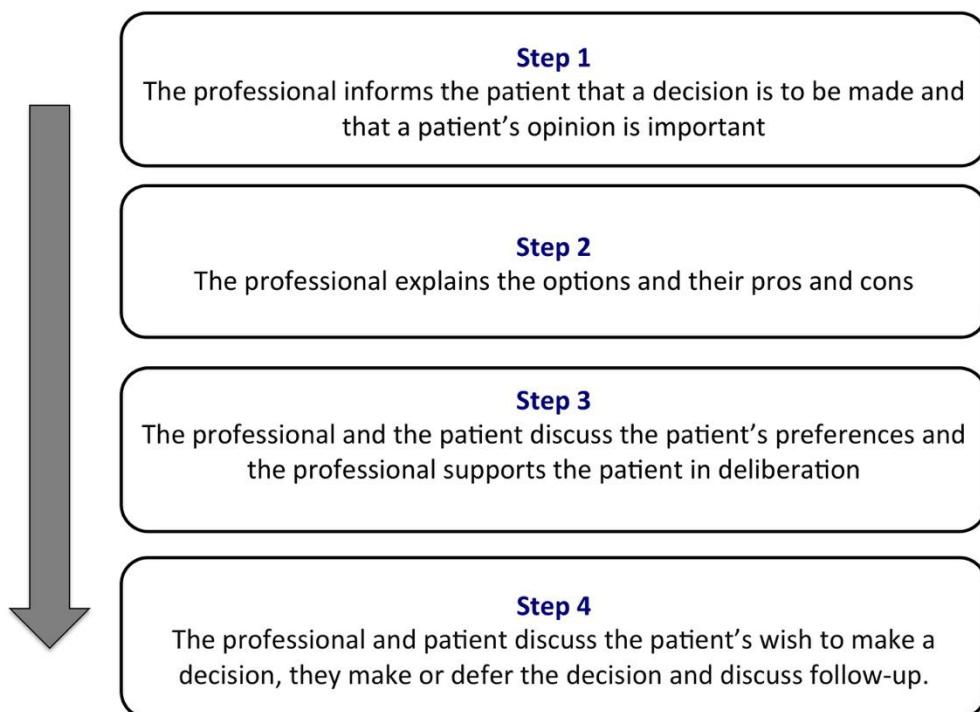
Truog (2012) notes that the shift in medicine to an idea of an autonomous patient can be linked to the right-based movements of the 1960's, with Veatch describing a social revolution through the idea that everyone should be treated equally, that healthcare should be for all and not only those who are able to afford access (Veatch, 1972 cited by Stiggelbout et al., 2015: p1173), whilst Charles and colleagues argue that this shift occurred in the 1980's (Charles et al., 1999: p652). However, general agreement exists on the reasons as to why the paternalistic approach in medicine was dominant for so long: doctors were seen as best placed to assess 'risk' versus 'benefit' of treatment; there were limited or small number of available existing treatments for particular concerns; they had access to the most up to date knowledge of an illness; that they were invested in restoring the health of their patient and were working within a professional code of ethics (Charles et al., 1999). Although largely considered out-dated and an unethical approach in medicine as a whole, the paternalistic custom is still practiced in situations where a patient is not considered to have capacity to make a medical decision. These paternalistic acts are debated in cases of patients refusing life saving treatment (Bingham, 2012), end of life care (McNamara, 2004), emergency care (Erbay et al., 2014; Clarke et al., 1980), compulsory admission or detention for psychiatric illness (Fistein et al., 2016) and dementia and Alzheimer's disease (McBrien, 2007).

Emanuel and Emanuel (1992) described three other types of doctor-patient relationships in addition to the paternalistic model. These included the 'informative model', where a physician provides technical detailed information relating to the patients medical concern, potential treatment pathways and associated risks. The patient is then said to be able to make a decision that is most closely aligned to their values and does not take into consideration the physician's values. The next model is the 'interpretative model', whereby a physician provides technical detailed information but also helps a patient 'to elucidate or articulate their values' and choose the course of action that corresponds with these (p2222).

Their final model is entitled the 'deliberative model', where physicians provide information to patients and offer advice as to what they would consider the most suitable course of action. Like paternalism these approaches have received criticism, with the informative model being considered too distant from the caring relationship expected of doctors and that it does not consider uncertainty experienced by patients. It is thought that the interpretative model is flawed due to the practicalities of time restraints and training of clinicians who may subconsciously impose their own values in consultation. Mismatched values between the patient and clinician are cited as the primary weakness of the deliberative model, as well a variation in values held by different clinicians towards a potential course of treatment. These models have largely been superseded by the proposal of shared decision-making (SDM); first defined by Charles et al (1997) but can be traced back to concept of sharing decision making by Veatch 1972 (Veatch, 1972 cited by Stiggelbout et al., 2015:p 1172).

### ***2.2.1 Shared Decision Making***

Those invested in exploring the best approach and practices to decision-making in the clinic have reached a general consensus that a shared decision-making process enables the right balance of patient autonomy and physician input (Stiggelbout, et al., 2015). This concept purports that in order to manage illness successfully patients and health care professional should work together. It acknowledges the expertise of the physician but also that the patient is the expert on their 'experience of illness, social circumstances, habits and behaviours, attitudes to risk, values and preferences' (Coulter, 1999: p719). The process of shared decision-making (SDM) is made up of four key components (Figure 2.1), which can be further separated into six elements (situation diagnosis, choice awareness, option clarification, discussion of harms and benefits, deliberation of patient preference and making a decision) (Stiggelbout et al., 2015; Wieringa et al., 2017). The practice of all four components in reality however is said to be limited (Stiggelbout et al., 2015; Couët et al., 2015). A broader approach to SDM and its components has also been proposed by Elwyn and colleagues (2012) and is discussed further in Chapter 6 section 6.4, in relation to a participant's specific reproductive decision-making consultation.



**Figure 2.1** Shared- Decision Making (SDM). Informed by Stiggelbout et al 2015.

By using a SDM approach, relationships between a health professional and their patient is said to be strengthened, with patients reporting an increase in physician satisfaction and relationship quality when implemented (Sullivan et al, 2006; Shay and Lafata, 2015). Despite widespread acknowledgement of the positives of SDM by professionals and patients, Shay and Lafata (2015) note there are limited data and also methodological issues that complicate assessing the impact of SDM on patient behaviour and health outcomes.

In this section I have described the changing perspectives of decision-making in clinical encounters, with emphasis now placed in the active participation of patients in deciding what course of action is appropriate for them. Decision-making in the context of this study is related to the reproductive options available to women and includes retrospective, current and hypothetical accounts of reproductive decision-making. Women are faced with assessing risk of affectedness of future children based on limited clinical information due to the complexities of mitochondrial inheritance discussed in Chapter 1. They also have

to consider a broad array of reproductive options that include a range of emotional, physical and social factors (discussed below in Chapter 3). As a result of this, their reproductive decision-making can be seen as largely within the social realm, reliant on assessing a number of social factors (Figure 1.7). In the following section I will describe an overview of the concepts of risk and uncertainty, before introducing reproductive decision-making in the context of genetic disorders (section 2.4).

## **2.3 Understanding Risk and Uncertainty**

### **2.3.1 Risk**

Historically concepts of risk were tied to probabilities and the process of losses and gains. In recent decades however the term has become linked with concepts of danger (Lupton, 1999). Beck (1992) notes that this may have occurred as a result of changing society and that risk could be 'defined as a systemic way of dealing with hazards and insecurities induced and introduced by modernisation' (p21). For Beck (1992), risk can only exist when there is knowledge of it.

In practical terms, Slovic et al (2005) note that risk perception and subsequent actions of individuals can depend on their preference for a specific activity or outcome. Those who are said to judge the activity or outcome as favourable will evaluate the risk as low but the benefits as high. In contrast, those who do not find the activity or outcome as favourable will evaluate the risk as high and the benefits low, a process defined as affect heuristic. However, such risk perception and assessment does not occur in a social vacuum, it is shaped by an individual's culture or subculture (Lupton, 1999). Centrally, definitions of risk are under constant revision within an individual, they are influenced by a person's core values, societal norms and societal institutions (Parsons and Clarke, 1993).

There is also debate about the role of emotion in risk perception and assessment. For example, Sjöberg (1998) notes that when communicating risk there should not be an assumption that an individual's response will be based on emotions. They argue that emotional responses can be superficial and that judgements should be based on values and beliefs. However, Slovic et al (2005) suggest the risk can be considered as both a feeling and analysis, the former being rapid and instinct driven and the latter being grounded in logic and reason. There are many

definitions of risk within the literature (Haimes, 2009; Kaplan & Garrick, 1981; Renn, 1998; Yates & Stone, 1992) but in the context of this thesis I found the inconsistent accounts between risk as 'emotional' or 'void of emotion' interesting due to the factors found to be influential in the reproductive decision-making in women interviewed, such as feelings of guilt and responsibility and the impact of their lived experience (Chapter 8).

### ***2.3.2 Risk and Reproduction***

Despite declining mortality rates associated with pregnancy, society has become increasingly concerned with risks posed to not only pregnant women, but to all women even those who may never become pregnant (Possamai-Inesedy, 2006; Ruhl, 1999). The experiences of women and pregnancy in Western societies can be described as shaped by the social constructs of risk in which they live. In modern day society women are bombarded with information relating to risk surrounding reproduction and pregnancies, such as their weight or BMI (Body Mass Index), their diet, their alcohol consumption and smoking (Possamai-Inesedy, 2006; Cedergren, 2004; Torloni et al., 2009; Wisner et al., 2000; Lindqvist et al., 1999; Chatenoud et al., 1998; Thorne et al., 2006; Kravetz and Federman, 2005; Abel, 1982). With increased pre-natal monitoring, especially in those mothers who are at increased risk, pregnancy can now been seen to be a continuous analysis of what is normal and what is defective, with a child's birth being reliant on meeting a specified criteria (Remennick, 2006). Pregnant women or women attempting to conceive who 'fail' to respond to risk appropriately could end up being labelled as irresponsible, not only to her own health but that of her unborn or planned child (Possamai-Inesedy, 2006).

Conflicts between clinicians and mothers over risk(s) posed to them and/or their unborn child are not uncommon, disagreements can include prenatal activities such as smoking or consuming alcohol, treatment regimes for mother and the foetus, and labour and delivery methods (Oberman, 2000). Escalation of conflicts beyond disagreement can result in pregnant women being the subject of a court order to comply with the treatment directed by their doctor, leading to incidents known as maternal-foetal conflicts (Epstein, 2013; Oberman, 2000). Despite agreement existing that it is 'impermissible to infringe upon pregnant women's autonomy rights' (Oberman, 2000: p452), maternal-foetal conflict remains highly

debated in areas of medicine, bioethics and law (Epstein, 2013; Johnsen, 1986; Oberman, 2000). Amongst the large number of prosecutions of women who have been said to have caused harm to their unborn child, there are women who have had these charges overturned, with women's autonomy being a key instrument of their defence (Epstein, 2013; Johnsen, 1986; Oberman, 2000). It has been argued that cases such as these, underpinned by the belief that foetal rights outweigh that of the mother could result in the ideas of pregnancy becoming a crime (Robertson & Paltrow, 1989), whereby all women are vulnerable to prosecution as no one woman is able to provide the 'perfect womb' (Paltrow, 1990 cited by Epstein, 2013: p145).

The notion of the 'irresponsible' or 'responsible' mother can be also been seen in the context of prenatal diagnostic testing. Some women believe that in order to fulfil the role of a 'good mother' they must act responsibly and undergo prenatal testing, to avoid having an ill child who may suffer in the future (Remennick, 2006) - parental testing and motherhood is discussed below in Chapter 3 and 2.5 respectively. Feelings of responsibility to children and other family members is an influential factor in the proposed conceptual model of reproductive decision-making in maternally inherited mitochondrial disease and is discussed in Chapter 8 section 8.7.2.

### ***2.3.3 Uncertainty***

Uncertainty in illness has been defined as the 'inability to determine the meaning of illness-related events' (Mishel, 1988) and can be applied to acute, life-limiting and chronic illness (Smith & Lieher, 2014). Uncertainty experienced in illness includes the period prior to diagnosis, diagnosis, considerations of treatments and their outcomes (Mishel, 1988). McCormick's (2002) review of the literature provides explanations of the five characteristics that can be viewed as situations of uncertainty: ambiguity, vagueness, unpredictability, lack of information and unfamiliarity. They note that these are situations in which uncertainty can arise from but that uncertainty is the result of a persons reaction to these situations. These reactions can be further separated into three areas: probability, temporality and perception (McCormick, 2002).

Providing information relating to the probabilities of outcomes in illness is an attempt to address uncertainty and can assist with decision-making. The lack of probabilistic information can contribute to uncertainty. The temporality of chronic illness is also defined as biographical temporality, whereby patients are unable to plan for the future and unsure of how their disease burden may increase, decrease or fluctuate in the future. Perception of events or situations as uncertain is required by the individual, if the person does not see their situation as ambiguous or vague uncertainty does not present itself (Mishel, 1984).

The presence of high level uncertainty has been linked with high levels of emotional distress, anxiety and depression (Carpentier et al., 2007; Chaney et al., 2016; Giannanco & Gitto, 2016; Haisfield-Wolfe et al., 2012; McCormick, 2002; Parker et al., 2016; Reich et al., 2006). Eliminating uncertainty can be seen as 'the solution', although for many people an unlikely situation. McCormick (2002) notes that emphasising the possible positives of uncertainty may be an approach for health care professionals to support a patient faced with uncertainty.

Ideas of ambiguity, vagueness, unpredictability, lack of information and unfamiliarity as well as probability, temporality and perception echo the experience of women with maternally inherited mitochondrial disease. This is especially in relation to areas such as their diagnosis, their family members diagnosis and reproductive decision-making. As a result, it is uncertainty that underpins this thesis due to its prevalence in the many areas of women's lives and in reproductive decision-making.

#### ***2.3.4 Risk, Reproduction and Decision Making***

Within medicine, negotiating risk of initiation, deferring or refusing treatment is complicated by the unpredictability of outcomes. Addressing the inherent uncertainty and complexity of decision-making in healthcare has led to the development of various approaches to risk analysis, including risk modelling (Hunink et al., 2014). Decision diagrams and balance sheets are said to enable the individuals to assess the impact of multiple factors that may occur at different time points in the context of the bigger picture that the 'unaided human cannot possibly accomplish' (Hunink et al., 2014 p:ix). Decision-making, predicting and negotiating risk in reproduction, pregnancy and parenthood has an extensive

literature base. Within this literature is a number of decision-making models and aids have been developed and reviewed in areas such as teenage pregnancy (Hoskins & Simons, 2015), fertility treatment (McLernon et al., 2014), mode of delivery (Schoorel et al., 2014), midwifery care (Noseworthy et al., 2013) general obstetric and maternity care (Dugas et al., 2012; Stevens et al., 2016) and breastfeeding (Martens & Young, 1997). This thesis argues that the assessment of risk for women with maternally inherited mitochondrial disease is predominantly informed by social factors due to uncertainty imposed upon them by the complex inheritance of mitochondria and therefore inheritance risk, as well potential risks in pregnancy and parenting ability. The proposed conceptual model of reproductive decision-making (see Figure 1.7) therefore includes aspects of risk as socially constructed, dependent on women's cultures and environment, lived experience, emotions, beliefs and values. I will now move on to discuss reproductive decision-making in the context of a known genetic disorder.

## **2.4 Reproductive Decision Making**

Reproductive decision-making in the context of a known Mendelian genetic disorder has been extensively researched (see Sivell et al., 2008 for review) but reproductive decision making in the context of a known mtDNA mutation less so. Complexities surrounding predicting affectedness of a future child/children makes the process of decision-making difficult for women, their partners, family members and the clinical teams involved (Gorman et al, 2016). Comparisons in the literature of reproductive decision-making can be made in part between X-linked genetic conditions such as certain muscular dystrophies and those that are categorised as late onset genetic disorders such as Huntington Disease. Prior studies into risk perception, its interpretation and retention in genetics can also assist understanding how an individual responds to risk including carrier and inheritance risk (Sivell et al., 2008; Gigerenzer and Edwards, 2003; Edwards et al, 2001; Meiser et al., 2001; Dommering et al., 2010; Parsons and Clarke, 1993). Literature surrounding reproductive decision-making processes is also helpful in understanding how individuals with a known genetic inheritance risk contemplate decisions (Downing, 2005; Lippman-Hand & Fraser, 1979; Myring et al., 2011).

#### **2.4.1 Lived Experience**

Lived experiences of a genetic disorder are complex and can be attributed to many different aspects of life including relationships with one's self and those around them. Lived experience has been reported to be a major influential factor in reproductive decision-making, with a large majority of accounts being of negative experiences impacting on decision-making although positive accounts are also present in the literature. This experience can also be referred to as an 'experiential knowledge', whereby those making reproductive decisions draw on either their own embodied experience of disability or via the close relationship they have with an affected individual (Boardman, 2017; Boardman, 2014). Lived experiences can be divided into those of closely affected relatives (parents/siblings) and the lived experiences of people having an affected pregnancy or child/children. Experience of growing up with an affected relative can result in individuals wanting to avoid having a child who may also be affected. Kay & Kingston (2002) described reports from women who were known to be carriers for an X-linked condition, where the experience of living with an affected brother strengthened their desire to avoid having an affected child. For some people, negative experiences of living with an affected parent (or relative) with Huntington's disease (HD) as a child meant that they not only wish to avoid having a child but also distanced themselves from entering into relationships (Decruyenaere et al., 2007; Klitzman et al., 2007).

Lived experience as a parent of an affected child has various influences on reproductive decision-making. Parents of affected children are said to remain undecided about future reproductive decision-making and have unresolved doubt surrounding decisions (Frets et al., 1991). A national survey of reproductive issues and carrier screening in cystic fibrosis (CF) conducted in the Netherlands showed that in 53% (154/288) of couples sampled plans for future pregnancies had been influenced by having an affected child, 40% of couples had not been influenced and 7% reported not knowing (Henneman et al., 2002). For those that reported being influenced 70% did not want to have another affected child, 14% were undecided about future pregnancies, 8% reported it easier to decide not to have any more children, with the remaining not providing an answer/other (Henneman et al., 2002). Myring et al's (2011) study into reproductive decision

making also in CF showed that couples in which both the male and the female carried a recessive gene for cystic fibrosis (resulting in a 25% chance of an affected child) were heavily influence by already having one child with a diagnosis of CF or by an affected family member. Finally, Dommering et al's (2010) study into retinoblastoma parents showed how they where influenced by the burden of disease on their children, wanting to avoid another child undergoing painful treatment.

Parents of affected children are mindful that having another child (affected or unaffected) may negatively effect their existing child and so impact that child's requirements (Dommering et al., 2010; Myring et al., 2011). Myring et al's (2011) participants recall opting to have a prenatal test result in subsequent pregnancies as they worried about the impact that another affected child may have on their existing affected child and the care they are able to provide them, with one couple reporting that they would have had a termination had they found out they were having another affected child. Couples have also reported worrying about the impact an ill sibling would have on their healthy child/children, taking them away from that child to meet the demands of a new 'sick child' (Dommering et al., 2010; Myring et al., 2011). Personal experience for these individuals helped them to determine if they could parent a sick child or multiple sick children. Parents who did feel that they would be able to cope with another child who was affected showed a sense of empowerment from their experience (Myring et al., 2011).

The desire to have a healthy child was stronger in the couples who had had an affected child which resulted in them being more likely to have another pregnancy, whereas those who had had healthy child were described as content and were less likely to have another child (Myring et al., 2011). They reported that seven of 13 influential factors in reproductive decision making were attributed to lived experience. These could be divided between those with an affected child and those without, these included: relational issues - love and loyalty towards first child and love of affected family member(s) – health issues - the health of child with CF and concerns of cross-infection – external sources of information - genetic counselling; internet and other media and issues around ability to cope with their first child

Lived experience of a genetic disorder, either their own embodied experience or that of a family member, including children is an important factor in reproductive decision-making in a number of genetic disorders. This is also the true of the women interviewed in this study, with lived experience featuring in the proposed conceptual model of reproductive decision-making in maternally inherited mitochondrial disease.

#### ***2.4.2 Guilt and Responsibility***

Guilt and responsibility are often discussed together in relation to reproductive decision-making and although guilt is different from responsibility they seem to be intrinsically linked in this context. Feelings of guilt and responsibility surrounding the idea of pregnancy and inheritance are well established within the literature (Barlevy et al., 2012; Decruyenaere et al., 2007; Dimond, 2013, 2014; Donnelly et al., 2013; Downing, 2005; Frets et al., 1991; Hallowell et al., 2006; Kay & Kingston, 2002; Klitzman et al., 2007; Raspberry & Skinner, 2011).

Kiltzman and colleagues (2007) presented a comprehensive list of emergent themes surrounding reproductive decision-making in couples with a known HD risk. Included amongst these were feelings of 'guilt' and 'blame'. Participants stated that they would feel guilt by having a child who was at-risk and that they believed that they may feel guilty in the future even if such feelings were illogical. They note that such feelings of guilt may be overwhelming with parents feeling that they may be blamed in the future. They were also concerned they may be blamed if prenatal testing and pre-implantation diagnosis (PGD) (see Chapter 3) became common techniques in HD in the future but that the decision to not undergo these was taken. However it was also noted that some individuals would feel no blame (Klitzman et al., 2007). We see here that change over time is a concern both for the potential to feel guilt in the future but also in relation the development and acceptance of technologies; change over time is further discussed in section 2.4.4. Guilt has also been linked to declining pre-natal testing, in that by choosing not to undergo prenatal testing, parents may have future feelings of guilt and regret at having had the chance to avoid having an affected child (Decruyenaere et al., 2007 p458). Couples making reproductive decisions can sometimes be faced with relatives who disapprove of their chosen decision with reactions of others being a known influencer on decision making

(Frets et al., 1991). Having such disapproving relatives also adds additional pressure onto couples (Frets et al., 1991).

In addition to reports surrounding guilt and blame, the notion of 'responsibility' in reproductive decision making in HD has also been explored. Responsibility towards others was said to constitute considerations to the individuals own interest, others' sense of the individuals responsibilities, input from family and health care professionals, costs, and wider 'moral, religious and political obligations' (Klitzman et al., 2007 p352). This thesis adapts a model of responsibilities proposed by Downing (2005), which shows the process in which participants in their study in HD progressed through in order to establish themselves as a 'responsible' decision maker. Downing's (2005) full model is shown in Chapter 4, section 4.7. Their model incorporates factors and elements influential in reproductive decision-making in HD, some of which have been retained in the model of decision making in maternally inherited mitochondrial disease where as others have been replaced (see Chapter 4, section 4.7).

Responsibility in reproductive decision-making has however been shown to be transferred outwardly from the individual, with beliefs of predestination or predestiny being seen in relation to risk and genetics. This is where an individual with a known risk believes that a health outcome is destined or fated to happen. The application of this belief in genetics has been termed 'genetic determination' and has been said to be used by those with knowledge of their genetic risk to free them from the responsibility of passing on a genetic condition (Hallowell et al., 2006 p979). In Hallowell et al's (2006) study of male *BRCA1/2* carriers, some men adopted this belief which allowed them to believe that their status as a carrier was an 'unavoidable fact of life' and to 'construct themselves and others as blameless' (Hallowell et al., 2006 p979). Understanding guilt, blame and responsibility in the context of reproductive decision-making in maternally inherited mitochondrial disease is important not only for reproductive counselling but also in diagnostic setting for women who may have a child/children and who may go on to suffer from these feelings post diagnosis (Chapter 6 section 6.3.2).

### **2.4.3 Perception, Interpretation and Retention of Genetic Risk**

Literature examining how individuals perceive genetic risk is extremely valuable in the context of reproductive decision making in maternally inherited mitochondrial disease, when risk of affectedness can be complex to make sense of for both clinicians and patients. As noted above, definitions of risk are said to be under constant revision within an individual and are influenced by a persons core values, societal norms and societal institutions (Parsons and Clarke, 1993). In this section I will highlight key literature on perception and interpretation of genetic risk followed by studies discussing retention of genetic risk.

#### **2.4.3.a Perception and Interpretation of Genetic Risk**

Understanding one's genetic risk is said to 'influence risk management decisions' (Sivell et al., 2008 p30). Couples who are said to perceive their inheritance risk as high have been reported to have struggled more with decision-making than others (Frets et al., 1991). Myring et al (2011) reported that a numerical inheritance risk of 25% was clearly understood amongst their participants. However complex inheritance risks are not always retained, understood or interpreted, with some individuals perceiving their risk to be higher than it is (Sivell et al., 2008; Gigerenzer and Edwards, 2003; Edwards et al., 2001; Meiser et al., 2001). In a study of retinoblastoma patients, who had between <1% and 50% risk of inheritance, opinions divided over what percentage would be considered above the risk threshold (Dommering et al., 2010). Some couples were happy to accept 50% whereas one woman who was pregnant at the time reported feeling that 2% was too high (Dommering et al., 2010 p338).

Parsons and Clarke (1993) investigated the difference in perceptions of risk between female carriers of the X-linked genetic neuromuscular disorder Duchenne Muscular Dystrophy (DMD) and health professionals. They found that health professionals cited numerical values from the literature, which were made up of numerous percentages relating to carrier and reproductive risk. Whereas mothers and female siblings of affected males with DMD used descriptive terms of 'high or low', 'bad, not so bad and high' (Parsons and Clarke, 1993 p563). Women appeared to confuse their carrier and reproductive risk and interpreted certain percentage risks as 'high' when health professionals considered these 'low' (Parsons and Clarke, 1993). Potential reasons for this were thought to be

related to women not understanding the differences between the two risks, as well as health professionals not imparting information clearly enough or defining the differences between carrier and reproductive risk. Also arbitrary “high” and “low” understandings were associated with certain percentages, with some women cautiously assessing their individual risk (Parsons and Clarke, 1993).

Gender difference in risk perception is especially important when considering that reproductive decisions often (but not exclusively) are made within heterosexual couples. In this thesis, I focused mostly on interviewing women with mtDNA mutations. I need to note that Newman et al (2002) showed that males and females differed in their perception of carrier risk in cystic fibrosis. They reported that men were more likely to assume that they were carriers and that any children they had may also be carriers compared to women, however the authors were unable to provide further explanation as to why this was the case.

There are also arguments that some couples believe that they may be able to ‘beat the odds’ surrounding reproductive risk. Myring et al (2011) described couples that had a 25% chance of having an affected child believing that ‘the odds maybe in their favour’ in their next pregnancy (p412) or that they had taken ‘a gamble’ in their first pregnancy (Klitzman et al., 2007 p358). In contrast to this, couples who have not yet had an affected child believe they may not be so lucky in their next pregnancy. The notion of being ‘lucky next time’ in a couple’s subsequent pregnancy was observed in retrospective study of reproductive decision-making in HD. Couples who had experienced previous terminations of affected pregnancies lived in hope that that a future pregnancy would result in an unaffected foetus and that that pregnancy would make up for their ‘pain and sorrow’ (Decruyenaere et al., 2007 p458). Hope in particular relation to reproductive decision-making in mitochondrial disease has been discussed by Herbrand and Dimond (2017), who report that women who had themselves received a mitochondrial disease diagnosis or cared for an affected child viewed mitochondrial donation as offering hope to women making reproductive decisions now, their female family members in the future and to society in general. Ideas of ‘luck’ and ‘hope’ are clearly important notions when considering risk perception in reproductive decision-making.

#### **2.4.3.b Retention of Genetic Risk**

Sivell and colleagues (2008) reviewed existing qualitative and quantitative literature showing a large body of evidence that over time risk perceptions may become more accurate compared to initial perceptions. Retention of numerical risk after genetic counselling has also shown to be poor, with women diagnosed with breast and ovarian cancer showing experienced difficulty in recalling risk six weeks after genetic counselling (Hallowell et al., 1997). In a qualitative study, some couples found it difficult to remember all of the information given to them (Dommering et al., 2010).

Critiques of genetic counselling and retention of information have argued that that there should be a focus on genetic counsellors practicing more 'effective risk communication strategies' (Sivell et al., 2008 p31). Counselling methods employed by clinicians and genetic counsellors have also been questioned in relation to how risk is presented to an individual. The presentation of risk has been shown to impact upon responses to information (Marteau, 1989). Non-directive counselling methodologies used seek to influence a person's 'thinking processes' whereas directive counselling is the process of 'influencing behaviours', with arguments existing that both forms have a place in genetic counselling (Kessler, 1992).

#### **2.4.4 Existing Models and Processes of Reproductive Decision Making**

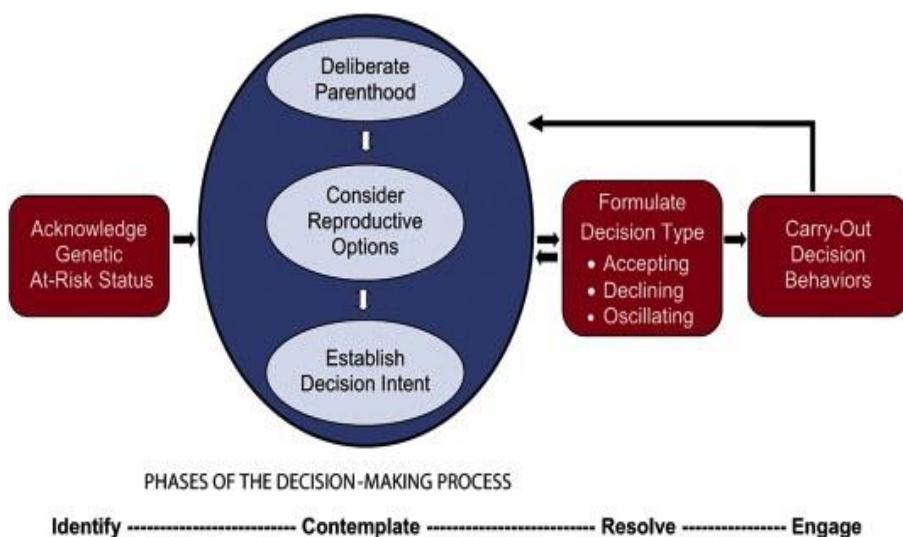
Reproductive decision making processes with knowledge of a genetic condition are said to be imbued with 'conflict and ambivalence' both 'consciously and unconsciously processed' (Decruyenaere et al., 2007 p460). Early work conducted by Lippman-Hand and Fraser (1979:73) into reproductive decision-making in the knowledge of genetic risk was said to occur in four ways:

- 1) 'binarisation of risk': decision making on the basis that something happens or it does not
- 2) 'diffusing the burden of responsibility': finding an outward reason to make a decision
- 3) 'reproductive roulette': avoiding making an explicit decision by leaving 'contraception to chance' and finally

4) 'scenario – based' thinking: that allows for a decision to be managed

Myring et al (2011) investigated retrospective reproductive decision-making and described that decision-making began in couples with CF towards the end of the phase of adaption to their child's diagnosis. They describe their participants engaging in scenario-based thinking - as described by Lippman-Hand and Fraser (1979) - which included parents thinking of all the possible outcomes of a decision.

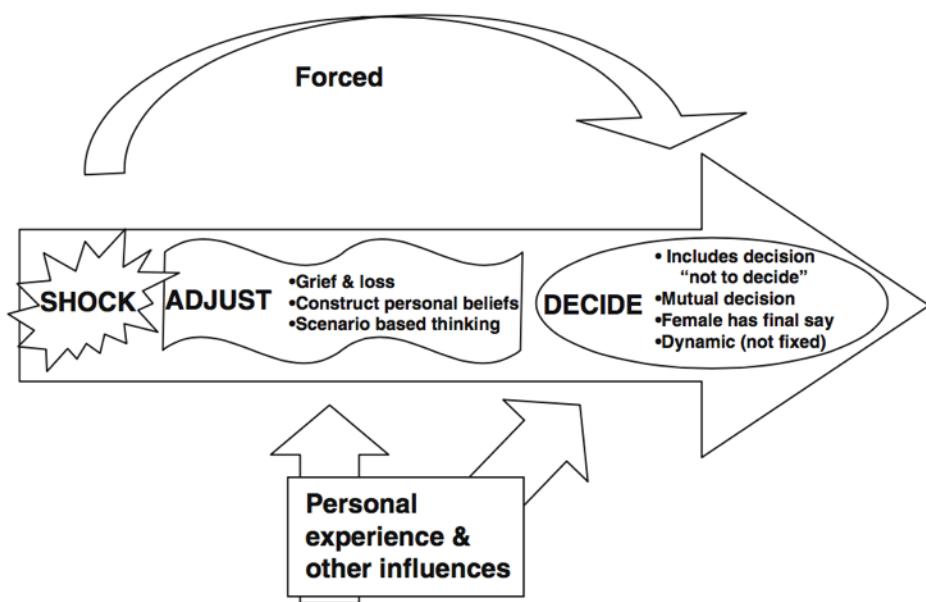
A model of reproductive decision-making for couples considering undergoing PGD (see Chapter 3) was developed by Hershberger et al (2012) and includes four specific phases of decision-making. The decision-making process is said to be iterative and includes multiple decisions (see Figure 2.2). The first phase is entitled the identify phase were parents acknowledge their at-risk status; contemplate is the phase of exploring reproduction options and parenthood and is said to be the longest; third is resolve where couples accept, decline or oscillate (neither for or against PGD) and finally, engagement (Hershberger et al., 2012).



**Figure 2.2** Decision-making process for at-risk genetic couples considering pre-implantation genetic diagnosis (PGD)(Hershberger et al., 2012). Used with permissions.

Some of the processes included in the Hershberger et al (2012) model mirror those proposed in this thesis regarding overall reproductive options decision-making in mtDNA mutations, which are discussed in Chapter 8.

Myring et al (2011) provided a model of decision-making in CF (see Figure 2.3), that include three main stages - shock, adjustment and decision - which were significantly influenced by personal experiences and time pressures if the woman was already pregnant which they label as 'forced'. Noticeably this model includes the decision 'to not decide', that women had the final decision (due to their role as primary care giver and the pregnancy implications) and that decisions were subject to change over time.



**Figure 2.3** Reproductive Decision Making in Cystic Fibrosis Carrier Couples. The process includes 1) Shock 2) Adjust 3) Decide, where 'Forced' represents finding out carrier status and risk whilst pregnant in accelerated decision-making conditions. Reproduced from (Myring et al., 2011)

Change over time is a significant process in reproductive decision-making. The perception of risk, which is not always related to health risk, can be seen to change over time. For example, Dommering et al (2010) reports that parents whose children were no longer receiving treatment, and who were living a relatively normal life, no longer wished to avoid having more children.

In addition to the above models and processes, some researchers have reviewed existing models of behaviour for their appropriateness in understanding decision-making in genetic disorders. In considering change over time in the context of reproductive decision-making, Klitzman et al (2007) refers to the Health Belief Model and how its application in reproductive decision-making in HD may be beneficial. The Health Belief Model is a theory that largely reflects the actions of adults and how ways of knowing (or beliefs) and their behaviour change over time based on temporal, linear and rational decision-making, as a result of interactions with other and environmental factors (Rosenstock et al., 1988; Kirscht, 1974, Finfgeld et al., 2003). Although this model does not take into account emotional factors or the impact of morals, unconscious and imagined elements of decision-making (Klitzman et al 2007). In an attempt to understand the suitability of Prochaska and DiClemente (1983) 'stages of change' model Houlihan (1999) applied the model to individuals undergoing pre-natal testing in HD. The 'stages of change' model was originally developed to understand smoking cessation and is reported to be primarily a linear process in which people cease to engage in harmful behaviours. The initial stage is termed pre-contemplation (unwilling/unaware of change), followed by contemplation (to consider the possibility), action and maintenance of change. Although the result was that the model was too simplistic and placed judgement values on undergoing prenatal testing or not, Houlihan concluded that it was useful in assisting nurses to provide stage matched interventions such as counseling, ensuring effective communication and ultimately decision-making.

## **2.5 Kinship, Parenthood and Genetic Relatedness**

Issues of kinship – social relationships between people – and how they are defined are also central to the experience of reproductive decision-making. We need to consider two types of kinship, 'biological' kinship (e.g. genetically-related child) and 'social' kinship (e.g. adopted child). Genealogically constructed kinship are relationships formed with those who are biologically related to an individual; this idea is also described as 'descent', 'lineage', 'biological' and 'bio-essentialist' kinship. However, socially constructed kinship is also central. Biological kinship focuses on a 'state of being', they either 'exist or they do not' whereas social

kinship focuses on social relationship formed by actions and interactions, on 'doing' (Schinder.,1984:p165).

### **2.5.1 Parenthood**

Traditional western theories of parenthood were built upon married male and female couples having children. This restricted view is no longer representative of modern day families, with many families comprising of step-parents and half siblings. Contemporary varieties of parenthood such as gay parenthood also exist, facilitated by assisted reproductive technologies (ART), adoption and surrogacy (Murphy, 2013). I will discuss below the impact of ART on parenthood, but I will first outline perspectives on what constitutes a 'parent' and 'parenthood'.

Berman (2014) argues that parenthood is a form of possession, whereby the birth mother primarily, and those around her, have control over the child. Steinbock (2005) summarised four of the key positions on defining legal parentage, which included: genetic relatedness, contract or intent-based parenthood via an agreement, social parenting, and the best interest approach whereby an adults interests are replaced by what is best for the child. These positions encompass the majority of reproductive options available to women with maternally inherited mitochondrial disease (with the exception of voluntary childlessness), which are described in more detail below (see Chapter 3). Taking the best interest approach idea of parenthood is said to move away from the perspective that children are possessions. However it is not without it's critics whom argue that after eliminating the risk of neglect or abuse, how is it possible to deem which parent (the biological or social) is best. It is therefore said to be 'too vague, too difficult to apply and reflects social prejudices' (Steinbock 2005:p302).

When investigating the reasons as to why people want to become parents, Murphy (2013) found that for some, parenthood was rooted in a feeling that they had always wanted to be a parent; they where pre-destined to be (Chatjouli et al., 2017). Rabin and Greene (1968) noted that respondents to their survey listed motivations of parenthood as being fatalistic, the purpose in which men and women where 'brought into the world' (p:39) to procreate as well as altruistic motivations, born from affection for children and the desire to nurture. Some people go on to enter into grandparenthood, whereby they take an active role in

the parenting of their grandchildren, either formally (by court order) or as social contracts with parents (Werner et al., 1998).

Issues pertaining to parenthood have been largely examined in relation to gender roles historically, with researchers examining the role of mothers and fathers often as discrete roles as opposed to in conjunction with one another (Fox, 2001; Rossi, 1984; Sanchez & Thomson, 1997; Song, 2012; Starrels, 1994; Thompson & Walker, 1989). Becoming a parent is often discussed as a transition into parenthood, which is said to be more stressful for prospective mothers than fathers, in part due to the woman's role as primary care givers (Pinquart and Teubert, 2010 cited in Widarsson et al., 2013), although it has been argued that couples experience equal stress which manifests in different ways (Widarsson et al., 2013). With the introduction of ART, traditional 'natural' theories of parenthood have been challenged.

### ***2.5.2 Assisted Reproductive Technologies and Parenthood***

Jones (2015) draws on Aristotle and the work of William Harvey (1651) when describing what constitutes a woman's role in reproduction. He lists women's roles as providing equal contribution of inherited material, providing the 'bulk' of the embryo and thirdly, gestation and labour. We will see below, in Chapter 3, that advancements in ART have led to these three roles no longer being restricted to one woman, and could in theory be played by three separate women (not forgoing the social mother after the delivery of a child). These advancements have led to parenthood no longer being confined by genetic relatedness, albeit, it could be argued that adoption has challenged this idea for centuries. Emerging reproductive and genetic technologies have allowed for reproduction, which was considered to be concerned with biology only, to be questioned. McKinnon (2015 p 462-464) argues that assisted reproductive technologies have the 'quality of procreative sex' in that they produce something natural (a child) and therefore a 'seemingly natural kinship' but that this is achieved by different means.

ART has been described as denaturalising conception, pregnancy and the idea of nature<sup>1</sup> (McKinnon, 2015) and dislocating the ‘natural fact’ of motherhood and family (Strathern, 1992, cited in Teman 2010 p8).

The introductions of ART that allows for a donor sperm or egg to be used to form an embryo means that the resultant child will not be genetically linked to one or both of the intending parents (see Chapter 3). As we have seen above, parenthood can be depicted by some as a form of possession of children. This can be further reinforced by the concept that genetic parents have a claim to the children because they ‘own’ the genetic material of which their children consist of. This belief originates from a criticised interpretation of the theorists Locke who wrote of children being the product of bodily labour (Franklin-Hall, 2012). This perspective of genetic ownership of children is therefore challenged by techniques that involve egg or sperm donation. Another approach to the prioritisation of genetic relatedness in parenthood can be linked back to anthropological debates on kinship and the notion of ‘blood is thicker than water’ (Schinder, 1984 p165). Schinder disagreed with this perspective and argued that by assuming that this is true, all other kinship relationships, including social parenthood were weaker than those created through a biological link, (Schinder, 1984). In addition to manipulation of genetics, surrogacy conflicts with ideas of the role of the mother as someone who gestates; providing nourishment and safety to the growing child. The role of the gestational mother has been considered as a form of ‘sweat equity’, whereby the gestational connection is said to lead to stronger claim to parenthood than genetics alone (Steinbock 2005:p298). I will go on to explore surrogacy in more detail in Chapter 3.

## 2.6 Summary

This chapter provides a summary of the literature surrounding the key issues in which this thesis interacts with. I have outlined the historical perspectives of decision-making in the clinic, showing that in large, the paternalistic approach is no longer considered an ethical practice in medicine (with certain exceptions). I

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<sup>1</sup> Questions of ‘nature’ or ‘nurture’ have been central to debates around adoption. Parents whom seek to be reunited with the children that they relinquished parental rights for have campaigned for recognition of their biological bond to their unknown children and protest to end the automatic assumption that the social parent is ‘superior’ in this context (Modell, 1986 p646). In some cultures the importance of gestational motherhood and genetic relationships with those who conceived a person are irrelevant, (Bamford, 1998; cited by Sahlins, 2011 p3).

have shown that changes in medical practices now strongly emphasises patient autonomy in decision-making regarding their care. I have detailed how SDM has become the gold standard approach to clinical decision-making, improving reported patient satisfaction and patient-doctor relationships. Despite these benefits the implementation of SDM in the clinic and its role in improved health outcomes has proven difficult to measure. Central to SDM are discussions with patients surrounding risk and uncertainty of treatment options. To understand this further I have discussed the premises of risk, risk in reproduction and how in today's culture women are bombarded with various potential risks in relation to planned or actual reproduction. I have highlighted briefly existing decision-making models or aids that have been developed to assist women in areas including contraception, fertility treatments and obstetric care. Uncertainty underpins this thesis, with women directly experiencing uncertainty due to their illness or that of their family members as well as in their own or their female family members reproductive decision-making. Uncertainty is made up of five key areas, including ambiguity, vagueness, unpredictability, lack of information and unfamiliarity. High levels of uncertainty have been linked to high levels of emotional distress, anxiety and depression.

A central objective of this study is to understand reproductive decision-making in maternally inherited mitochondrial disease, from the women's perspective is missing from the literature. However by utilising empirical research into Mendelian genetic conditions, including X-linked and late on-set disorders I have been able to show core components of reproductive decision-making. These included lived experience, feelings of guilt and responsibility, the retention of genetic risk and existing models/process of reproductive decision-making. Finally this chapter includes an overview of kinship, parenthood and genetic relatedness, as well as highlighting how ART have been said to denaturalise conception, pregnancy and ideas of nature. A number of the reproductive options are available to women present challenges to the traditional thoughts of kinship and parenthood, which I will now go on to discuss further in Chapter 3.

## **Chapter 3. Reproductive Options**

### **3.1 Introduction**

This chapter presents a summary of the reproductive options available to women with mtDNA mutations. Women's ideas and preferences to these options are rooted in their values, these values can then be seen as influential in reproductive decision-making in maternally inherited mitochondrial disease. The thesis explores how reproductive options that enable a genetically related child are compared against those that restrict genetic relatedness or provide parenthood via a social kinship relationship are presented in Chapter 8. I will detail the biological procedures (where relevant) and key social perspectives of each option and where possible their already known application in mitochondrial disease. Due to the constraints of this thesis and the number of options available to women, these summaries will serve to inform the reader of the primary issues relating to each option and I recognise that the debates on each option are more extensive than provided here.

### **3.2 Genetic Counselling**

The National Society for Genetic Counsellors (NSGC), an American organisation define genetic counselling as 'the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease' (Resta et al., 2006 p77). With ever increasing advances in genetic technologies and screening, there is a greater need to address the support required by the recipients of genetic information, especially those individuals who may be more vulnerable than others (Lerman et al., 2002). The distinct roles of genetic counsellors have been summarised as the 'interpretation of family and medical histories to enable risk assessment', provide 'education relating to inheritance, preventative options including genetic testing and personal risk' and to 'facilitate informed decision making and adoption of personal risk' (Trepanier et al., 2004 cited in Smerecnik et al., 2009 p 217) .

As described in Chapter 1, the complexities of mtDNA can be challenging to impart and understand for all those involved (Poulton et al., 2017; Gorman et al., 2015; Nesbitt et al., 2014; Vento and Pappa, 2013; Taylor and Turnbull, 2005;

Burgstaller et al., 2015; Read and Calnan, 2000; Thorburn and Dahl, 2001). When asked about these challenges, 20 mitochondrial specialists from across Europe who took part in Bredenoord et al (2010) qualitative study of professionals views and experiences of decision-making in mtDNA disorders discussed four distinct themes surrounding their reproductive counselling experiences. The themes included: how ethically and biologically different mitochondrial genetics were to that of Mendelian disorders; their discomfort and doubt posed by the uncertainty of disorders even after testing; the struggle between patient autonomy and their own role and responsibilities in complex decision-making; and lastly, the strategies employed to attempt to control uncertainty. Professional's described anxiety and discomfort in communicating ambiguous results with patients and describing 'heated discussions' with colleagues about such results (Bredenoord et al., 2010:p11). The mitochondrial professionals included agreed in patient autonomy in decision-making, however they were less certain, due to the levels of complexity and uncertainty posed by the disorder, whether or not couples could make autonomous decisions, with a certain 'intellectual capacity' required (Bredenoord et al., 2010:p14). In relation to clinical strategies to tackle uncertainty, some clinics avoided testing certain mutations whereas others described large collaborative networks in which diagnostic and genetic expertise from multiple centres could be accessed. Finally professionals appear to question the difficulty in defining and explaining risk to patients and whether or not the desire to seek accuracy is asking too much, conflicting with their role as the provider of expert knowledge (Bredenoord et al., 2010). Women's experiences of reproductive and genetic counselling, both from a genetic counsellor and mitochondrial specialists are discussed in Chapter 7 section 7.2.

### **3.3 Conception without Medical Intervention**

Conception without medical intervention in the context of this thesis is defined as conceiving a child through sexual intercourse and choosing to not engage with any prenatal tests above those offered as standard care to all women. For a large number of women with mtDNA mutations they do not show signs or symptoms or receive a diagnosis until after they have had an affected child/children, that translates into many women having had pregnancies without the knowledge of a

potential risk. Some women who are in receipt of their diagnosis may also assess their risk and decide to become pregnant without engaging in any medical intervention. This study seeks to understand the reason behind this decision and the risk assessment processes that women conduct and is discussed further in Chapter 7 and Chapter 8.

### **3.4 Voluntary and Involuntary Childlessness**

The concept of 'just not having any children' was raised by women themselves in this study. Prior to this, voluntary childlessness was not a reproductive option that was included in the list of those presented to women either in the original scope of this study (discussed further in Chapter 4 section 4.3.5) or those generally offered to women in the clinic. This may be that reproductive options are considered to be those available or offered to women after women are believed to have already made the choice between having a child and childlessness.

Research into voluntary childlessness gathered pace in the mid 1970's and Houseknecht's 1987 review of the literature on the topic set out clear definitions of childlessness. Involuntary childlessness is defined as those who want to have children but are unable to due to 'medical, physical, behavioural conditions' whilst voluntary childlessness is termed as those who would 'prefer to have no children' and that both the intent and degree of commitment of these choices should be ascertained before assignment (Houseknecht, 1987 p369-370). Houseknecht (1987) also defined permanent and temporary childlessness, with temporary childlessness being a significant 'state' in which women with mtDNA mutations appear to occupy (discussed further in Chapter 7 section 7.6) (Houseknecht, 1987 p369). Caution is given to researchers in this area that attempt to distinguish between voluntary and involuntary childlessness, in that the former is 'the combination of choice and permanence' whilst the later is 'due to impaired fecundity, delayed childbearing and uncertainty' (Houseknecht, 1987 p370).

More recent definitions of voluntarily childlessness are

women of childbearing age who are fertile and state that they do not intend to have children, have chosen sterilisation or women who are past childbearing age but when fertile chose not to have children (Kelly, 2009 p157).

There have also been investigations into the sub-groups of women who choose childlessness, which can see women further divided into 'transitional, postponers, ambivalent and passive decision makers' (Kelly, 2009 p158) all of whom may have made a different choice in different circumstances. Women who choose to not mother in a biological or social capacity are often stereotyped as selfish or desperate (Letherby, 2002), with the most significant demographic stated as the older, European American, unmarried woman with a high socioeconomic status, with a long history of employment and little or no religious beliefs (Kelly, 2009).

Negative attitudes and stigma have been associated with voluntary childlessness because it is seen to deviate from society's norms that couples should want to have children with many negative perceptions attributed to these couples, such as being unhappily married, career driven, selfishness, psychologically maladjusted and emotionally immature (Lapham et al., 1996). Those who have chosen to not have children face 'social pressures to alter or justify their status' and find themselves developing strategies that help them do 'identify work' to combat this negativity (Park, 2002 p21). This study seeks to offer a unique contribution to the ideas and preferences of women with mtDNA mutations towards voluntary childlessness as a reproductive option (discussed in Chapter 7 section 7.6).

### **3.5 Adoption**

Adoption as a reproductive option has been traditionally associated with infertile couples (also referred to as involuntary childless in adoption literature) that seek a child to bring into their family, but it is also an option for parents who have a known genetic condition that they may wish to avoid transmitting to a biological child. Advances in reproductive technologies and the techniques available are said to be centred on the wants of the intending parents; whereas those services that manage adoption are seen to assess what intending parents can provide to a child (McGlaughlin & Grayson, 2001). It is important to note that the view of adoption presented in this thesis is one of Western societies reflections, with the practices of adoption also referred to as child circulation (Berman, 2014) in other cultures, excluded.

In the UK, governmental regulations state that to be eligible for adoption the adoptee must be under the age of 18 and must not be or have ever been married or in a civil partnership. For a child to be eligible for adoption both biological parents have to provide consent unless they cannot be found, do not have capacity to consent or if the child is deemed to be at risk if they were not adopted. The intending parent(s) must be over the age of 21, have a permanent address in the UK and have lived in the UK for at least one year. Intending parent(s) can include people who are single, married, in civil partnership, an un-married couple or the partner to the biological parent. It is cautioned that there may be different specifications in place for private adoptions or for a 'looked after child' (those placed under the care of local or national authorities) (GOV.UK, accessed 06.09 2017).

Adoption is commonly associated with lengthy and intrusive processes that are stressful for intending parents (Bird et al., 2002). In the UK the process of adoption is listed as the following: an initial meeting before being provided the application form, the application form, preparation classes, assignment of a social worker to review suitability, police checks on the person and adult family members, collection of three references and a full medical examination (GOV.UK, accessed 06.09 2017). Adoption in the UK has changed over the years, with less and less infants being given up for adoption, in their place there are a number of children who are unable to live with their biological parents, who tend to be older and have siblings also in need. Leading UK adoption organisation 'Adoption UK' outline on their website that there are more than 4000 children living in foster care who have had an 'unsettled start to their lives' and may have suffered from abuse or neglect (adoptionUK, accessed 06.09.2017).

Routes to adoption for the intending parent(s) are said to have started once a couple have failed to achieve the societal norm of a biological child and during this process are required to come to terms with the loss of hope to become a biological parent and identify as an adoptive parent (Daly, 1990; cited in van den Akker, 2001 p148). A study of 131 infertile couples showed that 80% had sought medical options to enable them to have a child and were motivated by the need to understand the reasons behind their infertility, whereas adoption and fostering were considered secondary to medical options and considered much later (van

Balen et al., 1995). In another study, when asked about the importance of a genetic link, 81.4% (48/59) of adopted parents/prospective adoptive parents recorded that they did not believe a genetic link was important, with the remaining believing it was (van den Akker, 2001). Within this sample 100 people responded to a question regarding their motive for adoption which included; altruism (40.8%), wanting a family (35.7%), adoption as a permanent solution (11.2%), other options failed (8.2%), the only remaining option (3.1%) and that one person was an adopted child themselves (1%) (van den Akker, 2001). Stages involved for families who adopt a child are said to include welcoming of the child into the family and community, disclosing information to the child and dealing with the child's responses and managing social stigma, which are also argued to apply to conception via donation and surrogacy (van den Akker, 2001).

Although discussed in debates surrounding mitochondrial donation below, adoption as a reproductive option for women with mtDNA mutations has not been investigated empirically. This study offers a unique contribution to both mitochondrial disorders and adoption literature (Chapter 7 section 7.5).

### **3.6 Ovum Donation**

It is argued that the most 'obvious and reliable method' (Thorburn & Dahl, 2001 p105) to 'completely eliminate the risk' (Burgstaller et al., 2015 p13) of transmitting the pathogenic mutation to their offspring, for women with mtDNA mutations would be ovum/egg donation. This is the process in which a donated ovum is used in place of the at-risk woman's ovum, it is important to note that this ovum should not be that of a maternal relative who might also be at-risk. Ovum donation is the process in which a donor ovum/egg is fertilised with the intending father's sperm through in vitro fertilisation (IVF) and transferred into the intending mother's uterus, with the first record of a successful procedure being in 1984 in California (Bustillo et al, 1984). In this thesis I used the term ovum and egg interchangeably. When discussing this technique with women I used the term egg donation as opposed to ovum to prevent potential confusion, as all women understood the term egg.

Predominant issues in gamete (ovum/sperm) donation include disclosure/anonymity, payment for gametes, exploitation of donors (centering on

egg donors and less so on sperm donors), parent-child relationships in ovum donation and the overarching sentiment of the meaning of motherhood (Kirkman, 2003). As of April 2005 in the UK, donor anonymity was replaced with donor identity release, which means that individuals conceived through gamete donation, can seek identifying information about their donor from the age of 18. However this is only possible if the procedure is done at a licenced clinic (which does not take into account informal arrangements seen in sperm donation or treatments conducted abroad). Issues surrounding disclosure to children about their conception are complex and are at the centre of donor conception studies, a primary reason cited is that heterosexual couples utilising gamete donation are able to 'adopt the mantle of a traditional family' and therefore are able to conceal their use of gamete donation (Nordqvist & Smart, 2014 p7).

In the UK it is illegal to pay for gametes, but expenses to the donor are provided, limited to £35 per visit up to a maximum of £750 for a 'course of donation' (HFEA accessed 07.09.2017). It has been argued that the practice of 'payment' for sperm and not eggs (in some clinics) implies that eggs are not an entity that can be 'sold' and that there is a maternal attachment placed on them (Braverman, 1993; Murray & Golombok, 2000 cited in Kirkman, 2003 p3). The availability and choice of donors available to women is more limited in the UK compared to some parts of Europe and elsewhere in the world and so some intending parents choose to access gametes from outside the country, contributing to the multibillion dollar industry that has developed from reproductive tourism (Nahman, 2016) also known as 'fertility tourism' and 'cross border reproductive care' (Deonandan, 2015). Beliefs regarding exploitation of egg donors (and surrogates) centring around this 'tourism' are complex and each 'destination' country can be viewed individually by its political, economic and religious past (Pfeffer, 2011).

Issues relating to legal parentage in the UK are however more simpler for women who conceive via egg donation than in surrogacy (discussed below) as in the UK the gestational mother is recognised as the legal parent of a children born through egg donation. Kirkman (2003) argues that disengaging from genetic continuity can be seen as a threat to motherhood. Parent-child relationships have been investigated in gamete recipient parents in comparison to natural

conception parents by Golombok and colleagues (2002) who found that parent-child relationships were more positive in the gamete recipient group than those in the natural conception group and that gamete recipient parents had greater emotional involvement with their child. Gamete recipient mothers have also been shown to take greater pleasure in their children but also perceive them to be more vulnerable (Golombok et al., 2005). Both studies conclude that although a genetic link may not exist between the parent and child this does not negatively impact on the relationships (Golombok et al., 2005; Golombok et al., 2002).

Although ovum donation can be seen to be a very simple solution for women with mtDNA mutations, qualitative investigations of its suitability for women is unknown. This study seeks to provide insight into women's ideas and preferences surrounding ovum donation as a reproductive option (Chapter 7 section 7.4).

### **3.7 Surrogacy**

There is an extensive base of literature surrounding surrogacy, with primary perceptions being on issues pertaining to how contentious it is within social, moral, ethical and legal frameworks around the world (Nahman, 2016). For women with mtDNA mutations surrogacy offers an option to women who may be physically unable to carry a child to term due to their disease burden, taking into account the potential risk to mother and baby as well as offering the option to use a donor ovum/egg to avoid transmission of their mtDNA mutation.

Surrogacy is traditionally described by the link in which the surrogate mother has to the resultant child and includes two forms of surrogate parenting, 1) genetic or partial surrogacy in which the surrogate mother and the intended or commissioning father are the genetic parents of the child and 2) non-genetic or full surrogacy in which the intending or commissioning mother and father are the genetic parents (HFEA, accessed 04.09.2017). The usual routes of conception in genetic surrogacy is artificial insemination, whilst with non-genetic surrogacy is in-vitro fertilization (IVF) (Golombok et al, 2004). There are also circumstances in which there can be up to three potential 'mother' roles, including biological, gestational and social mothers. For the purpose of this thesis I choose to use the term 'intending' parent as opposed to 'commissioning' parent as I believe

commissioning is more suited to legislative aspects of surrogacy whilst I aim to present surrogacy as a mode of enabling parenthood.

Surrogacy laws differ dramatically across the globe with some countries or states outlawing surrogacy outright, while others allow altruistic surrogacy (no financial gain to the surrogate) but prohibit commercial surrogacy (a debated term but general consensus is that this describes payment to the surrogate above reasonable expenses), to some countries or states having no legislation in favour or in opposition (Teman, 2010). Many viewpoints can be linked to the thinking that surrogacy is a 'cultural anomaly', especially in western society and said to be in relation to beliefs surrounding 'nature' and motherhood as a 'natural fact' (Teman, 2010 p6-8). This is coupled with stigma of the woman who relinquishes her child, disturbing societies views of motherly commitments (Teman, 2010).

In the UK commercial surrogacy arrangements are illegal and surrogacy arrangements are not enforceable (*Surrogacy Arrangements Act 1985 c49*). There are many criticisms of this act and subsequent amendments and reports in which the UK government has been said to have had a knee-jerk reaction to 'cash for babies' scandals that had emerged in the 1980's, moving to a more altruistic approach of a 'gifting relationship' (Fenton-Glynn, 2016 p 60-61). As a result it is only legal in the UK to cover the expenses of the surrogate, such as loss of earnings and transport to and from hospital visits. In the UK surrogacy may be legislated against but is not a regulated activity and fertility clinics are unable to assist with the 'matching' of a surrogate to intending parents. In addition to expenses paid to the surrogate, intending parents can face preliminary costs to register with not-for-profit organisations that assist with 'matching' them to a suitable surrogate.

Organisations in the UK that aim to assist intending parents include Surrogacy UK and Brilliant Beginnings; agencies that claim to offer 'surrogacy through friendship' (Surrogacy UK, accessed 04.09.2017) and support during the 'family building process' (Brilliant Beginnings, accessed 04.09.2017). Surrogacy UK reported via the HFEA that the process of surrogacy can cost intending parents from £7,000 to upwards of £15,000, although it is cautioned that this can increase depending on the type of clinical procedure utilised to achieve pregnancy (HFEA,

accessed 04.09.2017). In addition to these costs intending parents face issues relating to who is considered the legal parent at birth and whose names are added to the birth certificate.

In the UK, the surrogate or gestational mother is recorded on the child's birth certificate even if the child is not genetically related to her (i.e. is genetically related to the intending mother). In order for intending parents to be granted parental rights, they must apply and be granted a parental order; once this is in place the surrogate and the named second parent (if not the intending parent) will have no further rights or obligations to the child, although parental orders themselves are not simple to obtain (Fenton-Glynn, 2016). This remains a complex process (Fenton-Glynn, 2016) and although appropriate forms regarding legal parenthood are provided by the HFEA on their website, seeking legal advice is strongly encouraged regarding their completion and later application for the Parental Order (HFEA, accessed 04.09.2017).

Reproductive tourism is common amongst for not only ovum/egg donation but also within surrogacy due to the variation in legislation and commercial surrogacy practices available in some countries. This is compounded further with supply and demand principals, in that the demand for surrogates outweighs the number available in the UK (Fenton-Glynn, 2016). There are many ethical debates surrounding reproductive tourism and surrogacy which are outside the scope of this thesis (Nahman, 2016,; Fenton-Glynn, 2016), but UK parents are cautioned that if they consider this option that they take expert legal advice around the transfer of legal parenthood and parental rights in relation to the nationality of the surrogate and the country of birth of the child (HFEA, accessed 04.09.2017).

Intending parents in the UK live with uncertainty during their surrogacy journeys in that there is no legal contract that ensures their planned child will be relinquished by the surrogate mother after birth as well as anxiety over establishing the 'right' type of relationship with the surrogate (Golombok et al., 2004). Golombok and colleagues (2004) summarised the impact of surrogacy on intending parents, which included effects on psychological wellbeing (including parental anxiety, depression) marital conflict as well as interference in the quality of parenting due to feelings of inferiority compared to other parents.

From a social perspective surrogacy is said to differ from gamete donation in that it separates the role of biological and social motherhood (Golombok et al., 2004). Jones (2015) argues that even in consideration of advancing techniques 'it cannot seriously be disputed' (p101) that the woman who carries a child to term and gives birth is not the biological mother. Surrogacy raises issues about identity and how embodied experience of pregnancy can construct a new self-identity for some women (although for some this happens after birth) (Teman, 2009). In the case of the intending mother this change in self-identity must be managed by their access and desire to undergo this change (Teman, 2009). Teman (2009) highlights the blurred physical boundaries experienced by surrogates who are said to do a lot of 'classification work' (p52) to distance themselves from experiences that may elicit emotional ties to the growing foetus such as 'kicks' and other fetal movements, whereas intending mothers appear to take on the surrogates body as an 'appendage' (p54). The embodied experiences of pregnancy in surrogacy described by Teman (2009: p47) include 'initiating, challenging, validating, shifting, merging and birthing of the shifting body'.

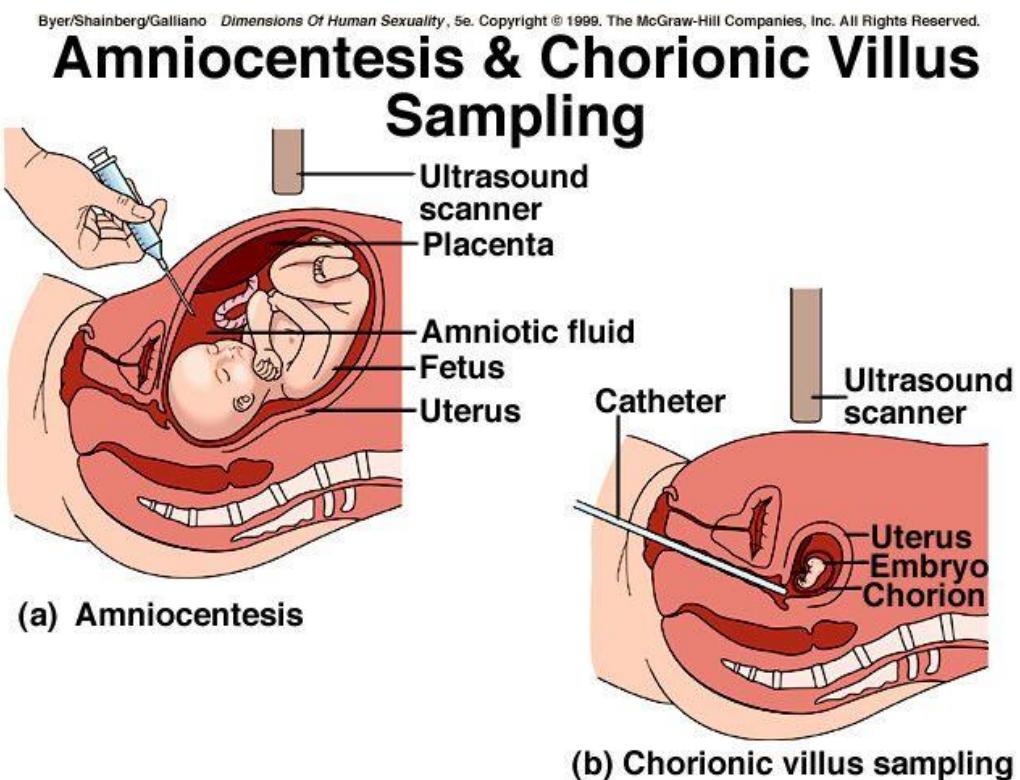
There have been no empirical studies detailing experiences of surrogacy in patients with mitochondrial disease, nuclear or mitochondrial in origin.

References to surrogacy alongside mitochondrial disease are included in debates surrounding the introduction of mitochondrial donation as an alternative option to undergoing the novel technique. The original contribution that this work adds to the field is that it presents the views and preferences of women with mtDNA mutations regarding surrogacy as a reproductive option (discussed in Chapter 7 section 7.4).

### **3.8 Prenatal Diagnosis and Prenatal Testing**

Prenatal diagnosis (PND) or prenatal testing are techniques that permit the genetic testing of a foetus before birth and include chorionic villus sampling/biopsy (CVS/CVB) or amniocentesis. Chorionic villus sampling is the process in which placental tissue is sampled for chromosomal abnormalities and is the earlier of the two tests, taking place between approximately 10-14 weeks gestation. The procedure can be done by the percutaneous transabdominal approach (needle puncture procedure through the abdomen) or as a transcervical approach (via the uterine cervix) (Bhatt, 2017) (Figure 3.1). Amniocentesis is a

later prenatal test, which can be performed between 16-20 weeks gestation and includes the withdrawing of amniotic fluid from around the foetus which contains fetal exfoliate cells, urine and secretions by a transabdominal approach (Dimri & Baijal, 2016 p131). Test results are available between 1-7 days post procedure depending on diagnostic tests performed on the sample (Bhatt, 2017 p81; Dimri & Baijal, 2016 p134).



**Figure 3.1** Prenatal testing techniques a) Amniocentesis testing procedure and b) Chorionic Villus Sampling procedure. Reproduced from (Byer, Shainberg, & Galliano, 1999).

Prenatal testing is offered to women in a number of different scenarios such as when there is a known genetic risk to a future child, when an earlier diagnostic test has raised concerns or when the mother will be over the age of 35 at time of delivery. Both procedures carry a risk of fetal loss or fetal injury; the percentages however vary from one report to another. Bhatt (2017) review of 16 cohort studies reports that the risk of fetal loss 14 days post transabdominal CVS is 0.7%, 1.3% 30 days post transabdominal CVS and 2% loss at any time during pregnancy

(Bhatt, 2017). Dimri and Baijal (2016) review of nine studies showed that miscarriages post-midtrimester after amniocentesis ranges from 0.75% to 3.3% (Dimri & Baijal, 2016). Nesbitt et al (2014) stated that the 'aim of prenatal testing in mitochondrial disease is to identify fetuses harbouring mutations that will cause severe disease and offer termination at a relatively early stage' (p1257).

Chorionic villus sampling was first offered to women with mtDNA mutations in 1992 but reservations surrounding the sensitivity of tests continued for a number of years after. These concerns were related to whether heteroplasmy levels tested at these time points were predictive of mutation load in other tissues or at birth (Thorburn & Dahl, 2001). These tests depended on heteroplasmy levels found in the cells taken during prenatal testing to be largely representative of all cells in the fetus and that they remain at these levels as the pregnancy progresses. As with predicting inheritance risk, understanding heteroplasmy results from prenatal tests in relation to the affectedness of a future child is especially difficult (Nesbitt et al., 2014). Prenatal testing is not advised for women with a known homoplasmic mtDNA mutation, as the foetus will also be homoplasmic and therefore the test will not offer any beneficial information (Poulton et al., 2017). The so called 'grey zone' can make it difficult for a clinician to counsel parents and for parents to decide whether to continue with or terminate the pregnancy (Nesbitt et al., 2014; Smeets et al., 2015). Thorburn and Dhal (2001) argue that interpretation of results proves difficult, with heteroplasmy below 30% considered low risk, whilst those over 90 % are considered high risk (Thorburn & Dahl, 2001).

Nesbitt and colleagues (2014) reviewed data on prenatal tests offered within their combined clinical services from April 2007 to January 2013, totalling 62 procedures of which 17 were mtDNA mutations, the remaining 45 were nDNA mutations. These tests were offered to women who already had an affected child, were a known carrier of a mtDNA mutation or who had a severely affected sibling (Nesbitt et al., 2014). Of these 62 procedures, 59 were CVS (gestation time between 8-15 weeks) and 3 were amniocentesis (gestation time of 15-17 weeks) (Nesbitt et al., 2014). The findings of this study are said to have shown that prenatal testing in mitochondrial disease is 'reliable and informative for nuclear mutations and selected mtDNA mutations' and that the provision of appropriate

reproductive counselling is important for patients considering all their reproductive options (Nesbitt et al., 2014 p 1255).

Social perspectives of prenatal diagnosis include the view that individuals presented with genetic information that may then require them to choose between continuing with a pregnancy and termination may be focusing only on the disability and show little regard for the fetus and to disabled people (Boardman, 2014). This leads into the belief of 'expressivist objection' or EO which is the belief that there is focus on correcting and preventing disability rather than the value of a disabled person (Buchanan, 1996 cited by Boardman, 2014). Boardman (2014) highlights that genetic testing and selective termination in families with experience of the condition is however very different to that of decision-making in the general public or with those with no experience of the condition (Boardman, 2014). There has been critique of what constitutes 'balanced' information in consultations with women who have screened positive for Down's syndrome, where physicians and midwives have only practical 'textbook' knowledge. This can lead to a focus on the medical problems associated with the syndrome as opposed to providing information of the broader subject of living with disability (Williams et al, 2002). There are however those who believe that EO is too simple an idea and does not represent the complexity of reproductive decision-making for intending parents in these situations, being overly critical of them and not taking into account broader arguments surrounding reproductive technologies (Shakespeare, 2006 cited in Boardman, 2014). Although studies have been conducted into prenatal testing in mitochondrial disease, little is known about the patients and their partners opinions of these test, this study seeks to add to this literature with unique insight in to views of women with mtDNA mutations of CVS and amniocentesis as reproductive options (discussed in Chapter 7 section 7.3)

### **3.9 Pre-implantation Genetic Diagnosis**

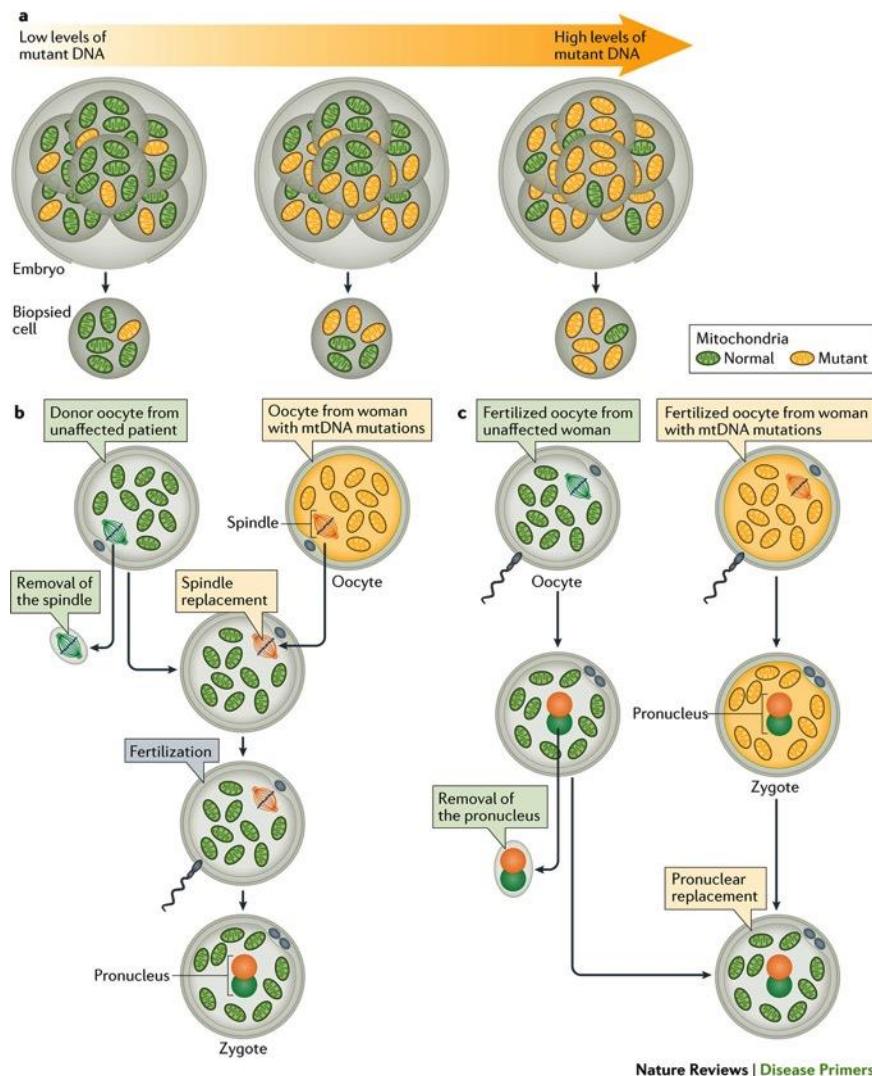
Pre-implantation genetic diagnosis (PGD) is the process in which embryos created via *in-vitro* fertilisation are biopsied and tested for genetic abnormalities the outcome of which can enable decision-making between the clinician and intending parents about whether to transfer the embryo(s) or not (included in Figure 3.2a). As well as having a mutation load thought to be below the threshold

level for clinical affectedness the embryo(s) must also meet standard IVF grading standards to be considered suitable for implantation. The first report of PGD as an option in human disease was in 1989, for X-linked conditions and was reported in 2006 to have been used successfully in mitochondrial disease, namely in the m.8993 T>G mutation, associated with NARP (Neurogenic Muscle Weakness Ataxia Retinis Pigmentosa) phenotype ( Steffann et al., 2006 cited in Brown et al., 2006). The HFEA website lists the mitochondrial conditions for which license has been to allow for PGD, these include NARP, MELAS, MERRF, Leigh Syndrome, PEO, Mitochondrial DNA Depletion Syndrome 2 (myopathic type), Mitochondrial Complex 1 Deficiencies (multiple gene origins) and LHON (HFEA, accessed 08.09.2017). The primary advantage of PGD is that it can prevent intending parents from facing possible termination of their pregnancy, as is the possibility with prenatal testing.

In PGD embryos are tested at either blastomere (an eight-cell embryo, or Day 3) or blastocyst (approximately 70-100 cells or Day 5) stage (Smeets et al., 2015; Poulton et al., 2017). There are however conflicting reports about the accuracy of PGD in mitochondrial disorders due to difficulties in confirming if the results are indicative of mutations loads of the whole embryo. These concerns centre largely on the stage at which the embryo has developed at the time of the biopsy (Smeets et al., 2015; Poulton et al., 2017). PGD is reported to raise issues of uncertainty for parents and is intensely emotional due to the strong desire to avoid having an unhealthy child or experience another unsuccessful pregnancy-in couples accessing nuclear genome PGD (Roberts & Franklin, 2004). Roberts and Franklin (2004) conducted an in-depth ethnographic study of two PGD clinic's in the UK over 18 months, they found that those women who took part in the study reported that finding out that they were candidates for PGD was 'an enormous relief' (p228) and that for some their decision to undergo the technique was a 'choice of necessity' (p228) and not really a free choice due to prior experience.

As noted above, the complexities of counselling patients with heteroplasmic mutations and being able to indicate what levels of mutation may result in an affected child is especially difficult. It is advised to counsel these women and their partners on a case-by-case basis, with Smeets and colleagues including parental

perceptions of risk as an important factor to be considered alongside the biological concerns (Smeets et al., 2015). This study seeks to understand how women with mtDNA mutations perceive PGD as a reproductive option (discussed in Chapter 7 section 7.4).



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**Figure 3.2** a) Pre-implantation Genetic Diagnosis (PGD) procedure involves IVF of all oocytes harvested from the intending mother; these are then biopsied and analysed for mutation. Embryos that meet IVF grading criteria and acceptable mutation percentage (to parents and clinicians) are implanted b) Metaphase II Spindle Transfer involves the removal of the spindle from donor oocyte, which is replaced by the intending mothers spindle; this oocyte is then fertilised with intending fathers sperm c) Pronuclear Transfer involves of the removal of the pronuclei from both the donor and intending parents zygote and inserting the intending parents pronuclei into the enucleated donor zygote (Gorman et al., 2016). Used with permission

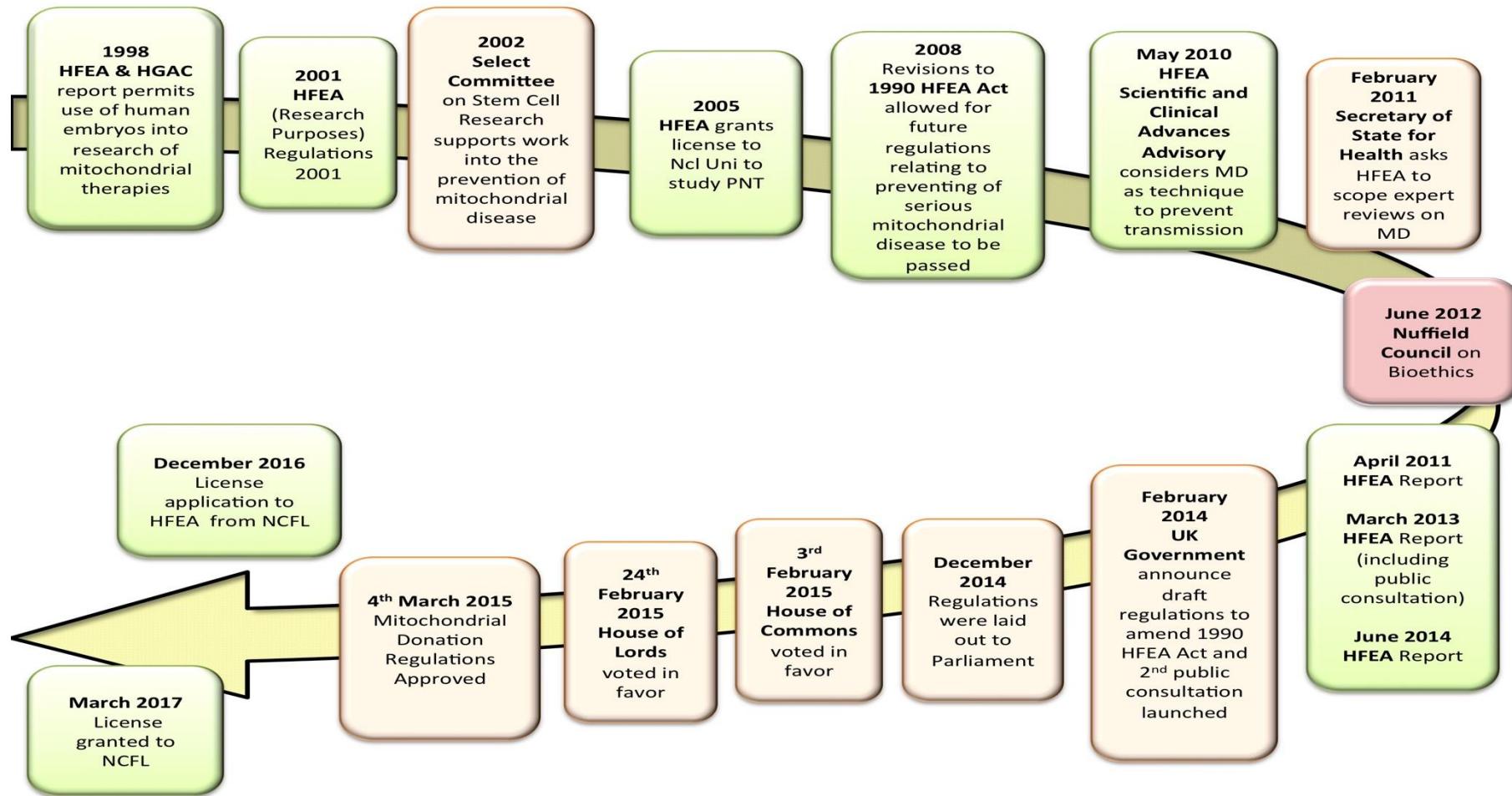
### 3.10 Mitochondrial Donation

Mitochondrial Donation is the term used to describe two reproductive techniques that have been at the centre of international scrutiny for a number of years, with intensive biological, ethical, legal, moral and religious debates emerging in advance of UK parliamentary debates and licensing of the techniques. The two

techniques include pronuclear transfer (PNT) and metaphase II spindle transfer (MST). Figure 3.2 (b and c) shows the difference between the two techniques, which are sometimes also referred to as mitochondrial replacement. In pronuclear transfer the pronuclei from the fertilised donor oocyte is removed and replaced with that of the pronuclei from the intending parents (the pronuclei from the early stages of the nucleus that contains chromosomes from the egg and sperm). In metaphase II spindle transfer the transfer occurs before fertilisation and involves the replacement of the donor spindle complex with that of the intending mothers spindle (the spindle is a microtubule apparatus that is involved with the movement of chromosomes during cell division- the complex includes the nuclear chromosomal material). Both techniques result in the nuclear genetic material from the intending parents being incorporated into a zygote that contains mitochondria from the donor and therefore free from the mtDNA mutation (Gorman et al., 2016).

Research into the potential of these techniques to prevent mitochondrial disease transmission dates back to 1995 (Rubenstein et al., 1995 cited in Craven et al., 2015) eventually cumulating in the award of the first licence to practice these techniques being granted to Newcastle Fertility Centre, Newcastle Upon Tyne, UK in March 2017 as an amendment to the Centre's existing Treatment and Storage license. Milestones encountered and required to facilitate this amendment to licence are summarised in Figure 3.3. During this period, clinical use of mitochondrial donation, specifically MST was first reported by Zhang et al (2016) and later described in full by Zhang et al (2017). The team reported the birth of a male child, whose percentage of mtDNA mutation ranged from undetectable to 9.23% across a range of tissues after the use of MST (Zhang et al 2017). News of the first clinical application of mitochondrial donation was met with controversy due to the clinical team having been said to have purposively travelled to Mexico where no legalisation exists against such IVF techniques (Palacios-González and Medina-Arellano, 2017; Chan et al, 2017). The team involved in this pregnancy have also reported the potential use of MST in a further 20 pregnancies in the first half of 2017 (New Scientist, 2016). In addition to this announcement, clinical teams in the Ukraine announced the birth of a child

born through mitochondrial donation, for the treatment of infertility as opposed to the prevention of transmitting mitochondrial disease (Coghlan, 2016).



**Figure 3.3** Timeline of Mitochondrial Donation UK approval process (1998-2017). Green boxes denote regulator activity, orange denote political activity. HFEA: Human Fertilisation and Embryology Association. NCFL: Newcastle Fertility Centre. Informed by (Craven et al., 2015) and extended with recent advance.

Mitochondrial donation has attracted worldwide attention and with it many varied opinions on its suitability as a technique. Controversy has centred on 1) introduction of a third persons DNA (donor mtDNA) and implications for the identity of children born via mitochondrial donation 2) that it is a germline technique that will see donor mtDNA passed onto the children of females born of this technique 3) safety and efficacy of the techniques to prevent mitochondrial disease and also the proposed surveillance of children 4) status and welfare of the mitochondrial donor 5) the wider societal impact of the techniques as well as 6) investigation of the debates themselves (Castro, 2016; Haimes & Taylor, 2017). Critiques have also centred on the misleading terminology of mitochondrial donation and mitochondrial replacement (Jones, 2015; Lane & Nisker, 2016; Nisker, 2015). Worries were that these may be heard by some to mean that the mitochondria ‘travel’, where it is the pronuclei or the spindle complex that is inserted into the donor oocyte or zygote. On this basis it has been suggested that ‘nuclear DNA hosting’ would be a more accurate description (Haimes & Taylor, 2015 p364).

As outlined above mtDNA account for a very small proportion of DNA present in a single cell, approximately 0.1% (Taylor & Turnbull, 2005). The introduction of this small percentage of DNA resulted in media tag lines of ‘3 parent babies’ ‘3 person IVF’ that then made their way into scholarly debates and public consciousness surrounding these techniques (Baylis, 2013; Dimond, 2015; Haimes and Taylor, 2015; Turkmendag., 2017; Dimond and Stephens, 2017). Claims that children born via mitochondrial donation would have three parents or two mothers was not supported by the Nuffield Council of Bioethic’s review of the techniques. The Council concluded that this should not be considered the case from a biological or legal perspective (Nuffield Council on Bioethics, 2012). The emphasis of healthy biologically related children were criticised by some in that they lacked information relating to other options available to women and ‘valorising genetic connection’ (Haimes & Taylor, 2017 p5) a point at which this study addresses by deliberately seeking the opinions of women on all reproductive options available to them. In recognition of the intensive debates surrounding mitochondrial donation as a reproductive option for women with maternally inherited mitochondrial disease I sought to add a patient’s perspective

of these techniques to the body of literature via this study, which I believe is lacking in comparison to other commentaries.

A consideration by the Nuffield Council included potential identity issues for a child conceived via mitochondrial donation, that he/she may have 'confused or conflicted' self-identity. In response to this query key research stakeholders responded that genes present on mtDNA were not linked with those responsible for identify-forming characteristics (Nuffield Council on Bioethics, 2012). The many different facets of identity and how mitochondrial donation may or may not impact upon them are discussed in-depth by the working group within the Nuffield Council and others (Watts et al., 2012; Dimond, 2015; Wrigley et al., 2015)

Mitochondrial donation is what is termed a germline technique because female children born of mitochondrial donation will pass the donor's mitochondria on to their children, therefore genetic modification will occur in future generations and further down the maternal line, the unknowns of which underpin safety concerns relating to the technique. Safety and efficacy of these techniques have been investigated over a number of years directed by the core research team and in alignment with the calls for additional testing by the HFEA over the course of their scientific reviews (Figure 3.3) (Craven et al., 2015; Wise, 2014). During the consultation process it was advised that mitochondrial donation be offered to couples as part of a research study only and that couples accessing mitochondrial donation should commit to long term follow-up of their child (Nuffield Council on Bioethics, 2012). Common critiques of the introduction of mitochondrial donation in parliament were in relation into the breach of the EU Clinical Trials Directive if mitochondrial donation were to be approved, despite this directive only being applicable to medicines and medical devices and would having no place in the implementation of reproductive technologies (HC Deb 2015-02 col.163.169. 171.177.181.183.185). To address concerns of safety, efficacy and long term survilaance, in advance of the licensing application, a study to assess the fetal and postnatal development of children concieved using mitocohndrial donation was approved by a UK Research Ethics Committee as well as the preparation of a dedicated Mitocohndrial Donation Clinical Care Pathway for long term follow-up of children.

The role of the mitochondrial donor has been heavily debated, with many preferring the term egg providers as a more adequate description of their contribution (Baylis, 2013; Haimes & Taylor, 2015). For the purpose of this thesis I have decided to use the term mitochondrial donor. For those proposing mitochondrial donation the status of the mitochondrial donor was that of a tissue donor, whilst critics questioned if donors should be afforded the same status as gamete donors (Brandt, 2016; Turkmendag., 2017; Appleby, 2016) The implications of gamete status would mean that children born via mitochondrial donation would be able to contact the donor once they reached 18 years of age. In addition to contacting their mitochondrial donor, theoretically they would also be able to contact any siblings born via mitochondrial donation also (HFEA, accessed 08.09.2017). The rights of the mitochondrial donor would also be that of an egg donor, enabling them to access information regarding the outcomes of their donation as well as being restricted in the number of donations they can make (HFEA accessed 08.09.2017). The defence of the status as tissue donor was argued that although the genetic contribution of the donor was significant enough to prevent disease, it did not compare to that of a gamete and therefore should not be placed in the same category (HFEA, accessed 08.09.2017). As above in the case of surrogacy, UK law does not recognise 'genetic motherhood' but only that of gestational motherhood (Nuffield Council on Bioethics, 2012 p46).

In addition to donor rights, concerns relating to the donor and the process in which eggs are collected were debated. In order to become an egg donor, women must undergo controlled ovarian hyper stimulation (COH) of their ovaries in order to produce a significant number of eggs to harvest at their collection date (this is also the case in IVF). Those campaigning against the introduction of mitochondrial donation raised concerns over the possible dangers of this (Baylis, 2013; Dickenson, 2013; Palacios-González, 2016). Ovarian hyperstimulation syndrome (OHSS) is caused by an excessive response to gonadotropins used to stimulate ovaries. Symptoms can range from the mild to the severe. It is estimated that 1% of women who undergo COH will experience moderate or severe symptoms (Royal College of Obstetricians and Gynaecologists, 2016). Serious complications such as venous thromboembolism (VTE) –the development of significant clots –are rare. Baylis (2013) writes that mitochondrial

donation poses a risk to egg providers, paying specific attention to the physical and psychological risks involved in providing eggs, and that these risks have to be considered by women regarding their role in 'some else's reproductive project' (Baylis, 2013 p533). Haimes and Taylor (2015) argue that despite the essentialness of donors for both the development (research) and application (therapeutic) of the techniques they were 'rendered invisible' (p:360) from the debates surrounding them and that this was a conscious decision as part of the 'strategy of persuasion' (p:361) to obscure and diminish the role of egg donor.

### **3.11 Summary**

This chapter presents a summary of the nine reproductive options available to women. Women with maternally inherited mitochondrial disorders have, if they so wish, the option to access genetic counselling, provided by mitochondrial specialists and/or genetic counsellors. Genetic counselling aims to provide women with information on their individualised inheritance risk to facilitate informed decision-making. Providing genetic counselling to patients about inheritance of mtDNA mutations is troublesome to trained mitochondrial specialists, who find imparting complex information, which cannot be considered accurate, particularly discomfiting. To combat this, specialists work in large networks enabling access to expertise and technologies. For a number of women with mtDNA mutations, their reproductive decision-making precedes their diagnosis, therefore resulting in a proportion of women who had little or no reason to consider another option other than natural conception without intervention. There are also women who choose this option after receiving their diagnosis. Understanding this process is a unique contribution of this study.

With the knowledge that they harbour about a pathogenic mutation, women may decide that they do not want to raise children, which is termed voluntary childlessness, where others may find themselves in a temporary state of childlessness. Adoption is an option for women, enabling them to fulfil a mothering role to a child, but is strictly regulated by authorities and can be perceived as a difficult and challenging process. Ovum or egg donation has been said to be the most logical ART to prevent the transmission of mtDNA mutations, but no empirical evidence is present in the literature around women's views and perceptions of this method in maternally inherited mitochondrial disorders.

Surrogacy provides women who are unable to carry a child the opportunity to have a biologically related child, which may be related to both intending parents or if used alongside ovum donation, related to the intending father. Surrogacy splits the role of intending mother and gestational mother whereby both women are required to work at their role, the gestational mother in distancing herself from the growing fetus and the biological/intending mother in establishing the desired relationship with the gestational mother and taking on her body as an appendage. Surrogacy however brings with it levels of uncertainty surrounding the relinquishing of the resultant child to the intending parents in which UK law cannot assist.

Prenatal diagnosis and PGD techniques allow for parents to be informed of potential mutation loads of their growing child or their fertilised embryos respectively. Both offer women and their partners the opportunity to obtain information that could be important in establishing clinical affectedness of their future children, however PGD allows for the discarding of embryos in place of pregnancy termination. Although both techniques are available, little is known of women's ideas and preferences surrounding these techniques for mitochondrial mutations. The newest clinically available option is mitochondrial donation. Although the two techniques involved differ in the point at which the nDNA is removed from oocyte or zygote, both techniques result in an embryo that has donated mitochondria, and therefore preventing the transmission of mutated mitochondria. Due to the germline implications of these procedures, lengthy debates in numerous areas have taken places over decades. This thesis explores how women, who themselves may be eligible for this treatment (as well as their daughters and maternal family members) view mitochondrial donation techniques.

Throughout this chapter, key components that make up uncertainty present amongst reproductive options especially in relation to ambiguity, vagueness, unpredictability, and unfamiliarity. In the following chapter I will detail the methodological approach that was taken to conduct this study and the practical methods of designing, setting up, conducting the study and analysis of study results.

## **Chapter 4. Methodology and Methods**

### **4.1 Introduction**

Within this chapter I address the theoretical and practical issues that presented throughout the conduct of this study. Initially, I outline the methodological framework that was chosen for this work and the underpinning theories behind this framework. I then move on to the ethical and institutional approvals required to initiate the study. I describe the research population, sampling methods and introduce the participants along with the key health professionals they encountered. I further define how interviews were conducted and recorded and provide a step-by-step guide to the data analysis methods used throughout the study and how the resultant themes were revealed. I will show in detail how the proposed conceptual model of reproductive decision-making in maternally inherited mitochondrial disease evolved across a number of different versions. I will, throughout each section, include my personal reflective practice and where applicable any amendments to processes and reasons why they were implemented.

### **4.2 Methodology**

Qualitative methodology was chosen to examine the experiences of women with mtDNA mutations and reproductive decision-making as it allows for rich and varied data to be collected. However qualitative research is commonly associated with a lack of scientific rigor. This criticism is often based on ideas that data is only anecdotal, subjective to the researcher and therefore open to bias and that findings lacks reproducibility (Mays and Pope., 1995). Ways in which to address the reliability and validity of qualitative research is discussed in Section 4.8.

In this section I will detail the methodology used in this research. Krauss, (2005: p758) defines methodology as identifying 'the particular practice used to attain knowledge'. Guba and Lincoln (1994: p108) note that 'inquiry paradigms define for inquirers what it is they are about' and within this, the limits of legitimate enquiry are set out. They believe that a researcher's response to three fundamental questions can define an inquiry paradigm, these being the ontological question, the epistemological question and the methodological question. I will therefore outline the theoretical approaches used and how aspects of constructivist grounded theory was

employed throughout fieldwork and interpretation. To begin, I will discuss the ontological and epistemological stance taken in this study.

#### ***4.2.1 Ontological Approach***

It is argued that ontology and epistemology sit alongside one another and that ontology informs the theoretical perspective as, 'Ontology is the study of being' (Crotty, 1998:p10). Paradigms or a person's set of beliefs can be charted on a spectrum ranging from positivism, the belief that enquiry enables you to know exactly what something is or how it works through to constructivism where there is an assumption that knowledge is created between the researcher and the respondent during inquiry (Guba and Lincoln 1994). Positivism as a theoretical perspective is underpinned by objectivism (Crotty, 1998) and has been described as dominating science, focusing on the quantitative analysis of phenomena, independent of social relationships or encounters and 'providing a single apprehensible reality' (Perry et al.,1999: p16).

Differing from positivism, realism is an ontological perspective that acknowledges multiplicity of realities and goes further by suggesting that each reality has equal validity (Krauss et al., 2005 p761) and that a difference exists between reality and a person's perception of reality (Bisman 2002 cited in Krauss et al, 2005: p761). This understanding is grounded in the phenomenon described as 'multiple realities' (Krauss et al., 2005), where each person experiences life from their own perspective and therefore has multiple different realities.

As we have seen in Chapter 2, decision-making is complex and can be dependent on an individual's lived experience, beliefs and values, meaning that each person's views on an issue or decision renders them in their own internal reality. The study described in this thesis is primarily concerned with woman's experiences of reproductive decision-making, understanding women's multiple realities and how these are influenced by their experiences and what meanings are placed on them. Acceptance of these multiple realities is essential in order to be open to emergent phenomena not previously described in this study group. Taking this approach also accepts that social conditioning of a researcher impacts on their knowledge of reality and is not independent of social actors (Dobson, 2002).

The ontological approach taken in this study was one of 'subtle realism' (Hammersley, 1992; Seale, 2006) where I acknowledge that realities discussed in this thesis are only known via my own interpretation of accounts constructed by others. By adopting this approach, I am attempting to explore and represent these realities as opposed to 'truth'. I seek to compare these multiple realities to one another and to existing literature on associated topics.

#### ***4.2.2 Epistemology***

It is argued that knowing the lens in which a researcher approaches an inquiry is an important step in understanding the study design methodology employed within a study (Dobson, 2002). Choosing the appropriate theoretical approach to take to examine decision-making as opposed to a set paradigm was an important step in the design of this study. For this I see myself as adopting an epistemological approach of social constructionism, which is in harmonisation with ontological perspective of subtle realism. Crotty (1998) defines constructionism as an epistemology where

'Truth or meaning comes into existence in and out of our engagement with the realities in our world. There is no meaning without a mind. Meaning is not discovered, but constructed' (Crotty, 1998:p 8-9)

In this, Crotty (1998) tells us that people construct meaning differently to one another and that an object or a phenomenon does not have an existing meaning already attributed to it, simply waiting to be discovered. Social constructivism states that it is a person's culture that dictates how they see or don't see an object or a meaning (Crotty, 1998). In taking this approach, I have actively considered the culture in which I have been part of prior to and during the course of this project and how this is reflected in the meaning that I have attributed to the phenomena I seek to present in this thesis.

#### ***4.2.3 Symbolic Interactionism***

Blumer (1969) notes that every individual has the capacity for thought, which is shaped by our social interactions (as cited in Crooks, 2010:p14). This capacity lends itself to the ability to associate meanings and symbols with the expression of thought, which is further modified by interactions with others and with one's self (Crooks, 2010). These interactions go on to enable a person to understand a

situation they find themselves in and to make choices. Symbolic interactionism is an established theory in health and illness research (Crooks, 2010).

#### **4.2.4 Constructivist Grounded Theory**

The research strategy for this study was fundamentally informed by Constructivist Grounded theory. Constructivist grounded theory requires no defined hypothesis of the phenomenon under study but for the phenomenon to emerge from the data as it develops. It originates from the work of Glaser and Strauss (Glaser, 1978; Glaser & Strauss, 1967) and informs recruitment, sampling, method and analysis.

Grounded theory was first introduced when positivist epistemology was dominant, in response to claims that qualitative inquiry was not 'scientific enough'. Defining components of the practice of grounded theory included the simultaneous involvement of data collection and analysis, developing analytical codes from the data, memoing, comparing data throughout the inquiry to permit the development of theory, using sampling methods that sought to construct theory as opposed to representing a population and to conduct literature searches after analysis (Glaser, 1978; Glaser & Strauss, 1967).

The original form of grounded theory received criticism from other qualitative researchers over time in that it assumed that the researchers performing the analysis did not bring their own interpretation to the data, echoing the positivist approach to inquiry. In its earliest form Glaser and Strauss had provided strategies to be applied to data analysis in an attempt to reflect the language and tone of quantitative methodologies. Over time grounded theory has been developed. Constructivist grounded theory, developed by Charmaz (2006) is the methodology that was applied to this study. Charmaz (2006) not only acknowledges the researcher in the process of data analysis but that their approach 'assumes that any theoretical rendering offers interpretative portrayal of the studied world not an exact picture of it' (Charmaz 2006:p10). Charmaz (2006) writes that unlike traditional grounded theory

'Neither data nor theories are discovered. Rather we are part of the world we study and the data we collect. We construct our grounded theories throughout past and present involvements and interactions with people, perspectives and research practices' (Charmaz 2006:p10)

A feature of constructivist grounded theory then, is how it frames the interviewee-interviewer interaction as collaborative (Crooks, 2010). Crooks (2010) notes that selecting grounded theory the 'researcher-participant relationship becomes the interactive context', this relationship allows for the researcher 'to understand the perspectives of women, women's ways of coming to know their health issues' including 'strategies and processes to help them through a situation' (p24). Rapley (2004) states that qualitative interviews are collaboratively produced between the interviewer and the interviewee and that the interviewers are active participants in the construct of the interview.

In addition to the above grounded theory methodologies of data analysis, Charmaz (2006) also included mapping of data as part of memo writing. Mapping or clustering of data allows for a visual perspective of data and can assist with analysis of complex and overlapping codes and relationships.

This approach has shaped both data collection, analysis and interpretation of data in this study. Throughout this thesis I aim to be transparent with regards to my worldview, my concurrent role as a member of the 'sometimes known' research team, which can be seen in my field notes and memos (omitted from the appendix to prevent patient identification but available upon request).

Interactions with my participants as a researcher led to changes in the interview schedule and most notably the interview aid relating to reproductive options (see section 4.5).

### **4.3 Data Collection**

#### ***4.3.1 Ethical Approvals***

National ethical approval for this study was obtained from North East Newcastle and North Tyneside NRES Committee 1 in June 2014 (14/NE/0144). Two substantial amendments were notified to and approved by the Committee (Amendment 01 28.03.2015 and Amendment 02 11.03.2016). Details of these amendments are described below. I attended the review meeting and received favourable opinion after one minor typographical change was made to the Partner/Relative and Close Friend Information Sheet.

The ethical challenges foreseen within this study included

- a) The emotive nature of the topic in both study arms (retrospective and current and prospective decision-making groups)
- b) The potential of clinical questions being directed to the non-clinical researcher
- c) Discussions on topics that raised safety concerns for the women or others
- d) Data Protection and Confidentiality
- e) Managing and supporting the emotional needs of the researcher.

#### **4.3.1.a Emotive Nature of Reproductive Decision Making**

Women who suffer from or who harbour a mtDNA mutation may face difficult decisions regarding their reproductive options, complicated further by the difficulty in predicting risks to both the mother and future child. Researching topics of this nature requires a sensitive approach and study design. Discussion around what constitutes a sensitive topic has been discussed by a number of authors, including Siber and Stanley (1988) who state that sensitive research is that which can be harmful to the participant and/or the research team investigating it. Lee and Renzetti (1990) explore the meaning of sensitive topics and they consider the costs incurred by the participant during the process, these costs may include psychological costs such as guilt or shame but also consequential costs of prosecution if disclosing an illegal act. Lee and Renzetti (1990) define a sensitive topic as

one which potentially poses for those involved a substantial threat, the emergence of which renders problematic for the researcher and/or the researched the collection, holding, and/or dissemination of research data (Lee and Renzetti 1990:p513)

This approach believes that the topic itself is of less concern but when introduced into the context of the research interview, it becomes sensitive. Cassell(1980) and Ramos (1989) both argue that by assuming that a research topic is harmful you exert power over the participant, taking away their own ability to control how and what is said during the interview process. I approached interviews with an understanding that the topic may be more sensitive to some women than others, which was in fact what was observed. To address the potential of distress at the outset of this study, detailed information sheets for each study group were provided (along with a specific information sheet for potential interview attendees - Appendix A2). These information

sheets outlined that the topic of reproductive decisions would be covered in the interview, which may cause some distress to some women, and that their participation was voluntary.

Eighteen women were interviewed as part of this project; they were offered a choice of locations in which to take part in the study. Women were informed that on the day of the scheduled interview or at any point during the interview they felt distressed or upset they could cancel, postpone, pause or terminate the interview. Women were offered a choice of interview location to reduce the inconvenience of taking part in the study, nine interviews took place at the participant's home, one interview took place in a public space (coffee house), four at their place of work (meeting room), two in the outpatient clinic at Data Collection Centre 1 and two at a clinical research facility at Data Collection Centre 1. Interviews conducted at Data Collection Centre 1 occurred in private consultation or meeting rooms and were arranged before or after the woman's scheduled clinical review. The interview conducted in a public space was at the request of the participant, when asked if confidentiality of the location would pose an issue, the woman was happy to conduct the interview without concern. Two follow-up interviews were conducted over the telephone.

Participants in qualitative enquiry are said to have more control of the research they are taking part in than in other biomedical research (Cassell, 1980) often having the control over the research setting and the context especially in unstructured interviews. Elwood and Martin (2000) suggest that allowing research participants the choice of interview location may enable them to feel more empowered with their interaction with the researcher and that this permits the researcher to observe the social geographies of the participant (Larossa et al 1981 cited in Corbin and Morse 2003). Corbin and Morse (2003) claim that research conducted in the homes of participants is more likely to elicit information that may not have been offered had the interview been conducted elsewhere. Whereas other writers believe that interviews in the homes of participants may disrupt power hierarchies, they do not erase power differences (Oberhauser (1997) and Falconer-Al Hindi (1997) cited in Elwood and Martin 2000). I do not believe the location of the interviews necessarily affected the topics discussed by women but providing a choice permitted women to be able to choose the space in which they shared their experiences. This choice of location

was commented on by participants as helpful and convenient and enabled them to take part in the study more easily.

Information sheets and consent forms were provided to any attendees who accompanied women during the interview. No questions were directed to attendees, however it was felt that to best support women they should be given the option for their partner/ relative or close friend to be present. Three of the twenty interviews included the woman's male partner - these were all in the clinical setting - in two interviews conducted at home, male partners were in an adjoining room with an open door.

Finally to support the women further, it was arranged with them that I would contact them by their preferred method (telephone/email) approximately seven to ten days following the interview. Smith (1992) states that leaving a participant in distress following an interview is 'morally wrong' and to ensure that this was not the case I purposively enquired as to whether they had been left feeling upset or distressed by any topics covered. Women were advised if at any point following the interview (immediately after/the weeks or months following) they felt distressed that they could contact me directly. With this information I could inform their clinical care team, who could then send a review appointment to the woman taking part or make a referral to the appropriate NHS service.

It was not uncommon during the interviews for women to become upset and there were often tears when discussing topics, especially the topic of inheritance risk and feelings of guilt. At these moments I asked women if they wished to suspend or terminate the interview. Only one interview was suspended with the tape recorder turned off to allow for composure before recommencing (at the request of the participant). The majority of the women wanted to continue to discuss the topic and afterwards told of how they felt better having had a chance to think and reflect on their feelings. This is seen also in the work of Elmir et al (2011) who described their participants experiences as cathartic and providing a sense of relief. Initially I felt uncomfortable in these circumstances but over the course of the study I felt better able to deal with these incidents, with support of the study support team (see section 4.3.1.e).

#### **4.3.1.b Clinical Questions from Women and Attendees**

As a non-clinical researcher it was a personal concern of mine during the design of the study that I might be misinterpreted as a clinician or someone with medical training. This raised the potential of participants asking clinical questions or clarifications and also women may not have felt able to give critiques of Data Collection Centre 1 to which I was associated by means of my employment. The potential impact of being known or being perceived as a medically trained individual performing qualitative interviews has been explored, with Hoddinott and Roisin (1997) comparing disclosure of professional training versus withholding in research interviews. Richards and Emslie (2000) reported the differences between the experiences of a GP's fieldwork compared to a sociologist researching the same patient population. Participants perceived the GP as having a high status and her profession over shadowed perception of her personal characteristics, whereas the sociologist was often asked if she was a student (which she was not) and identified as 'the girl from the university' (p74). Differences in interview content was also observed, with those interviewed by the sociologist discussing broader and not always health related issues, whereas topics in the interview with the GP remained predominately health based (Richards and Emslie 2000).

To try to prevent this I introduced myself to women as a member of the research group and that the project was to inform my PhD thesis. If at any stage a clinical question was asked, or they sought clarification of previously given clinical information I informed women that I was unable to answer or clarify but would feed any queries they had back to the clinical care team with their permission. This was acceptable to the women and did not raise an issue for them. I addressed the potential of women feeling that they could not provide a critique of the service provided by Data Collection Centre 1 by purposely asking for ways in which their experience could have been improved.

#### **4.3.1.c Discussions on Topics that Raised Safety Concerns from Women and Others**

As part of the informed consent process women and attendees (if applicable) were informed that their personal information and discussions would only be shared (without their consent) with their clinical team or other appropriate services if they raised safety concerns of the researcher. Two interviews raised concerns that were

discussed with supervisors and wider team, following transcription (Sarah) and immediately following the interview (Wendy).

Whilst transcribing Sarah's digitally recorded interview it became evident that she may have misunderstood a clinical diagnostic test. This was discussed with a supervisor and it was agreed that this should be feedback to her mitochondrial clinician. Sarah was then contacted to further explore her understanding of this particular test and the issue was confirmed resolved.

The second incident occurred in the hours following Wendy's interview. Wendy was evidently distressed at the outset of the interview (the interview was paused and only continued in accordance with her wishes) this distress was centred on her struggle to come to terms with her diagnosis and how she had received this. With her consent this incident and her request for specific counselling was communicated with the whole supervisory team, and then directed to her mitochondrial clinician.

#### **4.3.1.d Data Protection and Confidentiality**

The confidentiality of women, attendees and any other persons discussed during the course of interviews (clinicians/ family members) was of utmost importance throughout the lifetime of the study. As mitochondrial disease is a rare disorder care has been taken when discussing potentially traceable identifiers, use of quotations and tabulated participant information (Table 4.3). Where important to maintain confidentiality, aspects of the data have been amended to prevent potential identification, such as specific relationships to family members.

The mitochondrial research nurse contacted potential participants and obtained their consent that I may contact them, this was sought in advance of me being informed of their details. Women and their interview attendees were reassured that data collected would be anonymised when reported. As described to participants, all those who took part in the interviews were assigned a pseudonym, a conscious decision, as I did not feel that study numerical identifiers alone were appropriate. Any family member, friend or colleagues discussed in the interview were also provided with a pseudonym.

Care has been taken when participants have identified clinical professionals, not only from within the mitochondrial clinical community but across a multitude of medical

specialities. All medical doctors have been referred to as male to prevent the identification of female doctors who are easily identifiable in the UK mitochondrial and reproductive medicine community (see also section 4.4.6). Male gender was chosen as both a practical consideration, to avoid the amendment of large sections of data and out of concern that identifying all clinicians as female may lead to subconscious association to female clinicians by future readers. I decided to retain the gender of the nursing staff but there has been no distinction between nursing roles (clinical or research) when discussed by women to prevent identification of individuals. I have also removed NHS Trust Logos, names and contact details provided in appendices (Appendix A2)

Newcastle University requires that primary research data from this study be held for 10 years after study end. Newcastle Upon Tyne Hospitals NHS Foundation Trust acted as Sponsor for this study. In accordance with their policies, regulatory data from this study will be held for 5 years after the study end. Storage of research data and regulatory data will continue to be in line with the Department of Health's Research Governance Framework, Newcastle University's Policies and Procedures, the Data Protection Act 1998 and International Conference for Harmonisation Good Clinical Practice (ICH GCP) principles.

All paper-based data is stored in a locked cabinet in a locked office, behind access controlled entry doors in the Medical School at Newcastle University. All electronic data (including digital audio recordings) are stored on file servers, which are password protected and backed up regularly. Digital audio recordings will be deleted from file servers 6 months after final data analysis.

#### **4.3.1.e Managing and Supporting the Emotional Needs of the Researcher**

Lee and Renzetti (1990) tell us that research may also be harmful to the researcher. During the design of this study I prepared for interview conduct by attending training events about qualitative research. Identified early on in this process was the provision of emotional support for myself through the study. There is a great body of research which also documents the need to protect the researcher conducting interviews which are sensitive in nature (Dickson-Swift *et al.*, 2006 ; Dickson-Swift *et al.*, 2008). To try to minimise this, a support team comprising of study supervisors and nursing staff was formed, to allow for confidential discussions about topics

discussed in interviews. This was provided consistently through the study and on an ad-hoc basis when required. This was especially important for a particular interview that resembled personal experiences of my own family members. Thompson (1995) writes that a shared traumatic experience between the researcher and participant can benefit the research process, I felt that this particular interview analysis and subsequent data analysis was enriched by this experience. I managed the emotions that were raised at this time by discussing them with the support team, which was most important to me during the analysis and re-analysis of interview transcripts and associated memos. I am also grateful to fellow PhD researchers within the Institute of Health and Society who provided support with coping mechanisms for handling emotive topics during data analysis.

#### ***4.3.2 Institutional Approvals***

The study was sponsored by Newcastle Upon Tyne Hospitals NHS Foundation Trust (NuTH). Sponsorship included indemnity for the conduct and management of the study. Insurance for the design of the study was provided by Newcastle University.

In advance of the study start date I was required to update my research passport with Data Collection Centre 1 that permitted me to access clinical information for my position as clinical research manager. This allowed me the opportunity to include conducting patient interviews in my approved activities; this amended approval was provided in June 2014.

Research and Development (R and D) approval was obtained in July 2014, which enabled research interviews to physically take place at Data Collection Centre 1 if preferred by the woman. Additional clinical research department approval was granted May 2014.

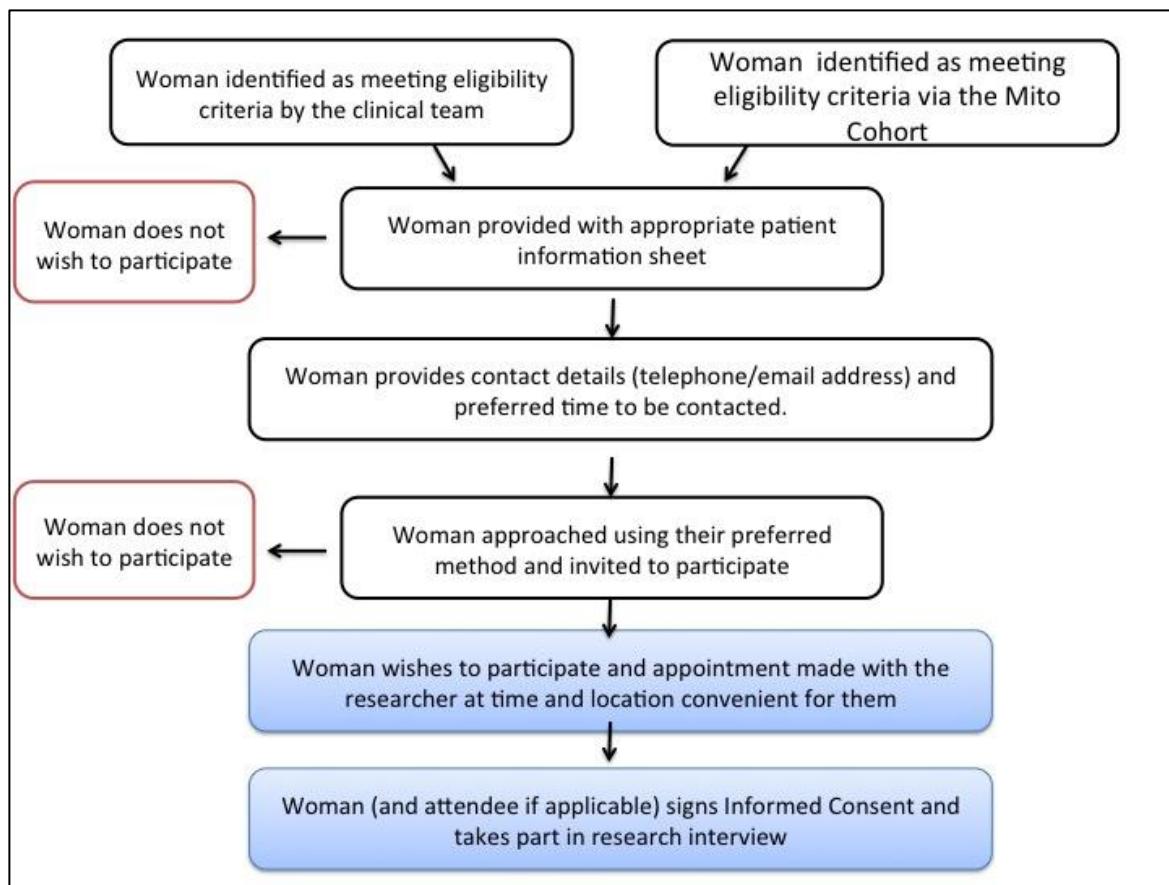
National Institute for Health Research (NIHR) adoption for the study was granted in August 2014. This status permitted access to service support costs to aid with study recruitment.

Described below in section 4.3.4 patient recruitment was facilitated by approval from the MRC Mitochondrial Patient Cohort - A Natural History Study and Patient Registry (13/NE/0326) Oversight Committee (MDOC). As the research manager of the Mitochondrial Cohort (MitoCohort), who processed all approvals I removed myself

from this role and was deputised by the Chief Investigator and mitochondrial research nurse. I was temporarily removed from the MDOC universal email address that provided national review of my application to contact potential patients (via research nurse as gatekeeper) and subsequently I refrained from accessing any of these documents when reinstated. MDOC approval was granted in May 2014. Although approved, postal invitation via the MitoCohort was not tested, as all participants who took part were approached in outpatients or via their family members.

#### ***4.3.3 Informed Consent***

Informed consent to participate in research has throughout my research career been extremely important to me and I felt this was even more so in this research setting. As described above, care was taken to inform the women of the potential for distress given the interview topic and the support mechanisms in place to minimise any distress to participants. I had attended previous NIHR Informed Consent training for my Masters research project and have continually renewed by ICH GCP certificates in research since 2008 to ensure up to date training in research conduct. Potential participants in the study were given a minimum of 24-hour period to consider taking part, but in most cases exceeded 7 days (Figure 4.1).



**Figure 4.1** Recruitment and Informed Consent Flowchart

#### 4.3.4 Research Population

In line with the research objectives I wanted to interview women who had previous experience of reproductive decision-making (retrospective group) and women who were currently or prospectively considering their reproductive options (current and prospective group). It was evident from the outset that these groups could also include sub-groups of women (Table 4.1). Gathering the experiences and opinions of these women would allow for a more detailed understanding of how reproductive decision-making has been and is being viewed by this patient population. An attempt was made to include women from each sub group within the study sample.

<b>Retrospective Group</b>	<b>Current and Prospective Group</b>
Affected women (diagnosis unknown) who went on to have an affected child/children	Women who are making imminent reproductive decisions (<2 years)
Affected women (diagnosis known) who went on to have a child/children who were affected/unaffected	Women who may be looking to make a reproductive decision in the near future (<5 years)
Affected women (diagnosis known) who did not go on to have a child/children	

**Table 4.1** Study Groups and potential patient sub-groups.

### ***Inclusion Criteria***

1. Females with a known mtDNA mutation between 16 and 65 years of age
2. Capable of giving informed consent
3. Able to read and converse in English (to ensure informed consent as funding for an interpreter was not available)

### ***Additional Inclusion Criteria (Retrospective Group)***

1. Females with a known mtDNA mutation who have made a reproductive decision in the last 21<sup>2</sup> years

### ***Additional Inclusion Criteria (Current and Prospective Group)***

1. Females with a known mtDNA mutation who were currently or who may be looking to make a reproductive decision in the near future (<5 years)

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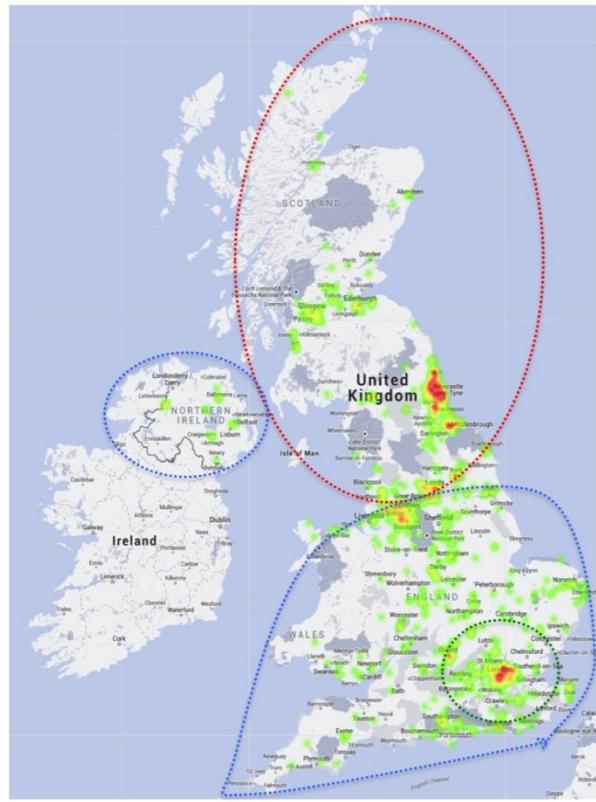
<sup>2</sup> \*Amendment 1 permitted the increase in age of 5 years (see section 4.4.2)

During the design of the study, the purposeful inclusion of partners (male or female) was discussed, although the investigation of this additional group was thought to be too difficult to accommodate within the scope of this PhD thesis. Their inclusion, if wished by the participant was included into the design, with specific consent to use any contributory data (Appendix A2). Their inclusion at the request of the woman, so that they could offer additional support to them, was especially important given the topic of the interview.

Analysis has not focused specifically on the attendee's data unless in direct relation to the topic being discussed by the woman (all 3 attendees were male partners of women interviewed). The study did not exclude homosexual couples, during sampling the inclusion of homosexual partners were discussed with the clinical team but there were no women known to be in a same sex relationship.

Inclusion to the study was also controlled for by geographical location. During the course of design and study set up, the MitoCohort had two other applications (Studies A and B) to interview women with a mitochondrial diagnosis regarding their reproductive options. In order to accommodate three similar studies and in the best interests of patients, the decision to split the country into three separate geographical areas (taking into account patient populations) was made by the MitoCohort Chief Investigator.

This study was assigned the North East, Yorkshire, North West of England and Scotland. The geographical split is illustrated in Figure 4.2; each allocated area was equal in the proportion of eligible patients. Study A recruited women with a single mtDNA mutation (m.3243 A>G) and Study B recruited women with either nDNA or mtDNA mutations.



**Figure 4.2.** Geographical sampling locations superimposed onto population map of reported mitochondrial disease patients. Red Area: local project, Blue Areas: Study A and Green Area: Study B

A study initiation meeting was conducted in which all those involved in eligibility review were invited and training on the protocol given when all approvals were received (July 2014). Eligibility screening was conducted by the clinical team, which included consultants in neurology and reproductive medicine, speciality training registrars, mitochondrial specialist nurses and research nurses. It was especially important that those who conducted eligibility were familiar with the women to take into account potential scenarios where approach to take part may cause distress, such as recent bereavement or personal or family members declining health.

This eligibility review included consideration of physical and emotional status before I was informed of their potential inclusion. This enabled the clinical and research teams to select women who were assessed to be emotionally stable to take part. Two potentially eligible patients were not contacted to take part in an interview when assessed due to their then current emotional distress surrounding dealing with

their progressing condition or still processing their diagnosis. A key benefit of the use of gatekeepers in this study was their expertise in the very specific and rare patient population (Arcury & Quandt, 1999). A criticism of this method of gatekeeping was that at times there were internal differences about the appropriateness of certain women to be approached to participate. This may have meant that some potentially interesting individuals were not included in this study. The roles of these gatekeepers were key to the study and to those who took part.

#### **4.3.5 Sampling**

Purposive sampling was used in this study, in order to understand the wide range of experiences of reproductive decision-making in maternally inherited mitochondrial disease. Patton (1990) tells us that 'qualitative inquiry typically focuses in depth on relatively small samples selected purposively' (p169), where logic and power is based on selecting information rich cases that allow for in-depth study. Charmaz (2006) supports this by writing that a study 'based upon rich, substantial and relevant data stands out' (p18). This approach allowed for me to adapt questions asked throughout the study and focus on emerging themes.

To include as many experiences as possible, those women who fell into the sub groups above (Table 4.1) were sought out. The purpose of which was to allow for in-depth illumination and explanation (Patton 1990).

Sampling occurred over three distinct time periods (Table 4.2) and included in Round One 'typical' case patients identified in outpatients at Data Collection Centre 1 (n=6). Round Two included mixed purposive sampling methods, 'extreme/deviant case' 'identification', 'convenience', 'chain identification' and 'stratified purposeful' (Patton1990) (n=9). Round Three was a final analysis checking round that included approaching former current and prospective women interviewed in Round One and Two for a follow-up interview (n=2). This was specifically to investigate the notion of change over time presented in the conceptual model of reproductive decision-making and was part of Amendment 2 to the study. A targeted sampling approach was used to recruit new participants into the current and prospective group (n=3), this was deliberate to address the imbalance between the two study groups previously observed and to interview women who in theory may have access to the then newly licenced mitochondrial donation technique. Women who were known to

have expressed a recent interest in discussing their reproductive options with their mitochondrial clinician were approached to participate in Round Three.

What is important to note is that Round One occurred before final parliamentary debates occurred in February 2015, in which both Houses of Parliament approved mitochondrial donation techniques for women at risk of transmitting a mtDNA mutation to their child. Therefore these first six interviews took place before anyone could be sure that these techniques could be developed further.

Round Two occurred in the months preceding the favourable vote and amendment in The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015. It was felt by many in the clinical and research communities that mitochondrial donation would be available within 12 months of this legislation, however the license required by the regulators (HFEA) for the introduction of this techniques was not granted until March 2017.

Round Three took place from May-June 2017, following the award of the license and after the introduction of a specific reproductive choices clinic at Data Collection Centre 1.

The timing of each round is important when assessing the context of the interviews, specifically relating to the political and regulatory landscapes governing access to the mitochondrial donation, as well as the intense focus on reproductive decision-making for these women from many different perspectives, including bio-ethical, religious and legal communities discussed previously in Chapter 3. Conducting study interviews over the last three years considering the above and in conjunction with grounded theory supports the research conclusions and recommendations.

Round	One	Two	Three
<b>Political/ Regulatory Landscape</b>	Prior HFEA MD Donation Amendment	Post HFEA MD Donation Amendment	Post MD Licence Award. Initiation of Reproductive Choices Clinic
<b>Type</b>	Typical case sampling	Mixed purposeful sampling	Opportunistic sampling (follow-up) and theory based sampling (new interviewees)
<b>Total Number of Women and Attendees</b>	6 (1 Attendee)	9 (2 Attendee's)	5
<b>Retrospective Group</b>	3	6	0
<b>Current or Prospective Group</b>	2	3	3
<b>Pregnant Group *</b>	*1	0	0
<b>Follow Up (Current or Prospective Group)</b>	N/A	N/A	2

**Table 4.2** Sampling methods and recruitment table. \* (included in retrospective group during analysis- see section 4.6)

Data from transcripts and field notes from Round One were analysed between October 2014 and March 2015 in which emergent categories and themes were identified and the interview schedule amended (Appendix B2). These categories centred on discovery of their diagnosis, when/how and who women spoke to regarding their diagnosis and inheritance risk (termed disclosure), relationships with clinical care teams and their own reproductive pathway. During this period of analysis, I was able to look critically at the data and to identify those women who had not yet been included in the sample. This included women who had continued to add to their family many years after diagnosis and what drove them, multiple family member perspectives and those who were extremely proactive in seeking future access to mitochondrial donation as their preferred option. Actively seeking out these groups lead to the mixed sampling approach of Round Two, which included participants identifying female members who met some of the above criteria (chain identification).

In addition, data from Round One was restricted with regards to what women thought about all available reproductive options. Instead only those options that they had personally considered were discussed. This lack of information meant that those options, which appeared, be the 'least popular' such as ovum donation, surrogacy or adoption were not included. This lead to the introduction of a specific Interview Aid (Appendix B2) into Round Two.

This interview aid listed available options and a short explanation of each option. The information provided was reviewed and approved by supervisors for accuracy and appropriateness. This aid was amended following the first interview, when Wendy identified that the option to 'just not have children' was not listed. This was added to version 2, which was used throughout the remaining interviews.

#### **4.3.5.a Sample Size**

In total, twenty interviews were conducted in this study, sixteen people were interviewed once (n=16 interviews), and two were interviewed twice (n=4 interviews). I collected data until I was satisfied that it was rich and sufficient (Charmaz, 2006), evaluated by assessing my data against Charmaz (2006), recommendations of

- a. Has enough data been gathered to understand the context of the study?
- b. Have detailed descriptions of a range of participant's views been obtained?
- c. Does the data expose what is happening under the surface?
- d. Does the data reveal change over time?
- e. Have multiple accounts of data (in this case decision making) been obtained?
- f. Has the data allowed for the development of analytical categories?
- g. Has the data provided the ability to make comparisons and how do these comparisons generate and inform ideas?

The third and final round of interviews (n=5) allowed for me to address the key codes and categories discovered further and to test the proposed conceptual model of reproductive decision-making in maternally inherited mitochondrial disease making (see section 4.7).

#### **4.3.5.b Recruitment Challenges**

An initial limitation of the sample included in this study was that the clinical team at Data Collection Centre 1, whom were acting as gatekeepers were familiar with more women who would be categorised in the retrospective group. Familiarity was built over a number of years caring for these women and may have already included their assistance in the reproductive histories of these women. The number of women actively seeking advice regarding their current and prospective reproductive options were fewer and this lead to the initial imbalance between the two study groups. This disparity was addressed by specifically approaching women in the third sampling round who would be considered in the current or prospective arm.

#### **4.4 Participants**

As specified above I refer to those who took part in this study as 'women' or 'participants'. I have assigned all those interviewed and the individuals discussed in their accounts with pseudonyms, I use these names throughout this thesis. I have chosen to do this to highlight the personal nature of this work.

In total I conducted 20 interviews, 18 of which were primary interviews and two follow-up interviews. Travel and accommodation costs incurred from participating in

the study were reimbursed. In total there were 10 women who were categorised as in the retrospective decision-making group and eight women categorised as in the current and prospective for data analysis. One woman was pregnant at the time of the interview, and was included in the retrospective group as she was actively trying to conceive at the time of her diagnosis. The number of pregnancies and the number of children were not specifically asked alongside the demographic information but were included in the Interview Schedule. This information has been excluded in Table 4.3 to maintain the anonymity of the women.

Demographic information was collected from participants directly at the outset of the interviews, outlined below. I did not ask participants directly, but only two of the participants were non-white British. All participants spoke English as a first language or were fluent in English as a second language. As previously outlined all participants accessed via the MitoCohort lived in the North of England and Scotland, with the exception of one participant accessed outside the scope of the MitoCohort who lived in South East England. Women represented a range of occupational class groups as defined by the ONS, 2010 (with the exception of group 8) and working in public, private and charitable sectors<sup>3</sup>. Educational attainment ranged from school leavers to those with postgraduate qualifications.

Giving the rarity of maternally inherited mitochondrial disease and the geographically restricted sample I have chosen to provide limited information on the participants in this thesis when not relevant to the issues explored. I have been cautious with the potential identification of participants to professionals who by the nature of the specialised care provided to women may recognise patients based on diagnostic pathways, family and reproductive histories.

The following demographic information was included in the interview schedule, considered initially to be potential influential factors.

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<sup>3</sup> Office of National Statistics Standard Occupational Classification (ONS, 2010) has been used as an objective tool to describe relevant participant demographics, based on information that was made available during the interviews.

1. Disease Mutation
2. Age
3. Religion
4. Relationship Status
5. Educational Attainment
6. Employment status and sector

#### ***4.4.1 Disease Mutation***

All women identified as eligible to participate had a known mtDNA mutation, but women were asked at the start of their interview whether they knew what type of mitochondrial disease they had and if they knew their particular mutation (see Chapter 5). As was expected, the most common mutation m.3243 A>G was most prominent in the study sample (n=11), with others including m.8344 A>G (n=2), single large-scale deletions (n=2), m.11778 G>A (n=1), m.3460G>A (n=1), and one other rare mtDNA mutation not yet defined at the time of the interview. The numbers of each mutation have purposively been included here but otherwise omitted from Table 4.3 and throughout this thesis to prevent potential identification.

#### ***4.4.2 Age***

The age of the women in both study groups ranged from 24 to 63 years of age, the age range in the current and prospective group was 24-39 years and the retrospective group, 34-63 years. Original ethical approval included women from 16-60 years of age, Amendment 01 included an increase in the age of eligible participants to permit the inclusion of potential grandmothers whose daughters faced current decision-making, increasing the maximum age to 65. Age ranges of 4 years have been included in Table 4.3 to minimise the risk of potential identification.

#### ***4.4.3 Relationship Status***

Relationship status was gathered to understand the position of each participant at the time of the interview. Within the sample, 12 women were married, two were engaged, two were cohabiting with a partner and two women who were single. All of those in the retrospective group were married, with the current and prospective group including married, cohabiting, engaged or single.

#### ***4.4.4 Religion***

Women were asked at the start of each interview if they followed a particular faith. For the majority of women their faith and beliefs were not discussed any further in the context of impacting reproductive decision-making. However the faith of three women was discussed in greater detail, these women self described themselves as Muslim, Methodist/Church of England and Church of Scotland. Other women described themselves as being christened or brought up within the Church of England but did not consider themselves as having a faith-based belief. One woman believed in 'something bigger' but did not describe this as any religion. This information has not been included in Table 4.3 but religious beliefs are discussed further in Chapter 8 section 8.7.3.

#### ***4.4.5 Educational Attainment, Employment Status and Sector***

Initial literature reviews of inheritance risk assessments had shown that those women with a lower educational attainment had difficulties in understanding risk probabilities and recurrences (Grimes & Snively, 1999). For this reason, I enquired into the level of education within my sample of women. A large proportion of women went on to further study or employment schemes that led to skilled or professional positions. I also enquired into as to their employment status and sector. This provided helpful context to the interview both during the process of conducting the interview and data analysis, especially with women whose background was in healthcare or healthcare provision.

<b>Pseudonym</b>	<b>Study Group</b>	<b>Age Range</b>	<b>Relationship Status</b>
Sally	Retrospective	34-38	Married
Sarah	Retrospective	34-38	Married
Joanna and Gary	Current/Prospective	34-38	Engaged
Emma	Current/Prospective	24-28	Cohabiting
Jenny	Retrospective	49-53	Married
Lisa	Retrospective	34-38	Married
Wendy and Mark	Current/Prospective	34-38	Married
Lesley	Retrospective	54-58	Married
Andi	Retrospective	44-48	Married
Alice	Retrospective	49-53	Married

Mandy	Current/Prospective	24-28	Single
Maggie	Retrospective	49-53	Married
Holly and Edward	Current/Prospective	29-33	Cohabiting
Pauline	Retrospective	44-48	Married
Miriam	Retrospective	59-63	Married
Lucy	Current/Prospective	24-28	Single
Zoe	Current/Prospective	38-42	Married
Ashley	Current/Prospective	38-42	Married

**Table 4.3** Demographic information on participants. mtDNA mutation, educational attainment, employment, religion, number of pregnancies & children omitted

#### **4.4.6 Health Professionals**

As outlined above in Data Protections and Confidentiality (section 4.3.1) the protection of the health professionals discussed in the course of the interviews was also important. Women discussed professionals encountered in often complex and lengthy diagnostic pathways across multiple primary, secondary and tertiary settings. This resulted in the removal of potential identifiers about a large number of professionals and their location/healthcare settings. Anonymisation of staff members occurred in interview transcripts, field notes, memos and in this thesis.

I have approached anonymisation in the following ways

1. For individuals encountered at primary care settings I have referred to them as 'GP' only. The rationale for this is, women did not routinely give the individual's name and referred to them only by their role.
2. For individuals encountered at secondary care settings I have distinguished them as Consultant or Registrar in their specific medical speciality at District (DH) or Regional Hospitals (RH). Given the large number of district and regional hospitals attended across the sample, providing the seniority and gender of these individuals was not considered as a potential identifier.
3. Physicians encountered at Data Collection Centre 1 were link anonymised to a numerical code in transcriptions and memoing. I do not make reference to this code in the thesis; I instead use Dr X. For professors, consultants and registrars I have identified them all with the prefix of Dr, in order not to distinguish between seniority that could lead to identification. I have purposively not distinguished between adult and paediatric training to protect the paediatric-trained members of staff amongst a larger number of adult trained colleagues. I have assigned all doctors as male gender to prevent the identification of female physicians who are in the minority. I chose to use male gender, both from practical perspective to avoid amending large sections of data and out of concern that future readers might subconsciously link quotes citing female doctors to a limited number of women practicing in the mitochondrial community. The majority of the time women interviewed referred to doctors with their professional prefix, in rare circumstances using their first names only. When specific identification was not relevant to the section in discussion within this thesis I have referred to staff as 'mitochondrial

specialist(s)', 'reproductive medicine specialist(s)' or 'mitochondrial and reproductive medicine specialist(s)'.

4. For nursing staff, past or present encountered at Data Collection Centre 1, I have not distinguished between their individual roles (specialist or research) to prevent identification of a limited number of nursing staff that provide care to mitochondrial patients at the centre. Nurses were also link-anonymised and assigned a numerical code, this included past and present nursing staff. The gender of nurses is referenced as female in transcripts, memos and in this thesis. Other professionals were prefixed by their role, such as allied health professionals that could include specialised genetic counsellors or speech and language therapists.

#### **4.5 Conducting Study Interviews**

Conducting study interviews with participants gave me the opportunity to enter into, at times, a very private and intimate space and share with them not only their experiences surrounding reproductive decision-making but also other personal stories about a range of topics. Over time I shared my related stories with some women, ranging from trivial to the more personal and relationships were formed, if only briefly. Corbin and Morse (2003) write that despite the number of times a participant may have told their story, the first time an interviewee and interviewer talk together 'it marks the beginning of a new relationship' and the course of the interview cannot always be predicted (p341).

A primary interview schedule for both study groups was constructed during regulatory submissions (Appendix B1) based on study objectives and initial literature review. As anticipated this document changed throughout the lifetime of the study in response to the emergent codes and categories and their importance to the women. Interviews were semi-structured and in some circumstance not all topics were discussed in order or at all. The issues important to the women participants guided the interviews following introductory questions. I reverted back to the schedule when the natural course of those topics came to a close. This approach was important to ensure that as a researcher I listen to stories and issues intrinsic to the participant, without restricting them to a predetermined set of ideas informed by other work or researcher's ideas.

As discussed above, interviews took place in a mixture of locations chosen by the women, the most popular choice was their home followed by their work place (meeting room) and then at their convenience before or after their clinical review or procedure.

Introductory question centred around risk and how, when and who made them aware of the risk of inheritance to their child/future child, 'Do you remember where you were when you were told about the potential risk of passing on your condition to a child?' The response to this question, provided by nearly all women was the story of their or their family members diagnosis, highlighting the often lengthy and complex patient journeys these women or their family members had already experienced (see Chapter 5). We will come to see how the lived experience of these women is crucial to their reproductive decision-making (see Chapter 8).

As discussed above in section 4.3.5, an interview aid listing reproductive options applicable to women with maternally inherited mitochondrial disease was introduced in Round Two. This aid was found to be invaluable and allowed for new discussions on reproductive options previously omitted by women in Round One. Options that did not naturally emerge in the first round included most notably adoption, ovum donation and surrogacy. With the introduction of the aid, and explanation of each given, women were able to consider how they felt about all the options and ordered them with regards to which they would consider the most appropriate or would completely discard.

Follow-Up interviews were conducted in Round Three during the final data analysis stage of the study, with an emphasis to test the proposed conceptual model of reproductive decision-making. Of the five women eligible for a follow-up interview (those in the current and prospective group), four women were approached to take part in a follow- up interview. One woman was not approached out of concern for her emotional wellbeing after her original interview. Two of the four women contacted for a follow-up interview did not respond. Of those two women who took part, both interviews were conducted by telephone interview. Follow-up interviews centered on the reproductive journeys of the women since their initial interview, the time between their initial interview and their follow-up interview was 23 months and 32 months.

Interviews and field notes were digitally recorded, this enabled easy transfer to secure password protect server following the interview. The recorder was used to

provide accurate transcription and analysis of data and allowed for me to be responsive to the women during the interview as opposed to note taking. Digital recordings of initial interviews lasted between 17 minutes and 120 minutes. Follow-up interviews lasted 10 and 34 minutes. Before the recordings were started, I confirmed informed consent. Written Informed Consent was obtained for interviews conducted face to face, for follow-up telephone interviews consent was confirmed on the audio recording and recorded in their medical notes. After the interview had ended and the digital recorder stopped, I engaged in informal conversation with the women, offering them another chance to ask any questions. In some circumstances additional relevant information was given after the digital recorder was stopped, this information was recorded in field notes. As soon as possible and in a confidential setting I recorded field notes directly onto the recorder. These included details of non-recorded conversations, areas of interest and my observations during the whole interview process (Rapley, 2004). These field notes were used alongside interview transcripts to form the complete data set analysed as part of this thesis.

#### ***4.5.1 Clinical Observations***

Throughout the process of gaining project approvals to initiate recruitment I attended mitochondrial and fertility clinics at Data Collection Centre 1. These observations have not been included in data collection as ethnography was not a planned method of data collection, instead these opportunities provided me with an understanding of the experiences of mitochondrial patients, general fertility patients and more specifically mitochondrial patients and their reproductive journeys.

Whilst observing assessments in the mitochondrial outpatient clinic, I witnessed patients from all over the UK who had travelled for their clinical review. Patients who attended the clinic (all of whom were female) showed varying differences in disease burden from one another, highlighting the phenotypic variations, which presents amongst different mtDNA and nDNA mutations.

Whilst observing standard fertility clinics, I was able to observe couples that were experiencing a number of barriers to achieving 'natural' conception, including medical conditions affecting the female and/or male and homosexual couples. Observations included initial assessment visits, visits where couples received their individual test results and clinics specifically to consent couples to their chosen treatment procedure.

I also observed a PGD clinical consultation with a couple considering PGD as a potential option to reduce the risk of transmission of the intending mothers mtDNA mutation. Topics discussed included the disease burden of the patient, their immediate and extended family, present and past medical history of both prospective parents, the technique and its required medical and emotional commitments.

#### ***4.5.2 Reflecting on Personal Position as a Researcher***

Briefly addressed in section 4.3.1, I considered my position as researcher from the outset of this study and the ways in which my personal and research background might shape the collection and analysis of the data.

Krauss (2005) states that qualitative researchers are 'encouraged to record their own biases, feelings and thoughts and to state them explicitly in the research report' (Krauss 2005:p764). Ambert et al (1995) write that a researcher should reflect upon class, ethnicity and gender when considering what influence the researcher, the interviewee and setting has on the data.

I have throughout this process examined my own relationship to the study. When this study was first discussed in April 2013 I had been employed as the clinical research coordinator (and later manager of clinical research) in the mitochondrial group at Data Collection Centre 1 for two years. This role at that time had also included supporting other rare neuromuscular conditions, with the design, approval and implementation of studies ranging from patient registries to clinical trials of new drug therapies. Prior to this I had spent three years managing Phase 1 (first in human) through to Phase 3 oncology drug studies in a tertiary hospital setting similar to Data Collection Centre 1. My academic background had included a degree in Pharmacology and a Masters in Clinical Research. The Masters included taught modules as well as a self-directed clinical research project. In this project I consented chemotherapy naive patients to take part in a biomarker study in which I studied the appropriateness of a novel enzyme assay to help determine the role of personalised medicine in cancer treatment. Prior to this study my research experience had been based on a positivist epistemology. It was this master project in particular that was the driving force behind my interest in qualitative research methods, discovering during the consent process of that study, the intricacies of patient journeys and their resultant behaviours.

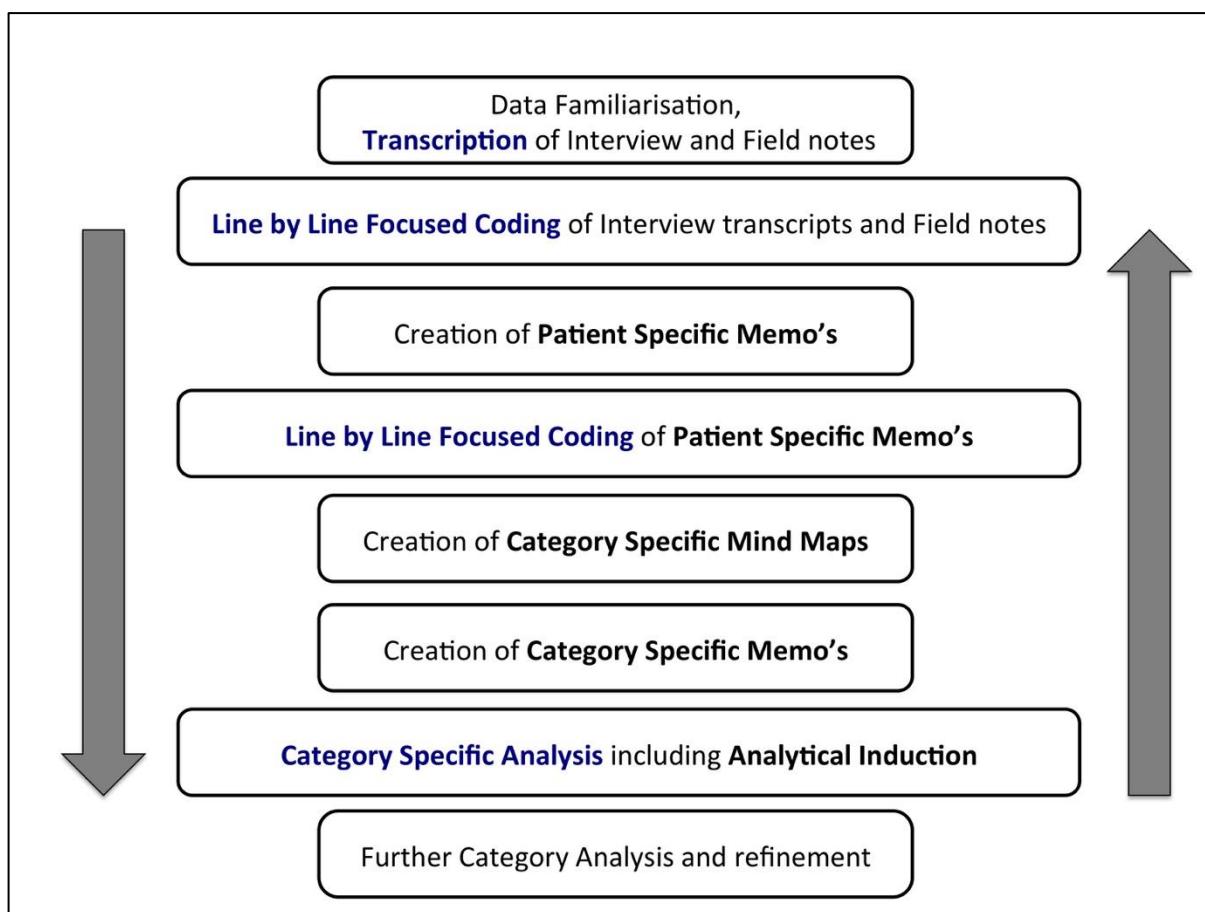
Before this study was initiated, I gave a lot of thought as to how I would be perceived by future participants, for some time I focused on how ‘not being a mother’ or how being myself a child of ‘assisted reproductive technologies’ might impact on how I presented myself or was perceived by the women in my study. I now realise that this did not require concern. I now know that perceptions and interactions with each individual could not be controlled, and as stated above these interactions were enriched by the social worlds that interviewees and I myself constructed before, during and after the interview process. I felt I established different relationships with every participant, some of which were of the same age, relationship status, even similarities in studying part time as I was, whereas others were at a different stage in their life course. Research has shown that taking part in research interviews can prove beneficial to patients in a number of ways, it can be (a) cathartic, (b) provide self-acknowledgment and validation, (c) contributes to a sense of purpose, (d) increase sense of awareness, (e) grant a sense of empowerment, (f) promote healing and (g) give a voice to the voiceless and disenfranchised (Hutchinson et al., 1994: p161).

At times, participants told me stories that they had not spoken about with any other person in their family, often asking if I agreed with their chosen actions. This was complicated further by the inclusion of multiple members of the same family, whereby women asked me what their family member had thought or said about a particular issue. I overcame this by reminding patients that I did not judge or have an opinion on their actions and that I was bound by confidentiality to not disclose other interviewees’ responses. All participants accepted this.

#### **4.6 Data Analysis**

Analysis of data was based on Charmaz (2006) constructivist grounded theory, which provides a framework to manage data, which included concurrent data collection and analysis, the assignment of ‘codes’ to the small fragments of data. The accumulation of these codes would in turn become the emergent categories that could then be compared to future data sets. Categories would then become ‘memos’, which would derive the phenomena directly from the data as opposed to a predefined hypothesis and where researchers were prompted to conduct their literature review after analysis.

Data were collected between August 2014 and July 2017, which included semi-structured interviews with women and researcher field notes. Data collection and analysis occurred concurrently, so that issues that arose in earlier rounds of interviews could be explored in subsequent ones. Analysis of data was a continual process, often returning to transcripts months and years later to re-investigate codes, categories and memos further. To illustrate the steps taken throughout the study I have summarised the process in Figure 4.3. As proficiency of data analysis increased some aspects such as line by line coding and mind mapping were required less but detailed patient specific memos and conceptual memos existed throughout the study.



**Figure 4.3** Data analysis flow chart

#### **4.6.1 Familiarisation with Data**

Ten of the eighteen interviews were transcribed verbatim by myself (ID001- ID009 and ID011). These included detailed non-speech tokens (Rapley, 2004) whilst the others (ID010 and ID's 012 - 015) were transcribed by a professional transcription service. Follow up interviews and interviews conducted in the confidence round

(Round Three) were partially transcribed by myself, transcribing data that was supportive or in conflict with existing ideas.

For the interviews I transcribed, this included listening to the interviews multiple times, often replaying sections to determine accurate transcription. For the interviews that I did not transcribe, I familiarised myself with the data by listening to each interview multiple times and reviewed transcripts twice for accuracy. I repeated this for field notes recorded and transcribed by myself following each interview. All transcripts and fields notes were edited during transcription to ensure anonymity of the participant and those family members and clinicians who may have featured in the interview as described above. Although these methods were time consuming this allowed for me to become immersed in my data and has led to a very detailed recollection of all the interviews conducted in the study (Rapley, 2004).

#### ***4.6.2 Line by Line Focused Coding***

All analysis was conducted according to the standard procedures of rigorous qualitative analysis (Rapley, 2010). Once transcribed, I reviewed the data using first and second line coding (Charmaz, 2006). This meant that I conducted focused line-by-line coding throughout the interview (see examples, Figure 4.4 and 4.5). This approach was especially useful to me as a novice qualitative researcher and allowed for me to capture extremely large numbers of codes grounded in the data that could be further define or discarded as categories emerged and developed.

Coding was carried out manually, with sporadic use of qualitative collation and management software (NVivo Software). I, however preferred manual coding and reverted to this method in the majority of the analyses.

131 IVR: Yeah

132 IVE: it should in Emily, so it's a little bit complicated really, it's not just a straight forward thing, erm

133 but I have have tried to make more awareness about mitochondrial disease in general by doing

134 tombola's and things like that

135 IVR: Oh right

136 IVE: around the local area, but not necessarily what we've found in our family

137 IVR: Yep

138 IVE: But I have kept it to close erm like I say friend talk about it and I had to tell all my family

139 members as I felt responsible for that

140 IVR: Yeah So how did the majority of people take, take what you were telling them?

141 IVE: Its was different from different people, my family are quite, most of my family feel like they just

142 shrug things off and not deal with it

143 IVR: Right

144 IVE: And that's their way that they have always dealt with things im the opposite I like to know

145 exactly what is happening what the possibilities are

146 IVR: Yeah

Julia 15/10/2014 20:35  
**Comment [34]:** In vivo code  
 "it's a little bit complicated really"  
 "it's not just a straight forward thing"  
 "more awareness"  
 "mitochondrial disease in general"

Julia 15/10/2014 20:38  
**Comment [35]:** In vivo code  
 "but not necessarily what we've found in our family"

Julia 15/10/2014 20:41  
**Comment [36]:** In vivo code  
 "but I have kept it close erm like I say"  
 "and I had to tell all my family members"  
 "as I felt responsible for that"

Julia 15/10/2014 20:42  
**Comment [37]:** Theme/Code: Responsibility supported by sub codes such as above?

Julia 15/10/2014 20:44  
**Comment [38]:** In vivo code  
 "different for different people"  
 "I just shrug things off"  
 "and not deal with it"

Julia 15/10/2014 20:49  
**Comment [39]:** In vivo code  
 "their way, that t he have always dealt with things"  
 "I'm the opposite"

Figure 4.4 Example of line-by-line focused coding.

377 IVE: No I didn't because erm .. my illness didn't affect the decision really it was (0.3) we made the

378 decision but there were, the factors to consider where was I going to get help or not

379 IVR: Um hu

380 IVE: Because I couldn't do it alone by the time I got to Abui I knew I couldn't do it alone erm so it

381 needed more people imputing so it was perhaps a family decision to have Abui

382 IVR: Yep

383 IVE: The youngest rather than my decision erm so in that way the mito affected it whether a baby

384 would have mito or not we'd have that baby anyway you know

385 IVR: That wasn't kind of (overlapping)

386 IVE: Yeah well we wouldn't go well I'd abort, I would never abort

387 IVR: Yeah

388 IVE: You know I've never done the amnio-gesis or whatever tests

389 IVR: Arh right so you haven't decided for pre (overlapping)

390 IVE: For in any pregnancy we've never done them tests we just had the normal scan cause we'd have

391 the baby whatever it was

392 IVR: Right, yeah

Julia 15/10/2014 20:41  
**Comment [34]:** In vivo code  
 "it's a little bit complicated really"  
 "it's not just a straight forward thing"  
 "more awareness"  
 "mitochondrial disease in general"

Julia 15/10/2014 20:38  
**Comment [35]:** In vivo code  
 "but not necessarily what we've found in our family"

Julia 15/10/2014 20:41  
**Comment [36]:** In vivo code  
 "but I have kept it close erm like I say"  
 "and I had to tell all my family members"  
 "as I felt responsible for that"

Julia 15/10/2014 20:42  
**Comment [37]:** Theme/Code: Responsibility supported by sub codes such as above?

Julia 15/10/2014 20:44  
**Comment [38]:** In vivo code  
 "different for different people"  
 "I just shrug things off"  
 "and not deal with it"

Julia 15/10/2014 20:49  
**Comment [39]:** In vivo code  
 "their way, that t he have always dealt with things"  
 "I'm the opposite"

Figure 4.5 Example of line-by-line focused coding

#### 4.6.3 Patient Specific Analytical Memoing

For every patient, I wrote extremely detailed patient specific analytical memo's ranging from 15 pages to 38 pages long. These covered each pre-identified or individually emergent codes and categories relevant to women as individuals. I was then able to order their interview into large categories such as diagnosis pathways, impact of diagnosis, clinical relationships, disclosure and reproductive decisions. I further interrogated these by re-coding the memos, so that ideas could be collected across each category (see Figure 4.6 for example).

164 [redacted] describes inheritance as passed through the egg and the inevitability of it being passed to a 165 foetus 'its invariably gonna be passed to a foetus there is no avoiding that' [redacted] 252-253. 166 then questions herself about the probability of it not being passed on and severity of the mutation if 167 it were. This conflicts the previous statement where she knows she cannot avoid the passing on of a 168 mutation 'is there a chance that it might not be passed and if it was what would be the severity' 169 [redacted] 254.	Julia 26/11/2014 18:48 Comment [68]: Inevitability of passing on mutation - Unable to avoid
170 [redacted] could not make this decision on her own but she needed her husband to make a joint decision 171 together. [redacted] describes her husband acting in a way you would expect, amazing and she described 172 his more relaxed approach to decisions, including this one. Her husband found a number of reasons 173 as to why the couple should not worry unnecessarily or as [redacted] describes it a 'you could just go into 174 absolute blind panic meltdown' [redacted] 259-260 in them interim weeks.	Julia 26/11/2014 18:55 Comment [69]: Uncertainty of severity - Hope (that it might not be passed on/transmission)
175 'he is a lot different to me in that he is quite laid back and he you know, what will be will be 176 and you know, do we need to worry about it were not even pregnant yet and erm you know 177 where seeing the consultant in two weeks let's get some more information there' [redacted] 178 257-259.	Julia 26/11/2014 18:55 Comment [70]: Needing her husband - Joint decision - Supportive partner
179 [redacted] describes the reason for taking part in the study and the decision she made was that she could 180 have well have fallen pregnant at any time in the last 15 years but not known her diagnosis	Julia 26/11/2014 19:11 Comment [71]: Different take on information they had - Acknowledging the need for more info - Decision hasn't been made yet - Dealing with it when we are pregnant

Figure 4.6 Coding of patient specific analytical memos

#### 4.6.4 Category Specific Mind Mapping

In order to make sense of codes for each emergent category, I mapped individual codes, allowing for issues to be better identified, that then ultimately made up the large main category components (Charmaz, 2006). I did this first manually (see Figure 4.7 for example) and then entered a selection of these into mind mapping software MindView 5.0.



**Figure 4.7** Manual mind mapping of disclosure category

#### **4.6.5 Category Specific Analysis**

After identifying the main codes of a category in Round One, I was able to produce Category Specific Memo's that then underwent further revisions. For example, Figure 4.9 is the third version of sub-code 'speed of disclosure' of the larger category Disclosure.

Disclosure: How do characters within the story of known diagnosis increase? **V3**

- The speed of disclosure of 'some kind of genetic condition' to those ***socially significant*** from the person receiving news of a potential diagnosis is relatively fast, even in circumstances when diagnosis not confirmed or even when told by a relative (with inherited significance) in the first instance.
  - The prognosis over the specific mutation is important to establish as soon as possible (linked to information provision and use of the internet!) to establish if fatal, life altering or mild (002)
  - This can be complicated by the lack of understanding and complexity of the disease. Bare minimum of information or learnt scripts/stories are used to assist disclosure and can also be a way in which to modify the level of disclosure to others (full or partial)
  - Frustration arises due to the lack of the individuals understanding and inability to answer/explain to others
  - The speed of disclosure 'of some kind of genetic condition' to others may legitimise their symptomatic illness to family, friends and employers

**Figure 4.8** Category specific memo of disclosure: sub-code speed of disclosure (Version 3)

The sub-codes were then entered into an Excel spread sheet that allowed for future participants to be plotted against the existing memo version (Kraman & Hamm, 1999; Mays & Pope, 1995; Seale, 1999). Over time the overall category memos were amended and updated in accordance with the new data collected and analysed.

Figure 4.10 highlights Version 4 of the Disclosure sub-category emerging when new information led to the amendment relating to script use; the boxes that remain white are in agreement with the data collected already in Round One, those highlighted represent areas that new participants have changed the sub-category or are not applicable.

Subtheme (V4) █	Sub- Theme Point Description V4	Evidence		
The Speed of Disclosure	<b>The speed of disclosure of 'some kind of genetic condition' to those <i>socially significant</i> from the person receiving news of a potential diagnosis is relatively fast, even in circumstances when diagnosis not confirmed or even when told by a relative (with inherited significance) in the first instance.</b>	Yes - Family also diagnosed with mutation - doesn't tell us how fast she tells her husband █, told her best friend (and inner circle) who was support system along with her mother but does	Yes - Family also diagnosed with mutation - discussed with family including stepmother after confirmation of genetic diagnosis.	Yes - siblings █ also diagnosed - spoken about openly with family, husband and █ told
	The prognosis over the specific mutation is important to establish as soon as possible (linked to information provision and use of the internet!) to establish if fatal, life altering or mild (█)	Yes - knowledge of family prognosis important- becomes more important when her █ develops █ and passes away	Yes - █ surprised that her mutation level was the same as her symptomatic █ . Concerned over prognosis	Yes - unique family position as little was known on the natural history of the condition when diagnosed

Figure 4.9 Redacted analytical induction category workbook: Disclosure sub category: speed of disclosure (Version 4)

#### **4.6.6 Data Clinics**

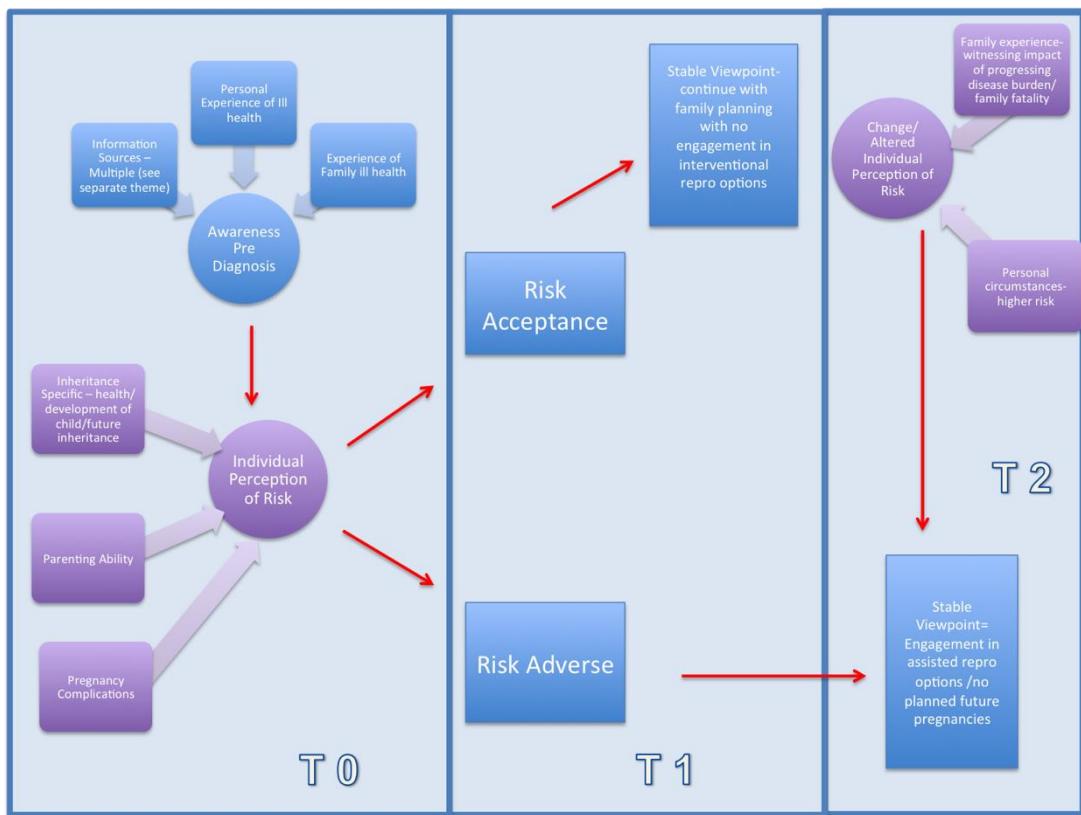
In addition to discussing analytical outputs at regular supervisory meetings, subsections of interview transcripts were reviewed at Data Clinics and included research associates, assistants and other PhD researchers based in the Institute of Health and Society. This allowed for a proportion of my data to be analysed collectively, where the researchers shared and exchanged interpretations of key issues emerging from the data (Rapley, 2010).

### **4.7 Conceptual Model Development**

Data collected and analysed over the course of the study allowed for the development of a disease specific conceptual model of reproductive decision-making. The process included three specific developmental stages, each resulting in an updated version of the conceptual model. Discussions of the final version are covered specifically in Chapter 8, but developmental stages are included here to show how this came in to being. The first two conceptual model versions were mapped from emergent study categories. Upon recognising the similarities between prior work by Downing (2005), categories were then super-imposed into their existing framework of responsible decision-making in HD. Similarities and differences are present between the Downing (2005) model and the proposed maternally inherited mitochondrial disease model and these were revealed through a process of refinement.

#### **4.7.1 Conceptual Model Version 1**

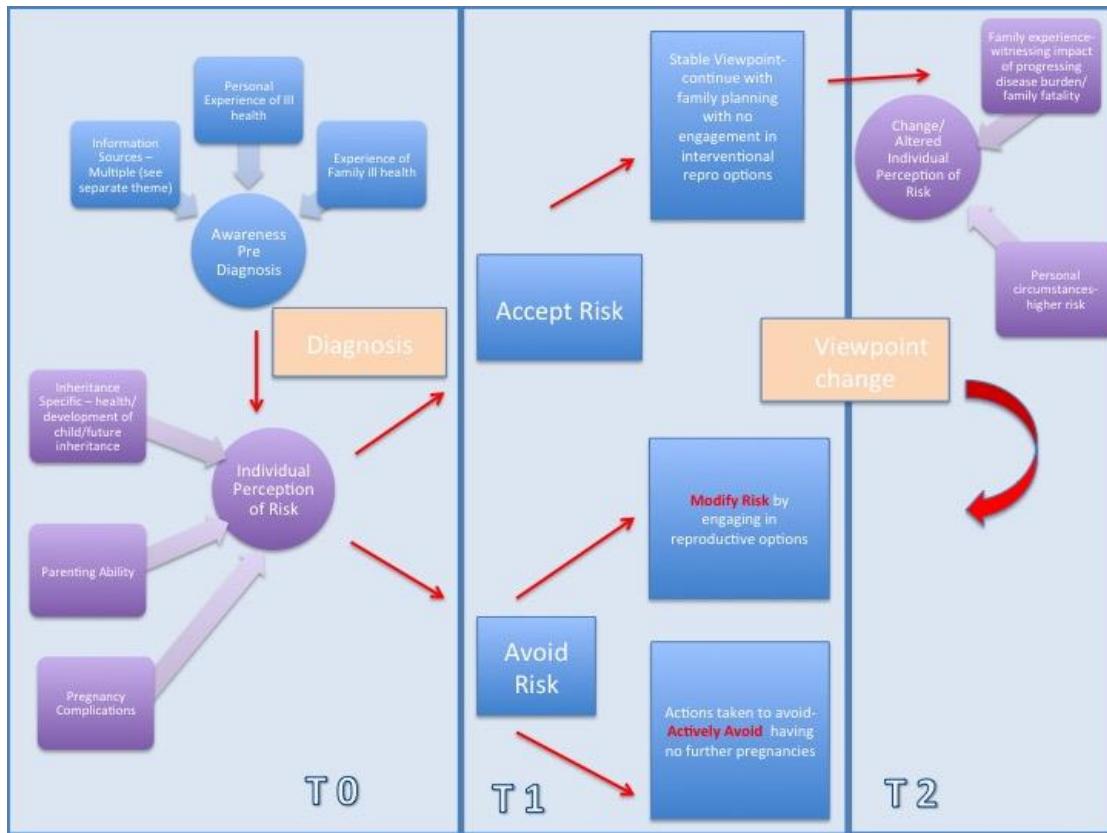
The following model was developed from categories discovered in interviews that showed three distinct time points throughout the process of reproductive decision-making. Initially these were broken down into time point zero (T0) which included pre- and post-diagnosis considerations, time point one (T1) that was response to T0's considerations and time point two (T2) where women experience a changed or altered perception of risk. A response to risk was framed as being accepting or adverse to risk, which dictated what reproductive options they engaged with.



**Figure 4.10** Maternally inherited mitochondrial disease reproductive decision-making conceptual model (Version 1)

#### 4.7.2 Conceptual Model Version 2

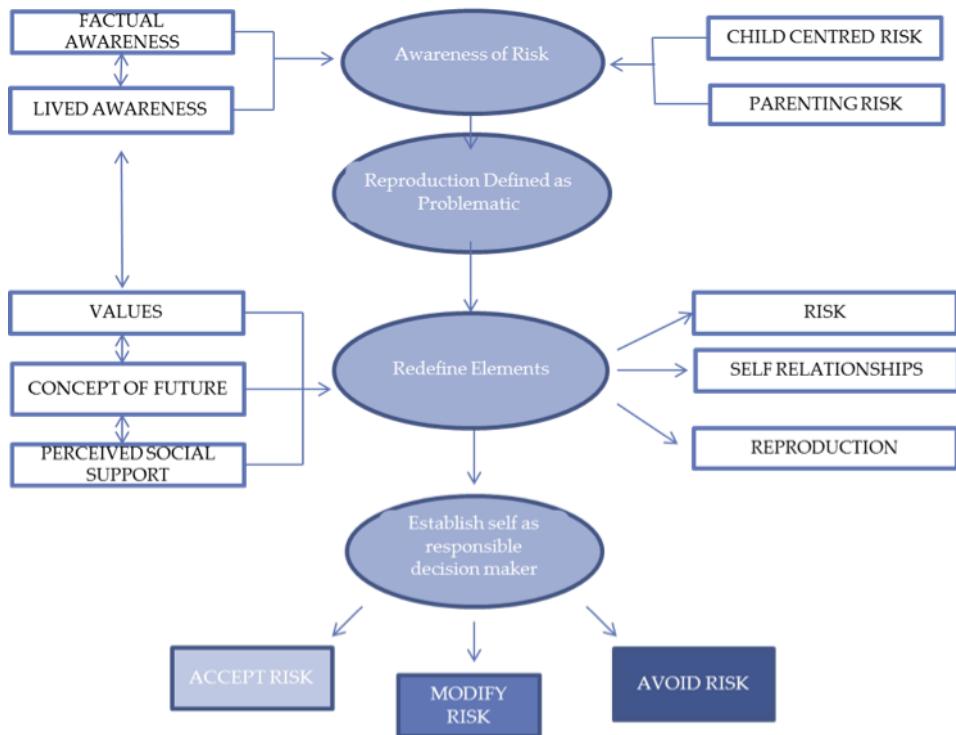
The second version on the model shows more clearly the differences amongst those women who were considered to be risk adverse and their reproductive decisions. This was done by dividing these into those who sought to modify their risk by engaging in reproductive options, which included a form of intervention and those who avoided further risk by having no further pregnancies. It also showed more clearly that those women whose perception of risk had changed or been altered sought ways in which to modify future risks.



**Figure 4.11** Maternally inherited mitochondrial disease reproductive decision-making conceptual model (Version 2)

#### 4.7.3 Conceptual Model Version 3

The model was then reviewed against Downing's (2005) model of responsibility in HD (Figure 4.12) and configured to the same framework. The refined model is outlined in the Chapter 1 (Figure 1.7) and discussed in detail in Chapter 8 (Figure 8.1) and 9 (Figure 9.1).



**Figure 4.12** Model of Responsibility of Huntington's disease (Downing, 2005)

With my refined model, factors and elements that corresponded with emergent categories in this study remained, but those that did not were replaced with elements specific to the study data (see Chapter 8). The novel time point, time point two (T2) was included into the model representing change over time in relation to risk perception, attributed to a change in personal circumstances or witnessing the impact of progressing disease or fatality in the family. Interviews in Round Three (post-licensing of mitochondrial donation) were specifically conducted to enable the categories of the final proposed model to be tested. The proposed conceptual model can be applied to the experiences of women in both the retrospective and current and prospective decision-making groups.

#### 4.8 Reliability and Validity

As introduced earlier, qualitative research is often criticised for lack of scientific rigor, therefore ensuring reliability and validity of these methods is not only key within the wider social science field but also within this study. Mays and Pope (1995) suggest that in order to ensure rigor in qualitative research a 'systematic and self-conscious research design, data collection, interpretation and communication' should be applied as would be in quantitative research (pp 110). In addition to this, clear

accounts of the methods of data collection and analyses should be included in the dissemination of research, an area which Mays and Pope (1995) describe as neglected in some articles.

When assessing reliability and validity in qualitative research Guba and Lincoln (1989) established the following as precedent of quality 1) credibility 2) transferability, 3) dependability and 4) conformability as well as the creation of a reflexive journal. Over time there has been suggestions that not all of the these recommendations are required in every study, Morse (2015) concluded that reliability and validity are intertwined and recommended strategies to enable them both to be achieved within a study. The strategies of thick and rich description of data, negative case analysis, peer review and debriefing, coding systems and acknowledging potential researcher biases have all been employed in this thesis.

#### **4.9 Summary**

In this chapter I have outlined the methodological framework and theoretical approach taken for this work, detailing the practicalities of data collection and analysis employed throughout the study. I have shown the step-by-step developmental process of the proposed conceptual model of reproductive decision-making in maternally inherited mitochondrial disease. It is important to reiterate that although these processes are presented here in a linear form, in reality these activities took place in overlapping cycles throughout the three years in which data was collected and analysed.

In total 20 interviews were conducted with 18 women with a known mtDNA mutation, allowing for a rich data set to enable integration and the formation of the results presented in this thesis. I am confident that the data, analysis, conclusions and recommendations to clinicians from this work are grounded in the data. They provide a solid foundation to support the disease specific conceptual model of reproductive decision-making, therefore informing the patient pathway for women with maternally inherited mitochondrial disease making reproductive decisions now and in the future,

## **Chapter 5. Diagnostic Pathways: Women's Practical Experiences**

### **5.1 Introduction**

This short chapter is the first of four findings chapters; it sets the scene for the remainder of this thesis and provides important context. It prioritises the experiences of women with maternally inherited mitochondrial disease and their diagnosis. This Chapter centres women's description of their illness unlike the bulk of the literature that views their condition via a clinical perspective. The focus of this thesis is reproductive decision-making for women with maternally inherited mitochondrial disease. However, to do this it is necessary to situate their experience of the conditions as an important feature of their life so far, as for many it has had important and long-term impacts on their life prior to being diagnosed. In some cases women were entirely asymptomatic whereas others negotiated a complex and varied collection of symptoms that they did not always attribute to having any particular condition. For some women the onset of symptoms and delay in diagnosis resulted in uncertainty. They didn't know why they were getting the symptoms, how they would develop or if they were related to a specific condition. Therefore their experience of living with maternally inherited mitochondrial disease pre-existed diagnosis and in some cases women's reproductive decision-making. For this reason, this chapter explores in particular how women understood and made sense of their embodied experiences, in combination with illness experienced by family members, including in some instances their own children, and how this in turn influenced their individual journeys to diagnosis. Interview data collected from women featured accounts of delay in terms of their diagnosis. In the literature this is referred to as diagnostic delay and can represent the time between them becoming symptomatic, or the diagnosis of a family member and the diagnosis of the woman herself. To further explore this I use two models of diagnostic pathways to explain the accounts of women.

### **5.2 Diagnostic Delay in Rare Disease**

Of the many challenges facing rare disease patients, delay in diagnosis and access to appropriate health care are a common problem across the many thousands of known rare disorders (Dharssi et al., 2017; Elliott & Zurynski, 2015; Zurynski et al.,

2017). The diagnosis of mitochondrial disease is no different, complicated by its dual genome origins and its complex and varied phenotypes that result in a number of investigations and expert interpretation required to obtain a diagnosis (Haas et al., 2008). Countries across the globe have established individual or collaborative strategies to address these along with other challenges facing rare disease patients (Dharssi et al., 2017). The UK Strategy for Rare Disease published a number of commitments to improve the lives of those living with rare disease by 2020, in which the eleventh commitment was to 'work to achieve reduced time for diagnosis' and to 'ensure that undiagnosed patients have appropriate access to coordinated care' (Department of Health & UK Government, 2013 p 32-33)

It is recognised that general practitioners in the UK health care system can play a role in 'spotting the zebra from the horses' and will play a bigger role in the long-term management of people with rare disease (Evans & Rafi, 2016 p550). However, delays can sometimes occur before patients have even made contact with health care professionals. Women in the study tell us about specific periods of delays between them first noticing an unexplained symptom(s) and making the first appointment with their GP. The Andersen Model of Health Care Utilisation provides a conceptual structure of seeking medical attention for a specific illness concern, which can be seen to be relevant to both the women and their family members in this study (Andersen et al., 1995). The general model of 'total patient delay' as proposed by Andersen includes 1) appraisal delay: time between detection of unexplained symptoms and concluding illness 2) illness delay: time between inferring illness and deciding to seek medical help 3) behavioural delay: time between a person deciding an illness requires medical care and deciding to act on this 4) scheduling delay: time between deciding to act on the decision to seek help and actually attending an appointment and 5) treatment delay: time between the first appointment with a health care professional and the onset of treatment (Andersen et al., 1995; Walter et al., 2012).

Throughout the section that follows, I will show how women experienced aspects of the Andersen model, as well as difficulties in being 'believed' and therefore accessing appropriate care services before finally receiving their diagnosis of a mtDNA mutation.

### 5.3 Accounts of Diagnosis as a Direct Result of Women's Symptoms

Of the 18 women included in the study, five women were diagnosed with their mtDNA mutation as a result of their own ill health. The length of time in which women had experienced symptoms ranged from approximately 12 months to over 30 years before receiving a diagnosis. I will describe their diagnostic journeys by first outlining the initial noticing of symptoms, their experiences of visiting health care professionals in primary, secondary and tertiary care settings and how they came to be diagnosed with a mtDNA mutation.

Throughout the data women report experiences of initial 'noticing' of unexplained symptom(s). Personal accounts of noticing symptoms which led to concern can be seen to be experienced throughout the life course of some of the women interviewed, some dating back to when they were at school. Given the historical context, Dimond (2013) notes that many patients lived with symptoms of mitochondrial disease before the development of the necessary diagnostic techniques. We see this in Jenny's accounts of her childhood fatigue and how it noticeably affected her when taking part in school sports, 'I'd known ... since I was a kid there was something wrong' (Jenny: 74-75), unfortunately for Jenny her GP had told her mother that she was 'just lazy', which meant that she remained undiagnosed for over 30 years. Difficulty participating in physical school or social activities was also true for Holly and Lucy, having both experienced symptoms since their childhood. Holly struggled to hold her arms in their air whilst dancing 'I was always getting into trouble for not keeping my hands up high enough' (Holly: 372-374) in activities outside of school whilst Lucy suffered anxiety when faced with her PE classes. When discussing how she was relieved to have received her diagnosis she tells us that:

Aw 100% because for years I've been poorly, first school, middle school, always tired, always, I hated PE with a passion, couldn't run, teachers used to shout at me, they used to call me lazy. I would make myself sick thinking about PE the next day, cause it was just, so now that I've got something it's good to say there is a reason why I am feeling like this (Lucy: 34-38)

For Lucy, her diagnosis now allowed her to understand why she had struggled for so many years, that this was not a product of being 'lazy'. Having a diagnosis enabled her to re-position her past experiences as emerging from her 'sick role' (Parsons, 1951) and so other's responses to her as somehow malingering where illegitimate.

Other accounts of noticing include deterioration in health over a number of years. Women noticed changes such as the onset of extreme fatigue, weight changes, loss of hearing, myoclonic jerks and episodes of syncope. Women commonly refer to 'something not being quite right', 'something is wrong', 'getting worse' or 'I've felt it for years'. Andi can be seen to have experienced appraisal delay (Andersen et al., 1995) at the initial onset of fatigue, as she did not believe that this may be of a medical aetiology but a sign that she had 'just taken on too much' (Andi: 86-87). She was working full time, headed a number of community and charity committees/events as well as having a young family 'I just thought arh I've just taken on too much'. To address this, she reduced her working hours and stepped down from some of the organisations she had been supporting. The first symptoms that prompted Andi to seek medical advice were visual inconsistencies that she described as 'getting worse and it was just getting weird' (Andi: 43).

Some women were conscious of physical changes over time, especially symptoms that they could not associate with any other cause. Maggie described being 'really concerned that I was losing my hearing' (Maggie: 217) in her early to mid-thirties. There was a period of time for Maggie where this concern had been delayed - described as behavioural delay (Andersen et al., 1995) - until she finally decided to make an appointment with her GP. She was told however that 'you're far too young it can't possibly be' (Maggie: 218-219). Like many of the women interviewed Maggie was told that it was 'something that you've got in your head' (Maggie: 220) or for those who experienced fatigue, that they were just 'lazy'. Muir (2016) argued that the experience of not being believed was not uncommon amongst patients with rare disorders, with many experiencing issues with persuading medical professionals to believe their symptoms and their condition often being written off as psychological in origin. Living with medically unexplained symptoms can leave sufferers unable to achieve society's sick role as a result of not having a medical diagnosis, access to the appropriate medical care, and often a lack of visible illness. This leaves them facing accusations of malingering, hypochondria and mental illness (Glenton, 2003). Some of these women also experienced treatment delay (Andersen et al., 1995), which in Maggie's case was the eventual placing of two hearing aids. It took a number of years and the onset of an additional symptom, initially spotted at a high street optician, before Maggie would be diagnosed and receive appropriate advice, support and care.

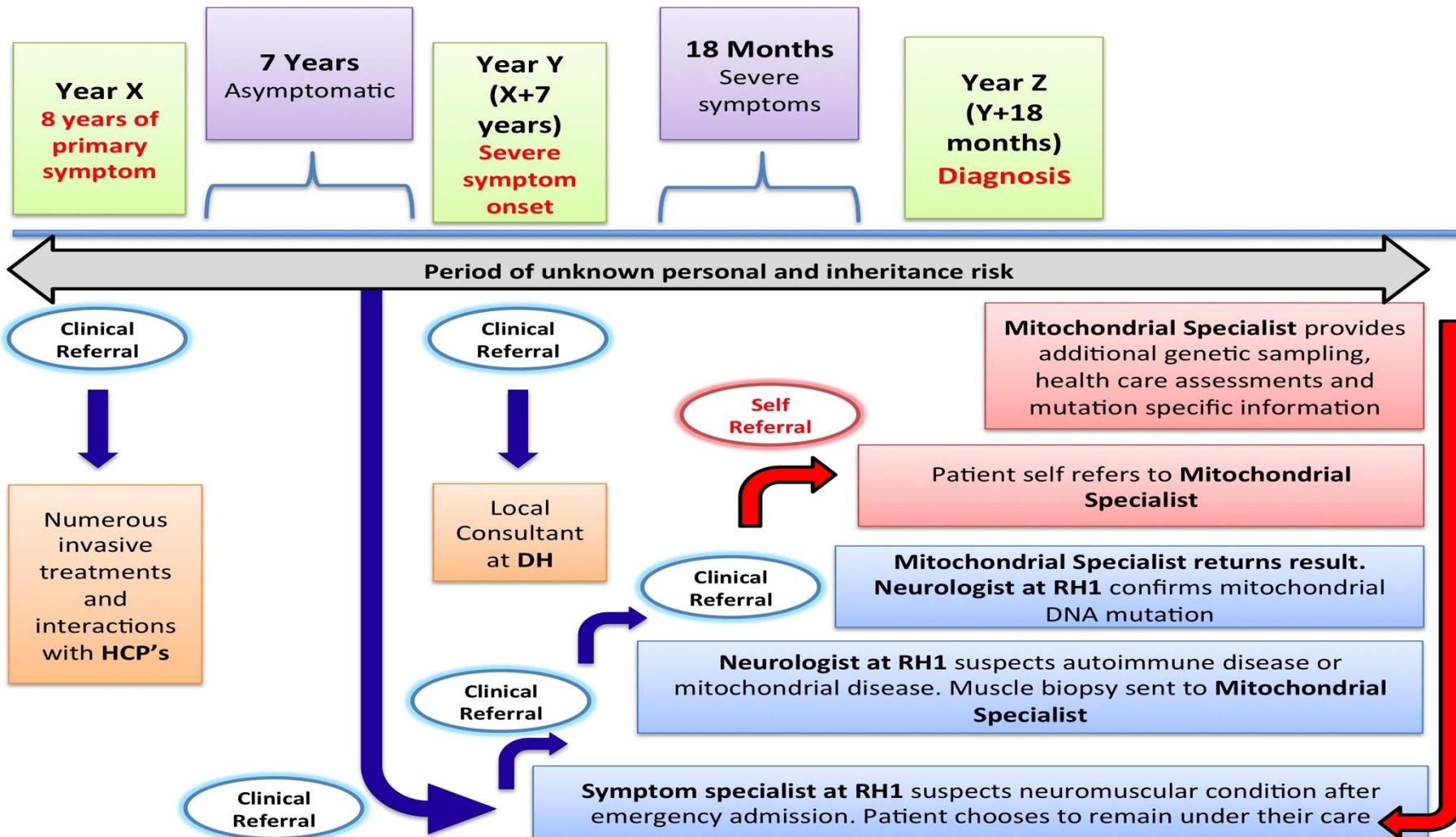
Women who received a diagnosis as a direct result of their ill health saw a number of health professionals over the course of their diagnostic pathway. After navigating a referral from a primary care setting to their local hospital they were seen by a specialist in the major symptom that they were exhibiting. None were seen by a neurologist in the first instance. Specialities encountered included audiology, ophthalmology, cardiology and diabetology, with subsequent referral times to neurology ranging from a matter of months to 16 years. In three cases, ophthalmology specialists at regional hospitals made the potential link to a mitochondrial disorder and made a referral to a regional neurologist or directly to a mitochondrial specialist. For two of these women, they were told that they might have 'mitochondrial disease' or 'myasthenia gravis', an autoimmune disease that causes muscle weakness and fatigue. They were informed that the latter would be the worse of the two.

Sarah experienced a very lengthy and traumatic diagnostic pathway, undergoing a number of invasive operations and emergency admissions. At one point, she received advice from a specialist that suggested a procedure that would leave her with sight in one eye only, at the prospect of which Sarah described feeling 'absolutely like devastated' (Sarah: 195) by the prospect of. Shortly after this encounter she had an appointment with another ophthalmologist who suspected a neurological explanation. The onset of recurrent infections prior to Sarah's eventual referral was described as a 'traumatic 18 months leading up to that diagnosis' (Sarah: 148). Sarah was referred a regional neurologist who performed a muscle biopsy.

Sarah: They thought it might have been something called myasthenia gravis  
Int: Ok yeah  
Sarah: But the neurologist wasn't convinced so did the muscle biopsy that was sent to [mitochondrial specialist centre], suspected mitochondria, then the biopsy came back, I got the results, when I was given the information I was told that it was a more positive diagnosis than myasthenia gravis (Sarah: 112-114)

Sarah had read about both potential diagnoses before returning to receive her results, where she reports being told in a very hectic, rushed clinic that she had mitochondrial disease. Like many women in the study, Sarah was not able to recall if she had a mtDNA mutation or nDNA mutation when asked, but she did recall the

specific mutation. What was important to Sarah was establishing the seriousness of her condition first for herself and then if it would have any impact on her plans to start a family (see section 7.4.1). The complexities of Sarah's diagnostic pathway are shown in Figure 5.1, highlighting the number of clinical referrals she experienced after the onset of severe symptoms and how she actively sought advice from a mitochondrial specialist to understand her diagnosis more and to undergo additional testing and health assessments.



**Figure 5.1** Example of primary complex diagnostic pathway in maternally inherited mitochondrial disease. HCP: Health Care Professionals. DH: District Hospital. RH1: Regional Hospital.

In this section I have termed these women's experiences of diagnosis as the 'primary complex diagnostic pathway of maternally inherited mitochondrial disease', in which they themselves have experienced both symptoms and multiple encounters with health care professionals. For these women their experiences of ill health, unnecessarily prolonged due to delayed diagnosis, is a factor of consideration with regards to reproductive decision-making, which I explore further in Chapter 8.

#### **5.4 Accounts of Diagnosis as a Result of a Childs Symptoms**

The majority of the women interviewed in this study were diagnosed as a result of a family member's ill health. This could be a product of their own child's diagnosis, which will be discussed here, or as a result of their parent or sibling's diagnosis, which I will discuss below. Three women who took part in the study received their own diagnosis of a mtDNA mutation as a result of their child's diagnostic pathway. Again, these were lengthy, taking place over approximately three to seven years. Like the women above there was a period of 'noticing' of symptoms that went onto to initiate their child's pathway at first and then their own.

For one woman their own mother had initially 'noticed' symptoms. Historically, Jenny's mother had noticed her own daughter's abnormal level of fatigue but, at that time, was unable to progress further than their GP. However, Jenny went on to recognise the same symptoms in her child years later, 'I could see it happening when [child] was younger' (Jenny: 103) and described the situation as 'history repeating itself' (Jenny: 105). Jenny delayed seeking medical advice 'you try to (0.2) ignore it' (Jenny: 107), demonstrating a period of illness delay before seeking a referral when she saw her child's symptoms worsening (Andersen et al., 1995). Jenny reflects on the delay as 'which rightly or wrongly you do, but it just got to the stage where [child] was getting worse then what I was' (Jenny: 109-110). It could be inferred that Jenny delayed seeking advice given her own experience of not being believed. Only when her child became noticeably worse than she had been, she acted to seek medical advice.

Jenny does not provide a description of her child's diagnostic pathway but that all three generations of her family gave blood for a DNA test. Whilst Jenny's mother's test came back 'minutely', Jenny and her child's results were 'just like you'd think that someone had just got a big black dabber [marker] and just went duhh' (Jenny:

118-119). Jenny made an action with her hand indicating heavy highlighting of an imagined piece of paper, this relates to a type of diagnostic test where the absence or presence of a protein is measured by the appearance of a protein band on a film. Heavy thick bands denote a high concentration and in comparing these across family members showed that both Jenny and her child had the same concentrations as each other, resulting in them both having the same diagnosis.

For women who described themselves as having no prior experience of ill health that they could relate and compare their child's symptoms to, they described noticing symptoms including vomiting, weight lost, 'failure to thrive', 'walking wobbly or oddly', 'wobbly eyes' and myoclonic jerks. Mothers of affected children experienced delays in accessing the appropriate care or prolonged treatment delays (Andersen et al., 1995). Notably, the mothers interviewed did not appear to experience the other delays (appraisal, illness, behavioural or scheduling) described by Andersen, with these women making contact with their GPs at the outset, unlike in the personal accounts above. Sally observed symptoms in her youngest child when they were very young. She described experiencing a complication at her GP initially, 'we went to our local GP and there was a bit complication' (Sally: 39-40), that we can take to understand as a delay. After 'eventually' being referred to a local hospital, Sally was told that they would implement a 'kinda watching and waiting' (Sally: 41) approach. It went on to take a number of years, three referrals to three different hospital settings along with many blood tests, multiple MRI's and a muscle biopsy before Sally's child would be diagnosed with a mtDNA mutation. Sally was told of the inheritance link when she and her husband were told of their child's diagnosis, the impact of which is described in Chapter 6 and Chapter 8.

Miriam was diagnosed after the eventual diagnosis of her middle child who had experienced symptoms for almost seven years before receiving a mtDNA diagnosis. Miriam and her family experienced many difficult, emotional and frustrating encounters with medical professionals during this time.

So I kept going back, as mothers do, this isn't right, [they] not just got that [they have] got something else (Miriam: 148-150).

Muir (2016) also reported that alongside adult rare disease patients being considered to experience psychosomatic illness, parents of children with rare disease were considered to be neurotic.

Women of affected children in the study expressed concern, anger and frustration that their child was not being seen by the right kind of specialist. Delayed diagnosis of children suffering from a rare disorder due to the perceived lack of knowledge amongst health professionals has been shown to have serious consequences to both parents and children, including stress, worry and frustration (Zurynski et al., 2017). Miriam and her family had seen a number of doctors over the seven years before their diagnosis, including a number of neurologists. After their diagnosis, Miriam felt that even though the neurologists they were seeing were 'nice' enough for certain aspects of her child's illness they weren't mitochondrial specialists.

"Well who do we need to see, who knows more about this condition?" 'Cause obviously our doctor was a neurologist and he dealt more with like Parkinson's, MS and this [mitochondrial disease] was off the radar  
(Miriam: 419-422)

For Miriam attending an appointment with a regional neurologist that could only treat certain symptoms of her child's phenotype was not good enough, an opinion shared by her husband and their then adult children. Upon receiving a diagnosis via their regional neurologist she and her family insisted that they saw a mitochondrial specialist together. What was key for Miriam was that she and her family were seen by an expert in mitochondrial disease, specifically with a focus on receiving treatment or participating in 'clinical therapy trials' (Miriam: 442).

For these women, although they themselves did not experience a lengthy diagnostic pathway, I suggest that their diagnostic pathway was one of secondary complexity; and I have described this as the secondary complex diagnostic pathway of maternally inherited mitochondrial disease. For Jenny and Miriam, they considered their families complete and were not intending to add to their family, Sally was less certain of this and at different points of the interview she was less certain that she had completed her family than at other times. I will explore further how lived experience of family ill health, along with factors relating to concerns of safety for a

future child and maternal guilt and responsibility relating to inheritance impact upon reproductive decision-making in Chapter 8 section 8.7.2.

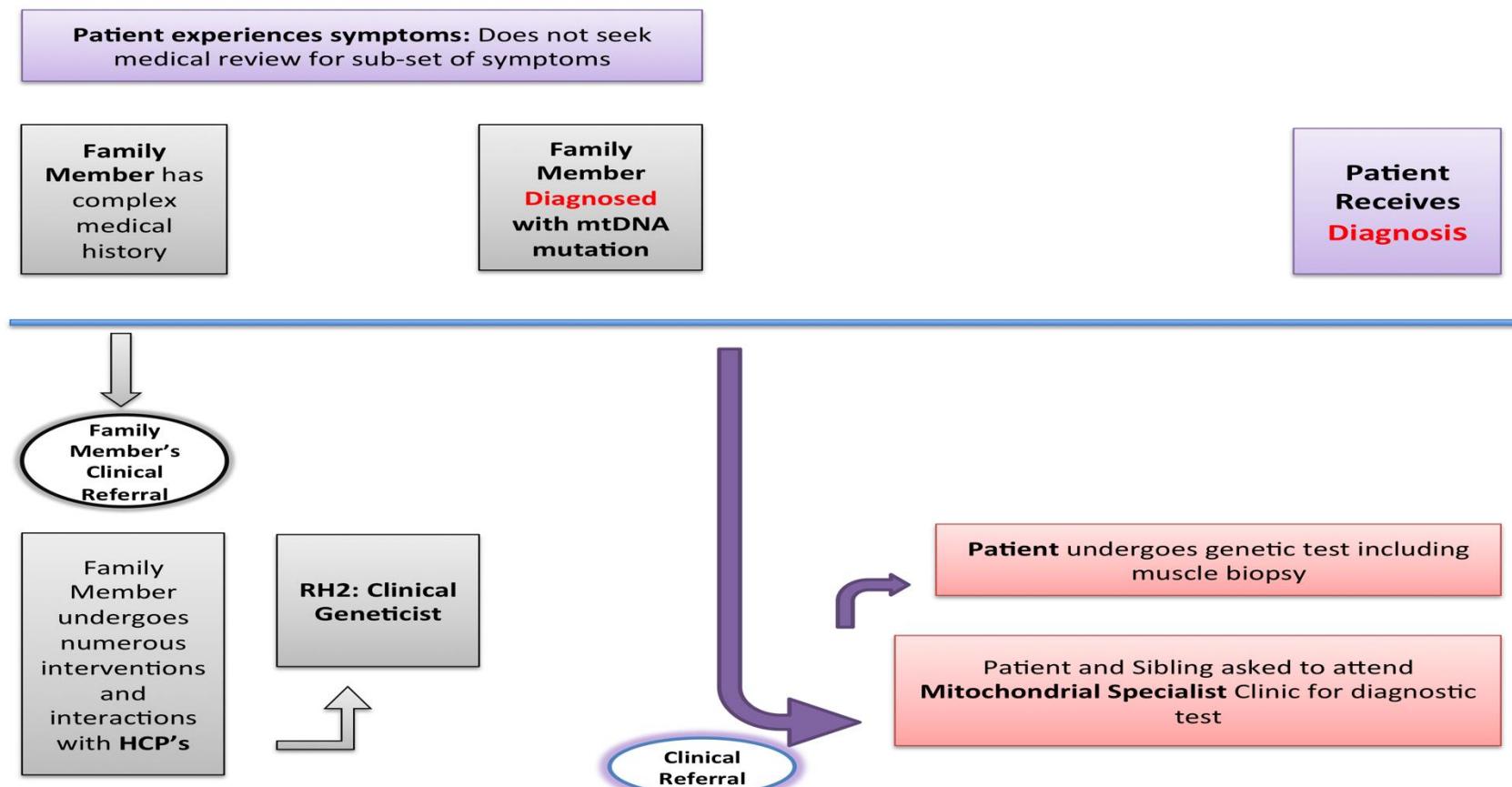
### **5.5 Accounts of Diagnosis as a Result of a Family Members Symptoms**

Family accounts of noticing are seen in women whose parents or siblings exhibited symptoms that were later attributed to a mtDNA mutation or a posthumously suspected mtDNA mutation. These symptoms commonly presented over many years, including over decades. The accounts of noticing include their mothers experiencing deafness, seizures, organ failure, stroke like episodes and early dementia. One woman's mother was thought to have been suffering from Creutzfeldt-Jakob disease, commonly known as mad cow's disease or as they also described it, the one you get 'from eating beef' (Ashley: 30). Accounts relating to siblings included episodes of black outs, learning difficulties, blindness, seizures and deafness, some of which dated back to their siblings' childhood or in the years preceding their diagnosis. It is interesting to note that many women's families also included symptomatic maternal aunts and uncles who had also presented as early as childhood, most of whom were not aware of a genetic cause of illness, except in one case (see Chapter 8 section 8.7.2)

For ten of the women interviewed, their family members diagnosis was what led them to receive their own diagnosis, five of whom were diagnosed as a result of their own mother's experience of ill health and five women as a result of their siblings' ill health (including both female and male siblings). Within this group of ten, four of these women had not experienced any signs of ill health that may have been related to their mitochondrial mutation before or after their diagnosis. Additionally, one woman, Ashley, offers a contradictory account. Ashley tells the interviewer that 'I'm not really affected it's kind of OK, cause you can't change it anyways' (Ashley: 44) but also that she was 'handling the symptoms and hoping for the best' (Ashley: 45). Ashley offered no additional information of what these were. For Ashley there may have been a potential appraisal and illness delay (Andersen et al., 1995). Dimond (2013) argues that asymptomatic individuals who live with the knowledge of a mtDNA mutation experience the phenomenon of being 'a patient without symptoms' like those with recessive disorders or late onset disorders such as Huntington's disease. I too make this link to similarities experienced by patients with mtDNA mutations to those with known risk of HD in Chapter 8, with regards to the proposed

conceptual model of reproductive decision-making in maternally inherited mitochondrial disease.

The remaining five women in this group had experienced symptoms that they had either deemed not worthy of visiting their GP for, or whose symptoms were treated but not investigated further. For Joanna, she had experienced fatigue levels that were of concern for her and noticeable to others, in particular her partner, but had never sought medical advice. Alongside this Joanna, also had 'few' other health problems but did not provide any further information. It was clear that for Joanna her experience of fatigue was most notable. Upon receiving the news that she too had a mtDNA mutation like her mother, she felt relief in finding an explanation of her symptoms both for herself 'so kind of things made sense a little bit' (Joanna: 75) and others, in that the diagnosis had legitimised her fatigue 'and he [her partner] realised that I'm not just lazy after all these years (Joanna: 84). Relatedly, this relief echoes the work of Clarke (2000) who writes of the sense of relief those with chronic fatigue syndrome experience upon receiving their diagnosis. The relative simplicity of Joanna's diagnostic pathway compared to her mother's is shown in Figure 5.2, highlighting the interventions and clinical referrals her mother experienced prior to diagnosis, that led to Joanna and her sibling being asked to consider a diagnostic test, whilst experiencing noticeable fatigue.



**Figure 5.2** Example of secondary complex diagnostic pathway in maternally inherited mitochondrial disease. HCP: Health Care Professionals. DH: District Hospital. RH1: Regional Hospital.

Alice, had noticed extreme weight loss 'I'm not, like, particularly big but I'd lost so much weight. People, I, I think people thought I was, like, anorexic' (Alice: 943-945). It took 18 months for Alice to receive a diagnosis of diabetes given the complexities surrounding the presentation of the diabetes phenotype known to be associated with her mtDNA mutation (then undiagnosed). Interestingly Alice is medically trained. For Alice the then unexplained visible symptoms of illness caused concern not only with regards to the aetiology but that she was perceived to have an eating disorder by others. It can be deduced that Alice felt stigma associated with this perception, which is known to exist in eating disorders (Mond et al., 2006) as well as in rare disorders (Joachim & Acorn, 2003).

As with the parental accounts of diagnosis delay I believe that these women also experience complex diagnostic pathways, secondary to their relative(s) lengthy diagnostic journeys, as they observed their family going through investigations but they themselves were also unwell. Women in this group also had the option if they had wanted to, to defer their diagnosis once armed with the knowledge of their relative's diagnosis, which two women did after finding out their siblings diagnosis. They were not alone in this behaviour with many women describing other family members of theirs, who had at the time of the interview refused testing, including other siblings and extended family such as maternal aunts, nieces and nephews. When writing about genetic testing in families with a known risk of breast and ovarian cancers, d'Agincourt-Canning (2006) says that the decisions to have a genetic test is 'not made in isolation but is shaped by other life experiences, circumstances, responsibilities and commitments (p101).

For the two women in this study who delayed testing, their reasons differed from one another, but both had waited a number of years before requesting a diagnostic test. For Wendy it was her decision to defer until she was actively considering starting a family (see Chapter 8) and for Alice it was because she struggled with knowing whether it was something she wanted to know because 'once you know that's it' (Alice: 279). Alice made the decision to have the diagnostic test after finding out a younger member of her family had been found to have the mutation. This new information prompted Alice to be tested to enable her to contribute to research for the potential benefit of her family member and others.

And from then I checked, I, I wanted to go and get tested because I knew if, if I had it, that was it. But, like, I thought, "If [Family member] have got it, I've got to, like, contribute." I'm not, I, I know that sounds a bit selfish, not just my [Family Member] - other people as well. But that was the deciding factor, I think, when I found out my [Family Member] [had it]" (Alice: 300-305)

Both Wendy and Alice's eventual desire to undergo genetic testing echoes work done by others in *BRAC1* and *BRAC2* testing, where known carriers wanted to be tested to benefit family members (Goelen et al, 1995). In addition to helping family, Alice's motivation to help others who may be affected is described by d'Agincourt-Canning (2006) as the 'civic self', where women at risk of *BRAC1* and *BRAC2* gene sought testing to help other families and advance medical knowledge, acting out of concern for 'society at large'. For many women, experiencing their loved ones go through serious episodes of illness left lasting reminders of potential severity of their family's mtDNA mutation. Lived experience of family ill health is shown within this study to be a factor of consideration with regards to reproductive decision-making (see Chapter 8 section 8.3).

## 5.6 Summary

Women with maternally inherited mitochondrial disease travel varied and often complicated pathways to diagnosis. In some instances, women delayed accessing a diagnosis, either to put off a suspected diagnosis or on the assumption that their illness was not too severe and did not warrant testing. However, some women had experienced symptoms from childhood that remained undiagnosed for a number of years devoid of the legitimisation offered by the sick role (Parsons, 1951), especially for women who were not afforded it by the health professionals they first encountered when seeking help with their symptoms. Women were sometimes left in a long term, medically unexplained or misdiagnosed state. Upon receiving their diagnoses these women described feeling relieved to receive an explanation for their illness. Similarly, data in this Chapter also shows how mothers of affected children experienced upset and frustration in obtaining a diagnosis for their child. This data contributes to, and supports literature that suggests that receiving a medical diagnosis can result in individuals feeling relieved (Dimond, 2013; Glenton, 2003) and in some instances enabled women to shed the stigmatised identities generated

from a misdiagnosis or lack of diagnosis (Huibers and Wessely, 2006; Picariello et al., 2015; Ashbring and Narvanen, 2002; Tucker, 2004; Barlow et al., 2007).

Although relevant to some women at particular stages of their diagnostic journey, Andersen's model of total patient delay has limited explanatory potential in the context of complex diagnostic pathways in mitochondrial disease. In part this can be explained in the design of the model, which was developed specifically in relation to how family units accessed health care (Andersen et al., 1995; Andersen & Newman, 1973), with some researchers proposing disease specific adaptions or expansions (Walter et al., 2012). Because of the genetically inherited nature of mitochondrial disease, and the extensive variation in symptom manifestation, such a model is unlikely to deliver the scope necessary to satisfactorily incorporate the condition. However, as this chapter illustrates, it remains useful as a comparison point from which to develop understandings of alternative diagnostic pathways.

I have shown that all women in this study have an experience of living with mitochondrial disease and that if they themselves have not been physically affected they have at least one family member that has as a result of a mtDNA mutation. I will go to explore the impact of this diagnosis in Chapter 6.

## Chapter 6. The Social Implications of Diagnosis

### 6.1 Introduction

The previous chapter discussed the various routes to diagnosis travelled by women with mtDNA mutations who participated in this study. The effects of living with a rare disease have been shown to extend from the medical, biological and physical impacts into many areas of patients' lives (Muir, 2016; Nunn, 2017). This chapter continues to explore the social impacts of being diagnosed with mitochondrial disease, which in turn provides additional context to the reproductive decision-making discussed in the following chapters. Data introduced in this chapter explains women's experiences of being diagnosed, as well as their short-term responses to their diagnosis, which include fear of how the condition might progress and their attempt to seek further information.

Women also had to navigate disclosure, and make decisions about who they would and would not share their diagnosis with. For example, decisions not to tell were largely informed by privacy or in the case of immediate family not wishing to be the bearers of bad news. Further the chapter goes on to examine the longer-term disruptive implications of their illness on important relationships in their lives. This included navigating interactions with employment and educational organisations, which were ill equipped to manage the uncertainty posed by the women's conditions. The last section reflects on how the dynamic of clinical relationships could change post diagnosis, as some non-specialist health professionals appeared to have difficulty in providing support appropriate to the uncertain nature of the women's conditions.

### 6.2 Receiving the Diagnosis

#### 6.2.1 *Uncertainty and Fear*

Alongside relief of understanding what had caused their own or their family members' ill health for many years came the uncertainty surrounding their or their family members' future. The natural history of mtDNA mutations is still relatively unknown despite on-going research aimed at finding new associations and understanding all the potential phenotypes attributed to certain mitochondrial mutations (Mancuso et al., 2015; Nesbitt et al., 2013). As we have seen in

Chapter 5, some women were given their initial diagnosis by a non-mitochondrial specialist, the inability to provide specialised information at this appointment left some women extremely distressed ‘I just sort of panicked, and I thought, “Oh no, I’m going to die” you know?’ (Maggie: 516-517). Maggie like many others actively sought a consultation with an expert in mitochondrial disease following her diagnosis and was told that:

Maggie: [They] just said, “Well, you know, we really don’t know what your prognosis is. We won’t know because it’s a fairly new area of medicine, and we don’t really know what the future is for” erm  
Int: Yeah.  
Maggie: So, but I did feel, feel better  
Int: Yeah.  
Maggie: You know, that [they] sort of, erm, because I [Laughter] I mean that was one of the things I asked [them] what my life expectancy would be. Erm, and [they] basically said, “Well nobody can sort of tell you what that is, but he looked at like, I mean my mam’s [XX years old]. My, my nana lived till she was [XX years old] something, you know, so he says, you know, “It’s obviously been passed through generations, and it doesn’t seem to have caused any sort of shortening of your life expectancy” (Maggie: 533- 551)

Maggie’s specific concern was relating to life expectancy, which she deduced from the specialists advice unlikely to be adversely affected because of her mtDNA mutation. This had been based on the probability that her mother and grandmother had also carried the mutation. Although Maggie did not receive all the answers to her many questions at that appointment she did leave feeling more reassured.

The initial fear of a threat to mortality was not uncommon, with many women’s first question being ‘will I die?’ and in reference to any children or family, ‘will they die?’ Many women who experienced strong emotions surrounding their diagnosis called for more psychological support to help them come to terms with their diagnosis, I explore this further in section 6.3.2.

### ***6.2.2 Seeking Information***

Information seeking relating to mitochondrial disease is intertwined in many areas of women’s lives from the moment they find out about their diagnosis or the

potential that they may have a mtDNA mutation. They seek information on a broad range of topics, including coping with their diagnosis, learning to adapt their lifestyle through to disclosing to others their diagnosis and for reproductive decision-making. Women relied on a number of sources of information prior to and when first diagnosed, most notably their mitochondrial specialist, other trusted health care professionals and the Internet to learn about the risk of mitochondrial disease. Awareness of mitochondrial disease and inheritance risk is a contributing factor to the proposed conceptual model of reproductive decision-making, with many women using these information seeking practices to inform their decision about reproduction (see Chapter 8 section 8.3.1).

Information provision, especially during the initial phases of diagnosis is often key. Sally was shocked to receive the news that her daughter had a mitochondrial mutation after numerous hospital appointments, receiving at the same time the news that her child's condition was maternally inherited.

[they] gave us the information that what [they've] found I don't think that anything else could have been given to me at the time to make me feel better erm unless you know cos I had to go away do my own research and come to terms with stuff' (Sally: 278-280)

For Sally it was important that she was able to do her 'own research' and she saw this as a way of 'coming to terms' with her child's and eventually her own diagnosis, she did not feel more could have been done for her by her child's clinical team initially. Noorda et al (2007) conducted interviews with parents of children with mitochondrial disease and found that the attitude and availability of the person providing information about their child's condition was the most important item, that they wanted this person to be honest about what they did and did not know and that there should be resources available to allow them to ask questions.

Like Sally many women conducted their own 'research' as to who were the experts in mitochondrial disease and who could help them further 'it was me that kinda did further investigations and then I got in touch with [mitochondrial specialist]' (Lucy: 19-20) and that the internet 'opened the gate for me to speak to [mitochondrial specialist]' (Sarah: 413-414). A common criticism on the

information available to women from sources linked to specialist centres was that stories featured did not represent their experiences of mitochondrial disease; where stories of severe phenotypes were more present than stories of those more mildly affected. This caused some women to feel anxious about their diagnosis. Sarah found this was the case during her initial investigations using a dedicated mitochondrial disease website, after having established that her diagnosis was not fatal.

Sarah: Their newsletter, their website for patient information and it was all great I thought it was fab but also, I kept thinking well this isn't me, I'm not in a wheelchair  
Int: Yeah  
Sarah: You know it doesn't impact my daily life, yes it does impact sort of the [Symptom] thing erm but that not really the mitochondria it was more starting to make me worry about the future ... I just kept thinking aw these poor people  
Int: Yeah  
Sarah: All these poor people but that's not me but am I going to be like that' (Sarah: 405-417)

For Sarah, she had been very relieved that her diagnosis was not fatal, she was also satisfied that the information she had was enough for her not to alter her plans to start a family (see Chapter 7 section 7.4.1). However, she felt that information published about living with a mitochondrial disorder was not tailored to her, aimed at those much more affected than her and so was not comparable to her current or possible future experience. The disparity has also been reported in bipolar disorders, with caregivers reporting that in contrast to the above, on evaluation of the usefulness and acceptability of an information website respondents felt information was directed at those with milder symptoms, with less provided in relation to those supporting family members or friends with chronic, severe or complex symptoms (Berk et al., 2013).

Andi also felt this way with regards to the level of information available to adults in comparison to paediatric patients, where her experience of mitochondrial disease is of slow progression unlike that of severely affected adults and children: 'I don't know, it doesn't feel like it's for me; (Andi: 523). Andi found that information available for patients when she was first diagnosed, the pamphlets

and website she found, was adequate enough for her at first. Over time no new information had become available via these routes or via dedicated social media platforms. Andi suggests many different areas of research that could be shared with patients, not just research centring on mitochondrial donation (which had just been voted on in the houses of parliament prior to her interview) but how mitochondria have been linked with other disorders and how this would be very interesting to mitochondrial patients to know.

Andi: For instance I know there has been research in other field's erh connecting mitochondrial erm issues with Parkinson's or Alzheimer's and there's been research into whether a lot of the other illnesses the cause is in the mitochondria  
Int: Arh right yeah  
Andi: So that would be interesting to somebody who has mitochondrial disease  
Int: Yeah  
Andi: Cause you think well there's not a lot of research in our field apart from this IVF thing (Andi: 544-550)

Andi appears passionate about this subject and she feels that other mitochondrial patients would want to know about links to other conditions as well. There is little chance of people finding out about these advances 'because it's quite niche it's not something that's going to make the news unless it's a slow day' (Andi: 564). She feels that much of the relevant research is restricted to 'medical journals or research journals which we don't normally have access to' (Andi: 473-474), that require 'deciphering' so that 'ordinary' people can read them. She, like some others, is seeking to further her understanding of the disease in terms that make sense to her. In practical terms, she is seeking a more open, accessible and democratic knowledge about her disease.

Andi highlights that on-going information provision is important to her and could be to other patients, especially when research may go on to affect them in the future. The emergence of new knowledge from research and its communication to patients was also an issue for Miriam and her family; they felt that although there was lots of new information available she found it difficult to know what was relevant to her and her family. She describes that patient information days and

improved websites are helpful by that she feels that she does not receive answers to all 'her' questions.

Erm, so the last meeting we had was good information there. But sometimes you find when you ask, I always have questions to ask and I feel they're not always answered. They're kind of hmm, the one says to me, that's rubbish and that's not gonna happen  
(Miriam: 602-606)

This is specifically relating to potential participation in a clinical trial, a central question for Miriam was 'if the UK centres will not participate in the study then what else are they doing for patients?' Miriam like many others is frustrated with the lack of therapeutic options available and would like more information about potential experimental therapies that her child may take part in.

The receipt of a diagnosis led many women to seek further information about mitochondrial disease themselves, often online. Some women recounted that this was something they 'had to go away do' following their diagnosis, whilst others researched mitochondrial disease after a less than satisfactory consultation. Information seeking in this way has been said to be the start of the 'emotional work of grief and acceptance' for parents of children affected with rare disorders and that the knowledge gained by this helped parents to address uncertainty and re-establish a life in which their child's disorder can be managed (Gundersen, 2011:p91). Searches often produced worse case scenarios, leading women to fear that they or their family members prognosis may be fatal. These feelings were alleviated once they or their family member received an individualised specialist assessment. Factual awareness of mitochondrial disease and its role in reproductive decision-making is explored further in Chapter 8. Women felt that these search results did not mirror their experiences of the disorder, especially if they felt that they had mild symptoms; feeling sympathy for those more affected than themselves. Finally women wanted to be part of generating new knowledge, including recommendations for the dissemination of understandable science relating to mitochondria and its role in other diseases and participation in clinical research. This desire also mirrors Alice's in Chapter 5, who wanted to be able to take part in research not only for her family members but also the wider community affected by mitochondrial disease.

### **6.2.3 Disclosure**

Following the receipt of information that they, their child or their family member had a possible mtDNA mutation or had already been diagnosed, came the process of deciding who in their lives became privy to this information. Sharing of genetic information within families, especially with at-risk relative(s), and its complexities has been written about extensively within the literature, with many clinical and ethical guidelines along with policies of best practice published (Forrest et al., 2007; reviewed in Gaff et al., 2007). The process of informing others of their potential or diagnosed mtDNA mutation was complex for many of the women. Issues faced by women included decisions as to whom to tell and whom not to tell, disclosure of the genetic cause and how this disclosure or non-disclosure helped them in living with their disorder.

#### **a. ‘Telling others’**

As we have seen in Chapter 5 a large majority of women were informed of their risk of having a mtDNA mutation from either a maternal family member or from their child’s clinician and so were therefore not the primary receiver of the family’s diagnosis of mtDNA mutation. For those informed this way they still found themselves faced with scenarios regarding further disclosure to other family members. In this study women chose to tell those who were considered as socially significant that they might have ‘some kind of genetic condition’ relatively fast, even in circumstances when a diagnosis was not confirmed. Socially significant in this context was found to be their partners (if in a relationship), siblings, their parents, specifically their mothers and close friends. Many women also described telling their ‘in law’s’ but did not find it necessary to go into detail about their diagnosis as it was felt that they did not really understand. For those women who had strong relationships with in-laws, such as their sister-in-law, they were included in the socially significant group as both family and close friends.

Providing information to others about their specific prognosis was important for women and their family members. As we’ve seen above, establishing if their diagnosis was life threatening was a main priority.

I think he was more concerned is it something terminal, “it’s not terminal is it?” something erm can’t remember what the other things could be but … it wasn’t something, I think once you rule out that it’s not terminal you sort of arh well I’ve I’ve had it’ (Andi:137-139)

For Andi’s husband hearing that her diagnosis was not terminal was the most important thing to him, so much so that Andi cannot recall what other future potential symptoms she may have been told about at her diagnostic consultation. As for many women’s partners, friends and relatives, establishing the severity and prognosis of his wife’s diagnosis was Andi’s husband’s main concern.

Many women chose to tell those who may also be at-risk, maternal family members ranged from siblings and their mothers as well as at-risk cousins and their children. This was seen primarily to be related to their feelings of guilt and responsibility (discussed further in Chapter 8, section 8.7.2) and supports the existing literature on ‘genetic responsibility’, in that individuals take on not only responsibility for themselves but responsibility for other at-risk biological relatives (Arribas-Ayllon et al., 2011; d’Agincourt-Canning, 2001; d’Agincourt-Canning, 2006; Dimond, 2013; Hallowell et al., 2003; Novas & Rose, 2000).

Women described sharing genetic information in family groups as a form of support, especially in those families in which there were multiple people affected. This echo’s work done on the key reason for communication of *BRAC1* and *BRAC2* genetic test results amongst sisters, which showed that 74% of their sample shared genetic information in order to obtain emotional support (Hughes et al., 2002). For Alice finding out her diagnosis meant she felt that she could better support her affected family members ‘I felt better once I knew, I could support my [family members] more’ (Alice: 407). Although Alice did consider this might seem ‘silly’ to say, she recalls telling a relative about her diagnosis via text message after her consultation.

Alice: As I said, we’re in the, we’re in the, we’re in the gang.  
And, er, I can remember when I came out of the hospital  
and I text [Family member X] because [Family member X]  
and [Family member Y], I was-

Int: Yeah.

Alice: Only with [Family member Y] when I was diagnosed and,  
erm, [Family member X] was, I don’t know, [Family  
member X] might have been at work or something. And I

text [Family member X] to say, "I'm in the gang." And she went, "I knew you would be," type of thing  
(Alice: 2869- 2879)

For Alice, disclosure of her diagnosis to the family member who had first been diagnosed was relatively informal, via a text message following her appointment. Alice also wondered that had she not have tested positive for the family mutation, whether this would have somehow separated her from these relatives 'It would have changed things a lot, wouldn't it?' (Alice: 2887). Alice tells us throughout the interview that those members of the family who are affected share together their experiences of their illness that she finds very comforting 'I think we support each other a lot' (Alice: 2894).

Parental disclosure of illness and its aetiology to children varied depending on their 'at-risk' status and their age. For women whose children were affected, their child's illness meant that siblings were aware of the struggle to find out what was wrong with their brother or sister, irrespective of age. Inheritance patterns were also not withheld from siblings. Sally discussed their family mutation with her children who were still of school age 'I also want them to know that, about our condition and our gene and our family' (Sally: 404-405). It was important to Sally that they grow up with an understanding of their family's mutation - 'our gene' - but also that it affects people differently and to be empathetic to people with disabilities. Sally engages with social media to assist with this, included in more detail in Chapter 8 section 8.3.1. Johnson et al (2005) showed that parents of ill children shared their child's medical diagnosis more often than affected adults disclosed their own diagnosis, and parents were also less likely to regret this disclosure (Johnson et al., 2005).

Disclosure was complicated by women's own lack of understanding of the complexities of maternally inherited mitochondrial disease. Frustrations arose when women found it difficult to understand their diagnosis and when they were unable to answer questions from others. Sally found it difficult to tell people about her family's mutation because she did not believe her family showed typical signs expected from their mutation 'so it's a little bit complicated really, it's not just a straight forward thing' (Sally: 132-133). Lack of understanding was however

combated with the introduction of analogies used by mitochondrial specialists to explain mitochondrial disease to patients. Women found these helpful for their own understanding and went on to use these to tell others of their condition and how it affected them.

Liza: I didn't really know what it meant just sort of had this mutation erm in me you know DNA and at that point it was very hard to try and tell somebody what it meant, what [SYNDROME] meant erm you know it wasn't until good years later when they started using that term about the batteries

Int: Right

Liza: So at the time it was kinda like arh yeah we've got this family and were researching it through through the hospital but that was it really

Int: And did you then tell that it might be carried through the female line, through yourself or did you not

Liza: No no I don't think I did

Int: Or did you not go into it

Liza: I didn't really go into it no, I think it was just more because there wasn't much ... for me like information for me to pass on at that point

Int: Yeah

Liza: Erm so I kind of just just left it cause again it's very hard for other people to to understand when you're fine  
(Liza: 228-242)

Liza found it difficult to tell others about her family's diagnosis as she felt that there was not enough information available to help her do so. Liza showed signs of struggling to understand, as did other women, what the differences were between their family's genetic mutation and the phenotypic syndrome that someone in their family had or were currently suffering from. For example, Ashley described herself as having a severe syndrome 'I have [SYNDROME], if that helps, I am not sure' (Ashley: 10) but also that 'I'm not really affected' (Ashley: 11).

Liza chose not to disclose to others that her condition was maternally inherited but was comfortable informing others that it was to do with 'family DNA', again because of the lack of information available to her. Disclosure was further complicated for Liza as she herself does not experience any signs of illness, she's 'fine'. Liza found the introduction of the analogy of batteries very helpful,

this being that mitochondria are the batteries of a cell that provide energy to enable the body to function, without these or 'faulty batteries' the body is unable to function how it should. Women also used their own scripts to 'quicken' up disclosing how their mtDNA mutation affected them to others. Sarah tells us that she does not share information relating to her mtDNA mutation readily. When asked how Sarah had dealt with questions relating to her multiple hospital visits and time away from work, she tells us that she used a short script to explain her condition.

Sarah: Oh gosh ... well ... I say that ... it's about an energy supply that affects the cells in the DNA that makes muscles work and fortunately for me ... it's only affecting my [X organ] but they've got to keep an eye on me  
Int: Yup  
Sarah: and that's what I say ... now and that's the shortest quickest  
Int: Un hun  
Sarah: But I don't think that doesn't that in any way explain the severity of it ... at all (Sarah: 236-242)

Although she prefers not to tell others when asked Sarah, like Liza, is comfortable disclosing that she has a genetic condition. She discusses 'energy supply' and how this affects her that she is 'fortunate' that it affects only one organ and that it requires a level of monitoring from health care professionals. For Sarah this provides enough information needed by others, but she recognises that this script does not represent the 'severity of it at all', which could be heard as both the severity that Sarah experiences as well as the severity of mitochondrial disease as a disorder.

Difficulty in explaining to others about complex rare disorders and their implications has been reported in other conditions, scleroderma (Joachim & Acorn, 2003) and phenylketonuria (PKU) a disorder that has significant social implications due to diet restrictions (Diesen et al., 2015). Use of analogies is common practice in health care and can be used both to help patients to described their symptoms to their doctor and used by doctors to help patients understand and cope with symptoms (Fuller & Hughes, 2003). Most notably mitochondria as the 'battery of the cell' has been used extensively in ethical and legal scholarly debates, parliamentary consultation materials and in media

reports around the world during the UK parliamentary consultations and debates (see Chapter 2). Mitochondrial donation was explained by the analogy of ‘changing the batteries in a camera or a laptop’ (Barber & Border, 2015 p22; Watts et al., 2012 p53 & p78). The use of such analogies or scripts were memorable to women and used by many to tell others of their condition, they also permitted women to modulate how much information they provided to others, in that it did not require them to specifically mention what organ or system was not functioning correctly.

Close friends or the ‘inner circle’ (Wendy: 195), were included amongst the people informed of the illness. This was often as a form of emotional support for women. It provided an explanation as to why some woman had made lifestyle adaptions such as walking at a slower pace, taking naps, using walking aids and in one case explained a woman’s anxiety about looking after small children in the family. There was a mixture of those who provided either information regarding the maternal inheritance pattern, a ‘genetic condition’ or provided no specific information regarding either. This disclosure was based on trusted relationships with friends. For some women their diagnosis legitimised their experience of unexplained illness to others who may have questioned them, as we’ve seen in Chapter 5 in relation to Jenny’s childhood GP, Lucy’s PE teachers and Joanna’s partner. For some this seemed to be experienced at a much more significant level, especially when prior comments had caused them lasting upset as we have seen with Lucy’s experience of being stigmatised as ‘lazy’.

Some women also found it helpful to discuss their diagnosis and how it affected them with their employers and colleagues, this allowed them to tackle issues such as hearing impairments, ataxia, fatigue and mobility issues in the work place. Sometimes this disclosure upon diagnosis was due to concerns over employment contracts that required medical conditions that could affect their performance or pose a safety risk to be disclosed: ‘I’m contracted to tell them’ (Alice: 1528). It also emerged with regards to arranging working hours, a suitable office layout and helping colleagues to understand what they are living with.

I was quite open about it. I believed that erm keeping it, like not telling people, erm, and having them kind of judge me based on what they were seeing without understanding what was actually wrong, erm was, wasn't going to do anybody any favours. I thought it was better taking it out in the open and I actually printed off sheets about mitochondrial disease and gave them to like my team at work and my manager and things like that, to help them understand a bit more about what I was dealing with (Holly: 612-621)

Holly was the most proactive amongst the women who informed their employers, as well as providing medical letters or visiting occupational health as others had, Holly printed off information sheets for her managers and colleagues to enable them to understand more about her condition. For Holly, she had made a number of employment decisions in the past relating to symptoms that were later attributed to her mitochondrial disease, these had included leaving full time study and giving up a place on a workplace training scheme. She felt that being open about her diagnosis helped to prevent other people from judging her with regards to her working hours and patterns.

Disclosure and confidentiality were synergistic for many women, however some women were faced with losing their anonymity either partially or completely when participating in charitable fundraising or via political engagements that involved local, national and international media. During parliamentary debates many women contacted their MP to vote on their behalf and as result were then known to them as an 'affected family'. To prevent any possible identification, I have actively chosen not to include supportive quotes relating to personal media campaigning (available on request), however a proportion of women spoke about how their interaction with media at the time of debates meant that friends, acquaintances, employers and colleagues became aware of their diagnosis and their lived experience of mitochondrial disease if this was shared. This disclosure to those around them and to a broader public was not considered problematic by those women, but does raise awareness of what it means to be a 'public patient' and its impact on confidentiality and disclosure.

### **b. 'Not telling'**

For some women disclosure was problematic and included hesitancy to inform at-risk female siblings or children and non-disclosure to elderly maternal grandparents and employers. Hesitancy to inform their adult at-risk siblings was seen when women wanted to delay their family members from experiencing the parental guilt that they felt toward their own children. Those women who had hesitated to tell their adolescent or young adult children did so because they believed them to be healthy and wanted to delay them informing them. For Maggie this included brief disclosure to her teenage children around the time of her diagnosis, but this was more to abate their concerns that their mother was very ill and may have been told she had a terminal illness.

so I sort of explained to them what it was, but I didn't really sort of say to them, "And yous have probably got it as well" ... I said that it was a genetic condition. That was all I sort of said (Maggie: 607-616)

For Maggie ensuring that her children did not worry about her was the driving force behind telling her children; she did disclose that she had a genetic condition but did not explicitly tell them they may also be at-risk of having the same mutation. Maggie eventually went on to tell them when they were older after discussion with a mitochondrial specialist, although she was not entirely comfortable with doing so.

Disclosure of a genetic condition was often withheld from elderly mothers or maternal grandmothers, with many women citing that this was to protect them from feeling the guilt that they themselves felt towards their own children. In addition to this, the complexities of mtDNA mutations also meant that their mothers or maternal grandmothers may not harbour a mtDNA mutation responsible for their child or grandchild's illness and they may evoke distress for no reason. The role of guilt and responsibility is discussed in detail in Chapter 8 section 8.7.2.

Disclosure to employers however was seen, in comparison to examples above, as problematic for some women. For Wendy, concerns that knowledge of her diagnosis may negatively impact her employer's perception of her ability to

perform at work. When discussing whom Wendy has chosen not to tell about her diagnosis, Wendy tells us that

Well it's not affecting my health and my work but also I don't want it to in anyway sort of jeopardise my career (Wendy: 206-207)

Wendy had two reasons as to why she had chose not to tell her employer, the first being that she did not experience any symptoms associated with her mtDNA mutation (having been diagnosed via a sibling) – and is in contrast to Holly (see above) who experienced significant disease burden and was very open with her employer. Secondly, Wendy felt strongly that it could jeopardise her career, in that knowledge of her diagnosis may in some way result in discrimination against her, not uncommon amongst patients with genetic disorders (Lapham et al., 1996). Wendy sees this as a serious concern due to the nature of her work and the mental capacity that it requires.

In summary we can see that disclosure is complex for women with mtDNA mutations and can affect every aspect of their life, including relationships with family members, friends, colleagues, employers and in some case the public. The role of 'genetic responsibility' and its impact on reproductive decision-making is explored in detail in Chapter 8 section 8.7.2.

The receipt of diagnosis, either directly or indirectly meant that women were faced with decisions as to whom else to share this information with. Women shared information of their diagnosis with socially significant individuals relatively fast, with news of their prognosis being the most important to these individuals. For those women who shared this information with family members, they felt a sense of support, where as some chose to withhold information either temporarily or indefinitely from family members whom they did not feel able to tell or who they felt it was unnecessary to tell due to the upset caused. These feelings of 'genetic responsibility' are closely linked with guilt and responsibility which is included as an influential factor in the proposed conceptual model of reproductive decision-making (section 8.7.2)

### **6.3 The Long-Term Impacts of Diagnosis**

For a number of women in this study, the long-term impacts of their condition pre-existed their diagnosis. In this section I discuss both these long-term symptom related experiences and if and how they were impacted on by receiving a diagnosis. This section is central to women's experiential knowledge of mitochondrial disease and highlights its disruptive nature on their lives.

For a proportion of women in the study their mitochondrial disease had become progressively worse over the years, requiring additional care and lifestyle adaptations (Garrino et al., 2015). Additional care often included being referred to other specialists and managing symptoms as well as possible, given that no specific mitochondrial treatments are known to date. Women discussed how their progressing symptoms affected them at home or work, more than they did their medical care. For Alice and her family, it was arranging for a hairdresser to come to their home as removing hearing aids in busy salons was distressing. For Andi it was using a walking stick to help her when out with the family on day trips. Some women however experienced more significant changes to their lives as a result of their or their child's changing requirements including impact on social relationships, emotional needs, education and work, which I will discuss in turn.

#### ***6.3.1 Social Relationships***

For those women physically affected by their mtDNA mutation they experience biographical disruption, as they undergo a 'period of adaption' to the emerging symptoms but have 'access to periods of classic sick role behaviour' when they experience symptom progression or exacerbation of existing symptoms (Bury, 1982. p168). When discussing who knows of her diagnosis, Andi tells us that she had had to explain to others more as time goes on due to her disease progression. A sign of progression for Andi had meant that she had started to drop items but only noticing that she had when they hit the floor, due to lack of feeling in her fingertips, 'there's an adjustment period you adjust to that and then you're fine again' (Andi:168-169). For Andi, managing and adapting to her disease progression was central to her feeling 'fine again', a reaction also reported in other rare diseases (Garrino et al., 2015). For Liza, she had grown up in a family affected by mitochondrial disease and was already aware of the potential disruptive impact of certain known symptoms. She therefore felt

prepared to deal with the symptoms associated with their family's mtDNA mutation if her future child was to suffer from these.

Liza: I was like well we can cope with [Symptom A], [Symptom A] fine, you know [Symptom B] yep its very rife now can deal with that, you know other bits and bobs and so my view was ... even if I, I knew I was passing on I knew that was the one thing

Int: OK

Liza: I knew I was passing onto my child but I thought whatever I pass on ... is going to be fine it's its manageable millions of people manage it (Liza: 120-125)

These 'socially acceptable and manageable' symptoms did not pose a concern to Liza when considering her reproductive decision-making she felt that society as well as her family would be able to help support a child if they were to experience these symptoms. For Lisa her lived experience of mitochondrial disease did not impact her reproductive decision-making in her first pregnancy but a family fatality had a profound effect on Lisa feelings towards risk and uncertainty associated with their shared disorder (see Chapter 8 section 8.3.1).

Experience of chronic illness is also said to lead to individuals retreating from social interactions because of the impact of their symptom (Jefferies & Clifford, 2011; Jeon et al., 2010). Strauss (1975) argues that although this can be seen as understandable it can become problematic. Uncertainty and unpredictability of symptoms have been linked to anxiety and depression due to lack of social contact and increased dependency on others (Barlow et al 2007). For Holly she felt that relationships with some of her friends became strained both before and after her diagnosis, with many believing her symptoms were psychosomatic (see section 5.3). She describes incidents when she lost friendships she had had since childhood and that even recently she felt that some friends had been 'really, really angry' (Holly: 682) with her 'spoiling' events.

Erm, I lost a couple of friends because of it, because erm I had a, like because my symptoms were meaning that when I was going out I was having to, I was taken unwell and I was having to leave early, or I wasn't, I was just going out and, or I just wasn't able to go to things ... And I think it

got to the point that it was easier just to not invite me to things as to actually invite me and deal with the outcome of it, sort of thing, which was hard. It's hard to (Holly: 622- 650)

These losses and strained friendships had impacted on Holly quite considerably and she expressed feelings of selfishness for feeling like 'I want to be like everybody else. I want to join in and have fun' (Holly: 725-726). These feelings had led her to seek counselling to address this impact.

Holly was not alone in feelings of isolation. Miriam describes how her child who is affected feels isolated from people their own age. There was a strong sense throughout Miriam's interview that the lack of communities for affected mitochondrial patients was troublesome for her and her family. She was very upset when discussing this topic and returned to it as a major issue throughout the interview. Miriam's feels that these communities exist in other conditions, notably Duchenne Muscular Dystrophy 'they all keep in contact with each other, they all see each other' (Miriam: 370-371) but that her family are unable to fit into any of these neuromuscular groups.

Miriam would like to meet people with the same mutation as her family's, she would like this because of how unpredictable her child's phenotype can be. She ponders whether or not her family's mitochondrial specialist team may be less forthcoming with details of similar patients to her child in order to protect them from witnessing how severely it can affect a person.

But all we want to know is because of this unpredictability we, we should know of the people have got this condition. Maybe they're worse than they think they are. We don't know whether they're [mitochondrial specialists] trying to protect us, we don't know, but it would be nice for [Child Y], who's got something similar to [them]. They truly understand each other. (Miriam 634-640)

Throughout these segments of the interview, what is key to Miriam is that she wants to locate peer support for her child. Miriam had also exhausted symptom specific support groups but to no avail, 'we always ask, well what kind of people go to the thing 'cause we've had some really odd experiences' (Miriam: 524-525). Many of these groups included elderly members only and when specifically asked if there were any younger members or groups known

to them, Miriam was told there was not. Given that Miriam's affected child was a young adult these groups were not suitable to their requests for peer interaction and support.

Miriam: but [they] wants some people to understand and they are [their] age  
Int: Yeah  
Miriam: More fun for [them] rather than people our age, older than us, what on earth [do they] want to be around them for, "cause we're older, we've lived our lives"  
(Miriam: 536-543)

It was distressing for Miriam that she was unable to find the peer support that her child had wanted. However, just before taking part in the interview, Miriam and her family had been approached by a stranger whilst in the park who ran a sailing club for people with disabilities. Miriam and the family were excited to go along to the club in the near future and were hoping that this would be what they had all been looking for.

### ***6.3.2 Emotional Support***

For some women, receiving news of their diagnosis and the diagnosis of their family members was a particularly emotional experience and continued to be for months and years afterwards. Two women specifically spoke about their desire to seek counselling for themselves and family members in relation to their diagnosis, with both women becoming very emotional when describing how they felt that they or their family member had not been offered or received any support such as counselling.

Jenny had and is still struggling with her and her child's diagnosis, who at the time of this interview was a young adult. She tells us a number of times throughout the interview that she wished there was emotional support via a counselling service to help them come to terms with their diagnosis and to manage their disease progression, she feels that this is where the care provided to her and her child is lacking.

Jenny: Yeah I think yeah that probably were the [service] falls down  
Int: Right  
Jenny: There is no counselling and there's erm no  
counselling for the kid either (Jenny: 299- 301)

Jenny had hoped that there would have been more emotional help for her child as their disease burden had become, 'worse and worse and worse' (Jenny: 355-356), she becomes emotional when recalling these memories. Jenny would like to have seen these services available to her child to deal with their changing body especially as this was occurring during their teenage years. Jenny had requested assistance from her child's mitochondrial specialist but as this specific counselling service were not available via the team, it took many months for an appointment letter to arrive from what appeared to be a generic counselling department. This appointment was not attended, as it was felt by Jenny's child that it was too late, "it doesn't matter" (Jenny: 401). Jenny recognises that there is now more of an emphasis on talking therapies available via GP's in primary care than there was at this time 'I mean now they're more into talking therapies and stuff like' (Jenny: 404). Jenny also recognises that there are budgeting pressures that can prevent the level of care that she would have wanted 'it all boils down to funding and money and stuff' (Jenny: 312). Jenny feels that they would have also required a specialist counsellor with an awareness of mitochondrial disease.

Jenny: It's changed a lot erm so probably even then even had  
have went to see a counsellor the counsellor probably  
wouldn't have been ... able to deal with it you know  
what I mean  
Int: Yeah  
Jenny: Cos it's like completely like, it's not like just somebody  
going in and going arhh I'm stressed and my work is  
driving me mad where as you go what's happening to  
us and I don't know what is happening to us  
(Jenny: 406-412)

For Jenny an ordinary counsellor would not have been able to help them, as she and her child weren't like other people and their stressors were not 'ordinary'. Jenny describes wanting to know more about what was happening to her and her

child's bodies but less from a medical side and more in order for both her and her child to cope and understand these changes more. Jenny also struggles with the emotional burden of the maternal inheritance of their mutation (see Chapter 8 section 8.7.2) and believes that, even after more than a decade of living with this knowledge, she would like the opportunity to discuss this with a trained counsellor.

### **6.3.3 Education and Work**

Uncertainty features in the lives of women with mitochondrial disease in relation to the education including mandatory and higher education and women's employment. Women provided a number of varied accounts of both educational and employment institutions failing in their ability to cope with the uncertainty and unpredictability of mitochondrial disease, both pre and post diagnosis. As a result, some women found themselves needing to leave university courses and employment training schemes as well as seeking roles that offered flexible working to accommodate in most circumstances, feelings of fatigue. These experiences contributed to women's lived experience of mitochondrial disease, which is discussed in Chapter 8 in relation to reproductive decision-making. The long-term effects of restricted access to education and employment and their associated negative financial implications have not been assessed in mitochondrial disease. Although outside the scope of this thesis it is evident that mitochondrial disease impacts upon these areas, leaving some women (and their children) navigating complex relationships with societal institutions.

Jenny offers an insight into her child's experience in compulsory education and how having mitochondrial disease affected their schooling. Jenny was a fierce advocate for her child during their time at school, particularly in relation to their time at secondary school, which she describes as not being equipped to accommodate someone with the needs that her child had or making an attempt to after they were advised by a specialised physiotherapists, citing that adaptations 'never got done' (Jenny: 367-368). This unwillingness or inability to address the needs of Jenny's child highlights an area of society that is ill adapted to accommodate the needs of mitochondrial patients, which in this case resulted in not only frustration but also restricted GCSE options due to physical access to classrooms and excursions.

For Maggie, her employers and colleagues were initially very compassionate and accommodating to her symptoms and news of her diagnosis. Over time and in conjunction with an increasing number of symptoms such as stumbling and loss of balance, Maggie's employers became frustrated with her unspecified disease prognosis. Maggie felt that this was due to their anxiety that a serious incident may occur whilst at work. As symptoms progressed Maggie changed job roles within the same company, retrained and secured a promotion. For some time this was suitable, until additional symptoms meant that Maggie needed to reduce her hours. Unfortunately, this request was not suitable and Maggie felt that she had 'had enough' and that she had 'no support'. After some time off work, Maggie returned to a new part time role in another company that offered flexibility around her symptoms.

Living with unpredictable and uncertain symptoms has been reported in those living with blood clotting disorders, who reported that their disorder had had a negative impact on their education and their employment, with some losing their job or retiring on health grounds (Barlow et al 2007). As a result these individuals also suffered from 'severely reduced' incomes (Barlow et al 2007:p238). When exploring the impact of symptoms on women and their education and employment it is key to not underestimate the societal and individual value of 'work' and the potential impact of being labelled as 'disabled' at work can have on a person's identity. Fryers (2006) discusses how those workers with disabilities may suffer 'discrimination as non-workers' and loss of their identity (p4). In the accounts provided from women within this study, this could include the loss of their identity as departmental managers, employment training program candidates and as university students.

#### **6.4 On-going Clinical Relationships**

Being diagnosed with a mtDNA mutation generated new clinical relationships with mitochondrial specialists for the women in this study. However, they also had to continue to negotiate pre-existing relationships with health care professionals with their new diagnosis. This section provides context by reflecting on women's negative encounters with health care professionals prior to being diagnosed, before exploring their accounts of these relationships after being diagnosed as well as detailing women's positive experiences of engaging with specialist care.

#### **6.4.1 Negative Encounters with Non-Specialist Healthcare Professionals**

In Chapter 5 we saw multiple examples of women who struggled to convince their GP that their symptoms were 'not in their head', with many waiting until further symptoms appeared to seek further medical advice. Some women however struggled to be 'believed' even when under specialist review. Holly experienced personal ill health for a number of years before her diagnosis with ever increasing disease burden over these years. When referred for further investigations Holly tells us that she was made to feel that her symptoms were 'all in my head' until the point where her examination showed that something was not right.

Holly: When I went to the [Symptom Specialist] the first time he erm, I left that appointment in tears because he basically told me that erm, like he, before I went on the treadmill he initially was saying you know, "Your medical file is massive for somebody your age. Is your family supportive of you getting all these tests?" And he pretty much accused me of having, of it all being psychological and said

Int: That's not helpful.

Holly: You know, there's this great psychosomatic disorder that can be if you're, you know, it can be like to do with stress and different psychological factors, and it can present itself and cause physical symptoms. I left that appointment thinking, "God, is this all in my head?" Like, he had me sort of believing that, right up until I went on the treadmill and then he totally changed his tune when he seen the reaction that I had on that.

Int: Yes.

Holly: But it was hard. But yeah, having a name for it made a difference. It, it kind of validated basically everything that I had said, and the fact that I had had all these symptoms, and really that it wasn't in my head, and they were all real.

(Holly: 319-333)

Like previous examples, Holly experienced an accusation that her illness had no physical cause. This encounter and how she was made to feel after seeing this specialist is clearly very memorable for her. As discussed previously, for her and many others in the study, validation of their illness from a medical professional was a very important milestone for them.

Unfortunately for Holly, negative experiences with health care services have continued since her diagnosis, with more than one incident relating to the provision of emergency care via the ambulance service in her region. The events

described by Holly were in relation to the ambulance services call handler's lack of knowledge of mitochondrial disease and how serious Holly's symptoms were. Holly describes falling very ill at a friend's house party

Holly: And then there was in issue because I had mitochondrial disease, erm there was nobody there that could run me, like to drive me to the hospital, so they said well the best thing would just be to phone an ambulance, but when we phoned the ambulance they had never, they didn't know what mitochondrial disease was. They couldn't understand the need for me to have an ambulance because they were like, "Well, just put her in a taxi, why do you need an ambulance?" Erm, and it took three hours for them to actually put a, get an ambulance out' (Holly: 689-698)

Holly stayed in hospital for two days after this event, and went on to experience many more episodes of hospitalisation during the course of that year. Lack of knowledge in the wider medical community of the potential dangers of mitochondrial disorders meant that even with a diagnosis, Holly's symptoms and the seriousness of them was overlooked by emergency call handlers. Holly's experience not only reiterates the unpredictability of the disorder and how uncertainty affects social relationships and can lead to isolation, but also how lack of knowledge in the wider medical community causes practical, emotional and health problems.

Distress from not receiving the appropriate care even after diagnosis due to lack of medical knowledge of mitochondrial disease was not uncommon. Miriam found that because her symptoms were different from her child's presentation that her GP did not believe that she was actually affected. When discussing how she had tried to seek help from her GP regarding her concern for herself and her family, Miriam tells that:

Miriam: But you mention mitochondrial, you mention the word [SYNDROME] they just laugh at you, what on earth and they describe what [Child Y] got and they want to look for [SYNDROME]. Well for goodness sake, it's just sounds like a made up name, 'cause they're all made up like that. They sound a bit weird and I think [GP] for my doctor I see, he's great with [Child Y]. He doesn't understand the condition affects us all, you know. So when I go down I said - he said,

“You haven’t got that condition.” I say, “Well, I have.” ... So when we go with [Child Y] and I go, he doesn’t really associate it as us all having it. He doesn’t really understand it. Erm, so one day I think I went to see him, erm, and I said, “My [Child X] made this appointment, I’ve not made it. They think I’m depressed, I’m not depressed, I’m just concerned.” And, erm, he just goes, “Oh I understand, you’ll be okay.” I’m thinking, “You don’t ...”

Int: He can’t say that.

Miriam: You know, he can’t, that’s kind of annoying (Miriam: 663-698)

Miriam finds that the complexities of the sub-types of mitochondrial disease make understanding mitochondrial disease even harder for her GP and other health professionals. Miriam feels that her GP is unable to associate the genetic condition to her and other family members, that he does not understand their mitochondrial mutation and as a result is unable to offer the level of care she and her family believe that she needs. Like Miriam, other women experience similar encounters with their GP post diagnosis, recalling events when they have been told by their GP that “I actually don’t know anything about it” (Maggie: 3232) and that ‘he says “I really must read up on it” (Maggie: 3255). This results in many women choosing to bypass their GP and instead directing all their clinical queries to their mitochondrial specialist, or to their trusted symptom specialist, which I will now go on to discuss.

The impact of being diagnosed for women who had negative experiences of health care provision prior to diagnosis, was not an improvement in their experience, but a change. Non-specialist health care professionals were ill equipped to manage the uncertainty and unknowns of mitochondrial disease. Whereas previously women felt that their symptoms were not necessarily believed, having been diagnosed, they now felt that non-specialist health care professionals did not know and were unwilling to learn how to support them adequately with their condition.

#### **6.4.2 Recognition and Referral**

Persistent negative encounters in primary care and misdiagnosis in other specialities meant that for some women their relationship with the person who signposted or referred them to mitochondrial specialists or mitochondrial

specialists themselves become very important to them. In addition to being the ones who initiated or confirmed their diagnosis, these specialist have assisted them in accessing various types of support since, which as we've seen above is not always easy for patients with mitochondrial disease. This translates to them seeing these health professionals as those they can really trust.

Specialists who signpost or referred women (or their family members) for diagnostic testing are seen to be the person that if they had they not met, they would have never received their diagnosis. In these circumstances women speak highly of these individuals and subsequently return to them not only for symptom specific care but to also discuss information provided by other clinicians who were unable to provide the level of clarity they required. When discussing how she received her diagnosis, Sarah tells us that:

Sarah: It was quick, during my appointment there was a fire alarm, so we all had to go outside so that was all interrupted erm ... so I had about 10 minutes with him that was it  
Int: OK  
Sarah: Where [Regional Neurologist] told me not to really worry about anything, then did [Investigative test] which obviously made me worry, but then I was seeing my [Symptom Specialist] ... erm about 3 weeks later  
Int: OK  
Sarah: So that was actually really quite helpful because it allowed me to go away  
Int: Absolutely  
Sarah: Think about the diagnosis, think about all the questions I had erm and come back to appointment my with [Symptom Specialist] prepared (Sarah: 112-121)

For Sarah returning to her symptom specialist after her diagnosis allowed her time to think of all her questions surrounding the news of her mtDNA mutation and was able to ask them at her appointment with them. Sarah speaks very highly of this individual many times during her interview 'amazing, absolutely amazing' (Sarah: 175-176) and when describing the care received at their clinic 'it's been a really good experience and their care has been amazing' (Sarah: 183-184). They were not only the person who prevented drastic measures being taken (a symptom related operation that would have left Sarah with sight in one eye only) but they were also the specialist with whom she discussed her

reproductive decision-making with. Sarah recalls discussing ideas of what is 'a normal life' and her symptom specialist's giving her anecdotes from earlier in their career about people living with disabilities and how everyone's normal is different. We will see in Chapter 7 that advice from experts was an important factor for Sarah in deciding to start a family.

Seventeen of the 18 women in the study had received their diagnosis from laboratories based in one mitochondrial specialist centre, and as we know not all received their diagnosis from a mitochondrial specialist. Eleven women were informed of their diagnosis from a mitochondrial specialist at the same specialist centre, whereas seven women were informed by either their general neurologist, symptom specialist or via a mitochondrial specialist located elsewhere. For those that did not receive a diagnosis at a specialist centre, consultations in which these women were informed of their diagnosis were often seen as somehow flawed, with not enough specific information being provided or simply being conducted via a letter or telephone. This resulted in women feeling distressed, confused and in some cases angry; anger which persisted to the day of the interview when recalling their diagnosis. The one exception to this is a woman who received her diagnosis from a mitochondrial specialist whilst living in another country.

All seven of these women went onto to actively seek a consultation with a mitochondrial specialist at the specialist centre, either immediately upon diagnosis, when they moved into the region or when they sought specific advice regarding their reproductive options. This was often through an Internet search and initial email contact directly to the mitochondrial specialists that their searches had found. Women recall receiving fast responses to these initial enquires 'from the first time I googled and then just sent [them] an email and [they] responded within 12 hours' (Sarah: 354-355). For those women who had themselves experienced symptoms they describe how important it had been for them to have met doctors that believed them and that there was a sense that these doctors 'were on our side', that they could be trusted with their care or the care of their family members.

Hmm, but as I say this was where I think [Dr X] I trust him, 'cause he knows about the condition and I know he specialises in [SYNDROME X] and [SYNDROME Y] and [SYNDROME Z] and that (Miriam: 854-856)

For Miriam she tells us explicitly that she trusts the mitochondrial specialist that she and her family members see, she trusts him because he specialises in many of the potential syndromes caused by mtDNA mutations. As we have seen earlier, ensuring that her affected child receives the most appropriate and up to date care is very important for Miriam. This trust extends to the wider specialist team, including specialised nurses and physiotherapists who make up an even larger clinical team that includes a speech and language therapist, dietitian and benefit advisor all specialising in mitochondrial disease.

Women feel able to directly contact these individuals, bypassing their GP and those symptom specialists whom they have not found particularly helpful or understanding in the past. Maggie's direct contact with the mitochondrial specialist team is as a result of not trusting her GP. Maggie describes a 'horrible' incident in which she lost feeling in her fingers and toes and was asked during her appointment with her GP whether or not she thought it was related to her mitochondrial diagnosis, when she replied that's what she had hoped they could help her with, her GP responded: ' "Well really you know I put, I hold my hands up," he says, "I hold my hands up and tell you. I don't really understand anything about it." '(Maggie: 1415-1416). Maggie experienced what seems to be a similar response on many occasions and as directed by her GP, she now contacts her mitochondrial specialist team in the first instance. The GP is reported as saying to her ' "I'm not really sure whether I should do anything. I think you need to speak to the, the [mitochondrial specialists] first" '(Maggie: 1439-1441). Maggie tells us with an air of humour that she feels able to discuss any medical concern that she has with specialist mitochondrial nursing staff 'I mean they're so approachable, and I don't even feel embarrassed asking them daft questions' (Maggie: 2846-2845). Maggie receives quick responses to emails and she and her family members have been seen for clinical reviews promptly when they had concerns.

The majority of women in the study felt the same way as Maggie and have many positive comments on the level of care and availability of their mitochondrial

specialists and the wider team. Women benefited from being able to contact the mitochondrial specialist team via email if they had hearing impairments and via tele- health clinics that allowed them to stay in regular contact when living far from the centre. Although not common, some women comment on the speed of receiving results of tests back and how they felt the speed of communication could have been quicker. Positive comments were given with regards to how they felt that their mitochondrial specialist had been an advocate on their behalf with other health care professionals. This included staying in regular contact with their local specialist clinicians, communicating with and providing support letters to local funding commissioners around required care packages, home adaptions and access to funding for assisted reproductive techniques such as PGD. When discussing how their mitochondrial specialist was helping them to access funding from their local clinical commissioning group, Joanna tells us on more than one occasion that she feels the team are 'on our side' (Joanna: 293) and that the team were 'gonna do all they can to help us' (Joanna: 293).

These attributes described by women concur with those described by Mechanic & Meyer (2000) as integral to trust between a patient and doctor, interpersonal competencies such as compassion and concern, listening and 'fighting' for patients access to health care. Trust in medical encounters has been defined and conceptualised by a number of researchers, see Hall et al (2001) for review. Trust between a patient and doctor has also been discussed in decision-making (Charles et al., 1999; Schildmann et al., 2013). Charles et al (1999) reported the importance of finding a clinician whom women felt they could not only trust but who would also treat them as individuals, was an important aspect of decision-making (p:655). Trust is also invoked when individuals believe in their doctor's expertise and when they feel that they have been provided with all the relevant information to their diagnosis (Coulter, 2002; Wright, 2004). As we have seen above, for patients who feel as though they have been misled by their doctor loss of trust can be 'irretrievable' (Wright, 2004:p3). Lack of trust between a doctor and patient may also prevent active patient participation in decision-making (Belcher et al., 2006).

Positive and trusting relationships with their mitochondrial specialist team meant that for those women who were considering their reproductive options they felt

able to discuss these with their care team. These discussions took place in either a patient requested consultation or later, specially designated reproductive choices clinics where women felt at ease, 'the clinic was lovely and they were really supportive' (Ashley: 90) and 'their approach was really nice and it was like don't worry we're here for you' (Zoe: 135-136). Even Sally, who thought she may have completed her family, noted that if she were to want another child in the future 'I would definitely discuss it with them if I did' (Sally: 295). Mandy was still some years away from starting a family but had felt able to ask for a specific reproductive information session with a member of the mitochondrial specialist team and reproductive medicine specialist.

Mandy: It was information based but then obviously I got a chance to ask any questions or I said obviously how I was confused as to where it was going erm and that's where they both kind of got together and said kind of obviously they can't give you what your gonna do but  
Int: Yeah  
Mandy: But it's given you the kind of wise option as to what they would advise (Mandy: 306-310)

Mandy describes this meeting, attended with her by a close friend as being extremely helpful, that she was able to discuss how she felt confused by the options that she thought were available to her. Mandy tells us that although the specialists were unable to tell her what options she should choose they were able to tell her the 'wise option'. For Mandy this relationship of trust meant that was able to request this consultation at a time when she felt she needed more individualised information and she also felt that she had been given the most appropriate advice for her and her mtDNA mutation.

## 6.5 Summary

Data presented in this chapter show some of the short and long term social impacts of women's diagnoses of maternally inherited mitochondrial disorders. Women responded to their diagnoses in different ways, though a number of women were concerned and fearful about the potential progression of their condition, or the condition of their child/children. This is comparable to literature on other chronic conditions, which explores people's fears of dying (Cinar et al., 2012; Jeon et al., 2010), illness recurrence (Koch et al., 2013; Oxlad et al., 2008)

or progression (Herschbach et al., 2005; Kwakkenbos et al., 2012). To allay these concerns, women sought information from varied sources. However, those that conducted research on the Internet found that it largely exacerbated their fears, (a finding supported by research in relation to a number of health conditions Ziebland et al., 2004; Ziebland & Wyke, 2012) whereas those that accessed information via mitochondrial specialists were more reassured, despite the uncertainty fundamental to their condition.

Experiences of illness are inherently social (Nettleton, 2006), and there are clear parallels between aspects of the women's accounts and Bury's (1982) notion of biographical disruption. Often their symptoms had a disruptive impact on their life that preceded being diagnosed, and the process of diagnosis brought with it a renegotiation of a number of important social relationships including with family and employers. Issues included disclosure of their or their family members diagnosis to other family members including those who may also be at-risk. This disclosure can be seen in the context of a spectrum from full, partial, delayed or none at all. Women quoted reasons for disclosure as establishing a social support, a sense of responsibility and openness. Being diagnosed with a rare disorder also affected the nature of some women's relationships with health care professionals. Their accounts featured disappointment in their pre-diagnosis interactions with (mostly) non-specialist healthcare professionals, suspecting that they were not believed or their symptoms inadequately understood (Glenton, 2003; Jeon et al., 2010; Muir, 2016). Having been diagnosed, these interactions did not necessarily improve, though they were subject to change. After diagnosis some women felt that non-specialist healthcare could no longer address their general health needs and so approached mitochondrial specialists directly, whereas others were encouraged to do so. Recognition of either the symptoms or aetiology of their condition and consequent referral or signposting to suitable services was also important to women in this study. Not only did it offer the legitimisation discussed in the previous chapter, it also resulted in the subsequent return of women to the 'referrer' as a trusted professional (Hall et al., 2001; Mechanic & Meyer, 2000). These trusting relationships with mitochondrial specialist team members meant that women felt not only comfortable in discussing their reproductive options but also requesting specific reproductive

consultations, sometimes years in advance. We can see from Mandy's description of her consultation that principals of shared decision-making were applied by her specialist team, in that she received high quality information from those with expertise and that she was supported in her deliberation of her options (Elwyn et al., 2012). Mandy's description of her consultation supports Elwyn and colleagues (2012) process of 'doing shared decision making' in that there was *Choice talk*, where Mandy's reproductive options were presented, *Option talk* in which more detailed information was provided and *Decision talk* where Mandy's preferences were sought. Providing this specific care to women can be seen to be very beneficial in helping them to decide amongst the many reproductive options available women, enabling a space in which to discuss their own individual inheritance risk, assisting women in understanding what some of the more complex options are and offering reassurance that the clinical team are available to answer questions now and in the future.

Insight into lives of women with maternally inherited mitochondrial disease helps provide the necessary context for the following two chapters, which specifically focus on women's ideas and preferences of reproductive options and the proposed conceptual model of reproductive decision-making. This chapter provides women's accounts of lived experiences of mitochondrial disease on a social spectrum, highlights the types of clinical relationships that exist between women and medical professionals and how trust is fundamental to these relationships. I will now move on to explore women's ideas and preference of available reproductive options in Chapter 7.

## **Chapter 7. Reproductive Options: Searching for the Healthy and Biologically Authentic Child**

### **7.1 Introduction**

The previous chapter explored some of the social implications of receiving a mtDNA mutation diagnosis, in combination with the social impacts of having symptoms that pre-existed being diagnosed. This chapter focuses explicitly on women's ideas and preferences for their reproductive options in the context of being diagnosed with harbouring a pathogenic mtDNA mutation. The initial section of this chapter explains how women first came to know of their inheritance risk through reproductive guidance and/or genetic counselling, whilst also providing a distinction between the two. The women's accounts demonstrated strong preferences for having children that were both healthy and genetically related to them. Whereas the preference for health is undermined by the uncertainty that features throughout experiences of mitochondrial disease, the preference for genetic relatedness represents an outcome women can be certain of, and could be constrained or enabled by the nature of the reproductive pathway the women took, or would consider taking. This chapter opens up discussions and understandings about kinship, as options such as raising 'someone else's child' or voluntary childlessness were largely problematised by women in this study. However alternate accounts are also explored.

### **7.2 Reproductive Guidance and Genetic Counselling**

In Chapter 3 I outlined that clinical professionals offering reproductive guidance to women with maternally inherited mitochondrial disease would consider reproductive options as a list of options to be presented to women. One of those within the list of options is 'genetic counselling'. Within this dataset we see that most women understand genetic counselling as part of the overarching process. For them, genetic counselling covers the period of time in which their reproductive options were being discussed. The women did not make the distinction between general discussions of reproductive options within a clinic from a meeting with a separate genetic counsellor.

For the women, genetic counselling – what health professionals would see as outlining reproductive options within consultation - is described as helping them (and their partner, when applicable) to choose between the options. When asked if she recalls being told about the risk of inheritance to future children, Emma says that

you know what the different options were and the things like for us to, to consider if starting family was something that we wanted to do and erm explained how you know it's females that kinda pass down that man carry and but they don't pass it down and those sort of things  
(Emma: 65-67)

Emma attended the clinic with her husband following her diagnosis via a relative, where they were told that her mtDNA mutation was passed down the maternal line and that men were unable to pass on the mutation. For her, the central issue is understanding that the disease is inherited, and inherited through the female line, and that, should they choose to have a family, they have different options.

For women in the retrospective group they recall being told about the maternal inheritance and in the specific context relating to the potential risk to their child/children. Pauline tells us about the analogy used by the specialist mitochondrial team to describe maternal inheritance - snooker balls in a bag. This is not to dissimilar to the use of analogies used to explain mitochondrial disorders to patients and then later used by patients to tell others discussed in Chapter 5.

Pauline: "And this is like, if, if you were gonna have children now," he said, "and I kind of picked three, and two are red, and one's black"  
Int: Yeah  
Pauline: "That one black might be the one mutation. But you might be really lucky, and get all red" (958-965)

Pauline recalls being told that there was, what would equate to, a one in three chance that if she had children now that they would inherit her mtDNA mutation, but that there was two in three chance that she would be 'really lucky' and a future child would not inherit the mutation. The presentation of inheritance as a game of chance is influenced by the classical decision-making theory of subjectively expected utility maximisation (SEU) theory (Edwards, 1961).

Bonomo and Johnston (1979) define SEU as a

case in which both the probabilities of decision outcomes and the worth or utility of each consequence to the decision maker cannot be objectively determined, but must be estimated in a subjective fashion by each individual (Bonomo and Johnston 1979:p177)

Shiloh et al (2006) notes that this approach has led to those practicing genetic counselling believing that providing accurate probabilities is the most important piece of information that a decision maker requires. Clearly, in Pauline's case, the analogy of the snooker balls in the bag is still memorable to her after all this time.

For those in the current and prospective groups the approach and methods of discussing genetic inheritance and reproductive options lead to a combination of feeling supported but not influenced or having made joint reproductive decisions with the clinical professionals, seen also in Chapter 5. Joanna, when asked if she felt influenced by clinicians, responded that

Joanna:	Erm no
Gary:	No, absolutely
Joanna:	I'd say no, totally left to make our own decisions
Gary:	Yeah
Joanna:	And they have given us lots of information about all our options and things like that and you know the implications erm for that (297-303)

Joanna and her partner Gary had attended specific reproductive guidance appointments with both mitochondrial and reproductive medicine specialists prior to the study interview. Both Joanna and Gary work together to show the interviewer how they reject any idea that they felt influenced. She notes that the clinicians only provided 'lots of information' and that they were 'left to make their own decision'. This style of decision-making, where the patient is offered the information, yet the clinician does not offer their preference, is known as 'informed' or 'consumerist' (Charles et al., 1997; Charles et al., 2000; Emanuel and Emanuel, 1992)

Within the data set, three women discussed seeing professionals they described as 'genetic counsellors'. Two of the women, Zoe and Holly, had been referred to this service via their regional reproductive centre prior to a mitochondrial specialist consultation. The third woman, Joanna, had been assigned a genetic counsellor nearer to her home whilst also at the same time receiving mitochondrial specific genetic counselling at a mitochondrial specialist centre. Holly and her family visited a genetic councillor soon after receiving her diagnosis, in part to discuss risks to her nieces and nephews. Zoe outlined that her appointment had covered what she and her husband already knew about her mtDNA mutation and she remembers specifically being told about PGD at a private healthcare clinic outside the region. When Zoe and husband returned for a second visit to the genetic counsellor they were told that that private fertility centre did not hold a licence for Zoe's mutation and it would not be possible to conduct PGD there. For Joanna, her genetic counselling sessions complimented those provided by her specialist mitochondrial and reproductive medicine team.

If I've been [mitochondrial specialist centre] and gone away and forgotten things then when I go see them then I can speak about things yeah, so that is really good (Joanna: 306-309)

The combination of seeing different services assisted with her recollection of inheritance risk information previously given and offered a dedicated space to consider inheritance. This was a positive experience for Joanna because she was able to further discuss inheritance risk. The approach of repeat follow up counselling dates back to Emery et al (1979), who recommended that it should be routine to conduct follow up genetic counselling. Especially in cases when the counsellor suspects the patient has had difficulty in comprehending complicated inheritance patterns (such as X-linked disorders) and where the chances of having an affected child are considerable.

Over the dataset, only one woman raised specific objections to genetic counselling from mitochondrial specialists. Andi tells us that had she been offered genetic counselling during the consideration of her two post diagnosis pregnancies she 'would have turned it down' (Andi: 599). Although she does not outline the direct reasoning, she tells us later in the interview that the decision to have more children was a family-based decision. Issues under consideration included her health and abilities whilst pregnant and the degree of support from her husband and elder children around the house if a new child was to arrive. She outlines that 'So our best would be to have a family that we wanted and to do our best when they got here whatever' (Andi: 684-685). Concerns relating to pregnancy complications and parenting ability in women's reproductive decision-making is discussed further in Chapter 8 section 8.5 and 8.6.

Women's understanding of the inheritance of their mtDNA mutation and reproductive options available to them or other women allowed them to form ideas and preferences on current and future reproductive options that they were aware of. This study sought to investigate these preferences and to seek information on all current and potential reproductive options. Their ideas and preferences have been developed into four areas: having a healthy child and keeping them safe; raising a child of my own; raising some else's child; and voluntary childlessness. I will now present them each in turn.

### **7.3 Having a Healthy Child and Keeping Them Safe**

This topic is further divided into two areas, which include having a healthy child now and in future generations and keeping their children safe, especially in relation to women's ideas and preferences regarding prenatal testing. I will discuss these in turn.

#### ***7.3.1 Having a Healthy Child Now and for Future Generations***

Throughout the project, the majority of women favoured mitochondrial donation as the most favourable reproductive option for women with maternally inherited mitochondrial disorders. This includes women from the current and prospective group considering their own options and from women in the retrospective group who were considering their younger sisters or daughters' future reproductive options. For women and their partners who were hoping to be able to access mitochondrial donation they described the technique as a 'real sort of lifeline, lifeline, you know' (Mark: 578). Whilst women in the retrospective group talk about mitochondrial donation as the only real option for their daughters, '[daughter] couldn't really have a baby anyway apart from trying this new syndrome method [mitochondrial donation]' (Miriam: 2118-2219).

Mitochondrial donation's popularity as the best option available to women was centred on their understanding that it would allow them (or other women considering the technique) the ability to not only reduce the level of uncertainty they faced with the knowledge of their mtDNA inheritance but potentially rid them of any burdens associated with inheritance and allow them to have a 'healthy child'. Liza had completed her family at the time of the study interview (Round 1- pre-parliamentary debates). When asked if she would support women choosing mitochondrial donation as an option in the future Liza says:

Liza: Yes definitely yeah cause I totally back it you know I've seen what it can do and I can see what it does erm and I just think ... why wouldn't you, why, if you had that opportunity and someone said that I can do this for you to make sure that you have a healthy baby then why wouldn't ya

Int: Yeah

Liza: Why wouldn't you do it, you know and so yeah for me it's totally a total positive thing

Int: And if it had been available to you might have considered that

Liza: Yeah I would have if it had been passed sorted, available then, yes I would have I would have probably gone for it erm yeah so (Liza: 710-717)

Liza tells us that she has seen what mitochondrial donation can do and if it had been available to her then she would have 'gone for it'. For Liza the key issue was the potential to be offered the chance to 'make sure' she would have a healthy baby.

Mitochondrial donation offered hope to women of not only having a healthy child as a result of the technique but also that future mitochondrial disease would 'be gone', as mitochondrial donation is germ line technique, in which it is hoped that female children born of the technique would no longer risk passing the disorder onto their children. When asked which options she would chose, Lesley discounted them all but mitochondrial donation:

Lesley: I would go straight for that en [mitochondrial donation]  
Int: Yeah  
Lesley: Um hu  
Int: And is that  
Lesley: And that is basically because then I would know that I would have a healthy baby  
Int: Yeah  
Lesley: Um hu, and it would it wouldn't be there anymore  
(Lesley: 633-639)

Similarly to Liza, Lesley's support of mitochondrial donation was the ability to know in advance that you would have a healthy child but also that 'it' - mitochondrial disease - would no longer be part of the next generations' lives. The importance of this inheritance link being broken by the introduction of mitochondrial donation is the significant factor for Lesley.

For Liza a motivation for her to support mitochondrial donation was centred on the chance that she may have had a daughter who could benefit from mitochondrial donation in the future: 'I want to be able to say well I fought and helped for you to be able to have this' (Liza: 604-605). Mitochondrial donation would have gone on to have enabled a daughter to have children who would not be affected by a mtDNA mutation, that the children would be 'normal and happy'.

When recalling her motivation to support mitochondrial donation and what she would have said to a daughter:

Erm you know so that you you can go on to have children that are perfectly normal and happy erm so that was my main motivation it was future. As it happens I've had [X] son's it's fine, it's great [Laughs]. Erm you know I've wiped it out in my family kind of thing but yeah that was the main sort of focus on yeah I'll I'll I wanna get it out there and people need to understand that you know because of the thrown this three parent IVF thing around (Liza: 607-612)

Women talked about their mitochondrial disease 'ending' when they had either not had children or if they or their relatives had had male children. For Alice she wonders if fate had been the reason why she and her husband had not been able to have children and that her family members had all had sons, 'because it's stopped now' (Alice: 3722). For Alice the end to the inheritance of the family's mtDNA mutation was poignant and seemed to offer a potential reasoning as to why she and her husband had not conceived a child. The notion of hope and the potential for mitochondrial donation to prevent inheritance has been reported by Herbrand and Dimond (2017), who described women's accounts of hope for themselves, their children and society.

Although there was overwhelming support for mitochondrial donation for the reasons outlined above, Miriam had concerns that mothers may still be faced with the uncertainty as to whether their child may develop symptoms even if mitochondrial donation was successful.

Miriam: You'll always be watching your child, saying, "Is that a mi- a mitochondrial ... there?" Could they see?  
Int: Yeah  
Miriam: And not to have this worry in the back of your mind. It won't be much fun for the mother having a baby with this new, new method. (Miriam: 5552-5556)

Miriam is supportive of both the mitochondrial donation as a technique and the prospect that her children may be able to opt for it in the future. She does not express concerns of risk(s) associated with the technique but she does question whether it would be enough to prevent women from worrying in the future as to whether their child may develop symptoms and how this worry would not be

'much fun'. We see here that for Miriam the uncertainty of a child's future affectedness is central to her view of mitochondrial donation. This can be likened to the experience of uncertainty reported by childhood cancer survivors (Zebrack & Chesler, 2002) and fears of recurrence in serious illness (Koch et al., 2013).

### **7.3.2 Keeping Them Safe**

All women interviewed expressed a strong desire to keep their developing child safe during a pregnancy and as a result prenatal testing was not considered an option for the majority of them. The reluctance to undergo prenatal testing was related to the risk to the unborn child as a result of the technique 'I was told was that prenatal diagnosis is kind of risky for the child' (Ashley: 155-156). However, the dominant objection was to the potential decision that may need to be made following a result, terminating their pregnancy. Uncertainty about what percentage mtDNA mutation load would result in an affected child and the severity, as well as objections to termination of an established pregnancy or moral objections to termination made this option even more complicated and dictated how women formed opinions on prenatal testing.

For some women being potentially placed in this situation led to immediately discounting the option. When asked which options Wendy would discount, Wendy quickly discounts prenatal testing:

we've ruled out ... because you've then got to make a decision about whether you abort and we don't really want to do that (Wendy: 518-519)

For Wendy and her husband being presented with the decision to terminate was something that they were not willing to consider. Similarly Maggie discounts prenatal testing as an option immediately from the lists as she considers 'it must be awful to actually be pregnant and then have to have a termination, decide whether you want a termination' (Maggie: 2667-2669). For both women the central objection was finding themselves in the situation where they would have to make a decision to terminate an established pregnancy. This supports women's and couples accounts of termination following prenatal testing in other genetic disorders (Boardman, 2017; Kelly, 2009; Myring et al., 2011; Rapp, 1998).

Prenatal testing for particular mtDNA mutations was not thought to be of any benefit for one woman as she foresaw knowing that their child would have a percentage mutation load. Zoe believed that her genetic mutation meant that any child she would conceive naturally would be affected 'I think they said that all my mitochondria will be, they know that obviously it's, be affected' (Zoe: 201-202). Whereas for Mandy the ambiguity surrounding mutation load percentages and predicting the affectedness of a child was more troublesome. Knowing the value of a prenatal result would not be helpful to Mandy, especially if she was then to be faced with the decision to continue or to terminate an established pregnancy. When asked which reproductive options she would discount Mandy says:

Mandy: I think you would, I think it would be too hard of decision to make to whether to go through with the pregnancy or to not and I think knowing that the difference between the percentages and the symptoms I don't think I could make that decision

Int: Right

Mandy: On for example if it came back ... that kind of if it had a percentage of ... I don't know [X] cent or something erm I know I'm sitting here and I've got [X + 10] and I'm very well

Int: Yeah

Mandy: And I think that's but then I know there are other children who are born with even less than that percentage and have a massive range of symptoms and are really complex

Int: Yeah

Mandy: So I just think that decision is just ... too hard (overlapping)

Int: Too difficult (overlapping) yeah

Mandy: I just don't think I could do that (Mandy: 503-515)

For Mandy the key issue is the uncertainty surrounding any result from a prenatal test – given different ways that the symptoms can express themselves - and that making a decision about the future of her pregnancy based on a result would be too difficult.

For one woman interviewed, engaging in any prenatal testing over and above standard clinical procedures was not an option 'You know I've never done the amnio-gesis or whatever tests' (Andi: 388). The reasons given for not engaging in any additional testing was that the outcome of the testing would not have no impact on her decision to continue with the pregnancy 'we'd have the baby

whatever it was' (Andi: 391) and that she would not terminate a pregnancy 'Yeah well we wouldn't go "well I'd abort", I would never abort' (Andi: 386). For Andi prenatal testing was not a reproductive option as it provided no relevant information that she and her husband would act upon and was therefore unnecessary.

For a small number of women, they saw prenatal testing as a benefit in that it would allow them time to prepare for a potential difficult pregnancy and the arrival of an affected child. Ashley tells us that 'it might have been important for us to know erm where the levels are' (Ashley: 155) but that even considering this advantage 'I am not sure if we have gone through with it to be honest' (Ashley: 156). This was echoed by Pauline who would not consider a termination of a pregnancy but 'I suppose then you could prepare, that it might be a difficult birth or it might be' (Pauline: 1185-1186) or that there may be 'something wrong with the baby at the end of it' (Pauline: 1190). However, for these women the advantage of 'being prepared' for potential difficulties ahead did not mean that they themselves would have chosen prenatal testing as an option.

At the time of the interview many women had not considered prenatal testing as an option let alone experienced undergoing a prenatal test, with the exception of two women. Miriam had been offered and accepted amniocentesis testing in her three pregnancies, 20-30 years prior to the interview because 'it was just done, you're meant to have it' (Miriam: 2110-2111). Miriam describes how she had considered the potential outcome that she might receive a positive result for Down syndrome and what this would have meant for her 'I would still keep the baby' (Miriam: 2120-21021). Miriam did not discuss knowing of any risks associated with an amniocentesis test at the time. For Liza, she and her husband had been unable to access PGD via the NHS as they already had one child and private treatment was not an option 'I would have to pay for any treatment through IVF [PGD] ... upfront and obviously it just wasn't an option' (Liza: 264-266). Liza and her husband deferred starting a family for a number of years after receiving the news that they were not eligible for NHS treatment and that prenatal testing was the only other option available to them 'then after that it was the CVB or you do nothing just go ahead and don't know' (Liza: 484). Not knowing the

potential risk to her child was not an option for Liza, so after finding out that she was pregnant she requested a test, although she didn't 'fully realise what exactly it meant' (Liza: 270-274). Liza had two pregnancies and underwent two prenatal tests and both experiences were very difficult for Liza and her husband. Lisa and her husband made the difficult decision to terminate her second pregnancy after much consideration with not only the mitochondrial specialist team but with extensive consultation with her extended family. Based on this and the percentage mutation load Liza and her husband decided that their baby 'wouldn't have had a very nice life so erm we terminated the pregnancy based on that information' (Liza: 278-279). The option to undergo a second prenatal testing was because 'nothing really else available to me' (Liza: 285) but that this meant that Liza was undergoing another emotional 'CVBS gamble' (Liza: 287). Liza felt that she had no other option but to undergo prenatal testing to ensure that she was able to make the best decision possible for her future child based on the mutation load and how the child may be affected by their family's specific mtDNA mutation.

We see from interviews that women wanted to be able to combat the uncertainty that exists with the inheritance of mtDNA mutations to ensure, as best as possible, that their future child would be healthy and free from the burden of mitochondrial disease both in their generation and future generations. We see that some women were unwilling to risk the safety of their unborn child to undergo prenatal testing when they would not terminate a pregnancy whilst others used prenatal testing results to assess future risks to their unborn child and made decisions based on preventing future suffering. Having a healthy child is a central finding in this study as well as the idea of having a 'child of my own'.

#### **7.4 Raising A Child of My Own**

Frequently seen across the reproductive options was the idea of a 'child of my own' and that some reproductive options restricted or enabled women to achieve this goal. I have chosen to specifically distinguish between restricting and preventing this goal as the women set different parameters to what a 'child of my own' meant. In those cases where women spoke of 'their child' they seemed to be speaking specifically of the genetic link to themselves as mothers whereas the genetic link to their partner or future partner only was specified in relation to options such as ovum donation and surrogacy (with or without a donor ovum). In

the following sections I will discuss issues that applied to options that enabled or restricted genetic relatedness.

### ***7.4.1 Reproductive Options that Enable Genetic Relatedness***

Reproductive options that enable women to have a genetic link to their child or future child include conception without medical intervention, prenatal testing, PGD and mitochondrial donation. Women discussed all of these options across the three interview rounds, with the introduction of the interview aid facilitating more detailed discussions. Over the course of the interviews, the women offered four different responses to these options. They were: lack of knowledge, awareness and understanding; not concerned; not an option and that such an option was to be used as an interim option. I will discuss each of these in turn.

#### **7.4.1.a Lack of Knowledge, Awareness and Understanding**

For some women interviewed, lack of knowledge of their mtDNA mutation or naivety regarding potential risk(s) to a future child featured when discussing conception without medical intervention. For the purpose of this study I define conception without medical intervention as, natural conception without prenatal testing (CVS/CVB or Amniocentesis).

For example, Maggie had 'completed' her family before her diagnosis and she reflected on the position she was in then and how she had conceived naturally 'in ignorance':

And if I had known that I had, had this when I was younger, whether I would have even, whether I would have had any kids. I don't know (Maggie: 1705-1707).

Maggie questions whether she would have had children had she known of her diagnosis early. In contrast, Liza had known of her diagnosis for a number of years beforehand and had considered the potential inheritance risk. She was aware of symptoms including deafness, diabetes and gastrointestinal symptoms but she deemed these as socially acceptable symptoms. She conceived her first child without medical intervention. Liza tells us that she did not consider the seriousness of the symptoms arising as a result of their family mutation before her first pregnancy.

I was sort of before my mam died I was actually very naïve about what could potentially happen so with [first child] I never did anything, I never spoke to anyone about it, I think I remember going ... well when I was pregnant they knew I was pregnant but you know I and I do remember being offered a erm CBV test. And I just kinda said "arhh no it fine dur dur" and again very naïve at the time erm and so it was offered to me but ... I just had [first child] sort of normal, everything fine you know, erm left it at that

(Liza: 91-97)

Liza describes herself as naive a number of times when discussing her first pregnancy. She also tells us that she did not discuss her pregnancy or any inheritance concerns with the mitochondrial specialist team in detail. Liza's reflections on her first pregnancy and the actions she chose in her future pregnancies after her mothers death can be seen in relation to her experiential knowledge of their families mutation and a change in risk perception (Boardman, 2017), discussed further in Chapter 8 section 8.3.1.

#### **7.4.1.b Not Concerned**

For some women, after receiving genetic counselling and expert assessment of their individual inheritance risk they were not overly concerned to either continue trying to become pregnant or to plan to become pregnant without medical intervention in the future. Sarah fell pregnant with her first child soon after her diagnosis and declined prenatal testing. She relied on the information from her regional neurologist who had informed her of her diagnosis to assess the risk of inheritance to a future child. When asked if she felt she was informed enough to make her decision Sarah tells us that:

the first thing that I said "well what does this mean for my decision to start a family?" And he said "I really think that it is low risk and that I don't think that it should let you, it should affect your decision; continue as you are" (Sarah: 390-392)

For Sarah this level of information from 'an expert' (Sarah: 400) was enough to not deter her from continuing to try to conceive naturally, although she acknowledges that this was not very scientific 'That was helpful, how scientific it was, he's an expert so that was all I need to hear to not stop' (Sarah: 392-392). However, it provided her with the reassurance she needed at the time. It was

important for Sarah that her child not be affected by the mutation more than she was:

Sarah: Nobody would choose to have, to put, to have a child and put them at that risk so for me it was just incredibly hard cos I just kept clinging onto all I need to hear from somebody is that (0.2) that if I had a baby with mitochondrial disease it wouldn't be any more severe than what I've got  
Int: Right OK  
Sarah: And that would be enough for me (Sarah: 273-276)

Information from a trusted expert about the risk factors to her child was important to Sarah in managing her uncertainty and knowing that her child would not be more severely affected than herself the key factor.

Emma had previously considered her reproductive options in more depth. She recalls that her mitochondrial specialist at the time was not encouraging couples to seek alternative options to establish a pregnancy:

I think what erm what he was saying at that time was that he, you know he wasn't strongly encouraging that we, we erm you know that we took up any of the alternate options and was saying that you know "a lot of people just make the decision to kinda of go ahead naturally", I think that was quite quite reassuring erm and he did offer us an appointment erm with one of the specialists (Emma: 76-81)

Again, we see how advice from a trusted expert is central to decision-making. The advice was reassuring for Emma and her partner at the time as conceiving naturally was a 'sanctioned' option, a norm that she was told many others like her already undertook.

Finally, Andi offers a different perspective, one where advice and trust is still central, but that advice and trust is based on religious faith. Andi went on to have two further pregnancies after her diagnosis. For her conception without intervention was the only option that would permit her to have a biologically related child. Andi tells us earlier that she believes that she would have turned down the offer of genetic counselling but that she did receive information on inheritance 'I think it was mentioned at the very beginning erm' (Andi: 419) and that she hadn't needed any additional information. Therefore, for Andi and her

husband, they did not require an expert opinion on risk to inform their future reproductive choices.

Well being [religious] has affected all my decisions to do with it because it's just been ... it's just something that we accept, you know everybody has got. You know it's a progressive disease but you don't know what the future is, you don't know where you're going to be, you don't know what your kids, you don't know anything about the future, so I don't dwell on it and when it comes to so when it comes to family and things making a decision whether to have a family or not it doesn't really affect it, we'd we'd want, you try you're best  
(Andi: 675-682)

For Andi and her husband their religious beliefs were central in informing their views on having a potentially affected child. If this were to occur then they would accept and work with the emergent situation. As a family all they could do would be to try their best: 'so our best would be to to have a family that we wanted and to do our best when they got here whatever' (Andi: 844-845). In this way, a doctrine of predestination means that such information is unnecessary and therefore of no concern.

Relatedly, Andi also told us that she has not actually 'had to consider' mitochondrial donation as an option. She noted that she was unsure as to where she stands in relation to it. In response as to whether her uncertainty was because she had not considered it previously, she outlines that:

Andi: I've not had to consider, I'm not sure whether it would be from a religious point of view  
Int: Ok  
Andi: Erm but I don't have to consider that, that my kids will have to think about that one [slight laugh] (Andi: 641-644)

It is not that her religious faith directs her reasoning, but rather such an option is not a concern for her, as she has already completed her family. She notes, albeit with a tone of humour, such considerations, including those of how such a technique could be understood from a religious perspective, is for the next generation of her family.

#### 7.4.1.c Not an Option

Reproductive options that enabled genetic relatedness that women framed as not an option to them included conception without medical intervention, prenatal testing, PGD and mitochondrial donation, which were related to their perception of inheritance risk and risk of having an affected child.

For some women in both the retrospective and current and prospective arm, conception without medical intervention was defined as 'not an option' as soon as they were informed of their diagnosis. Multiple accounts from women and their partners show that 'to conceive naturally has never really been an option to start with' (Joanna: 383-384) and 'you couldn't do it with our condition, I would not recommend that with this condition, no, absolutely not, no' (Miriam: 1866-1876). For Holly, at the time of the interview, natural conception was not an option after receiving her diagnosis. In addition to receiving her mitochondrial diagnosis she had also received medical advice that as a result of her specific phenotype she would not be physically fit enough to carry a child to full term safely. When asked Holly tells us that:

Holly: But it was never, once I knew I had mitochondrial disease and like erm the fact that it had got so bad, erm especially as the years went on, it was never something that I would have wanted to  
Int: Considered since the diagnosis  
Holly: Consider doing, no. (Holly: 1856-1861)

For these women, and in some cases their partners, knowledge of a mitochondrial diagnosis would reconfigure beliefs and expectations, such that the 'natural' birth would become too risky to begin to consider.

#### 7.4.1.d Interim Option

For some women reproductive options that enabled biological relatedness were actively considered when their preferred option was not available. In the majority of cases this was women and their partners who had sought specific advice about PGD because their preferred option of mitochondrial donation was not yet available. This is complicated further by the assumption that PGD is suitable for all mtDNA mutations and that all women would be considered candidates for the procedure. PGD is dependant on the type of mtDNA mutation that a woman has

as well as typical IVF screening factors such as ovarian reserve and age which can significantly influence the chance of a live birth (Craven et al., 2017; Salleveld et al., 2013).

A number of women in the study had sought or were actively seeking advice regarding PGD as a reproductive option. For all of these women their preferred option at the time of the interview was mitochondrial donation. For example, Joanna and her partner Gary were pursuing PGD as an option and had attended a joint mitochondrial and reproductive medicine consultation prior to the interview. For both Joanna and her partner, PGD was their chosen option:

Joanna: since the very first time we were sort of told you know we would, we could go through IVF and this is you know this is the implication, we've both sort of, before we even knew too much information I think that we would go  
Gary: yeah I think we've already made owa minds up  
Joanna: I think that we would go with (Joanna: 386-392)

Since they first found out about PGD (described by them as IVF) and with only brief information on the technique, they had already decided that it was what they wanted to try as their first choice. However when asked – pre the parliamentary debates - if they knew anything about mitochondrial donation both Joanna and Gary tell us how mitochondrial donation would be their preferred option:

Joanna: I think it be fantastic  
Gary: Yeah I think it [overlapping]  
Joanna: And if we could go for that then  
Gary: Then I'd rather  
Int: Really would you?  
Gary: Yeah (overlapping)  
Joanna: We'd both rather go for that if that could eradicate the mitochondrial disease almost completely or completely  
Int: Yeah  
Joanna: Then I think it's you know  
Gary: Fantastic  
Joanna: Really good yeah, fantastic (Joanna: 350-361)

They work together enthusiastically to tell the interviewer how 'fantastic' mitochondrial donation is and if it were now 'we'd try it yeah' (overlapping: 377). Their belief that mitochondrial donation will be able to eradicate mitochondrial

disease 'almost completely or completely' was the primary factor for it's preferential status.

Wendy and her husband Mark took part in the study interview shortly after the favourable parliamentary debates and up until these debates were considering PGD as their only option 'we thought that we we may want to do PGD cause that was all that was available then' (Wendy: 143-144). As a result of the parliamentary debates, Wendy and her husband had contacted specialists to request a mitochondrial and reproductive medicine consultation. This consultation was to specifically discuss mitochondrial donation as an option, as they had changed their minds about undergoing PGD at their local mitochondrial specialist centre. When telling us why PGD was no longer their preferred option they outline that:

Wendy: But because my percentage is so high that the advice that we've received is that the kind of best-case scenario is that we'd probably have fifty per cent an embryo with about fifty per cent which is still is at the lower end of the grey category of risk  
Int: OK  
Wendy: So ... because I've got [XX percent] PGD ... PGD isn't a perfect solution  
Int: Right ok  
Wendy: Because we could ... we could have a child ... that's in the kind of ... probably gona be OK but it's still in the grey area  
Mark: Yeah  
Wendy: In the lower end of the grey area (Wendy: 526-533)

Their understanding is that the probability that an embryo created through PGD would still have at least 50% mutation load. For Wendy and Mark the uncertainty that PGD brings with regards to the possible mutation percentage load of the embryos created and the possible 'grey area' of affectedness for a future child has meant that they now would now prefer to explore mitochondrial donation. Wendy tells us that her and Mark had spoken to the mitochondrial specialist team via telephone and email prior to their specialist mitochondrial and reproductive medicine appointment. They had also received a counselling session and that they had all their questions about mitochondrial donation answered:

our assessment of the risk is that we want to have our own biological child ... ideally erm and this is a way to get a very very low percentage of mutational load like the studies are showing it's could that the carry over is likely to be should be less then sort of five per cent (Wendy: 544-546)

For them, having a biological child with the lowest inheritance risk is key to their reproductive decision-making and their preference for mitochondrial donation and the reason why PGD is no longer an option.

Ashley is another woman, who's preferred reproductive option was mitochondrial donation and had been for a number of years prior to the interview:

so our hopes were already really high up to get it developed in time kind of for us to have a chance to have a child of ours without it being affected in the end (Ashley: 63-65)

Ashley and her husband has spent a number of years tracking the progression of mitochondrial donation through parliamentary and regulatory approval in the hope that they would be able to undergo the technique. Their preference for mitochondrial donation was the chance to have a 'child of ours' who would not be affected by an mtDNA mutation. Ashley recalls being advised that mitochondrial donation may not be approved in the time frame that her and her husband would wish and that they should consider other potential options. She was told by a mitochondrial specialist that:

'well it is an option, he can't promises us it's going through in time for us, possible for us to go through with the treatment and we should already look into other options, he told us that' (Ashley: 70-72)

They had been trying to conceive without medical intervention for a number of years prior to the licencing of mitochondrial donation. It seems that for this period of time Ashley was able to accept the potential risk.

Even though Ashley and her husband were trying to conceive naturally she stills describes this period of time as waiting for mitochondrial donation 'we took our chances' to wait (Ashley: 73) and 'hoped' it would be approved before she reached an age that she believed would prevent her from accessing mitochondrial donation. Over time Ashley's perception of risk associated with 'natural' conception as an option changed:

Ashley:	but within me it developed kind of that I don't want to bear the responsibility of having a child that is getting really sick, either as a child or later on in life depending on how severe it is
Int: Ashley	yeah and that's a common thing that's been said yeah so it did change over time and I am taking now the contraceptive pill again until we can figure out what were gonna do about egg donation (Ashley: 126-130)

Over time, her perception of the potential impact of her mutation on a future child and the potential burden of guilt and responsibility shifted their preferences and practices (see Chapter 8 section 8.9). Ashley and her husband had hoped to be candidates for mitochondrial donation or PGD but after an assessment at their regional reproductive centre they were informed that Ashley did not meet the requirements to be considered a candidate for either of the techniques and as a result they were now considering egg donation (see section 7.4.2.b). We see from the response given to the options that enable genetic relatedness that having a biological child with the lowest inheritance risk is high priority for the women interviewed in this study.

#### ***7.4.2 Reproductive Options that Restrict Genetic Relatedness***

Options that women considered restrictive to genetic relatedness included ovum donation and surrogacy (with or without a donor ovum). It should be noted that women in Round One did not discuss either of these options. However, with the introduction of an interview aid in Round Two and Three I was able to initiate a conversation about them as potential reproductive options (see Appendix B2). This itself could be seen to denote their almost irrelevance to women in their consideration of reproductive options, despite the potential of ovum donation ability to provide certainty of preventing transmission of mtDNA mutation and allowing for the embodied experience of pregnancy. Over the interviews, the women offered two types of responses to options that restricted genetic relatedness to a child. They were that they were 'not an option' or that such an option would only be used as 'a last resort'. I will discuss these in turn.

### 7.4.2.a Not an Option

Ovum donation was also considered as a non-option for some women in relation to the child not having the genetic link to the mother or carrying the family's genetic lineage down through the generations. Opinions of surrogacy were also often included with options to ovum donate or pitted against ovum donation. For Lucy her objection to both ovum donation and surrogacy were formed from the desire to carry her own genetically related child 'I would want to carry my own baby. I want it to be related to me. I want to carry it myself' (Lucy: 71-72).

Such ideas about genetic lineage are central to some women. Holly's account centres on a continuation of 'my family line':

Holly: I would want a baby that was linked to me genetically. I wouldn't want to use like a donor egg because I, I know for some people it doesn't matter and being genetically linked doesn't make you the mother sort of thing.

Int: Right, so that is important.

Holly: But for me it was important to feel that it was like a continuation of like my family line as well, sort of thing. So I wanted to, I wanted to feel as though it was a part of me sort of thing, like my baby was going to be a part of me and obviously [partner]. And if it was a donor egg I would almost feel like I wasn't part of that. So I think it would be harder (Holly: 1171-1184)

For Holly, and others, ideas about family and belonging are centred on ideas about genetics. A donor egg would remove a key link between herself and her child, as she feels that that child would not be 'a part of me'.

Miriam thinks about ovum donation in comparison to surrogacy and believes that ovum donation is 'probably a better option in some ways' (Miriam: 2030) but that 'it's still somebody's egg you're carrying' (Miriam: 2033). Additionally, with surrogacy she envisages potential complications, including the surrogate unwilling to give up the child once born, as well as the potential of bonding between the surrogate and the biological father.

If it's going to work, if if it's going to be that the mother will give up the baby that she is carrying for nine months, if they don't change their feeling, if the father doesn't get involved with the woman carrying his eggs (Miriam: 1962-1965)

Miriam considers that the 'there's too many complications, too many emotions' (Miriam: 1975) with surrogacy. Miriam also considers that if resemblance was to exist between the surrogate and the intending mother, the father may feel somewhat conflicted by this.

She's going to be a young, healthy woman, probably looking like his wife, hav- the same hair colour and the same eyes; all the kind of- he'll think about that (Miriam: 1981-1983)

For Miriam, concerns about not 'receiving' the child that the couple had planned together and the emotional burden were central to her objection of surrogacy. Objections to options that women saw as restricting genetic relatedness seem to raise questions about what it means to be a member of a family. The sharing of genetic material with a child was important for them to ensure feelings of belonging and a core requirement to ensure insider status in a family.

#### 7.4.2.b Last Resort

For some women reproductive options that restrict genetic relatedness would be considered but only after other avenues had been fully explored. As Wendy outlines:

if our preferred option didn't work then we would consider them, so we've not eliminated them they're just not at the top of the list (Wendy: 487-491)

When considering ovum donation, Wendy and her husband tell us that they 'haven't really spoken that much about just using a donor egg in its entirety' (Wendy: 477-478). Ovum donation would permit the child to be related to her husband Mark as well as providing her the chance to carry the child. On reflection Wendy finds it interesting that they hadn't considered ovum donation more:

Wendy: Erm and interestingly that's probably one that we haven't really discussed (0.5) Yeah and I suppose the difference between [adoption] and [ovum donation] is that is would be your biological child but not mine cause we would use a donor egg  
Mark: Arh right yeah of course  
Wendy: Erm but then I would carry the baby (Wendy: 433-484)

Wendy and Mark talk through ovum donation together in the interview and begin to see that it would result in a child genetically linked to Mark and that Wendy

would be able to carry the baby. Both of the mitochondrial specialist teams that Wendy and Mark had discussed their options with had not yet spoken to them about ovum donation and only in the interview do they seem to consider the potential benefits. For Zoe 'egg donation would be another option to the mitochondrial donation as well' (Zoe: 194-196). This is because she believes that her mutation would not be suitable for PGD and has been to date putting on hold having a family in the fear of passing on her mutation to a child.

For Ashley and her husband, Ashley describes having already reached their 'last resort' after receiving the news that she would not be a suitable candidate for either of the IVF technologies, her preferred method being mitochondrial donation. She and her husband had already initiated their own investigations into ovum donation from private clinics. They had chosen to search for private clinics as they were conscious of her age and long waiting times on the NHS. Ashley and her husband had expanded their search across Europe for a clinic that would permit them to review characteristics of a potential donor to enable them to try to match the potential physical features of the potential future child to their family.

Ashley: if possible we would love to have a child of our own again erm and if it's just half [laughter] with the egg donation process we would move forward with that

Int: is it more the genetic link with your husband or is that you would want to carry the baby?

Ashley: I think it is more the genetic link for my husband erm yeah it's kind of important for him I think... 'it's a closer link than adoption but no it's not that important for me to be pregnant (Ashley: 138-144)

Having 'our' child, even if 'it's just half' our child is seen as a good outcome. Ashley tells us that the genetic link to her husband is important to him, as it provides a closer 'link' to the child than adoption. Ashley had experienced complications in her previous pregnancy that required emergency surgery, a number of months in hospital and the eventual early arrival of their first child, which may account for lack of importance of carrying her child. Although Ashley does not specify whether the genetic link to her husband is important for her, she does tell us that it is important that the child resembles both her and her husband 'that the child would hopefully look a bit alike' (Ashley: 110-111). It could be

argued that having a child that could be perceived by others as not genetically related such as 'having dark hair' (Ashley: 112) is central to her concern of ovum donation and the reason why choosing a clinic that permits this matching is of importance to Ashley and her husband.

Holly and Edward were unique to the study in that at the time of the interview they were actively pursuing PGD with Holly's eggs (although like others their preferred option was mitochondrial donation) with a proposed plan to use a surrogate to carry their biological child to term. This was thought to be a requirement due to severity of Holly's mtDNA mutation 'I've been told that I should find a surrogate rather than carrying the baby myself' (Holly: 828). As we have seen above (section 7.4.2.a) a biological link to Holly was important and that surrogacy would allow for this genetic link to be possible, as she believed that 'I don't think I've got another option' (Holly: 1167). To enable this, Holly would need to freeze her eggs until they can find a surrogate. However finding a surrogate had a number of barriers. Holly and Edward described facing practical issues of costs of upwards of £20,000 to accommodate the surrogates medical care including a £1000 registration fee to the leading UK not-for-profit surrogacy organisation ([www.surrogacyuk.org](http://www.surrogacyuk.org)). Other pressing issues were around the legal aspects of the surrogate mother being the legal mother at birth who did not have to 'handover' the child to the 'biological mother' if they did not wish. However the main issue for Holly was concern relating to bonding or the lack of bonding if she were to not carry her child. When talking about whether surrogacy was an easy option to understand, Holly talks about her sister's pregnancies:

Because even like the kicks and like, like she'd say, "Put your hand here and you can feel the baby kicking," and I thought, "Oh it must be amazing to feel that," and you've, like that's a bond you just can't replace. And like I just think, "How hard is it going to be to watch another female carrying my baby?" And then just try and pick up almost where they've left off, I just think it'll be really like, I think it will be difficult, erm like the bonding side of it. (Holly: 1158-1166)

Clearly, for Holly the emotional issues that emerge out of not having an inter-embodied experience of pregnancy are central, especially around issues she describes as bonding. Holly and Edward were at the time of the interview prepared to accept surrogacy as their option of last resort, to enable them to have

a child that was biologically related to them both. Interestingly Holly took part in a second interview, outlining that she and Edward had conceived a child without medical intervention, had chosen not to undergo any prenatal testing and had a healthy child who was approaching their first birthday. This notion of change over time in reproductive decision making is explored in Chapter 8 section 8.9.

In conclusion, 'raising a child of my own' was important to women and reproductive options that enabled genetic relatedness were favoured over reproductive options that restricted a woman's biological link to the child. Women who conceive naturally without medical intervention were often those who had no prior knowledge of their mtDNA mutation and who had no reason to consider other avenues of having children. Whereas those who made their decision after receiving information did so either through self-proclaimed lack of awareness and understanding of risk or who were not concerned either after receiving expert guidance or because they did not consider there to be any risk. Conception without medical intervention was for a proportion of women too risky due to the uncertainty that surrounds predicting the affectedness of a future child. Whilst mitochondrial donation was the preferred choice of the majority of women, PGD was regarded by many as the interim option, due to concerns that mitochondrial donation may not receive approval or not be available in time for them. PGD provided women the biological link but still presented uncertainty, a 'grey zone' whereby children may still be at-risk of affectedness. For those reproductive options that restricted genetic relatedness, these were seen as less favourable, and either not an option or as a last resort. Ovum donation was considered not an option for women who placed importance in their biological link to a future child, for those women considering ovum donation as a last resort this link was less important, but interestingly genetic relatedness to the father was reported as important to one woman's husband. Surrogacy was considered problematic for concerns commonly cited, which included concerns that the intending parents may not 'receive' their child at birth and concerns relating to missing out on the inter-bodied experience of pregnancy and notion of maternal bonding (Teman, 2009). I will now move on to discuss women's ideas and preferences that centred on 'raising someone else's child'.

## 7.5 Raising Someone Else's Child

The idea of raising a child that was 'not their own' was in most cases problematic for the women interviewed, there were some women who may have considered raising a child that was not in any way biologically related to themselves or their partner given no other options and only one woman who had already decided that she would raise 'another woman's' child if she could not conceive.

### 7.5.1 Not an Option

For Alice to whom adoption was described as not being an option, her reasoning had centred around the desire for her and her husband to have their 'own baby'. Alice had experienced fertility issues for over 20 years at the time of the interview and as result she did not have any children. She and her husband had discussed adoption in the context of childlessness but not within the context of a known mitochondrial disease diagnosis. Alice recalls the information sheet on adoption she was given by a reproductive medicine specialist after approximately 5 years of trying to become pregnant, she remembers 'it was saying that that could take, like, four or five years' (Alice: 2062-2063). Sandelowski et al (1991) has outlined that the experience of long waiting times for adoption can cause distress to couples by disrupting the couple's social lives, creating prolonged transitions to parenthood and the stages of imagination. For Alice, like others, given the temporal uncertainty, adoption was not an option.

Alongside information on adoption, Alice was also provided with a leaflet about the then new IVF procedure 'the test tube baby'. At the time Alice, describes reading what she thought was science fiction 'it was like science fiction and I was like, "Oh my God." (Alice: 2079-2080). She outlined how 'I s- I was scared, the two of us were scared stiff, right? And I read it qu- the stuff quite a lot' (Alice: 2091-2093). Alice and her husband discussed their available options and decided:

We've got a good marriage and we talk about things and we decided that adoption wasn't what we wanted to do. And if we wanted to have a baby it was going to be our baby (Alice: 2125-2139)

For Alice and her husband the central issue was one of genetics. Despite the possibility that the new techniques of IVF offered a child with a genetic link, Alice and her husband continued to try to conceive 'naturally'.

Miriam offers a range of accounts as to why she would discount adoption. When discussing what options she would not consider she says that:

Miriam: Not have, no. That one adoption, of course, but it's not the same  
Int: yeah  
Miriam: I've not adopted so I can't really say, for that but I if I  
desperately wanted a family and I couldn't have  
mitochondrial donation I still don't think I could adopt. I don't  
think I could, 'cause you don't really know, it sounds awful, I  
don't think anybody I know has ever adopted' (Miriam: 1893-  
1905)

Even if she 'desperately wanted a family' adoption could not really be considered. It is 'not the same'. She alludes to the preference for genetic relatedness by contrasting adoption with mitochondrial donation. With a non-genetic child via adoption you are left with uncertainty 'cause you don't really know' about aspects of that child. She is aware that such a position is hearable as problematic by some. She comments that it 'sounds awful' and offers a range of justifications for her opinion: she has no experience and does not know anyone with experience. In response to adoption as an option on the interview aid another woman, Lucy tells us 'no I don't think that would be for me' (Lucy: 68) and when asked which options she would not consider 'probably adoption it sounds horrible but erm adoption' (Lucy: 69). However, unlike Miriam, Lucy did not unpack further as to the reasons why adoption was not for her.

Miriam then tells us that her daughter and son and law had discussed adoption as a possible option but that her son in law in a similar fashion to her was not in favour.

'But [daughter] and [son in law], have said they might adopt but [son in law] said "no". If they can't have their own children he doesn't want to have somebody else's children' (Miriam: 1909-1911)

Again we see a preference for genetic relatedness, that adoption means that you are having 'somebody else's child'. Miriam also offers concerns, as adoption may not 'bring a family closer' if someone then had a biological child.

Miriam: Mmhmm and what if they do then have another baby? How would it feel to be, you see so many programmes and films about that and you think "How would it be to have your own child and an adopted child?" (Miriam: 1924-1935)

Such a blended family, of 'your own child' and someone else's is not for Miriam. Similarly, Ashley acknowledges adoption as an abstract option but feels that it is not an option for her and her husband as

we are already having one child, were really happy with it, and we probably wouldn't adopt another child (Ashley: 132-133)

Ashley and her husband had been trying for a number of years to become pregnant. However, they would consider ovum donation (see above section 7.4.2), which we have seen can be linked to genetic relatedness to her husband and a preference to having a child that physically resembles them both.

### **7.5.2 Never Considered**

For women in the retrospective group who had completed their families before their diagnosis they recall never considering or had hoped to never have to consider reproductive options other than natural conception (without intervention). Pauline had not struggled to fall pregnant with three children.

I would hope not to have to adopt. I would still want, I think, to, to carry me own baby, so not to have to adopt (Pauline: 1134-1136)

Pauline like others does not discount adoption as an option but she tells us that her preference would always be to carry her own baby.

### **7.5.3 Last Resort**

For some women adoption would be considered but only when other avenues had been explored first, albeit is a 'last resort' (Zoe: 193). Holly and her partner had previously discussed adoption prior to the study interview as an option if their preferred methods of PGD with combined surrogacy were not successful.

Holly: It would be the last resort but it's certainly not something we would rule out. We, we definitely would look at adoption. Erm, we've also looked at, because of the issues with actually looking after a new baby erm, if we were doing adoption we would maybe look at adopting a slightly older child who is past that kind of really demanding stage where you are doing. You've got the sleepless nights and you really do need to have a lot of energy to kind of keep up with them and look after them

Int: So like an older toddler?

Holly: Yeah, yeah like somebody that is maybe past those, that kind of stage. But we haven't really talked about it in great depth

Edward: Not yet, no. We still, that would be our last thing once, if we had to decide then we would probably talk about it. But I think we will obviously go down that route I think, if we have to

Holly: Yes. It's really important for both of us to have a baby, so erm if, if what we are going to do isn't going to be possible and we end up then we'll certainly look at that option (Holly: 1868-1889)

As they note, they have not yet 'talked about it in great depth', but they have clearly thought through some of the implications, given their discussions about the age of the child that they would try to adopt. Adopting a child who was slightly older and not as dependent as a newborn may be more practical for them given that fatigue is a prominent symptom for Holly. However, centrally for them, adoption is only something that they would do 'if we have to', 'it would be the last resort', it would be 'our last thing'.

#### **7.5.4 Definite Option**

In contrast to the above outlooks Andi and her husband had discussed adoption prior to getting married in the event that once married they might find themselves unable to conceive. When discussing adoption as an option Andi tells us that:

Andi: No I wouldn't you know if I can't have a child I'm not meant to have a child I'll adopt, I'll look after somebody else's child

Int: Yeah, yeah erm and so if you, so the decision not to have a family wouldn't have happened you would have just gone on to have children via adoption?

Andi: Probably yes, yes adopt' (Andi: 666-671)

Again we see, the impact of her religious faith on her choices (see above 7.4.1). For Andi, a doctrine of predestination is central, if she had been unable to conceive then it must mean that it was not meant to be. In such circumstances she would care for 'somebody else's child' – note here how again, issues of ownership and belonging, tied to genetics is still central to these accounts.

Over all these accounts having a child is centred around ideas of genetic lineage and inheritance over, say, ideas of belonging emerging through the day-to-day practices of caring for a child. Raising someone else's child through adoption was primarily considered as a non-option or not even one at all. Those women in whom adoption had never been a consideration were those women who had not known of their diagnosis prior to having children and who had not experienced any issues in conceiving. Adoption was considered by some women to be problematic due to the lack of genetic relatedness and pre-existing beliefs that adoption can be a lengthy and disruptive process, resulting in it mainly being considered not an option. One exception was Andi and her husband, both of whom were in agreement that if they were unable to conceive naturally, they would care for someone else's child. For Andi and her husband, parenthood was founded on their actions of caring, and reflects Schinder (1984) definition of social kinship. Finally, I will discuss voluntary childlessness as an available option to women.

## **7.6 Voluntary Childlessness**

The reproductive option to decide to not have children was first introduced into the study by Wendy who upon seeing version one of the interview aid (see Appendix B2) suggested an addition; 'or seven don't have any children' (Wendy: 443). For the majority of women interviewed having a family was very important to them and had been since they were young, having a child/children was central to this imagined family. Individuals who are said to have always known that they wanted a child have been referred to as 'predetermined parents' (Murphy, 2013). We have seen above in section 6.4 that some women may have re-considered whether or not they would have had children had they known their mtDNA mutation and others who had actively been taking measures to not become pregnant whilst waiting for their preferred option to become available to them. The women who had spent time waiting for their options could be seen to be

practicing temporary voluntary childlessness in the hope that they could in the future have access to mitochondrial donation. As we have seen above, many women believed that having access to mitochondrial donation enabled them to reduce or eradicate the uncertainty of affectedness risk and offer them a greater chance of a healthy child genetically related to both them and their partner. For one woman interviewed, she believed that, had she had known of her mtDNA mutation she would have chosen to not have children. For Jenny the primary reasoning behind this is linked to the perception of the inheritance risk being too high for her to feel comfortable having a child (see Chapter 8 section 8.3.1). Interestingly she tells that she had never been very maternal and that having children had 'never really (0.2) really bothered me you know' (Jenny: 79) however she supports mitochondrial donation for women who are both desperate for a child and for that child to not be affected by 'anything mitochondrial'.

Jenny: I, if it's going to help people who want to have normal kids, healthy kids, go for it you know, if your that, if you really are desperate for a child and (0.2) and you would rather it not have anything mitochondrial related wrong with it  
Int: Yeah  
Jenny: go for it (Jenny: 226-230)

Jenny supported women whom would want to undergo mitochondrial donation in order to have a child who would not be affected by a mtDNA mutation.

## 7.7 Summary

This chapter shows the ways in which women with maternally inherited mitochondrial disease formed ideas and preferences based on current and future reproductive options available. These ideas and preferences were formed after receiving information from trusted experts regarding how mtDNA mutations are inherited and their own personal inheritance risk.

As we have seen in Chapter 6, receiving information on their individual prognosis and inheritance risk was especially important to women. Some women report their understanding of inheritance as chance, and that having an unaffected child would be 'really lucky', mirroring existing literature on beating the odds in CF (Myring et al., 2011) and luck in HD (Klitzman et al., 2007). Attending

appointments with both mitochondrial specialists and genetic counsellors meant that women were able to seek assistance in understanding and recalling risk. Retention of genetic risk is difficult for some couples due to the amount of information presented to them (Dommering et al., 2010) with it being reported that many people's perceptions of risk are said to be inaccurate follow counselling (Timmermans, 2005). Retention of genetic risk has also been reported to decrease over time (Hallowell et al., 1997; Michie et al., 1997) with genetic counselling assisting individuals with accurate perceptions of their risk (Bish et al., 2002; Evans et al., 1999). However, for Zoe, her experience includes being given inaccurate or out of date information in regards to a private PGD clinic, highlighting the possibility non-mitochondrial specialist genetic counselling could lead to inaccurate guidance provided to women. We have also seen previously in Chapter 6, that Joanna described aspects of SDM (Charles et al., 1997; Elwyn et al., 2012) in relation to her specific reproductive options consultation. Emma and Joanna and Gary presented their experiences of genetic counselling as informed or consumerist decision-making, whereby they were provided with detailed information but did not feel that the views of their mitochondrial or reproductive specialist was pressed upon them (Charles et al., 1997; Charles et al., 2000; Emanuel and Emanuel, 1992). Encounters relating to specific reproductive options consultations are described as positive, with women recalling feeling supported in making or planning future reproductive decisions. However, for one woman, genetic counselling was not a necessary requirement, this being that information about inheritance risk was irrelevant to her and her family's decisions.

We see that the core preference for most, but not all women was for 'my healthy child' with the focus first on the health of the child. As a result, mitochondrial donation is considered the most favourable reproductive option. In the face of uncertainty regarding possible affectedness of children, mitochondrial donation offers women and their partners both biological parenthood as well as a significantly reduced risk of having an affected child. Mitochondrial donation offers this hope to not only women making the decision in the present, but to maternal family members and future generations, echoing reports that mitochondrial donation provides hope to women, their children and society

(Herbrand and Dimond 2017). Women, whom considered prenatal testing as too risky, commonly described the importance of keeping their unborn child safe. In addition to this, prenatal testing was discounted by many women as receiving information about their unborn child's mutation load would then put them in a position of considering a termination, in which many did not want to find themselves.

After this we see a clear preference that women wanted 'my own child', which equated to a child that was genetically related to them, a child biologically connected to their wider family and one whom they had carried physically. There is a preference for maximising genetic relatedness to both parents provided by mitochondrial donation as the most favoured option whilst those options offering a partial biological link such as ovum donation or no biological link at all such as adoption were either never seen as relevant, never even considered or considered as a last resort.

This chapter shows the importance of women's ideas and preferences for certain reproductive options in the decision-making process. However, findings from this study show that these idea and preferences are set within a larger framework of reproductive decision making with other influencing factors and elements, which I will now go on to discuss in Chapter 8.

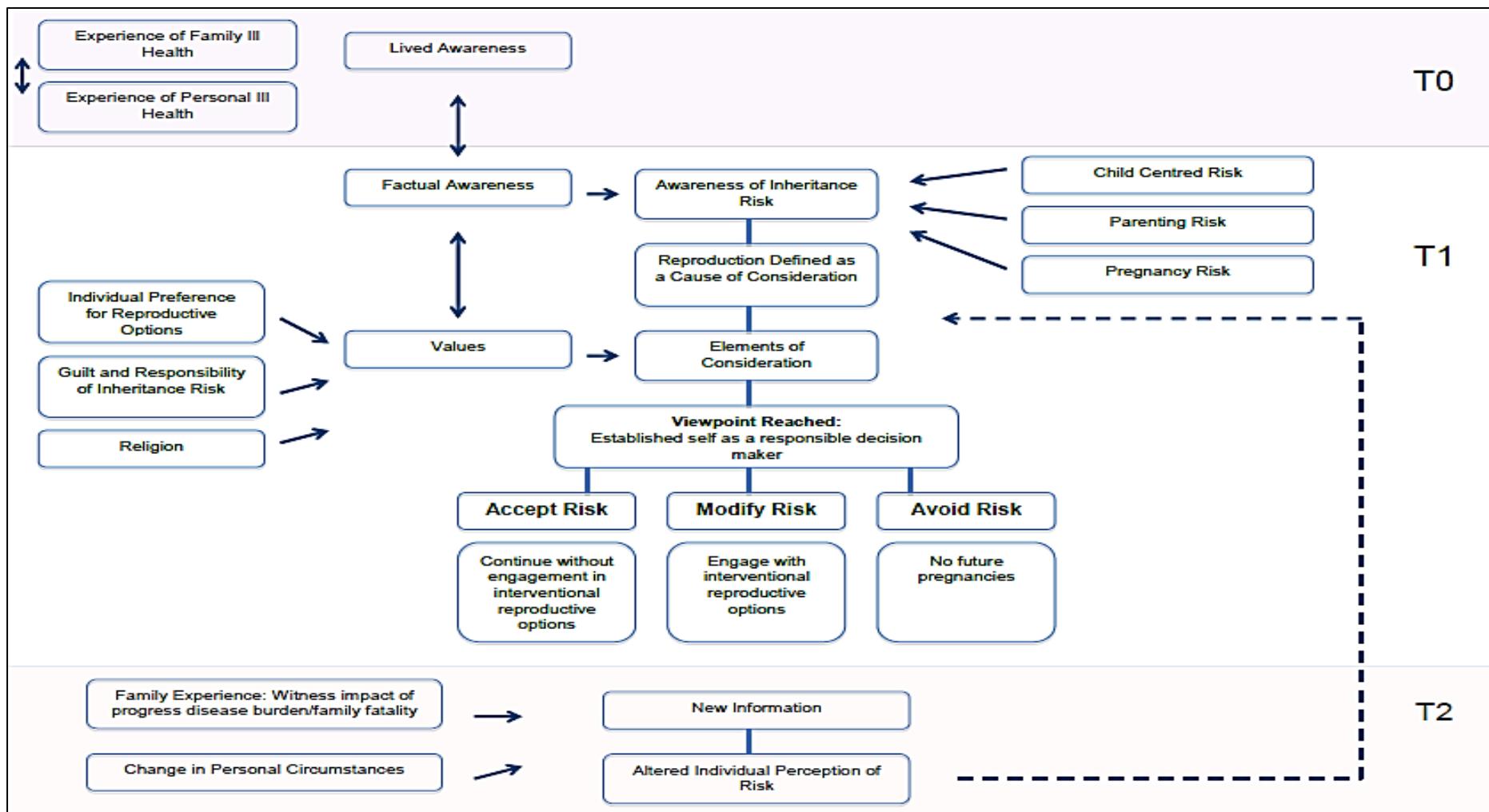
## **Chapter 8. Reproductive Decision-Making in Maternally Inherited Mitochondrial Disease: Conceptual Model**

### **8.1 Introduction**

In preceding chapters I have discussed how uncertainty features in the lives of women diagnosed with mtDNA mutations and their ideas and preferences towards available reproductive options. This chapter brings together these findings and organises them into influential factors and elements of reproductive decision-making. This chapter continues to explore each of these factors and elements providing justification for their status in the conceptual model proposed. Data presented shows that reproductive decision-making is influenced by women's awareness of inheritance risk, which can be further divided into lived awareness and factual awareness. Women consider a number of risks in the process of decision-making, which are primarily centred on the potential health risk to a future child. Some women consider the parenting risk associated with their ability to parent if their own disease burden were to increase and pregnancy itself, which can pose risks to both mother and baby. Women's values are intrinsic to reproductive decision-making, which have been shown in the data to comprise of their ideas and preferences surrounding the available reproductive options discussed in Chapter 7, their feelings of guilt and responsibility of transmitting a mtDNA mutation and for some, their religious beliefs. The conceptual model shows a number of influential factors or elements, however for some women their decision-making may be influenced by only one of these, whereas other women may consider a combination. These considerations enable women to reach a state of a risk acceptance, modification or avoidance, which in turn informs their decision-making relating to available reproductive options. Finally, the last section shows how the model accounts for decision-making as temporal and how women's perceptions of risk may change over time, based on new information or a change in personal circumstances, which can lead to a re-evaluation of available options.

## **8.2 Conceptual Model**

In Chapter 4 I showed how the below conceptual model was both initially developed and later superimposed into an adapted ‘model of responsibilities’ from Downing (2005) to provide a conceptual model of reproductive decision-making in maternally inherited mitochondrial disease. In this section I will discuss each of the influential factors and elements in detail, showing their importance in the model and the lives of women with maternally inherited mitochondrial disorders.



**Figure 8.1** Conceptual Model of Reproductive Decision Making In Maternally Inherited Mitochondrial Disease (adapted from Downing (2005))

### **8.3 Awareness of Inheritance Risk**

For the majority of women included in this study, reproduction was not defined as problematic prior to their or their family members diagnoses of mitochondrial disease. I have termed this time point in the lives of women interviewed as ‘time point Zero’ (or T0). During this time, women were not aware of the potential risk factors associated with the diagnosis of a genetically inherited disorder that would require deliberation as ‘at any time in the last 15 years I could have made that decision and been completely ignorant to having mitochondrial disease’ (Sarah: 214-215). However, during this time, women lived with the effects of mitochondrial disease, be it their own experience of ill health or that of a family member without knowledge of the actual cause. This experience is described in the literature on chronic illness, rare disease and reproductive decision making as lived experience (Barlow et al., 2007; Boardman, 2014; Christensen et al., 2016; Dimond, 2013; Downing, 2005; Frank et al., 2007; Garrino et al., 2015; Grinyer, 2007; Jefferies & Clifford, 2011; Jeon et al., 2010; Kelly, 2009). Although one woman in the study, Alice, she did have an experience of reproduction that was a cause for consideration prior to a mitochondrial diagnosis, and this was understood as being related to infertility issues (see Chapter 7 section 7.5).

Upon receiving a diagnosis and with the knowledge that they carry a genetic disorder that is maternally inherited, women enter a position in time whereby they consider one or a number of influential factors and elements, ‘time point One’ (or T1). Factors contributing to awareness of inheritance risk, either individually or in combination lead women to define reproduction as a cause for consideration and ultimately their reproductive decision to accept, modify or avoid risk. These factors included: factual awareness, lived awareness, child centred risk, parenting risk and pregnancy risk. I will discuss these each in turn.

#### **8.3.1 Factual Awareness**

Women discussed a number of different sources of information that have been defined as ‘factual awareness’ in the proposed conceptual model. These sources were either provided to or accessed by women at varying time points including: on receipt of their own or a family members diagnosis, whilst seeking strategies

of coping with their mitochondrial disease and in relation to their active consideration of reproductive options.

As discussed in Chapters 5 and 6, women sought information to help them understand their or their family members diagnosis, its potential impacts and to follow research updates specifically in relation to mitochondrial donation.

Receiving information from 'a mitochondrial expert' in a clinical consultation scenario for many women was necessary to enable them to process their diagnosis and understand further their individual inheritance risk. Women described other 'factual' sources of information as the Internet or 'Google', research organisations, patient organisations, mitochondrial patient newsletters, mitochondrial or neuromuscular patient information days, and traditional and social media platforms. Information sources including clinical experts and the information provided were scrutinised by women with regards to trustworthiness, resulting in a personal scale of usefulness for some women.

Many women described searching the Internet or 'I started googling it [mitochondrial disease]' (Sarah: 92) when they or their family member were told of the potential or actual diagnosis of mitochondrial disease. In Chapter 6 we see that diagnosis coupled with information seeking led to the majority of women being scared by what they found online, describing finding information relating to limited life expectancy and that they were concerned that they and their children may die prematurely from their diagnosis.

In Chapter 6 we see that Maggie's fears for her family were alleviated after she sought advice from a mitochondrial specialist as opposed to the symptom specialist who had informed her of her diagnosis. This non-specialist doctor was unable to offer much information other than that she had mitochondrial disease. This led Maggie to start 'looking on the Internet as you do' (Maggie: 393-394). Whilst awaiting an appointment with a mitochondrial specialist, Maggie cried nearly every day worrying about what she had read online and cried when retelling her story.

Er, people sort of dying. It's not, not sort of unusual for children to die from it, and then of course I mean I have got [X number of children], like [X children], and I was just thinking like, "What if they're gonna die?" (Maggie: 448-451)

For Maggie her experience of researching mitochondrial disease online was extremely distressing and that it led her to believe that both she and her children were at serious risk. Maggie, like other women interviewed who had researched mitochondrial disease online found a sense of relief when receiving more specific information relating to her mtDNA mutation and her inheritance risk. For women in the current and prospective group this factual awareness from an expert was an important factor to their reproductive decision-making, especially in Sarah's decision to continue to try for a baby (Chapter 7 section 7.4.1).

As discussed in Chapter 6 the variability in phenotypes associated with mitochondrial disease led to the common criticism that the multiple sources of information did not reflect their specific experiences of their disease. This made reflecting on their inheritance risk complicated as not all children were affected in the same way or with the same severity (especially when women may have unknowingly compared nDNA and mtDNA mutations). Sally was part of the retrospective group and tells us during the interview that she had completed her family but also that she would not rule out having another child in the future. Sally was diagnosed via her youngest child who had shown symptoms from a young age. When considering if what she had seen or read about mitochondrial disease online and via social media platforms had influenced how she felt about the inheritance of her mitochondrial mutation Sally tells us that:

Sally: I think that when I first erm heard about mitochondrial disease before [Child Z] I never heard about it before ever, erm when I did hear about it and I looked into it, and when you first type in mitochondrial disease it looks horrible and it is terrible erm but there are different scales of terrible

Int: Yeah

Sally: Erm so for me, that's what I found when I first when heard about mitochondrial disease it just looks dreadful and erm looks like it looks like it has a poor prognosis but like I said in our case were actually hopefully one of the lucky families that it can erm if it does (0.3) if it does give us symptoms it won't be as bad  
(Sally: 305-313)

Sally tells us that after researching mitochondrial disease online and in connection with the main UK patient charity there is a ‘scale of terrible’ in mitochondrial disease. Although Sally is concerned about the possibility that symptoms will present in her other children, particularly in one child whom she believes to be at greater risk, she is hopeful that it will not be to the extent of other families who are affected more severely. Sally does a lot of work throughout the interview to tell us that she feels her family are ‘lucky’ to have escaped the ‘horrible’ mitochondrial disease. For Sally the key issue was knowing that her family would not be affected as severely as others. Sally appears to exhibit what is known as downward social comparison, which can be applied to those living with a medical condition. This is the process in which people compare themselves to individuals whose experience of the same condition appears to be much worse than their own or who seem to be less fortunate. This then allows for them to form a more positive outlook on their experience (Standing et al 2017 in press) (Festinger, 1954; Taylor & Lobel, 1989; Wills, 1981).

Some women actively engaged in patient communities via the main UK patient charity or ‘private’ mitochondrial patient only social media groups where access and debates are controlled by appointed patient administrators/moderators. Some women used these groups for support in caring for affected relatives or as support to manage their own disease burden. These platforms were also used to raise awareness, inform family members, friends and co-workers of mitochondrial disease and for some to show their support in lobbying for the approval of mitochondrial donation in parliament. In one instance, these online communities were used as a direct source of information and support relating to reproductive options. Women who were not aware of these groups, expressed a wish to have an ‘online forum so if you wanted to speak to other people who were going through it you could’ (Wendy: 408-409).

Holly described being part of a global community of adult mitochondrial patients via a social media platform, which she described as offering peer support and a place ‘that they can be totally open and honest about whatever feelings and whatever issues they are going through’ (Holly: 1538-1540). In particular Holly was also able to connect with other ‘mitochondrial mums’ in America who had been through surrogacy to have their child/children and who were parenting with

a disability. When discussing how helpful this connection with other mums was to Holly she tells us:

Holly: Yes, they helped answer a lot of questions that I had about it, and even just the bonding side of it, and how, what they did and how because erm this, this lady is confined to a wheelchair and how she was able to just do things like, that you would expect a mum to do with her child. And how, what other types of things. So she told me about the things that she could do rather than focussing on all the things she couldn't do, sort of thing. And just trying to like turn it on its head and there are so many more things that you, you, you-  
Int: Positive.  
Holly: That you're not even aware of, that you can do with your child. Like you, you, until you actually sit and think about it. Whereas because people who are able bodied are running about and doing all these kinds of things, it doesn't mean to say that you can't do things just like sitting down. You don't have to be on the go constantly sort of thing (Holly: 1984-2002)

Holly used the social media platform to gain practical and experiential information from others, which helped shape her knowledge, hopes and expectations. Holly tells us that they discussed issues surrounding bonding with a child planned through surrogacy, recommendations on how to care for child when in a wheelchair and thinking positively about what can be achieved in spite of limitations caused by their mitochondrial disease. Engaging with other patient's experience (Ziebland & Wyke, 2012), their experiential expertise (Boling et al., 2015; Moreira, 2006; Ziebland et al., 2004; Ziebland & Herxheimer, 2008) is a central resource that helps to inform and support Holly's reproductive decision-making.

### **8.3.2 Lived Awareness**

Downing's (2005) model of responsibilities in reproductive decision making (Figure 4.13) in HD showed that lived awareness was an important factor in the awareness of risk, this was described in relation to the participant's experiences of HD in family members. Amongst women interviewed in this project we see that women's lived awareness of mitochondrial disease can consist of their

experience of family ill health and experience of their own personal ill health as a result of a mtDNA mutation. I will discuss both these in turn.

### **8.3.1.a Experience of Personal Ill Health**

Chapter 5 highlighted that for some women their personal experiences of ill health as a result of their mtDNA mutation dated back to their childhood. For Jenny, she had experienced over 40 years of symptoms at the time of the interview, that once diagnosed were attributed to her mtDNA mutation. Jenny had experienced severe fatigue from approximately 7 or 8 years old and despite being taken to see health professionals on a number of occasions she was not diagnosed with any illness other than being 'just lazy' (Jenny: 80-81). Jenny finally received a diagnosis when her only child presented with the same symptoms at approximately the same age, which led to the diagnosis of a mtDNA mutation in both Jenny and her child.

Jenny tells us that had she been aware of the inheritance risk associated with her mtDNA mutation she would have decided to not have any children.

Jenny: If I'd had had been diagnosed .... I wouldn't have had kids  
Int: You wouldn't have done?  
Jenny: No way  
Int: You have chosen not to?  
Jenny: Wey the risk is too great ain't it (Jenny: 290-295)

For Jenny the inheritance risk would have been too great. Jenny can be seen to have made this assessment of risk in part due to her lived experience of mitochondrial disease. Her decision therefore can be translated to the model as avoiding risk, resulting in the decision to not have children.

For others the uncertainty of being unable to predict the risk of affectedness of a child made it difficult for them to compare their own experience of ill health as a result of their mtDNA mutation to that of a future child's. Joanna struggled with not knowing what mutation percentage a future child may have and if they would have a percentage more or less than her own percentage. As we have seen in Chapter 5 section 5.5, Joanna was diagnosed via her mother whom she describes as having a 'really complex like medical history and things' (Joanna: 33) and she herself experiences bouts of chronic fatigue and other 'health

complications' that affect her daily living. At the end of the interview and when asked if there is anything that she wished to add Joanna adds:

Joanna: I have you know a few health complications and things like that and so it's the not knowing with mitochondrial disease  
Int: Yeah  
Joanna: I've got [XX] per cent, baby could have like [XX+11] – [XX+21], do you know the not knowing  
Gary: Umm  
Joanna: There is nothing to say that it would have less than me and you know  
Gary: Yeah  
Joanna: Cos it affects people in just different ways  
(Joanna: 398-405)

For Joanna the fact that there was no way of knowing what percentage mutation load her future child may have makes it difficult for her to compare her mutation percentage load with that of a future child. She tells us that a future child may have 11 per cent or 21 per cent more than her and that it may be more like her mother's percentage mutation load. The uncertainty described by Joanna and her partner Gary can be broken down to the unpredictability of mutation percentage, the lack of information relating to their specific risk due to the complexities of inheritance and unfamiliarity with the potential phenotype their future child may experience. We see that for both Joanna and Gary, this uncertainty is key to them seeking ways in which to modify risk by engaging with PGD (Chapter 7 section 7.4.1).

### **8.3.1.b Experience of Family III Health**

As seen in Chapter 5 it is often the case that some women with mitochondrial mutations do not experience any symptoms or experience low levels of symptoms that they deem to not require medical review until after they have had a child or children. A number of women interviewed had however experienced family ill health associated with undiagnosed mitochondrial disease for decades, which in some case included multi-generational experiences. Some women had witnessed their family members' health decline after a diagnosis of a mtDNA mutation, in line with the known natural history of these disorders. Both scenarios influenced how the women framed their own reproductive decisions.

For Wendy she had witnessed her sibling become seriously ill over 10-15 years, which was diagnosed as a mtDNA mutation after exhausting neurology services at their district and regional hospitals. Her mother who also experiences symptoms of the mutation, and her father, are her siblings' sole carers. When talking about how mitochondrial disease impacts their life as a family, Wendy tells us that

Wendy: Yeah [she] is severely disabled so [she] can't walk, [she] need's [she] can't [she] can't shower by [herself], [she] can't go to the toilet by [herself], [she] can't dress [herself]  
Int: Right so  
Wendy: Erm so yes so severely impacts my parent's life cause they're [her] main carers  
Int: Right OK  
Wendy: Well sole carers (Wendy: 259-264)

Wendy's sibling has a severe phenotype associated with the family's mtDNA mutation that requires both of Wendy's parents to care for them. The impact that her sibling's disability has had on both her and her husband's consideration of their options has led them to feel that they 'would rather not have a child, than have a child that's ... severely disabled like my [sibling]' (Wendy: 279-280). This strong desire to avoid having an affected child is in correlation with experiences of siblings with X-linked genetic disorders reported by (Kay & Kingston, 2002).

For Wendy it was important for her to tell her husband Mark of the possibility that she may also carry a mtDNA mutation before they were engaged. Although she had not wanted to take a genetic test to find out previously, she would have taken the test if Mark had wanted her to 'I offered to have the test (0.2) before before you'd even proposed to me and you were like "I don't care it doesn't matter"' (Wendy: 179-180). As discussed briefly in Chapter 5, Wendy had delayed undergoing a genetic test to find out if she too was affected by the family's mtDNA mutation for a number of years. The decision to have the test was as a result of her and Mark's discussions about having a family and how they wanted to know in advance Wendy's mtDNA mutation load. Upon receiving her result, Wendy and Mark considered Wendy's siblings quality of life, utilising their lived experience of mitochondrial disease. As a result of these considerations the

couple opted to seek guidance on PGD initially and then mitochondrial donation, with their preferred option being mitochondrial donation (Chapter 7). Both of these options would therefore allow for Wendy and Mark to modify the risk of having an affected child.

Awareness of the impact of mitochondrial disease could also impact on the reproductive decisions in other ways. For example, Lesley had grown up knowing that both her parents were ill, she attributes this firstly to the ages her mother and father were when she was born, describing her mother as 'in her forties'. Later she describes how her mother had started to experience serious health complications whilst she was still at school, including deafness, seizure episodes and dementia by the time Lesley was in her early twenties. For Lesley her older sister was 'more like wa mam than what my mam was actually like' (Lesley: 234). As a result of this lived experience of her families ill health Lesley decided, prior to any knowledge of the genetic condition, at an early age that if she were to have a family that she had to have a child before twenty six:

Lesley: No, no had me reasons  
Int: Is that related?  
Lesley: Yeah  
Int: To the diagnosis?  
Lesley: Erm even before that going back to when I was young all I can remember is illness ... I always said that if I didn't have a child by twenty six year old I'll never ever have a family and that's the way it worked out (Lesley: 211-214)

This was in order to reduce the chance that she too would become an ill parent, like her mother. Fortunately for Lesley she had a child by this age who was also the gender that she had always wanted and her husband was also in agreement that one child was enough for their family.

Lesley and her family believe that her mother's declining health over decades and early death was attributed to the severe phenotype associated with their family's mtDNA mutation, although they were unable to confirm this with any genetic testing. For Lesley becoming pregnant at an age that would allow her to parent without illness can been seen as central to shaping her and her partners reproductive decision making. She had initially decided this course of action prior

to the diagnosis of mitochondrial disease within the family, so her reasoning at that time point, was only informed by her lived experience.

Mandy had also experienced family ill health relating to her families then undiagnosed mitochondrial mutation. Mandy's mother was diagnosed when undergoing screening for a multi organ transplant, which was later found out to be have been a requirement due to her mtDNA mutation. Subsequently the rest of her maternal family was diagnosed, including aunts, uncles and her older sibling. When discussing factors that have influenced Mandy's reproductive decisions she tells us that:

it kinda was in the way that I wouldn't like to put my child through two transplants like what my mum has been through do you know what I mean erm and I wouldn't like to put them through just generally feeling weak and things like that erm (Mandy: 252-255)

Mandy tells us that she is not only concerned that her future child may require serious medical interventions as a result of the families mtDNA mutation but that she would want to avoid having a child that is affected by general weakness 'and things like that'.

In addition to her experience of family ill health, uncertainty as to what percentage mutation load would result in an affected child confused Mandy, as her mother's organ transplants had prevented clinicians from being able to accurately test her percentage mutation load. When discussing how mitochondrial disease affects her family Mandy tells us:

I mean my obviously my mum is more symptomatic than me so you would think her percentage would be higher or the same but then again it could be lower' (Mandy: 180-181)

The ambiguity of inheritance risk and the potential that her mother may have a percentage mutation load lower than her own but still be symptomatic was a real possibility to Mandy. We see that for Mandy both the uncertainty of inheritance risk and family experience of ill health are central to her desire to modify risk and her preference for mitochondrial donation as a future reproductive option (Chapter 7.4.1).

For women interviewed their lived experience of mitochondrial disease both personal and through family members impacted upon their reproductive decision-making (Decruyenaere et al., 2007; Dommering et al., 2010; Henneman et al., 2001; Klitzman et al., 2007; Myring et al., 2011). This experience, alongside women's concerns for their future child (child centred risk) as a result of the inability to predict inheritance risk accurately, impacted on their reproductive decision-making.

#### **8.4 Child Centred Risk**

We have seen in Chapter 7, and again above that women considered their future child's health and development as one of the most important factors in their reproductive decision-making. Sarah had considered the possibility of having a child whose mutation may have manifested in symptoms worse than her own but upon receiving advice from an 'expert', a regional neurologist, decided to continue with trying to become pregnant. When discussing how she made the decision to become pregnant following her diagnosis she tells us:

Sarah: I just think the world and life is hard enough as it is without proactively making a decision to bring a child into the world that is going to suffer  
Int: yeah  
Sarah: or is going to have problem (Sarah: 619-622)

Sarah believes that life is hard enough for what can be presumed as the 'average person'. Knowingly deciding to have a child who was going to 'suffer' or have 'problems' was not something that she would have wanted to do. For Sarah it was important for her child to be as healthy as possible.

As described in Chapter 7 section 7.3, women also considered the wellbeing of future generations, specifically relating to their daughters - living or imagined - who would be faced with reproductive decisions and the possibility of an affected child in the future. A number of women interviewed had been politically active in voicing their support of mitochondrial donation. For these women, this was in relation to not their own reproductive options but that of their female family members, predominantly their daughters. Sally was one of these women. At the time of Sally's interview, mitochondrial donation had not yet been discussed in parliament and the timeframe for debates relating to the technique were not yet

known. However, it was Sally's wish that mitochondrial donation be approved so that her daughters would be able to consider it as an option. When talking about how she will have passed on her mtDNA mutation to her children Sally says:

Sally: Obviously my ... girls will have the gene and will pass it and they have to make choice when they're older erm especially with all the ... things happening at the moment with the erm you know the IVF treatment that they are trying to do so erm I definitely keep up to date with that cos hopefully in another 20 years' time when my children decide to have it, that might be an option for them

Int: OK

Sally: I think I know that if I had the option that would make me feel a lot better that I could have that rather than take the chance and passing the gene on (Sally: 318-325)

Sally has kept 'up to date' with the progressing parliamentary campaign, including emailing her member of parliament to lobby in favour of the amendment to the 2008 Human Fertilisation and Embryology Act. Sally supported the new technique as she hoped that this would enable her daughters to be given the choice, one that she did not have, to prevent them 'passing the gene on'. What is central to Sally, and others, is preventing further inheritance to subsequent generations.

### **8.5 Parenting Risk**

Concerns over risk with regards to parenting ability is a factor in establishing ones self as a responsible decision maker in Downing (2005) model. With HD, the complexities of disease can manifest later in life and possibly after childbearing decisions have been made. As we have seen in Chapters 5 and 6, the onset of symptoms for some mtDNA mutations is the same, with many women interviewed not experiencing symptoms until after they had started or completed their families.

Women with mtDNA mutations also face the same predicament as patients with HD in that there is a lack of effective treatments to combat disease progression, which can lead to uncertainty regarding future parenting ability. We have seen previously in Chapter 7 section 7.4.1 that the risk of passing on her mitochondrial mutation was not a concern for Andi, however having a mitochondrial diagnosis

did impact on Andi in relation to whether she would be physically able to care for the new child, her other children and manage their home 'so in that way the mito affected it' (Andi: 383).

Andi experienced combinations of symptoms including chronic fatigue, visual disturbances including double vision, peripheral neuropathy and sometimes required the use of a walking aid. Andi and her husband discussed together the practicalities of having another child in relation to her mitochondrial disease.

Andi: No it was erm shared but he he did make sure that I wanted this because I was the one with the mitochondrial so it was going to be hard on me so with [Child Z] I said "yeah it would be nice for [them] to have a, with [Child Y] it would be nice for [them] to have erm to have a companion but I'm going to need a lot of help with this one so if were doing this", if we're getting pregnant then with another one he has to understand that he has got to put more work in  
Int: Um hu  
Andi: With me and around the house and everything so and he understood that and he was fine with that  
(Andi: 354-361)

Central to her decision-making was her husband agreeing to put 'more work in' to their family, to help her 'around the home and everything'. She also tells us that her elder children were involved in the decision, understanding that they would need to help their mum 'because I couldn't do it alone (Andi: 380) and so that it had been a 'family decision to have [Child Z]' (Andi: 381). For Andi, the practical support of her immediate family to help her through her pregnancy and raising her children in the future was important. For Andi and her family although her symptoms were taken into consideration when planning to have another child, any future parenting risks were alleviated with the extra input promised by her husband and older children. Therefore Andi can be seen to have accepted this risk.

Holly and her partner Edward had also discussed the possible affect that Holly's mtDNA mutation would have on both Holly's ability to parent in the future as well as Edward's ability to parent alongside, fulfilling the role of carer for Holly. When discussing how important it was to them both to have a child who would not be affected by a mtDNA mutation Holly tells us that:

I certainly wouldn't want to have a child that would potentially have a serious condition based on the fact that I've also got, like I've, I really struggle just every day, like generally, living day to day, without the added pressure of having to look after a child who has also got like complex needs as well, sort of thing (Holly: 944-950)

Holly was very aware the impact of her mitochondrial disease on her day-to-day life and that caring for an affected child with 'complex needs' would be added pressure and be 'extremely difficult' (Holly: 954). In Chapter 7 we also see that when considering adoption, Holly discusses adopting an older child who would be less demanding than a newborn and may be more suited to their family, given her specific disease burden.

Holly also considers the potential impact of her disease progression on Edward and how she would not want him to have to care for her and their child 'because that's not fair either' (Holly: 2262-2264). Edward tells us that his parents had discussed the issue.

I think my parents are concerned about having the baby and the pressure of it, so having to look after Holly with her condition and then also having a baby. So that adds a lot onto me (Edward: 2030-2033)

It is notable that Edward does report his parents being concerned about the health of the child. Edwards's parents are not alone in their concerns for Edward looking after Holly and their future child. Holly's family had also expressed similar viewpoints relating to the 'amount pressure that we will be under' (Edward: 2037-2038). It is evident that for both Holly and Edward a key issue to their decision-making is related to Holly's future parenting ability and the added 'pressure' of having a child may exert on them as a couple. Caring for a child with a mitochondrial disorder was reported by Read (2003) to be significantly more stressful and worrying compared to parents of another rare disease (PKU), with mothers experiencing dissatisfaction with social support and having multiple impacts on their personal lives. Parenting as a 'disabled parent' is of noticeable concern for Holly, and draws on the wider social studies of parenthood and disability and disabled parents raising children with a disability also (Olsen & Clarke, 2003).

## 8.6 Pregnancy Risk

Pregnancy complications in maternally inherited mitochondrial disease are varied and can be very dependent on the phenotype of the expectant mother. The majority of the women interviewed had not experienced difficult or traumatic births, although certain conditions of pre-eclampsia, appendix rupture, emergency caesarean sections, low birth weights of children, periods of hospitalisation and early deliveries were reported by women, concurrent with reports of pregnancy in mitochondria disease (Say et al., 2011).

For some women becoming pregnant when also being affected by a mtDNA mutation is however an issue. For one woman the potential that she may experience severe and possibly life threatening complications played a significant role in her reproductive decision-making. Holly had been told a number of years prior to the interview that her body would be unable to support the additional stress of pregnancy, due to symptoms associated with her mtDNA mutation. Holly had received this information in a consultation with her mother and before meeting her partner Edward, at this appointment Holly was told that she should find a surrogate to have a baby in the future. Holly goes in to detail about what was said to her during this appointment with a local doctor.

Yeah, so that was, that was erm, I'd went to the fertility one at the [local hospital] and then I'd seen like the obstetrician person. Erm, it was my mum that went to that appointment and [they], [they] basically went through it and, and like put the, like the absolute dread into me; the thought of actually carrying a baby. Because [they] said about how the rest of, erm like [organ] problems and there was a whole list of things, was much, much higher because obviously of having the mitochondrial disease, and just the added pressure in your body of carrying another, like carrying a child. Erm, plus the [symptom], I could potentially become [symptom] and [symptom] right through my pregnancy; I might end up having to spend most of it in hospital and it just, it scared the, it really scared me (Holly: 828-239)

For Holly finding out about the considerable risks to her health if she were to fall pregnant and carry a baby put the 'absolute dread' into her and 'really scared' her. Holly tells us that because of 'how much it kind of affected me' (Holly: 857) she was referred to a fertility counsellor, who she had continued to see at the time of the interview who had helped her 'come to terms with the fact that I wasn't

going to be able to carry' (Holly: 862-863). For Holly, finding out that she would have to seek an alternative option to have a child irrespective of inheritance risk influenced her reproductive decision-making before she had even met her partner Edward. As a result, Holly and Edward were actively seeking advice regarding options that would modify risk to both Holly and their future child, this being both PGD and surrogacy.

For Jenny the concern over the potential risk of complications during pregnancy was not for herself but for a female relative of hers. When asked if she felt that mitochondrial donation may be a suitable to her or her family members in the future, Jenny tells us that because of her female relative's symptoms and how they sometimes restrict her to a wheelchair she feels that 'Erm and you know, just, yeah I don't think it would, I don't think her body would cope ... you know' (Jenny: 252-253). For Jenny she did not feel that her female relative should risk becoming pregnant out of concern for her physical wellbeing.

As we have seen previously, some women do not experience any symptoms of their mtDNA mutation, are affected mildly (in their opinion) or who don't experience symptoms until after they have completed their family. However, for some women their individual experience of the disease and the complications that could potentially arise from a pregnancy do need to be considered when assessing their reproductive options, options that modify the risk of pregnancy complications would include surrogacy, adoption or voluntary childlessness.

We see that the factors identified in Downings (2005) model of responsibility in relation to awareness of inheritance risk also apply to women with maternally inherited mitochondrial disease. I have expanded upon these factors to include further detail relating to women's lived experiences of mitochondrial disease and inclusion of pregnancy risk that presents to some women as a result of their phenotype. I have shown that these factors either alone or in combination result in women defining reproduction as a cause for consideration. I have purposively chosen to assign these as 'cause for consideration' as opposed to problematic as the Downing (2005) model has defined them as we have seen that not all women describe them as problematic *per se* but rather a necessary consideration. I will

now continue to outline what I have termed 'elements of consideration' and how these play a role in the reproductive decisions made by the women interviewed.

## **8.7 Elements of Consideration**

Downing (2005) showed that once reproduction was defined as problematic participants went on to 'redefine certain elements of their situation' (p221). They argued that although some factors covering response to risk may be similar, responses are not consistent and that the process of redefining reflects elements that can be modified, therefore enabling people to tell different stories about risk acceptance, avoidance or modification. In her paper Downing (2005) outlines these elements as: values; concept of future; perceived social support; risk; self-relationships and reproduction. Emergent categories from interviews with women in this project support the inclusions of some of these elements into the mitochondrial specific model, whereas others were found to not be relevant as well as being difficult to define from their model and so therefore have not been included. In addition to those elements carried over, novel elements discovered within the data set have been added. These elements include values encompassing religion, inheritance guilt and responsibility and women's ideas and preferences surround reproductive options. I will discuss these each in turn.

### **8.7.1 Values**

Women's values were shown to be a major contributor in reproductive decision-making. Intrinsic to their values, were women's ideas and preferences surrounding available reproductive options. Chapter 7 showed how preference was placed on having a healthy and biologically authentic child, linked to women genetically. For the majority of women, mitochondrial donation was the most favoured reproductive option, as it enabled not only a genetic link but also maximised the opportunity to have a healthy child, either for themselves or for other female family members (real or imagined). Mitochondrial donation directly tackled the uncertainty of predicting the clinical affectedness of a future child, therefore significantly reducing the child-centred risk and feelings of guilt and responsibility (see section 8.7.2).

Other reproductive options that offered certainty in relation to having a child free of a mtDNA mutation included ovum/egg donation and adoption were problematic

to some women due to the lack of biological link and ideas of bringing up 'someone else's child', rendering them either a non-option or a last resort. Surrogacy for those women who had no reason to consider a potential pregnancy risk was primarily discounted, whereas in the one instance whereby pregnancy raised the potential of life threatening complications, it was seen as an option that would permit a genetically related child to be born. Issues pertaining to embodied experience of pregnancy and missing out on this experience were raised as a potential challenge to be overcome in surrogacy. PGD was often considered as an interim option for women and their partners who would have, given the chance opted for mitochondrial donation, with many couples believing that PGD still presented uncertainty in regards to its ability to reduce child centred risk, the 'potential grey zone'. Prenatal testing was in principal discounted by women, with women unwilling to take the risk of these procedures and their desire to avoid being placed in a situation in which they may have to consider the termination of an established pregnancy. These accounts were supported by one woman's experiences of how difficult decision-making was when presented with information that her unborn child may be affected. Some women reflected on not having any children/more children as a way to avoid transmission in both the retrospective and current and prospective groups. Although many women expressed that fulfilling the mothering role was something they had felt strongly about since they were young and therefore complete childlessness was not an option

### ***8.7.2 Guilt and Responsibility***

Notions of guilt and responsibility were present throughout the majority of interviews and these radiated out to not only real or imagined children but also to other family members. Chapter 6 explored how women had feelings of guilt when discussing their children or when faced with telling other family members about the diagnosis (see section 6.2.3). Women who deliberately sought to prevent their own mothers or grandmothers from feeling maternal guilt chose not to disclose that they had a genetic disorder and especially in relation to its maternal inheritance. Preventing their own imagined feelings of future guilt led to women seeking options that could modify inheritance risk to future children. Women also felt responsible to future children to do their best to reduce or prevent inheritance

and ill health as well as feeling responsible to disclose to family members 'at risk' of a mtDNA mutation (Arribas-Ayllon et al., 2011; d'Agincourt-Canning, 2001; d'Agincourt-Canning, 2006; Dimond, 2013; Hallowell et al., 2003; Novas & Rose, 2000). The realisation that their genetic disorder was passed down from mothers magnified these feelings.

For the women in the retrospective group who received their diagnosis after their children were born, they described feelings of guilt towards known affected children but also towards children whose risk of affectedness was unknown. They described feeling almost immediate guilt when initially learning about the inheritance pathway. For example, Sally's youngest child was diagnosed after almost two years of investigations at district and regional hospitals. Sally had assumed the visit when she found out about her child's diagnosis was going to be yet another appointment where they were told the cause was still unknown.

cos we weren't expecting it erm but at first when he said that he had found it and that it's came from me I felt really guilty and responsible for [Child Z's] conditions straight away, as soon as I came out of the room I was just in tears for a few days afterwards (Sally: 82-84)

For Sally, discovering that her child's problems had 'came from' her, led to an immediate emotional response. Sally's mother echoed her daughter's feelings later that same day.

my mum (0.2) didn't really take it on board until she got home but then she rang me a few hours later to say that she had been crying, upset because now she feels that now she is responsible (Sally:147-148)

Sally's mother had been looking after her other children whilst she attended the consultation with her husband. In this way, each generation felt guilt and responsibility towards the next generation.

Sally also felt the burden of responsibility towards her other two children who at the time of the interview showed no signs or symptoms, describing feeling 'really concerned', 'really responsible' and 'I didn't feel good at all' (Sally: 89). Clearly, she cannot change her past, but she can take responsibility for future actions. For Sally these feelings were central in her considerations around having more children.

Cos I did feel that immense guilt and I think that I would carry that on again if I had more children (Sally: 187-188)

Receiving her child's and her own diagnosis had 'put her off' thinking of having more children. Given her new knowledge, she now felt responsible to minimise the potential suffering of future generations. In this way, a desire to avoid any potential complications for future generations resulted in her avoiding this risk and believing, at the time of the interview, that she would have no future children.

For Sally it was also important at the time of finding out about the inheritance pattern that she disclosed her and her child's mtDNA mutation to her family as she felt 'I had this responsibility to tell the family' (Sally: 121). This disclosure to the family included a female sibling and cousins. Interestingly within Sally's family her maternal uncle had been diagnosed with a mtDNA mutation many years beforehand.

Yeah but I felt responsible again because I got to erm tell my family because because obviously my uncle has got this disease and we didn't know about it, he's had it for about [XX-XX] years (Sally: 115-116)

Unlike in other families in this study, Sally's uncle had known the reason why he had lost his vision after receiving a diagnosis of mitochondrial disease about the time when Sally would have been a teenager. Sally felt frustrated by this prior family knowledge because she felt that had she known her child could have received care sooner as opposed to taking over two years to be diagnosed. She also felt that through telling others in the family, they could then also have been tested or been able to seek an explanation for why they or their children might be unwell. It was important to Sally that this silence, the lack of collective knowledge about the condition, did not continue within the family.

We have seen in Chapter 7 and above that Jenny would not have had children had she been aware of her mtDNA mutation because of the risk relating to affectedness to a child. Jenny had had a child before her diagnosis and she describes very emotionally throughout the interview the feelings she experienced when she was first told of the inheritance pathway 'absolutely horrendous the

guilt' (Jenny: 55-56). When discussing how she had told others about feeling this way Jenny tells us through tears that:

Jenny: you sort of say you feel guilty, but you told that ridiculous cause like yeah it's ridiculous [inaudible]  
Int: Yeah  
Jenny: It's crazy yeah, you know, I mean I know (0.2) it's not me fault (Jenny) 323  
Int: Yeah  
Jenny: But it's still there (0.4) yeah (Jenny: 319-327)

She still feels this guilt, which she knows, in rational terms, is 'ridiculous', even after more than a decade since her and her child's diagnosis. Jenny talks throughout her interview as acting as an advocate for her child as they have grown to become an adult. As we have seen in Chapter 6, Jenny still feels that what was lacking throughout both her and her child's diagnostic process was access to appropriate counselling services that could help her come to terms with the diagnosis and the feelings of guilt she suffers from.

For women in the current and prospective group, they considered the potential health of their future child and for them to be as healthy as possible. As we have seen in Chapter 7 (section 7.4.2), Ashley and her husband were actively considering ovum donation as an option to have another child at the time of the interview. They had made this decision after finding out that they would not be suitable candidates for PGD or mitochondrial donation. For some time before seeking interventional reproductive options she and her husband had tried to conceive without medical intervention, over time this was no longer an option. When discussing why this was the case Ashley says that:

I don't want to bear the responsibility of having a child that is getting really sick, either as a child or later on in life depending on how severe it is (Ashley: 126-128)

Specifically for Ashley her decision to no longer continue with 'natural' conception was driven by the feeling that she no longer wanted to risk bearing the responsibility for an ill child or a child who may grow up to have complications later in life. A key issue for Ashley was to avoid this responsibility and to try to reduce the probability that she would have an affected child. This resulted in her

seeking to modify her risk by actively inquiring about interventional reproductive options.

For some women interviewed they were worried about how their own mothers or grandmothers may have felt when receiving the news of the maternal inheritance pathway. They were worrying that they may feel the burden of guilt that Sally's mother had. To prevent their mothers or grandmothers from feeling they were somehow to blame for their or other family members symptoms, some families had collectively agreed to not disclose the news of a genetic condition, especially that it was maternally inherited, to their mothers or grandmothers, raised earlier in section 6.2.3. This decision to not disclose this information seems to be led by the women's own feelings of guilt towards their own children, even if they did not know if their children were affected. This was further complicated by the ambiguity as to whether their mothers or grandmothers were affected, reporting that some of these women were in good health. There was also the potential that their mtDNA mutation may have been sporadic (Gorman et al., 2015) and had not originated in their mothers or grandmothers, such that disclosure could therefore cause unnecessary suffering.

As we have seen in Chapter 5, Joanna had received her diagnosis via her mother who had a complex medical history (section 5.5). Joanna's mother had made the decision to not tell her own mother, Joanna's grandmother, about their mtDNA mutation or the maternal inheritance pathway. When asked if there was anyone that Joanna had not told about her diagnosis she tells us that her grandmother did not know and that this had been because:

Erm she, you know my mum didn't want her to blame (0.2) to blame herself but now they say they think that it just started in my mum anyway not from my grandma (Joanna: 137-138)

Joanna's mother was herself struggling with the knowledge of inheritance and was often 'really emotional about it cos she blames herself' (Joanna: 91). Joanna herself found it quite hard to 'talk to my mum about it because (0.2) she feels like it's her fault' (Joanna: 96). Joanna therefore avoids talking about inheritance to prevent her mother from feeling 'terrible' or as if it were 'her fault' because the inheritance of their mtDNA mutation is 'just one of them things' (Joanna: 99).

What was central to Joanna and her mother was avoiding situations where their own mothers may feel guilt or blame themselves for the inheritance of their mtDNA mutation.

Maggie describes her mother being aware that she and her siblings were all unwell in similar ways and that she believed her mother may have thought it was a genetic condition but that she may be in 'denial' or may think that their symptoms may have come from either her or Maggie's father.

Maggie struggled with the idea of telling her mother that her symptoms were likely to have been inherited from her, she therefore decided to not tell her mother.

Maggie: It, it would only be something else for her to worry about.  
Int: Worry about.  
Maggie: And have the guilt to think that she's passed it on to her [X children], and that in turn that has been passed onto all of her grandchildren (Maggie: 1127-1134)

For Maggie she did not feel that her mother knowing about her mtDNA mutation would be of any 'benefit' to her and that this would only cause feelings of guilt for passing on the mutation to Maggie, her siblings as well as her grandchildren.

Maggie also struggled with disclosing inheritance to a cousin who would be at risk along with her children. When discussing who Maggie has discussed her diagnosis with she tells us that she was slightly hesitant in discussing her diagnosis and inheritance pathway with a cousin.

But I was sort of thinking my [cousin] got [X] kids, and I thought it's a horrible thing to have to tell her if she's got it, that she's going to have the same horrible feelings as I've got, that she might have passed it onto her kids as well (Maggie: 1040-1043)

Maggie was also concerned that telling her cousin would induce the same feelings of guilt that she had on to another person who also had children who were potentially at risk. What was central to Maggie was trying to prevent unnecessary feelings of guilt where possible but also being responsible to inform other family members of the potential risk.

Zoe was diagnosed via her older sibling, they were both teenagers at the time of their diagnosis. At the time Zoe was concerned about what her diagnosis meant for her in the future but has remained asymptomatic. Her sibling struggled with many aspects of their diagnosis, where symptoms had resulted in the loss of their job, driving licence, social life and independence. Zoe described them as feeling 'devastated, absolutely devastated cause I think at the time [they] felt that [their] life had been took away from [them]' (Zoe: 38-39). Zoe believes that for some time after her sibling's diagnosis they felt 'resentment' toward their mother and that 'I think [they] blamed me mam like a little' (Zoe: 48-49). This period of time was especially difficult for Zoe's whole immediate and extended family and that her mother 'was absolutely devastated [by the diagnosis] cause they didn't know' (Zoe: 77-78). Interestingly Zoe's maternal uncle was also affected by the family's mtDNA mutation prior to her diagnosis, similar to Sally, but Zoe's uncle had never received a diagnosis or explanation as to why he too experienced the same symptoms as Zoe's sibling. Like Sally, Zoe's mother struggled with knowing that the diagnosis was maternally inherited and felt a responsibility to tell her wider family, who along with their children may be at risk of the family mtDNA mutation. Zoe's account of her sibling's initial reactions to their diagnosis is the only account in the study of a 'child' being perceived as 'blaming' their mother for the inheritance of their mtDNA mutation.

All of the women who discussed their mothers described how they did not blame their mothers and how they wanted to prevent their mothers from feeling any guilt for the transmission, but that they had feelings of guilt towards their children. Only one woman described not having any feelings of guilt towards her children 'I don't feel guilty if my kids get it off me' (Andi: 117), as Andi believes that if her children were meant to inherit her mtDNA mutation there was nothing that could be done other than to care for them and look after them as best as possible (see section 7.2)

We see that a large proportion of women feel a sense of guilt when thinking about their children irrespective of whether they were known to be affected or not. For those women in the current and prospective group they felt a sense of responsibility to prevent transmitting their mtDNA mutation to future children. Women also felt a combination of responsibility to tell other family members who

may be at risk as well as hesitancy or avoidance regarding the disclosure of the maternal inheritance of their mtDNA mutation.

### **8.7.3 Religion**

All women were asked at the start of the interviews whether they followed a particular faith, in most circumstance women replied that they had been raised in a certain religion, christened or baptised for example but that they did not class themselves as religious. Three women within the study however answer that they had a faith, whilst one woman said she was not religious but believed there was a 'bigger force'. We see in Chapter 7 that Andi's religious beliefs impacted directly on how she both perceived inheritance risk and opinions of reproductive techniques including IVF technologies.

For Andi her beliefs affect 'all my decisions' (Andi: 675). When discussing how she and her husband considered future risk to their child and if they were to be affected by inheriting her mtDNA mutation, she tells us that:

religion affected it in that way, we don't, we would never have gone aw  
"I've got this illness, I can't, I'm going to stop now" (Andi: 698-690)

For Andi her religious views meant that she could accept and support any future children who were affected by a mtDNA mutation and that 'religions affected it more than science [laughter]' (Andi: 699). For her and her husband, faith was the central mediator through which they made sense of their life. For them, this meant that they accepted the potential risk and continued to add to their family without engaging in interventional reproductive options. Rapp (1998) reports that women with strong religious affiliations (as well as strong kinship and social communities) were 'most likely to decide against the biomedical information' provided by prenatal testing in their consideration of accepting or rejecting a pregnancy with known serious fetal abnormality (p67).

For the two women that described themselves as religious at the start of the interview they did not describe their faith as a mediator to their reproductive decision-making or their ideas or preferences of reproductive options. For Alice who believed in 'something greater' she spoke of her beliefs with regards to her and her husbands struggle with infertility and that perhaps she was not meant to

have children, to prevent having any affected children and from passing on her mtDNA mutation. When discussing how there were no younger females in her family who would be at risk of passing on the family's mtDNA mutation Alice tells us that:

Alice: This is the other thing I find funny.  
Int: Right.  
Alice: Because it's a maternal link and what you were saying about before, "Are you religious and do you believe in anything?" I've got [female family members] who've been diagnosed and they've got [X] sons  
Int: Yeah.  
Alice: The mitochondrial disorder ...and I don't have any children, so it's stopped.  
Int: Yeah.  
Alice: It's stopped now.  
Int: It's all stopped now.  
Alice: Hmmhmm. Isn't that funny?  
Int: Yeah.  
Alice: Hmm (Alice: 1276-1298)

Alice tells us that all the females at-risk of passing on their mitochondrial disease in their family had had sons who would not transmit the disorder to their offspring (but may still experience symptoms themselves). Alice finds it funny that this in combination with her being unable to have children has meant that their family mutation is no longer a risk to future generations, 'it's stopped now'. Alice talks about this as fate through the interview and it seems to have provided a comforting explanation of her and her husbands infertility and is supported by Tennen et al (1991) who showed that attributing an existential reason for infertility helped women make sense of 'what might otherwise seem like meaningless victimisation' (p110).

### **8.8 Establishing a 'Responsible' Viewpoint**

We have seen above how women or women and their partners reach a position that Downing (2005) states as a responsible decision maker, where women or couples have assessed all of the necessary factors and elements that apply to them. When women or couples have reached this stage they can then be seen to make a reproductive decision, which centres on accepting, modifying or avoiding risk. For those who can be seen to accept risk, they continue with planning or

adding to their family without engaging in interventional reproductive options, conceiving 'naturally'. For women that want to avoid risk, they opt to avoid becoming pregnant or to have no future pregnancies. Those women who want to modify risk are seen to seek information on or have already started the process of engaging with options that allow for risk to be modified such as egg donation, surrogacy, PGD and mitochondrial donation. However, not specifically explored in the model presented by Downing (2005) was the temporality of reproductive decisions, I will therefore explore how change over time was important in the lives of women in this study in relation to their reproductive decision-making and how this was incorporated into the proposed conceptual model.

### **8.9 Change Over Time**

The notion of time and change over time in relation to reproductive decision-making has been explored in other genetic disorders as well as in consideration of PGD as a reproductive option. Hershberger et al's (2012) model of decision-making in couples considering PGD described a decision type entitled oscillating, whereby couples were neither for or against PGD. Whilst Myring et al (2011) described decision making as dynamic and not fixed in CF. Dommering et al (2010) reported that parents of children whose treatment for retinoblastoma had ended no longer wished to avoid having more children. For some women in this study, change over time was an important influencer of their perception of risk and subsequent reproductive decision-making, and has been presented in the conceptual model as time point two (T2). The altered perception of risk meant that women could be seen to return back to the stage in the model where reproduction was defined as a cause for consideration. Using this new information alongside existing factors and elements women reached a new viewpoint regarding risk and acted according to this new perception of risk. This new information was either in relation to a family experience or a change in personal circumstances. Family experiences ranged from witnessing the impact of progressing disease burden or suffering the loss of a family member due to their mitochondrial disease. Changes in personal circumstances seen in the study included, women being made aware of new reproductive options, becoming pregnant unexpectedly or a relationship change that saw them view their prior options differently.

We have seen previously in Chapter 7, section 4.1 that Liza considered herself naive when she fell pregnant with her first child after she and a number of her family members were diagnosed with a mtDNA mutation. During the time of planning her first pregnancy Liza can be seen to have considered the potential child centred risks to a future child. Liza relied on her lived experience (Kelly, 2009) and experiential knowledge (Boardman, 2017) of the possible symptoms of which a future child may be at-risk of. Within her family these had included deafness, diabetes or gastrointestinal symptoms. For Liza she believed that she and society were able to accommodate these symptoms fairly easily. Liza conceived her first child 'naturally' and turned down prenatal testing. However Liza's perception of child- centred risk changed after her mother died from complications associated with a severe phenotype of their mtDNA mutation. When telling us about how her view of risk changed after the death of her mother, Liza tells us that:

Erm and I say it was when my mam died that aw hold on a second I maybe should be taking more interest in this and what's going on, erm I know my mam was very poorly with it but I never expected her to die kind of (Liza: 105-107)

For Liza the death of her mother made her stop and consider what having a mtDNA mutation may result in, she had known her mother was very unwell but 'never' expected her to die as a result of the mutation. Following her mother's death Liza started to learn more about inheritance risk 'so it was from that point really that I started to get involved with it' (Liza: 109). We've seen in section 7.3.2 that Liza and her husband went on to explore PGD as their preferred option followed by prenatal testing when denied access due to NHS funding criteria. Liza can be seen to have received new information that alerted her perception of risk resulting in her and her husband seeking ways in which to modify risk by engaging in interventional reproductive options.

Ashley acts in a similar way upon receiving new information, in her case this was the declining health of her sibling who had been diagnosed at the same time as her, just a number of weeks before the death of their mother. Ashley's mothers health had declined over 20 years with symptoms classically associated with their mtDNA mutation, later going onto to develop the severe phenotype associated

with the mutation. Ashley tells us that she is 'pretty much alright' (Ashley: 44-45) but also that she handles the symptoms and hopes for the best. At the time of her diagnosis Ashley did not live in the UK and received her result and information about inheritance from mitochondrial experts in two separate countries. Ashley and her husband had had their first child before becoming aware of her diagnosis, which she tells us was not easy, she had undergone a period of time on hormone injections, eventually conceiving her child after these interventions had ended. As we have seen in section 7.4.1, Ashley and her husband had been trying for a child naturally for 'quite some time now' (Ashley: 123-124) they could be seen to have considered risk and had chosen to accept risk by conceiving naturally.

However Ashley tells us that 'it changed over time and I got more scared' (Ashley: 162-163) and that she was no longer willing to take the risk of having a potentially sick child. Ashley tells us that this was because she has 'more time to think about it and seeing my sibling suffering' (Ashley: 166). Ashley's sibling experienced symptoms before they were diagnosed which were first identified when undergoing a medical examination as part of a job application, she also described them as suffering from short stature and mild learning disabilities. Over time they have experienced increased complications involving major organs and they have required intense and invasive medical treatments, she described them as 'really badly affected' (Ashley: 35) and 'very severely ill' (Ashley: 50). This new information altered Ashley's perception of risk and as a result she and her husband chose to prevent the chance of conceiving naturally by starting contraception and by actively seeking ways in which to modify their risk. Specifically enquiring about mitochondrial donation, PGD and ovum donation.

For Zoe her perception of risk changed when she and her husband saw on breakfast telly one morning that there was a new IVF technique approved that could prevent the transmission of mitochondrial disease. When telling us about how she had first heard about mitochondrial donation Zoe tells us that

so that's when me and my husband had seen, it was about a year and half ago I think or year, last year and we'd seen it on breakfast telly erm and that when we thought here's our chance, so it was like someone giving you a chance for something (Zoe: 100-103)

Zoe describes how finding out about mitochondrial donation was like being offered a chance, the chance to have a child who may not be affected. Prior to finding out about the '3 parent family thing' (Zoe: 118) Zoe had avoided becoming pregnant and had been practicing temporary childlessness to avoid the risk that she may have a child who could be affected like her sibling. When telling us about the potential risk to a future child she tells us that:

its not definite that they could... get it but there is a chance that they will you know and I, for me, its been hard to know that you want a family and physically able you can have a family but you've got that bit that pulls you back that says no (Zoe: 100-103)

For Zoe she had spent many years wanting to start a family with her husband but even with 'expert' advice regarding inheritance risk and knowing that 'it's not definite' that a child would be affected she had felt that something had pulled her back. During this time Zoe had assessed both factual and lived awareness of risk and can been seen to have chosen to avoid it, by actively preventing becoming pregnant. The new information for Zoe that led to alter her perception of risk was learning about mitochondrial donation, which had led to Zoe and her husband actively seeking advice on reproductive options that would modify the risk to a future child, specifically mitochondrial donation.

To further test the conceptual model for rigour after its development in relation to change over time, an amendment was made to the study protocol which allowed for those women who had been interviewed in the current and prospective group to be approached to take part in a follow up interview (see Chapter 4 section 4.3.5). Four women were approached; two women took part in a follow up interview. In both of these cases women had experienced a change in personal circumstances that had led to a change in reproductive decision-making.

At the time of her first interview Emma was unsure if she wanted to have children 'I don't know in the future as to whether I whether I will want them' (Emma: 169), but that she and her previous partner had had been given brief advice about their reproductive options when they were considering starting a family. At the time of her initial interview Emma's reasonings for potentially not having children was based on other factors including at the time the relationship she was in, 'it's not

something were looking at' (Emma: 189) and 'no it's nothing to do with mitochondrial diagnosis' (Emma: 192). Emma took part in the follow up interview, which centred on asking women if anything had changed with regards to their reproductive journeys since their previous interview. Emma responded that she was currently pregnant and in a new relationship. After congratulating her on the news Emma tells us immediately that:

Emma: But no we went ahead naturally, we didn't take up any of the options that were offered by the clinic, erm again we kind of looked at it before we made a decision and erm we were quite happy that we should go ahead naturally. We met up with the [mitochondrial specialist] from the clinic and sought some advice about that  
Int: Was that Dr X was it?  
Emma: Yeah, yeah  
Int: Aw wow, that's brilliant, so did you were your kinds of discussions were they brief or did you go into any depth or  
Emma: Erm no I think we did go into quite a bit of depth  
(Emma repeat interview: 11-19)

Before becoming pregnant, Emma and her new partner had contacted her mitochondrial specialist team, where they had an in-depth discussion about the reproductive options that were available to them. Emma was very aware of mitochondrial donation via the previous parliamentary campaigns. Emma and her partner 'looked at it' before making any decision and after considering their position they decided that they were happy with the information provided to them and opted to conceive naturally without any intervention. For Emma she tells us that she was 'aware of everything that [the clinic] could do and I've spoken to them quite a few times since erm to make sure everything is OK' (Emma: 27-29). Emma recalls being offered prenatal testing but like many women in the study declined this 'on balance' and that they did not think it 'necessary'. Emma has been offered additional care during her pregnancy from the mitochondrial specialist team but declined as she was already being monitored more closely for a condition that she describes as being linked to increased risk of other chromosomal abnormalities. Emma is relatively confident that this issue will right itself and she will be discharged back to standard pre-natal care. For Emma her change in personal circumstance has resulted in a change to her reproductive

decision-making, whereby she and her partner can be seen to have considered factual awareness and the reproductive options available to them and reached a viewpoint, which can be seen as accepting risk and conceiving their child without medical intervention.

### **8.10 Summary**

Data presented in this chapter supports the proposed conceptual model of reproductive decision-making in maternally inherited mitochondrial disorders. The decision-making model shows that for many women their lived experience of mitochondrial disease precedes their awareness of inheritance risk, be it personal or via a family member (T0). These experiences can be influential in women's assessment of risk including most commonly child centred risk and in some cases relating to parenting ability. Upon receiving a diagnosis, women are informed that their disorder is maternally inherited and that due to complexities of mitochondrial inheritance there is an unknown and difficult to predict risk to their current or future children. Women seek and receive information from a number of sources that can aid in the decision-making, with information from mitochondrial specialists being a trusted source of information relating to an individual's inheritance risk. Social communities including those made via charitable, political and online connections can be helpful to women as a source of information, whereas other women believe more could be done to represent the spectrum of mitochondrial disease and provide more information on on-going research.

Risks to a future child's health, risks surrounding future parenting ability and for some women potential risk of pregnancy are influential factors, alongside factual and lived awareness, that can see reproduction defined as a cause for consideration. Additional elements of consideration for women include their individual preference for reproductive options, their thoughts of guilt and responsibility in the context of a maternally inherited genetic disorder and for some their religious beliefs. These factors and elements allow for women to establish themselves as a responsible decision-maker, whereby they reach a decision to accept, modify or avoid risks. Acceptance of risk can be seen as continuing to have a child without engaging in interventional reproductive options, modification of risk included women or couples that chose to engage with an

interventional reproductive option and those who wish to avoid risk are those who would choose to have no future pregnancies.

The proposed conceptual model also takes into account the temporal nature of decision-making, accounting for change over time. The model accommodates the change in personal circumstances for women and their experiences of mitochondrial disease that can alter their perception of risk. This altered risk perception can then lead women acting/consider acting differently to their previous choice of accept, modify or avoid risk.

Through robust investigation of women's retrospective and current and prospective accounts of decision-making the proposed conceptual model is able to support discussions of reproductive decision-making with women and specialist clinicians, offering visual representation of the factors and elements that have been considered by a subsection of women with mtDNA mutations. The implications, strengths and limitations of the study and future evaluation of model are discussed further in Chapter 9.

## **Chapter 9. Discussion, Recommendations and Conclusion**

### **9.1 Introduction**

This study sought to understand the process of reproductive decision-making in maternally inherited mitochondrial disease, but also revealed the broader experiences of uncertainty faced by women with mtDNA mutations. Existing literature is dominated by ideas around the biomedical uncertainty of predicting the risk of transmission of mtDNA mutations, whilst the broader experience of social uncertainty in reproductive decision-making is under represented. In addition to this there is scarce empirical research exploring patients' experiences of living with mitochondrial disease and of women's experiences of reproductive decision-making.

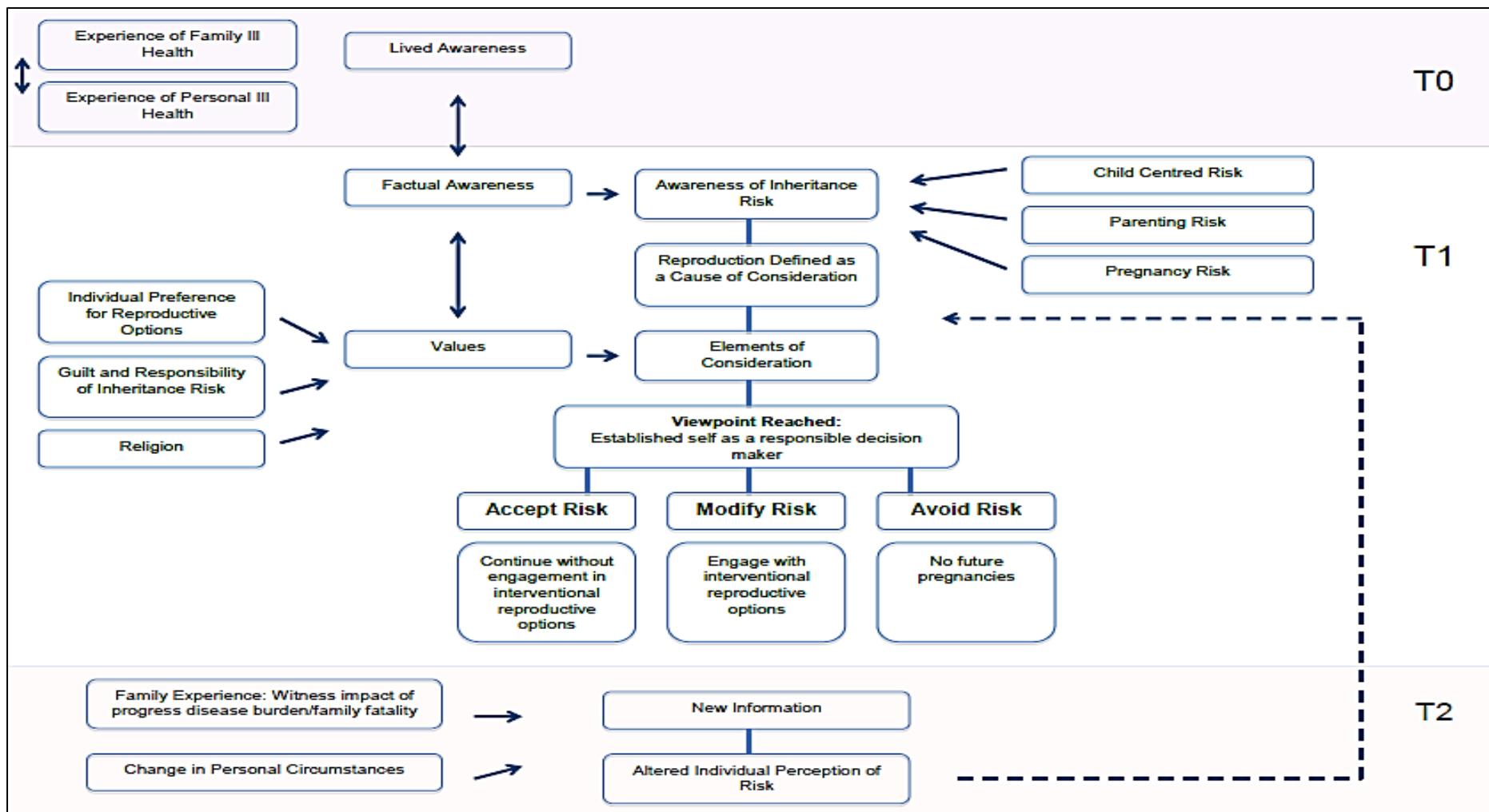
Primary objectives of this study included exploring women's experiences of living with a diagnosis of maternally inherited mitochondrial disease, their knowledge about the risk of transmission, genetic testing and reproductive options, the impact of health professionals on the process of reproductive decision-making and their information needs. The primary outcome of this study was to inform the development of a patient pathway and provide a conceptual model of decision-making to support discussions of reproduction with women with maternally inherited mitochondrial disease.

This chapter brings together the findings from the empirical chapters presented in this thesis, by summarising the key issues and outlining the implications for women with maternally inherited mitochondrial disorders, clinicians and the broader social science literature. I will examine these findings in relation to the study objectives, existing literature and highlight the unique contribution that this thesis offers. I will critically assess the limitations of the study, reflect on its strengths and conclude with recommendations for future research and the clinic.

### **9.2 Main Findings**

This thesis shows that uncertainty is fundamental to the experiences of women with mtDNA mutations, manifesting in personal accounts of their condition and in

reproductive decision-making. It demonstrates how reproductive decision-making is necessarily social and advocates for a more sociological understanding of uncertainty within the reproductive advice clinic. In taking this approach I have adapted an existing sociological conceptual model, developed in HD by Downing (2005) to develop the first disease-specific conceptual model of reproductive decision-making in maternally inherited mitochondrial disease. This model includes influential factors and elements of reproductive decision-making specific to women interviewed in the study, but which may also be applicable to decision-making for women with nDNA mutations.



**Figure 9.1** Conceptual Model of Reproductive Decision Making In Maternally Inherited Mitochondrial Disease (adapted from Downing (2005))

### **9.3 Implications for Women with mtDNA Mutations**

This study used qualitative interviews to investigate women's experiences of reproductive decision-making and included women who had already made reproductive decisions and those currently or prospectively making reproductive decisions. This thesis was particular centred on understanding reproductive decision-making from women's perspectives, but it highlighted that uncertainty as a predominant feature in the lives of women with mtDNA mutations. I therefore divide this section into implications of this study for women on their reproductive decision-making and the wider social implications of mitochondrial disease.

#### ***9.3.1 Reproductive Decision-Making***

Reproductive decision-making in maternally inherited mitochondrial disease is commonly reported as complex and reported in relation to the inability for clinicians to predict inheritance risk to a future child (Poulton et al, 2017; Thorburn and Dahl, 2001; Smeets et al., 2015; Nesbitt et al., 2014; Poulton et al., 2010; Gorman et al., 2016; Vento and Pappa, 2013; White et al., 1999; Craven et al., 2017). As a result, providing genetic counselling to this group of women and their partners (if applicable) is difficult (Vento and Pappa, 2013) and can also result in distress experienced by clinicians (Bredenoord et al., 2010). Supporting women with mtDNA mutations in making reproductive decisions has been at the centre of discussions surrounding their reproductive options.

The conceptual model illustrates the factors and elements that are considered by women in this study, either in isolation or in combination. It provides a tool to assist clinicians in discussions with women to comprehensively explore decision-making in the face of uncertainty. The conceptual model enables discussions around women's lived and factual experience of mitochondrial disease, their concerns over child-centred risk, pregnancy risk and risks surrounding their ability to parent with respect to their own disease burden, women's values and the possibility of change over time in relation to their risk perception.

The model builds upon Downing's (2005) model of responsible decision-making in HD, by highlighting that lived experience of mitochondrial disease can be a personal experience of ill health or experienced via an affected family member(s).

For some women this lived experience is translated into experiential or empathetic knowledge, which directly informs their reproductive decision-making, supporting Boardman who writes about experiential and empathetic knowledge and their role in decision-making in spinal muscular atrophy (SMA) (Boardman, 2017; Boardman et al., 2017).

The primary concern expressed by women was uncertainty with regards to the potential affectedness of a future child, with many women fearing that their future child may be more affected than themselves. Women feared that their child may be affected in similar ways to that of their affected family member or like those individuals they had seen as a result of their own information seeking activities. This particular concern surrounding the unpredictability of affectedness is directly related to complexities of mtDNA mutations. In contrast, Mendelian genetic disorders are able to predict probabilities of affected, carrier and unaffected, although the retention of these probabilities is not always accurate (Hallowell et al., 1997; Parsons & Clarke, 1993; Sivell et al., 2008). It is important to note that some X-linked conditions can affect carriers mildly, due to the deactivation of one of the X chromosomes (Puck & Willard, 1998).

Although less common, some women were concerned about their future parenting ability, with these women considering their disease burden currently and in the future. Although understanding of the natural history of mtDNA mutations has greatly increased in recent years (Nesbitt et al., 2013; Mancuso et al., 2015; Gorman et al., 2016) and recent developments in the identification of potential therapeutic targets (Gorman et al., 2016; Parikh et al., 2009), uncertain futures still featured prominently in women's accounts. With their understanding that their condition was progressive, their ability to look after a child, or more children, featured in accounts of women's deliberation over having a child/more children. These concerns were noted by Downing (2005) with regards to the late onset of HD, but are also supported in other rare disorders (Barlow et al., 2007) and chronic illness (Barlow et al., 1999).

The risk of pregnancy complications was of major concern for one woman included in this study and in direct relation to her phenotype. Pregnancy complications in mitochondrial disease have been reported to range from severe

to mild (Say et al., 2011), although further explorations of these has been called for. Multi-disciplinary clinical care is therefore recommended for women on an individual basis in an attempt to minimise potential pregnancy complications. Experiencing pregnancy complications can have a number of psychological effects on women (Morrison et al., 2014; Heaman, 1998), including uncertainty as to whether they will attain motherhood (Heaman, 1998). High levels of uncertainty have been reported in women hospitalised due to their high-risk pregnancy, which correlated with high levels of stress (Clouston, 1996). Uncertainty also features in parental accounts of children born prematurely (Lu et al, 2013), with threatened pre-labour a reported complication in mitochondrial disease. Providing advice on prenatal coping strategies and advocating for social support networks have been reported as ways in which to mediate the effects of uncertainty in high risk pregnancies (Giurgescu et al., 2006), with emotion based strategies advised over problem focused strategies (Lu et al, 2013). The provision of up to date information on potential risks posed by women's pre-existing conditions prior to conception and as early as their teenage years has also been called for to enable informed decision-making around pregnancy and possible risks (Crawford & Hudson, 2003).

Critics of debates surrounding the approval and introduction of mitochondrial donation centred on the lack of information and discussions on other available reproductive options (Haimes & Taylor, 2017; Herbrand, 2017) This thesis addresses this by presenting women's ideas and preferences in relation to the range of available reproductive options. This study shows that for the majority of women their preference is for their 'own healthy child', one that is biologically related to them and who will not suffer from a mitochondrial disease related illness. This finding is supported by US survey of women with a known mtDNA mutation, whereby 95% (20 of 21) of those considering childbearing placed biological relatedness as somewhat (43%) or very important (52%) (Engelstad et al., 2016). Mitochondrial donation allows for this biological link and significantly reduces, with the potential to eradicate, the uncertainty faced by women and their partners as to whether their child and future generations will be affected by mitochondrial disease. As a result, mitochondrial donation is the most favoured of the reproductive options in this study.

Findings showed that prenatal testing was problematic for women due to the perceived risks of the procedures and their reluctance to be placed in a scenario of deciding between continuing with or terminating an established pregnancy. These accounts are supported by others including Boardman (2017), Myring et al (2011), Kelly (2009) and Rapp (1998).

Ovum donation has been cited as the most obvious option to women who wish to prevent transmission of their mtDNA mutation (Thorburn and Dahl, 2001; Burgstaller et al., 2015). However, for the majority of the women this option has never been considered. For those women who would consider the technique this was as a last resort and if in the event they were ineligible for their preferred options (mitochondrial donation followed by PGD) and for those that had already received news that they would not be candidates for either. Lack of biological relatedness was the main objection to ovum donation, with the couple actively pursuing ovum donation specifically seeking a clinic that would allow for matching of physical characteristics to resemble both parents. The significance of resemblance between a parent and child can be related back to cultural ideologies of what family is (Becker, 2000), and how a physical 'resemblance is seen as the outward bodily expression of biological relationships' (Becker et al., 2005:p1301).

Surrogacy is an option for symptomatic women whose presenting phenotype may pose a significant risk to mother and baby. Surrogacy in this study was specifically viewed as the way in which to have a genetically related child, this biological link and carrying on of the family lineage was of particular importance. In addition, concerns relating to the use of a surrogate in this study are supported by the literature and included legal status of the biological mother (Fenton-Glynn, 2016), relinquishment of the child to the intending parents (Teman, 2008), financial costs (MacCallum et al., 2003) and negotiating pregnant embodiment and maternal identity (Teman, 2009).

Adoption was viewed by a number of women as not an option due to their preference for a genetically related child and corresponds with accounts of the 'prioritisation of biology' in women who experienced infertility but decided against adoption (Slauson-Blevins and Park, 2016:p248). Women who offered additional

explanations as to why adoption would not be suitable for them centred on pre-existing beliefs of the lengthy and disruptive processes associated with adoption (Sandelowski et al., 1991). For those women who did not discount adoption, it was considered as a last option and only after other medical options had failed, and support van Balen et al's (1997) report of couples choosing medical interventions for infertility before considering adoption or fostering. A deviant account existed in the study sample, whereby the couple had discussed the possibility of infertility prior to their marriage and were both in agreement that they would parent 'someone else's' child in the event they could not have their own biological child. This couple can be seen to view parenthood as a collection of caring activities for a child and not contingent on a biological link and this is supported by Miall (1996) whose respondents reported a 'sameness of maternal and paternal' feelings' between adoptive and biological parents (p315).

For the majority of women in this study, fulfilling the role of mother was an intrinsic desire experienced since childhood, referred to by Murphy (2013) as a 'predestined parent'. Women's accounts of having their 'own child' or raising 'someone else's child' concurs with theories of parenthood as a form of possession (Berman, 2014), as well as western ideologies of family that prioritises biological kinship (genetically related children) over socially constructed parental relationships (adopted child) (Suter et al., 2011).

Health professionals that signposted, referred or diagnosed women were considered trusted individuals, whom women felt comfortable in approaching for expert advice relating to reproductive decision-making. Women described consultations that utilised shared decision-making (Charles et al., 1997, 1999; Elwyn et al., 2012) and informed/constructivist decision-making (Emanuel and Emanuel, 1992; Charles et al., 1999; Charles et al., 2000). Both approaches were received positively by women and their partners (if applicable) and reported feeling supported in their autonomous decision-making. Rapley (2008) notes that decision-making is distributed and is an activity that includes a number of people as well as being on-going in nature and evolutionary, supporting the need for continued review of women (and their partner's) current perceptions of risk. It was particularly important to women that they received individual assessment of their inheritance risk, at diagnosis and when considering their reproductive options and

this is supported by Durand et al (2010) who highlighted women's needs for personalised information when considering prenatal testing, along with their request for this to be 'presented in multiple ways, remaining simple and unbiased' (p125). I advocate that the conceptual model can aid decision-making discussions by providing visual representation of the potential considerations for women, their partners and family members.

### ***9.3.2 Wider Social Implications***

Diagnostic delay is a common experience shared by patients suffering from a rare disease (Dharssi et al., 2017; Elliott & Zurynski, 2015; Zurynski et al., 2017). Delay in diagnosis meant that some women were devoid of the legitimisation that is offered by the 'sick role' (Parsons, 1951) with accusations that 'it was all in their head'. This supports Dimond's (2013) account that diagnosis allowed mitochondrial patients a 'legitimate patient identity, treatment and support' (p3), as well as other accounts of delay in diagnosis in rare disease (Nunn, 2017) and chronic illness (Glenton, 2003). These findings were also reflected in parents of children presenting with symptoms, with women describing complications at their GP surgeries and multiple repeat visits, reinforcing Muir's (2016) description of parents being branded as hypochondriacs or neurotic. This study showed that for women who had experienced symptoms for decades or even since their childhood, their diagnosis helped them to address feelings of stigmatisation which had resulted from symptoms that went undiagnosed or misdiagnosed. This is particularly apparent when they experienced severe fatigue and so were categorised as lazy. This echoes researchers investigating delayed or misdiagnosis of Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME) (Ashbring & Narvanen, 2002; Huibers & Wessely, 2006; Picariello et al., 2015; Tucker, 2004).

A large proportion of women recalled negative experiences with medical professionals who did not recognise or explore the potential reasoning for their or their family members symptoms. Noticeably, this was often directed to primary health care professionals as well as some symptom specialists. Experiences like these have been documented in other rare diseases where, alongside diagnostic delay, lack of knowledge in primary care was attributed to mistreatment (Barlow et al 2007), delayed access to social care (Grut & Kvam, 2013), conflicting

information (Frank., 2007) and inadequate or missing information (von der Lippe et al., 2016). Upon receiving recognition that there may be an underlying cause for their symptoms, subsequent referral and eventual diagnosis, can create positive and trusting relationships between women and those who had sign-posted or diagnosed them or their family member. These were formed out of the feeling of being 'believed' and 'listened to', that they were being looked after by experts with the most up to date knowledge and that these professionals were 'on their side'. This has also been reported in rare disease by Garrino et al (2015) and in relation to serious illness by Mechanic and Meyer (2000). These new relationships of trust resulted in women bypassing their GP or other neurologists when seeking advice on presenting health complaints of all severities and non-health related issues, such as assistance with home adaptations and funding for reproductive techniques (PGD).

An objective of this study was to explore the information needs of women with mtDNA mutations in relation to reproductive decision-making. In addition to this, the findings show that women also desired more varied information about mitochondrial disease. Women felt that sources of information, in particular results of Internet searches were not representative of some women's experiences, especially those who considered themselves to be mildly affected or somehow different to others with their mutation. With the tendency for searches to show extreme cases or information of the life-limiting and potential fatal consequences of mitochondrial disease many women were left in fear and panic following their diagnosis, more so when informed by a non-mitochondrial specialist. These fears were alleviated for women when receiving advice from mitochondrial specialists who were able to provide a more individually specific assessment of their own and/or their family members prognosis. In addition to this some women found online communities via social media platforms helpful in terms of support from other patients around the world, particular in relation to having a 'safe place' in which to share their frustrations, whilst other women were unaware of these. For one woman in particular, she felt that information provided by the main mitochondrial patient charity was irrelevant, as they did not consider adult patients experiences of disease and that mitochondrial research organisations provided limited and repeated information. A request for research

into the wider role of mitochondria in other disorders, written in a way that is accessible to patients, was desired.

For some women the initial emotional impact of their diagnosis remained for months and years following. For these women, they expressed the centrality of emotional support, specifically in relation to their diagnosis, feelings of guilt and responsibility and managing changing or progressing symptoms. At the end of one interview, the on-going distress experienced by one woman resulted in her permission being given to discuss this with her clinician in the hope of seeking specialised counselling. The lack of counselling support for people diagnosed with a rare disease was recognised in the UK Strategy for Rare Disease (2013) with commitment number 45 addressing the need to provide support to specialist centres to enable the provision of local counselling for patients (Department of Health & UK Government, 2013, p35).

Uncertain futures and unpredictability of mitochondrial disease resulted in women and their family members experiencing biographical disruption (Bury, 1982). Periods of illness and disease progression had educational, financial and social implications for women. This included experiences of mainstream and higher education and employment being interrupted or terminated, renegotiation of important social relationships along with feelings of isolation. These findings show that educational and employment institutions were also unable to adjust to the uncertainty of mitochondrial disease, with some institutions incapable of accommodating a flexible working approach or physical access. Relationships with family and friends were impacted as a result of disclosure of their diagnosis, especially in families where others may be at risk, with feelings of guilt and responsibility at their core that determined the level of disclosure in families. Some women's experiences were positive, where a collective family diagnosis offered a sense of a shared or mutual understanding of what it was to have mitochondrial disease. For one woman this experiential knowledge of certain symptoms directly influenced her reproductive decision-making. Disclosure of illness was further complicated by the complexities of mitochondrial diagnosis, which proved difficult for some women to fully understand and then in part to others. This was combatted with the use of analogies and scripts as tools to help

others understand what caused their symptoms and how in particular they were affected.

The thesis has shown that uncertainty is fundamental to the lived experiences of women with mitochondrial disease, and encroaches into many areas of their lives. In turn this then impacts upon their reproductive decision-making.

#### **9.4 Study Limitations and Strengths**

In this section I critically review the study and discuss its limitations and reflect on its strengths.

##### ***9.4.1 Methodology***

Utilising qualitative methodologies to explore the experiences of women and reproductive decision-making is a strength of this study as it has allowed for the collection of rich and varied data. Without this approach it would not have been possible to create the proposed conceptual model of reproductive decision making, as data collected allowed unique insight into uncertainty in reproductive decision-making and more broadly the lives of women with mtDNA mutations. Data collected within this study allowed for a very specific knowledge of women's experiences to be highlighted, an area that is currently lacking in the existing literature.

Qualitative research allows for in-depth illumination of a phenomenon and is especially useful in understanding the experiences of individuals (Atieno, 2009). It is particularly useful in exploring 'complex, new and relatively unexplored areas' (Clarke and Jack, 1998:p845). In taking this approach to explore the experiences of women and reproductive decision-making I have been able to gather rich and varied data that has shown how uncertainty features across the lives of women. Limitations commonly associated with qualitative research however include restriction of generalisability, as qualitative research does not seek to be 'statistical generalisability and representativeness' but 'aims to reflect diversity' (Barbour, 2001:p1115). Purposive sampling was used to identify a range of experiences of reproductive decision-making.

A key consideration in qualitative research is reflexivity, evaluating my role as researcher and my influence on the data – and in return its influence on me (Finlay & Gough, 2008). I discuss in Chapter 4 my position as a researcher,

reflecting on my previous research experience and personal background. Throughout the conduct of this study, reflections on data were included in field notes and patient and theme specific memos, as well as discussions with peers and supervisors. Researchers are said to gravitate to research areas that explore their own experiences, however this may make them more sensitive to data (Dickson-Swift et al., 2008). Some stories shared by women resonated with my own family's experience of prenatal testing, genetic disease and uncertain futures, which at times were emotionally challenging. By undertaking self-reflection, I was able to pay close attention to how my own experiences and pre-existing beliefs and values could shape the process of the research.

#### ***9.4.2 Longitudinal Interviews and Changing Political Landscape***

This study was initiated prior to parliamentary debates relating to the introduction mitochondrial donation as a reproductive option and continued until after the first centre licence to perform the technique was granted. A strength of the study is that it captures pre-parliamentary debate, post parliamentary approval and post licencing perspectives of reproductive options whereby mitochondrial donation transitioned from a research technique to a clinically available option. This was in part strengthened by the study design, informed by constructivist grounded theory. This permitted data to be collected and analysed throughout the course of the study. This enabled emergent categories and key areas within the data to be explored in future interviews. A criticism of this approach is that it can be exhausting, especially for novice researchers like myself who may become preoccupied with coding of data (Hussein et al., 2014). To ensure that that was not the case, data was discussed with supervisors and in a confidential peer setting that allowed for further exchange and interpretation of key issues emerging from the data (Rapley, 2010).

#### ***9.4.3 Recruitment***

Recruitment into this study was dependent on clinical gatekeepers with prior knowledge of the women who took part. This approach had a number of strengths but could also be considered a limitation. Research in rare disease is inherently difficult, however to address this problem in research into mitochondrial disease, mitochondrial experts from across the UK developed the MRC Mitochondrial Patient Registry and Natural History Study (MitoCohort) for the

purpose of rapid identification of eligible patients for research. This resource enabled potential participants for this study to be pre-screened by the department's mitochondrial research nurse more easily and that these women could be approached to consider participation at their next clinical review. This approach was especially helpful in regards to the purposive sampling methodology employed within the study, as I was able to enquire and request contact with women who matched certain criteria. Women who believed that their family members might also be willing to take part communicated this to the mitochondrial research nurse, often after reading the study information. If these women had previously consented to the MitoCohort to be contacted for research the mitochondrial research nurse was then able to approach them and provide study information if willing. For the one participant who was not identified by the MitoCohort, their mitochondrial specialist informed them of the research project in advance of their clinical visit. Although approved, mailing study information sheets to women identified via the MitoCohort only and not seen in the clinic was not tested, as those women that fulfilled the purposive sampling strategy were identified as attending upcoming clinics. It is an unknown as to whether a mail shot approach would have yielded different accounts from women.

Clinical gatekeepers were an important step in identifying women they believe to be suitable to take part in the study. This took into account women who may be known to have experienced a recent bereavement, be it experiencing their own or a family members declining health or those who may be struggling with issues such as their recent diagnosis. Without this up to date personal and medical knowledge of women there may have been occasions whereby women who received an invitation to the study and the study information sheet in the post may have been left distressed by its arrival. These considerations occurred twice within this study, whereby two women were not approached to take part in the study due to their own disease progression and that they were still processing their own diagnosis.

A strength of having a connection with the clinical specialist team meant that - as described above - with patient's permission, their clinical team could be informed of any distress and assist women with seeking additional support. Without this link I would have been unable to refer women to specific mitochondrial support,

due to the current lack of adult based support networks outside specialist clinical care teams.

The limitation of using gatekeepers in identification of research participants is that there may be additional screening criteria consciously, or sub-consciously, applied to the sample or even disagreements between gatekeepers as to the appropriateness of participants. In this study there was one incident where the clinical team discussed between one another as to whether a certain woman should be contacted, with concerns from some that an approach to take part would cause distress. To avoid this potential, that particular woman was not contacted. A limitation of recruiting women by their association with the MitoCohort was that these were women who had previously expressed a wish to be contacted to take part in research associated with their diagnosis and therefore may not have been entirely representative of the wider population of women, who may have previously declined participation in the MitoCohort.

The rarity of mitochondrial disease coupled with some women's confusion regarding the aetiology of their mitochondrial disease would have meant that general advertisement for women with mtDNA mutations willing to discuss their reproductive decision-making would have been extremely difficult, most likely receiving little response and may have led to a mixed sample of mitochondrial and nuclear mutations. Although general advertisement of the study would have been impractical, utilising the main mitochondrial patient charity may have enabled a mitochondrial specific population to be targeted (however this may not have addressed the potential to recruit women with nDNA mutations). This recruitment strategy was utilised by another study, identified in Chapter 4, it therefore may not have been feasible to approach this charity for their assistance.

During the course of the study I was informed of a large online social media group for mitochondrial patients, maintained and administered by patients themselves. It is possible that connections with this group could have been made, to post an advertisement for the women in the UK to contact myself directly. This approach may have permitted a geographically wider and therefore diverse sample, as the sample included in this study represents women - with the exception of one woman - living predominantly in the North of England and

Scotland. It is possible that recruitment of women in other regions of the UK and the Republic of Ireland may have led to different experiences of mitochondrial disease and reproductive decision-making. This recruitment approach may be suitable for future qualitative studies into the array of experiences of mitochondrial disease, which are currently missing from the literature (see section 9.5).

#### ***9.4.4 Insider Research***

As discussed in Chapter 4, there were concerns that women would associate me with their clinical care team and perceive me as someone with medical training and/or feel unable to critique the clinical service provided to them and their family members. Study information sheets declared that the study was for the purpose of my PhD, although some participants had met me or seen me previously in my role as clinical research manager at patient engagement events, patient focus groups or study steering group activities. I also went on to see participants at future events following their interview. In addition to these encounters, my staff profile was also present on Data Collection Centre 1's website, further reinforcing my role as a member of staff. It is therefore possible that some women may have consciously decided to refrain from criticisms or alternatively over complimented the service out of concern of possible identification and potential negative repercussions in their relationships with clinical team members. A strength of my sometimes-known status may have meant that women knew I had a level of understanding about mitochondrial disease, how it presented and its potential clinical implications. This may have been beneficial to establishing a relationship at start of the interview as opposed to feeling as though I had no insight into what mitochondrial disease was.

#### ***9.4.5 Couples Perspectives of Decision-Making***

This study was designed to specifically explore women's experiences of reproductive decision-making. Although interviewing couples was considered during study design it was thought not possible to accommodate, with a possible negative impact on recruitment. However, the study allowed for an attendee of the woman's choice to be present and contribute to the interview if they wished, which led to the inclusion of three couples. This approach was taken to allow women the opportunity to feel as comfortable as possible during the interview,

with support from an individual of their choosing. Interviews that included partners were those that took place before or following clinical reviews and were conducted in an outpatient clinic or research facility. Therefore, their participation may have been purely coincidental as opposed to purposeful attendance. Upon noticing this, I asked future women if there was a reason as to why their partners were not present. Reasons centred around availability as opposed to declining to take part. Existing research into reproductive decision-making has included both women's accounts (Raspberry and Skinner, 2011; Herbrand and Dimond, 2017; Kay and Kingston, 2002; Rapp, 1998; Dudding et al., 2000; Donnelly et al., 2013) and accounts of couples and families (Dommering et al., 2010; Downing, 2005; Frets et al., 1991; Helbig et al., 2010; Hershberger et al., 2012; Kelly, 2009; Myring et al., 2011; Snowdon & Green, 1997).

Myring et al (2011) reported that couples in their study believed women had the 'final say' in decision making, in part due to their role in primary care giving and pregnancy implications. Women (and partners where applicable) in this study reported their decision-making to be joint decision between couples and that they were not made in isolation, with some women discussing their options at length with family members. Interviewing couples can offer insight into their relationship and their shared realities, in this case their experience of reproductive decision-making (Valentine 1999). It is reasonable to assume that the presence of a partner may have limited or directed responses from women or vice-versa. To combat this, interviews could have been conducted with women and partners separately, followed by a combined interview, enabling viewpoints to be discussed that they may have felt unable to in front of their partner. This methodology would have added a layer of practical complexity to the study that may have negatively affected recruitment and the timely completion of the study.

#### ***9.4.6 Multiple Perspectives of Decision-Making***

This study utilised retrospective and current and prospective accounts of decision-making. When discussing which options women would consider and those they would discount. For those in the retrospective group these were largely hypothetical, as the majority of the women had completed their families. Hypothetical lines of questioning have been criticised for the potential to cause confusion for the participant, which can interrupt the interview and therefore the

quality of the data (King & Horrocks, 2010). The approach taken in this study can also be related to the technique of imagined variation, which is essentially a thought experiment used in interviews. This is the process whereby the interviewer encourages interviewees to reflect further on their experience of the specific area of study and then tell the interviewer how they think their experience would differ (King & Horrocks, 2010) if for example in this study, they had received their diagnosis prior to having completed their family. King and Horrocks (2010) advise caution when approaching this question, with recommendations that variations in the directions of questions be made. In the example of this study I asked women in the retrospective group which options they thought they may have been more likely to have chosen and those they would have discounted. I believe however that including multiple perspectives of decision-making was a strength of the study; especially as it uncovered a key area, change over time. This was then followed up by the inclusion of a repeat interview in Round Three to examine further.

#### ***9.4.7 Conceptual Model***

A key strength of the proposed conceptual model is that it is the first proposed model of reproductive decision-making in maternally inherited mitochondrial disease. As Hunink et al (2014) noted, decision models or balance sheets allow for the individuals to assess the impact of multiple factors that present at varying times, which most people would be unable to do unaided. A strength of the model has been its rigorous development, which occurred over a number of versions before being superimposed into Downing's (2005) model and then further adapted to reflect the women's accounts. The conceptual model was presented to the local mitochondrial specialist team to permit content review and feasibility. The conceptual model also aligns with influential factors reported in other genetic conditions (Myring et al., 2011) and considerations of PGD as an option (Hershberger et al., 2012 ).

#### **9.5 Areas of Future Research**

Further evaluation of the conceptual model needs to be conducted with women, their partners and health professionals. Accessible, user-friendly versions need to be developed, prototyped and evaluated. These could take the form of decision-aids, either for women (and their partners) to use alone, or to use within clinical

consultations. A more formal, long term, development process would need to be undertaken in light of the International Patient Decision Aids Standards (IPDAS). Such formal evaluation often occurs in the context of randomized controlled trials (RCTs) or via user-centred acceptability and feasibility testing.

The IPDAS collaboration outlines four criteria for the development and evaluation of patient decision making aids: 1) provide information in sufficient detail for decision making 2) present probabilities of outcomes (where/if available) 3) include methods for clarifying and expressing patient values 4) include structured guidance in deliberation and communication (Elwyn et al., 2009). The proposed conceptual model, and the information used to develop it, currently offers a lot of detailed information about the reproductive options that women face. This would need to be further refined and tailored, so as to be clear and accessible to women. Additionally, as outlined throughout the thesis, given the rare disease status, probabilities of outcomes are not yet available. Finally, in relation to the third and fourth criteria, there are to date, only a relatively limited number of ways that people design these features into decision aids, and these would need to be reviewed and then discussed and evaluated with women. The IPDAS collaboration also recommend that following the development of a decision-making aid with patients and specialised clinicians, 'beta' testing in real life scenarios should then take place (Coutler et al., 2012; Elwyn et al., 2006). This should include critical appraisal by those not involved in the developmental process and such a review could be conducted those with expertise in shared decision-making and clinicians not involved with the development to date. Not only would the inclusion of additional stakeholders enable further validation of the model in accordance with these recommendations but may also offer new areas of interest to explore, including its relevance for nDNA mutations.

Findings from this study also showed that mitochondrial disease impacts on the lives of women and their family members in a multitude of ways, which is largely missing from the literature. Feelings of guilt, responsibility and concern for maternal family members has been discussed in this thesis surrounding disclosure of genetic risk and reproductive decision-making, but uncovered also were impacts of mitochondrial disease on social relationships including those between partners, mothers, children, affected siblings, aunts, uncles,

grandparents and friends. For women who experienced symptoms, they spoke of their partners acting or potentially acting's as caregivers in the future.

Investigation of this role in relation to partners/primary caregivers could provide further understanding of disease burden - uncover unknown emotional and financial costs for patients and caregivers (Awad and Voruganti, 2008 in reference to mental illness) - identify the needs of caregivers (Houldin, 2007 in reference to cancer; Cameron and Gignac, 2008 in reference to stroke) and develop caregiver specific information (Given et al., 2008) and support networks (McCabe et al., 2016 in relation to dementia).

Some women described feeling a sense of support when more than one person in their family was diagnosed with mitochondrial disease. Research into these existing support networks could provide further understanding as to what it is like to live in 'family of affected people' and how these families negotiate varied symptom presentation and severity. Feelings of isolation arose out of the unpredictability of symptoms and their impacts of social life as well as the lack of peer support. Further work on this could lead to understanding of how to address these and possibly implement future interventions.

This study primarily examines clinical relationships in relation to reproductive decision-making, however it is evident that women's experiences of these relationships in relation to mitochondrial disease can pre-exist diagnosis for sometimes decades. This study highlights the lack of awareness of mitochondrial disease in the wider medical community, in particular the GP setting, which continues after diagnosis. Specific investigation into the wider experiences of patients and health professionals may allow for the development of targeted information portals, accessible to these health professionals. In addition to further exploring patients perspectives of clinical relationship, there is little qualitative exploration on health care professionals perspectives of caring for patients with mitochondrial disorders (Bredenoord et al., 2010; Read & Calnan, 2000). Insights into these individuals' experiences of caring for patients could assist with understanding the emotional, practical and financial implications of providing care to patients, all of which could support appeals for increased funding to commissioners.

Uncertainty of mitochondrial disease affected some women's education from compulsory through to higher education and work place training schemes. The long-term impact of being unable to complete education for patients with mitochondrial disorders may have emotional (Barrera et al., 2005 in relation to childhood cancer), and financial implications (Smith, 2009 relation to childhood illness) as well as potential implications on identity. This also highlights wider topics of the understandings of rare disease in education sectors and disability rights of access to education (Bines & Lei, 2011). Findings also showed that some women who experienced symptoms, commonly fatigue sought flexible working arrangements, reduced working hours and community commitments or left their jobs. None of the women who modified their working patterns to fit around their symptoms spoke about personally accessing any governmental support such as the previous disability support allowance or the newer personal independence payment (PIP). It is arguable to say that these women experienced a negative impact on their earnings or potential earnings due to reduced hours and interruptions to career development opportunities as a result of navigating work around their symptoms.

The cost of illness in mitochondrial disease has been reviewed in relation to the cost of treatment, in an impact assessment report of mitochondrial donation (HFEA, 2014) with an estimated lifetime cost of between £100,000 and £300,000 for patients with serious mitochondrial disease. A specific case study of one patient's treatment costs showed that of the estimated treatment cost of £222,906 over a ten-year period, £212,443 was attributed to their inpatient care in their final year of their life, highlighting the drastic decline of health some patients suffer as a result of their serious mitochondrial disease (HFEA, 2014). No investigation of cost of illness has been conducted in patients with mitochondrial disease on a microeconomic level (individuals and households). Investigations in other rare disease and chronic illness have shown a significant correlation between financial stress, disability and poor physical and mental health (Jeon et al., 2009). Rare disease and chronic illness can not only incur significant financial loss (Barlow et al., 2007) for sufferers but also psychosocial losses (Meenan et al., 1981), effects on social relationships (Cohen, 2004) and impacts on identity (Fryers, 2006). Women's experience in the workplace highlights the broader issues of disability

and work (Shier et al. 2009). Specific investigations of the impact of mitochondrial disease and employment would be required to support this claim further.

Finally, women described feeling as though their experiences of mitochondrial disease were not portrayed when searching online. Patients requested lay summaries of new and on-going research that could be easily accessed, with information shared to interested patients via patient engagement events, websites and social media platforms. I also propose that carrying out some of the above suggested research may address these feelings of under-representation, with qualitative investigations providing a mechanism to document the diverse spectrum of experiences in individuals and families affected by mitochondrial disease. Future work could also aim to explore the phenomenon of the 'patient without symptoms' (Dimond, 2013) which would allow for the experiences of these women to feature in the wider narrative of mitochondrial disease.

## **9.6 Recommendations for Clinical Practice and Policy**

Based on the findings of this thesis, I suggest the following recommendations to clinical practice and policy in relation to reproductive decision-making.

### ***9.6.1 Considerations of Lived Experience***

Findings from this study have shown that women are influenced by their personal and family experience of ill health associated with mitochondrial disease (in some case more general ill health). Discussions with women about their experiences of mitochondrial disease are encouraged to understand how these experiences and experiential and empathetic knowledge gained as result may potentially impact on decision-making.

### ***9.6.2 Reflections of Normality and Socially Acceptable Symptoms***

Findings from this study have shown that for some women, perceptions of disease severity and symptom management and acceptability in modern day society impact upon reproductive decision-making. Understanding of symptoms or phenotypes women are accepting of may assist with discussion around negotiating child-centred risk.

### ***9.6.3 Factual Awareness and Representation***

Findings from this study have shown that during both diagnosis and reproductive decision-making, women used Internet searches to seek information relating to

mitochondrial disease. Women reported that the information available reflected more severe accounts of mitochondrial disease and that they felt their experiences were not relatable. Providing more readily accessible accounts of the varied experiences of mitochondrial disease may assist women who undertake information-seeking activities as part of their factual awareness during decision-making.

#### ***9.6.4 Change Over Time***

A specific influential factor in the proposed conceptual model of decision-making is the potential for women's perceptions of risk to change over time, based on new information or personal circumstances. For some women in this study, this change in risk perception led to women considering reproductive options they had not considered previously. Mindfulness of this potential and discussions with women surrounding awareness of this change may support women further in their reproductive decision-making.

#### ***9.6.5 Emotional and Psychological Support***

Findings from this study have shown the role of guilt and responsibility in women's reproductive decision-making and its impact on women many months and years following their diagnosis. I recommend that specialised counselling be provided to women who are considering their reproductive decisions as part of their reproductive decision-making patient pathway and in addition offered to all women who attend the clinic who may be struggling with feelings of guilt and responsibility since receiving their diagnosis.

#### ***9.6.6 Central and Local Funding of Reproductive Options***

Findings from this study highlight that some women and their partners were prevented access to PGD as a reproductive option or where in the process of appealing a decision to prevent access. These funding barriers were in relation to the couple or one parent (father) already having a child or as an issued of devolution and access to NHS services. I recommend that central and local commissioners should be informed of health and social implications of mitochondrial disease and a request a review of the current funding criteria in relation to access to PGD.

### ***9.6.7 Implementation of Recommendations***

One aspect of the recommendations is that extended discussions could be offered to women. These would, ideally, focus on their lived experiences, reflections of normality, change over time and emotional and psychological support dedicated mitochondrial disease reproductive advice clinics should be offered to women. Such discussion would need to be incorporated into the patient care pathway for women and their families who wish to explore the multiple reproductive options available to them now and in the future. However, with specialties in both mitochondrial disease and associated reproductive options limited (on a global level as well as in the UK) offering these services locally to women and their families could prove challenging, resulting in attendance being restricted due to travel costs. Advances in tele-health clinics (Armfield et al., 2015; Langenau et al., 2014 Hommel et al., 2003) may address the uneven distribution of services routinely seen in rare disease, with regards to accessing appropriate care (Department of Health and UK Government, 2013; Cialone et al., 2011), providing personalised support to patients (Dorsey et al., 2013) to those patients living long distances for specialist's centers.

Clearly, such extended discussions would also take up additional health professional time, whether undertaken face-to-face within clinics or remotely, through tele-health clinics. In part, women's desire for more accessible information about mitochondrial disease could also be supported by a dedicated website. Such a dedicated website, with easily accessible information in multiple formats, may offer both additional support to women and families before, during and after reproductive decision-making and those wishing to have access to more varied accounts of other's experiences of disease. Women and their family members could be directed to it prior to any extended discussion to both provide important information to them as well as, potentially, focus the discussion on specific topics most relevant to them.

## **9.7 Conclusion**

In summary, this study adds to the limited qualitative literature of reproductive decision-making in maternally inherited mitochondrial disease. This study was conducted during intense global interest of mitochondrial donation from clinical, biomedical, social, ethical, religious, legal and policy researchers and offers

valuable insight into women's perspectives of their available options. It centres women's narratives of reproductive decision-making at its core and offers a unique contribution to scholarly debates.

This study demonstrates the uncertainty fundamental to the experience of women with mtDNA mutations which manifests in both their personal accounts of the condition and in reproductive decision-making. Women with mtDNA mutations harbour the desire for a healthy biologically authentic child and decision-making is essentially the process in which women consolidate their desire for healthy children and how they negotiate risk.

Qualitative research in mitochondrial disease is relatively novel, this study explores women's experiences of reproductive decision-making as well as highlighting the impact of mitochondrial disease in everyday life. It makes suggestions of further research to explore how uncertainty posed by mitochondrial disease affects the lives of patients and their interactions with society.

The outcome of the study has been the adaptation of an existing sociological model to support reproductive discussions between clinicians and women regarding decision-making in the face of uncertainty. The central finding of this thesis is the women with mtDNA mutation live an uncertain existence and highlights the importance of sociological understanding of this uncertainty in the mitochondrial reproductive advice clinic.

## Appendices

### Appendix A - Recruitment

#### *A.1 Invitation Letter and Expression of Interest Forms*



**To be on Hospital Headed Paper**

Dear *[Patient]*

**Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of  
Women's Experience**

I am contacting you to invite you to consider taking part in a research study being done at Newcastle looking into how women with mitochondrial disease or carry a mitochondrial DNA mutation make reproductive decisions.

I have enclosed an information sheet, which explains the study in greater detail and it also contains contact details for the research team should you wish to ask any further questions about the study.

If you would like to take part in this research, I would be grateful if you could complete the enclosed expression of interest form and post this back to us in the pre-paid envelope provided. Alternatively you can contact Julia Maddison on 0191 208 5982 ([julia.maddison@ncl.ac.uk](mailto:julia.maddison@ncl.ac.uk)) to express your interest.

Many thanks for taking the time to read this information.

Yours sincerely  
*[Research team member]*

### Expression of interest

We would be grateful if you could return this reply slip within 6 weeks of receipt. Please  
return to

Julia Maddison  
Clinical Research Office – M4.008  
Mitochondrial Research Group

I would be interested/not interested (please delete as appropriate) in finding out more  
about participant in Reproductive Decision Making in Mitochondrial Patients study

My name is .....

My date of birth is.....

My address is .....

My phone number is .....

My email address is .....

The best way to contact me is by phone/email (please delete as appropriate)

The most convenient time for me to be contacted (if I wish to be contacted by phone) is:

Mornings (9am-12pm)  
Afternoons (12pm-5pm)  
Early evenings (5pm-8pm)  
Late evenings (8pm-11pm)



## To be on Hospital Headed Paper

Dear *[Patient]*

### **Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of Women's Experience**

**Repeat Interview Arm**

I am contacting you to invite you to consider taking part in an extension to a study that you participated in, in the past. This previous study looked into how women with mitochondrial disease or carry a mitochondrial DNA mutation make reproductive decisions.

I have enclosed an information sheet about the extension study, which explains why this being done in greater detail and it also contains contact details for the research team should you wish to ask any further questions about the study.

If you would like to take part in this research project again, I would be grateful if you could complete the enclosed expression of interest form and post this back to us in the pre-paid envelope provided. Alternatively you can contact Julia Maddison on 0191 XXX XXXX ([xxx xxxx@ncl.ac.uk](mailto:xxx xxxx@ncl.ac.uk)) to express your interest.

Many thanks for taking the time to read this information.

Yours sincerely  
*[Research team member]*

### Expression of interest

We would be grateful if you could return this reply slip within 6 weeks of receipt. Please

return to

Julia Maddison  
Clinical Research Office – M4.008  
Mitochondrial Research Group

I would be interested/not interested (please delete as appropriate) in finding out more about  
participating in the extension of the above study

My name is .....

My date of birth is.....

My address is .....

My phone number is .....

My email address is .....

The best way to contact me is by phone/email (please delete as appropriate)

The most convenient time for me to be contacted (if I wish to be contacted by phone) is:

Mornings (9am-12pm)  
Afternoons (12pm-5pm)  
Early evenings (5pm-8pm)  
Late evenings (8pm-11pm)

***A.2 Participant and Attendee Study Information Sheets***



## To be on Hospital Headed Paper

### **Reproductive Decision Making in Mitochondrial Patients: A qualitative investigation of women's experiences**

**Patient Information Sheet for**

**Women who have made a decision**

You are being invited to take part in a research study. Before you accept or decline the invitation, it is important for you to understand why the research is being done and what it will involve. Please read the following information and discuss it with relatives, friends and your GP, if you wish. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 3).

#### **Why are we asking you to take part?**

You are being invited to take part in this research because you have mitochondrial disease or carry a mitochondrial DNA mutation and you have made a reproductive decision in the last 16 years

#### **Do I have to participate?**

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time, without giving any reason. This would not affect the standard of care you receive.

#### **What is the purpose of this study?**

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age.

The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some woman may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We would like to conduct interviews with two groups of women, women who have made reproductive decision/decisions in the past 16 years (Retrospective Group) and those women who are making decisions now (Current/Prospective Group).

We are interested in learning about topics like:

- how you made this decision (or multiple decisions),
- what was important to you at the time,
- what information you received or did not receive at the time that would have helped you to make a decision
- and how you feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

### **What happens if I agree to take part?**

The study will involve a one to one interview with the researcher. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. There will be some areas we are keen to discuss but you are free to talk about anything you think is important about how you made your reproductive decision/decisions.

If you are interested in taking part in this study, a member of the research team will contact you to arrange a time and date for your interview; you will be asked to sign a consent form before the interview starts.

The interview will take place at a time convenient to you, usually coinciding with your planned clinic visit. If this is not possible we will make an appointment at a time most convenient for you to attend the Clinical Research Facility at the xxx.xxxxx, xxx.xxxxx or the researcher will visit you at your home or a location that you feel the most comfortable.

If you prefer, someone else, like a partner, a member of your family or a close friend, can also take part in the interview with you. Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; you can decline to take part at any time. Not taking part in this study will not affect the standard of care you receive. If you decide after the interview has taken place that you would like collected data to be destroyed and not used, this will be done at your request.

### **Will information about me be kept confidential?**

All information we receive from you will be treated confidentially. Your personal details and replies will be kept safe and secure. The interview will be audio-recorded so that the researcher can transcribe the information accurately. The audio-recording will be destroyed six months after we have finished analysing and writing up the data. Written information will be kept secure in a locked office and only members of

XXXX XXXX team will be given permission to look at this information. Your personal details will be converted into a code and stored on a secure computer located at Newcastle University. If we publish any research, we ask your permission to use direct quotes; this will not identify you in any way.

Research records and data may also be inspected by regulatory bodies for audit purposes. This is a normal part of research and it is just to make sure that we are doing everything right.

### **Are there any benefits to taking part?**

We cannot promise the study will help you personally, but we hope that the information we get from this study will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

### **Are there any disadvantages to taking part?**

Giving up your time to take part in this project has to be considered. We also recognise that the topic of this interview is sensitive and may cause some distress.

Taking part in this study is voluntary and you do not have to take part if you feel that you would be too upset discussing this topic. We will do our best to make you feel as comfortable as possible. If you feel on the day of the planned interview that you would like to rearrange, this would not be a problem. If you feel before or during your interview you would like to take some time out, or stop the interview it is completely acceptable to do so.

We would like to support you as much as possible. Approximately 7-10 days following your interview the research team will contact you to make sure that you have not been left feeling upset or distressed. If you feel that after taking part in the interview (either immediately or in the weeks/months following) you would like to discuss things further, the research team can make a referral to your doctor or other appropriate NHS services and can also provide you with details of counselling services. This will only be done with your consent to do so.

The only time we will disclose your personal information without your prior consent would be if during the interview you disclose any information that could be deemed related to your safety or safety of others. We would then contact your health care team or other appropriate services.

### **What happens at the end of the research study?**

We hope to interview 15 women from each group, a total of 30 women over 1 to 2 years. At the end of the study, we will be able to inform you of the outcomes of the study in a newsletter. You will not be made identifiable in the newsletter or any published work. You will be welcome to have a copy of the results once they are published.

### **Who has reviewed this project?**

All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your personal information in this project.

This research has been reviewed by NRES Committee xxxxxxxxxxxx who have decided they are happy for us to go ahead with the study.

## **Who has funded this project?**

The project is being funded by the Medical Research Council who has allocated funds to Newcastle team for research into Mitochondrial Diseases. None of the research team will receive any direct (or indirect) payment for you entering this study.

## **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you can contact either xxxxxxxx xxxx on 0191 XXX XXXX (xxx.xxxx@ncl.ac.uk) or the Principal Investigator xxxx xxxx on 0191 XXX XXXX

You may also contact the xxx.xxxxx Hospitals Patient Advice Liaison Services department on telephone xxx xxxx.

If you feel that you have been treated unfairly throughout the research, or would like to make comment about the conduct of any aspect of this research, please contact the xxx.xxxxx NHS Foundation Trust complaints department on 0191 XXX XXXX.

Thank you for reading this information sheet

**To be on Hospital Headed Paper**

**Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of  
Women's Experience**

**Patient Information Sheet for**

**Women who may be faced with a decision**

You are being invited to take part in a research study. Before you accept or decline the invitation, it is important for you to understand why the research is being done and what it will involve. Please read the following information and discuss it with relatives, friends and your GP, if you wish. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

**Why are we asking you to take part?**

You are being invited to take part in this research because you have mitochondrial disease or carry a mitochondrial DNA mutation and you have expressed an interest in discussing your reproductive options for the future with your doctor.

**Do I have to participate?**

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time, without giving any reason. This would not affect the standard of care you receive.

## **What is the purpose of this study?**

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some woman may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We would like to conduct interviews with two groups of women, women who have made reproductive decision/decisions in the past 16 years (Retrospective Group) and those women who are making decisions now or in the future (Current/Prospective Group).

We are interested in learning about topics:

- what is important to you at this time,
- what information you have received or have not received at this time that would help you to make a decision
- and how you feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

## **What happens if I agree to take part?**

The study will involve a one to one interview with the researcher. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. There will be some areas we are keen to discuss but you are free to talk about anything you think is important about the decision you are making now or in future.

If you are interested in taking part in this study, a member of the research team will contact you to arrange a time and date for your interview; you will be asked to sign a consent form before the interview starts.

The interview will take place at a time convenient to you, usually coinciding with your planned clinic visit. If this is not possible we will make an appointment at a time most convenient for you to attend the Clinical Research Facility at the xxxx.xxxx , xxxx xxxx or the researcher will visit you at your home or a location that you feel the most comfortable.

If you prefer, someone else, like a partner, a member of your family or a close friend, can also take part in the interview with you. Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; you can decline to take part at any time. Not taking part in this study will not affect the standard of care you receive. If you decide after the interview has taken place that you would like collected data to be destroyed and not used, this will be done at your request.

#### **Will information about me be kept confidential?**

All information we receive from you will be treated confidentially. Your personal details and replies will be kept safe and secure. The interview will be audio-recorded so that the researcher can transcribe the information accurately. The audio-recording will be destroyed six months after we have finished analysing and writing up the data. Written information will be kept secure in a locked office and only members of XXXX XXXX team will be given permission to look at this information. Your personal details will be converted into a code and stored on a secure computer located at Newcastle University. If we publish any research, we ask your permission to use direct quotes; this will not identify you in any way.

Research records and data may also be inspected by regulatory bodies for audit purposes. This is a normal part of research and it is just to make sure that we are doing everything right.

#### **Are there any benefits to taking part?**

We cannot promise the study will help you personally, but we hope that the information we get from this study will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

## **Are there any disadvantages to taking part?**

Giving up your time to take part in this project has to be considered. We also recognise that the topic of this interview is sensitive and may cause some distress. Taking part in this study is voluntary and you do not have to take part if you feel that you would be too upset discussing this topic. We will do our best to make you feel as comfortable as possible.

If you feel on the day of the planned interview that you would like to rearrange, this would not be a problem. If you feel before or during your interview you would like to take some time out, or stop the interview it is completely acceptable to do so.

We would like to support you as much as possible. Approximately 7-10 days following your interview the research team will contact you to make sure that you have not been left feeling upset or distressed. If you feel that after taking part in the interview (either immediately or in the weeks/months following) you would like to discuss things further, the research team can make a referral to your doctor or other appropriate NHS services and can also provide you with details of counselling services. This will only be done with your consent to do so.

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## **What happens at the end of the research study?**

We hope to interview up to 15 women from each group, a total of up to 30 women over 1-2 years. At the end of the study, we will be able to inform you of the outcomes of the study in a newsletter. You will not be made identifiable in the newsletter or any published work. You will be welcome to have a copy of the results once they are published.

## **Who has reviewed this project?**

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## To be on Hospital Headed Paper

### **Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of Women's Experience**

#### **Partner/Family Member/Close Friend Information Sheet for Women who have made a decision**

Your partner, family member or close friend has been invited to take part in a research study. If you choose to accompany them it is important for you to understand why the research is being done and what it will involve. Please read the following information and discuss it with your partner, family member or close friend. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

#### **Why are we asking you to take part?**

Your partner, family member or close friend has been invited to take part in this research because they have mitochondrial disease or carries a mitochondrial DNA mutation and they have made a reproductive decision in the past.

#### **Do I have to participate?**

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time, without giving any reason. This would not affect the standard of care your partner, family member or close friend receives.

## What is the purpose of this study?

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some women may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We would like to conduct interviews with two groups of women, women who have made reproductive decision/decisions in the past 16 years (Retrospective Group) and those women who are making decisions now (Current/Prospective Group).

We are interested in learning about topics like:

- how they made this decision (or multiple decisions),
- what was important to them at the time,
- what information they received or did not receive at the time that would have helped them to make a decision
- and how they feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

## What happens if I agree to take part?

The study will involve a one to one interview with the researcher and your partner, family member or close friend. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. There will be some areas we are keen to discuss but your partner, family member or close friend are free to talk about anything they think is important about how they made your reproductive decision/decisions. We will not be asking questions to you directly, but if you want to add anything that is fine.

If your partner, family member or close friend is interested in taking part in this study, a member of the research team will contact them to arrange a time and date for their interview.

If you choose to attend the interview both yourself and your partner, family member or close friend will be asked to sign a consent form before the interview starts.

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## To be on Hospital Headed Paper

### Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of Women's Experience

#### Partner/Family Member/Close Friend Information Sheet for Women who may be faced with a decision

Your partner, family member or close friend has been invited to take part in a research study. If you choose to accompany them it is important for you to understand why the research is being done and what it will involve. Please read the following information and discuss it with your partner, family member or close friend. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

#### Why are we asking you to take part?

Your partner, family member or close friend has been invited to take part in this research because they have mitochondrial disease or carry a mitochondrial DNA mutation and have expressed an interest in discussing their reproductive options for the future with their doctor.

#### Do I have to participate?

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time,

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### **What is the purpose of this study?**

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some woman may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

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We are interested in learning about topics:

- what is important to them at this time,
- what information they have received or have not received at this time that would help them to make a decision
- and how they feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

### **What happens if I agree to take part?**

The study will involve a one to one interview with the researcher and your partner, family member or close friend. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. There will be some areas we are keen to discuss but your partner, family member or close friend are free to talk about anything they think is important about how they made your reproductive decision/decisions. We will not be asking questions to you directly, but if you want to add anything that is fine

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## **Are there any benefits to taking part?**

We cannot promise the study will help you or your partner, family member or close friend personally, but we hope that the information we get from this study will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

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## **To be on Hospital Headed Paper**

### **Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of Women's Experience**

#### **Patient Information Sheet for**

#### **Women who may be faced with a decision**

You are being invited to take part in a research study. Before you accept or decline the invitation, it is important for you to understand why the research is being done and what it will involve. Please read the following information and discuss it with relatives, friends and your GP, if you wish. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

#### **Why are we asking you to take part?**

You are being invited to take part in this research because you have mitochondrial disease or carry a mitochondrial DNA mutation and you have expressed an interest in discussing your reproductive options for the future with your doctor.

#### **Do I have to participate?**

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time, without giving any reason. This would not affect the standard of care you receive.

## What is the purpose of this study?

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some women may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We would like to conduct interviews with two groups of women, women who have made reproductive decision/decisions in the past **21 years** (Retrospective Group) and those women who are making decisions now or in the future (Current/Prospective Group).

We are interested in learning about topics:

- what is important to you at this time,
- what information you have received or have not received at this time that would help you to make a decision
- and how you feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

## What happens if I agree to take part?

The study will involve a one to one interview with the researcher. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. **If you would prefer, a telephone interview can be arranged.** There will be some areas we are keen to discuss but you are free to talk about anything you think is important about the decision you are making now or in future.

If you are interested in taking part in this study, a member of the research team will contact you to arrange a time and date for your interview; you will be asked to sign a consent form before the interview starts. **If you have a telephone interview verbal consent will be taken over the phone and documented.**

The interview will take place at a time convenient to you, usually coinciding with your planned clinic visit. If this is not possible we will make an appointment at a time most convenient for you to attend the Clinical Research Facility at the xxx xxxxxx or the researcher will visit you at your home or a location that you feel the most comfortable. **If you would wish to take part over the telephone the researcher will ring you at a time most convenient for you.**

If you prefer, someone else, like a partner, a member of your family or a close friend, can also take part in the interview with you. Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; you can decline to take part at any time. Not taking part in this study will not affect the standard of care you receive. If you decide after the interview has taken place that you would like collected data to be destroyed and not used, this will be done at your request

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## To be on Hospital Headed Paper

### **Reproductive Decision Making in Mitochondrial Patients: A qualitative investigation of women's experiences**

#### **Patient Information Sheet for**

#### **Women who have made a decision**

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#### **Why are we asking you to take part?**

You are being invited to take part in this research because you have mitochondrial disease or carry a mitochondrial DNA mutation and you have made a reproductive decision in the last 16 years

#### **Do I have to participate?**

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time, without giving any reason. This would not affect the standard of care you receive.

#### **What is the purpose of this study?**

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age.

The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now.

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The study will involve a one to one interview with the researcher. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. **If you would prefer, a telephone interview can be arranged.** There will be some areas we are keen to discuss but you are free to talk about anything you think is important about how you made your reproductive decision/decisions.

If you are interested in taking part in this study, a member of the research team will contact you to arrange a time and date for your interview; you will be asked to sign a consent form before the interview starts. **If you have a telephone interview verbal consent will be taken over the phone and documented.**

The interview will take place at a time convenient to you, usually coinciding with your planned clinic visit. If this is not possible we will make an appointment at a time most convenient for you to attend the Clinical Research Facility at the xxxx xxxx xxxx or the researcher will visit you at your home or a location that you feel the most comfortable.

**If you would wish to take part over the telephone the researcher will ring you at a time most convenient for you.** If you prefer, someone else, like a partner, a member of your family or a close friend, can also take part in the interview with you. Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; you can decline to take part at any time. Not taking part in this study will not affect the standard of care you receive. If you decide after the interview has taken place that you would like collected data to be destroyed and not used, this will be done at your request.

#### **Will information about me be kept confidential?**

All information we receive from you will be treated confidentially. Your personal details and replies will be kept safe and secure. The interview will be audio-recorded so that the researcher can transcribe the information accurately. The audio-recording will be destroyed six months after we have finished analysing and writing up the data. Written information will be kept secure in a locked office and only members of XXXX XXXX team will be given permission to look at this information. Your personal details will be converted into a code and stored on a secure computer located at Newcastle University. If we publish any research, we ask your permission to use direct quotes; this will not identify you in any way.

Research records and data may also be inspected by regulatory bodies for audit purposes. This is a normal part of research and it is just to make sure that we are doing everything right.

#### **Are there any benefits to taking part?**

We cannot promise the study will help you personally, but we hope that the information we get from this study will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

## **Are there any disadvantages to taking part?**

Giving up your time to take part in this project has to be considered. We also recognise that the topic of this interview is sensitive and may cause some distress. Taking part in this study is voluntary and you do not have to take part if you feel that you would be too upset discussing this topic. We will do our best to make you feel as comfortable as possible. If you feel on the day of the planned interview that you would like to rearrange, this would not be a problem. If you feel before or during your interview you would like to take some time out, or stop the interview it is completely acceptable to do so.

We would like to support you as much as possible. Approximately 7-10 days following your interview the research team will contact you to make sure that you have not been left feeling upset or distressed.

If you feel that after taking part in the interview (either immediately or in the weeks/months following) you would like to discuss things further, the research team can make a referral to your doctor or other appropriate NHS services and can also provide you with details of counselling services. This will only be done with your consent to do so.

The only time we will disclose your personal information without your prior consent would be if during the interview you disclose any information that could be deemed related to your safety or safety of others. We would then contact your health care team or other appropriate services.

## **What happens at the end of the research study?**

We hope to interview 15 women from each group, a total of 30 women over 1 to 2 years. At the end of the study, we will be able to inform you of the outcomes of the study in a newsletter. You will not be made identifiable in the newsletter or any published work. You will be welcome to have a copy of the results once they are published.

## **Who has reviewed this project?**

All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your personal information in this project.

This research has been reviewed by NRES Committee xxxx xxxx who have decided they are happy for us to go ahead with the study.

## **Who has funded this project?**

The project is being funded by the Medical Research Council who has allocated funds to Newcastle team for research into Mitochondrial Diseases. None of the research team will receive any direct (or indirect) payment for you entering this study.

## **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you can contact either Julia Maddison on 0191 XXX XXXX (xxxx.xxxx@ncl.ac.uk) or the Principal Investigator XXXX XXXX on 0191 XXX XXX

You may also contact the xxxx xxxx Hospitals Patient Advice Liaison Services department on telephone xxxx xxxx

If you feel that you have been treated unfairly throughout the research, or would like to make comment about the conduct of any aspect of this research, please contact the xxxx xxxx NHS Foundation Trust complaints department on 0191 XXX XXXX.

Thank you for reading this information sheet



## To be on Hospital Headed Paper

**Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of  
Women's Experience**

**Partner/Family Member/Close Friend Information Sheet for  
Women who may be faced with a decision**

Your partner, family member or close friend has been invited to take part in a research study. If you choose to accompany them it is important for you to understand why the research is being done and what it will involve. Please read the following information and discuss it with your partner, family member or close friend. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

### Why are we asking you to take part?

Your partner, family member or close friend has been invited to take part in this research because they have mitochondrial disease or carry a mitochondrial DNA mutation and have expressed an interest in discussing their reproductive options for the future with their doctor.

### Do I have to participate?

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time, without giving any reason. This would not affect the standard of care your partner, family member or close friend receives.

## What is the purpose of this study?

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now.

Reproductive decisions to some woman may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We would like to conduct interviews with two groups of women, women who have made reproductive decision/decisions in the past **21 years** (Retrospective Group) and those women who are making decisions now or in the future (Current/ Prospective Group).

We are interested in learning about topics:

- what is important to them at this time,
- what information they have received or have not received at this time that would help them to make a decision
- and how they feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

## What happens if I agree to take part?

The study will involve a one to one interview with the researcher and your partner, family member or close friend. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. **If they prefer, a telephone interview can be arranged.** There will be some areas we are keen to discuss but your partner, family member or close friend are free to talk about anything they think is important about how they made your reproductive decision/decisions. We will not be asking questions to you directly, but if you want to add anything that is fine

If your partner, family member or close friend is interested in taking part in this study, a member of the research team will contact them to arrange a time and date for their interview; if you choose to attend the interview both yourself and your partner, family

member or close friend will be asked to sign a consent form before the interview starts. **If your partner, family member or close friend takes part in a telephone interview verbal consent with be taken from you both over the phone and documented.**

The interview will take place at a time convenient to your partner, family member or close friend, usually coinciding with their planned clinic visit.

If this is not possible we will make an appointment at a time most convenient for them to attend the Clinical Research Facility at the xxxx xxxx xxxx or the researcher will visit them at their home or a location that they feel the most comfortable. **If your partner, family member or close friend wishes to take part over the telephone the researcher will ring them at time most convenient to them.** Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; yourself and your partner, family member or close friend can decline to take part at any time. Not taking part in this study will not affect the standard of care your partner, family member or close friend will receive. If your partner, family member or close friend decide after the interview has taken place that they would like their collected data to be destroyed and not used, this will be done at their request. This is also the case if you wish that your collected data to be destroyed (if you choose to add anything to the interview).

#### **Will information about me be kept confidential?**

All information we receive from your partner, family member or close friend and yourself will be treated confidentially. Your personal details and replies will be kept safe and secure. The interview will be audio-recorded so that the researcher can transcribe the information accurately. The audio-recording will be destroyed six months after we have finished analysing and writing up the data. Written information will be kept secure in a locked office and only members of XXXX XXXX team will be given permission to look at this information. Your personal details will be converted into a code and stored on a secure computer located at Newcastle University. If we publish any research, we ask your permission to use direct quotes; this will not identify you in any way.

Research records and data may also be inspected by regulatory bodies for audit purposes. This is a normal part of research and it is just to make sure that we are doing everything right.

### **Are there any benefits to taking part?**

We cannot promise the study will help you or your partner, family member or close friend personally, but we hope that the information we get from this study will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

### **Are there any disadvantages to taking part?**

Giving up your time to take part in this project has to be considered. We also recognise that the topic of this interview is sensitive and may cause some distress.

Taking part in this study is voluntary and yourself and your partner, family member or close friend do not have to take part if you feel that it would be too upset discussing this topic. We will do our best to make yourself and your partner, family member or close friend feel as comfortable as possible. If your partner, family member or close friend feel on the day of the planned interview that they would like to rearrange, this would not be a problem. If they feel before or during the interview they would like to take some time out, or stop the interview that is completely acceptable to do so.

We would like to support your partner, family member or close friend as much as possible. Approximately 7-10 days following your interview the research team will contact them to make sure that they have not been left feeling upset or distressed. If they feel that after taking part in the interview (either immediately or in the weeks/months following) they would like to discuss things further, the research team can make a referral to their doctor or other appropriate NHS services and can also provide them with details of counselling services. This will only be done with their consent to do so.

The only time we will disclose personal information without your partner, family member or close friend or your prior consent would be if during the interview any information is disclosed that could be deemed related to the safety of you both or the safety of others. We would then contact their health care team or other appropriate services.

## **What happens at the end of the research study?**

We hope to interview 15 women from each group, a total of 30 women over 1- 2 years. At the end of the study, we will be able to inform your partner, family member or close friend of the outcomes of the study in a newsletter. Your partner, family member or close friend and yourself will not be made identifiable in the newsletter or any published work. You will be welcome to have a copy of the results once they are published.

## **Who has reviewed this project?**

All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your personal information in this project.

This research has been reviewed by NRES Committee xxxx xxxx who have decided they are happy for us to go ahead with the study.

## **Who has funded this project?**

The project is being funded by the Medical Research Council who has allocated funds to Newcastle team for research into Mitochondrial Diseases. None of the research team will receive any direct (or indirect) payment for entering your partner, family member or close friend or yourself into this study.

## **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you can contact either Julia Maddison on 0191 XXX XXXX (xxxx xxxx @ncl.ac.uk) or the Principal Investigator XXXX XXXX on 0191 XXX XXXX

You may also contact the xxxx xxxx Patient Advice Liaison Services department on telephone xxxx xxxx

If you feel that you have been treated unfairly throughout the research, or would like to make comment about the conduct of any aspect of this research, please contact the xxxx xxxx NHS Foundation Trust complaints department on 0191 XXX XXXXX.

Thank you for reading this information sheet



## To be on hospital headed paper

**Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of Women's Experience**

**Partner/Family Member/Close Friend Information Sheet for**

**Women who may be faced with a decision**

Your partner, family member or close friend has been invited to take part in a research study. If you choose to accompany them it is important for you to understand why the research is being done and what it will involve. Please read the following information and discuss it with your partner, family member or close friend. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

### Why are we asking you to take part?

Your partner, family member or close friend has been invited to take part in this research because they have mitochondrial disease or carry a mitochondrial DNA mutation and have expressed an interest in discussing their reproductive options for the future with their doctor.

### Do I have to participate?

It is up to you to decide whether you want to join the study. If you agree to take part, we will then ask you to complete a consent form. You are free to withdraw at any time, without giving any reason. This would not affect the standard of care your partner, family member or close friend receives.

## What is the purpose of this study?

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some woman may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We would like to conduct interviews with two groups of women, women who have made reproductive decision/decisions in the past **21 years** (Retrospective Group) and those women who are making decisions now or in the future (Current/ Prospective Group).

We are interested in learning about topics:

- what is important to them at this time,
- what information they have received or have not received at this time that would help them to make a decision
- and how they feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

## What happens if I agree to take part?

The study will involve a one to one interview with the researcher and your partner, family member or close friend. Interviews will last between 45-90 minutes; they can be paused or stopped at any time. **If they prefer, a telephone interview can be arranged.** There will be some areas we are keen to discuss but your partner, family member or close friend are free to talk about anything they think is important about how they made your reproductive decision/decisions. We will not be asking questions to you directly, but if you want to add anything that is fine

If your partner, family member or close friend is interested in taking part in this study, a member of the research team will contact them to arrange a time and date for their interview; if you choose to attend the interview both yourself and your partner, family member or close friend will be asked to sign a consent form before the interview starts.

**If your partner, family member or close friend takes part in a telephone interview verbal consent will be taken from you both over the phone and documented.**

The interview will take place at a time convenient to your partner, family member or close friend, usually coinciding with their planned clinic visit. If this is not possible we will make an appointment at a time most convenient for them to attend the Clinical Research Facility at the xxxx xxxx or the researcher will visit them at their home or a location that they feel the most comfortable. **If your partner, family member or close friend wishes to take part over the telephone the researcher will ring them at time most convenient to them.** Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; yourself and your partner, family member or close friend can decline to take part at any time. Not taking part in this study will not affect the standard of care your partner, family member or close friend will receive. If your partner, family member or close friend decide after the interview has taken place that they would like their collected data to be destroyed and not used, this will be done at their request. This is also the case if you wish that your collected data to be destroyed (if you choose to add anything to the interview).

#### **Will information about me be kept confidential?**

All information we receive from your partner, family member or close friend and yourself will be treated confidentially. Your personal details and replies will be kept safe and secure. The interview will be audio-recorded so that the researcher can transcribe the information accurately. The audio-recording will be destroyed six months after we have finished analysing and writing up the data. Written information will be kept secure in a locked office and only members of XXXX XXXX team will be given permission to look at this information. Your personal details will be converted into a code and stored on a

secure computer located at Newcastle University. If we publish any research, we ask your permission to use direct quotes; this will not identify you in any way.

Research records and data may also be inspected by regulatory bodies for audit purposes. This is a normal part of research and it is just to make sure that we are doing everything right.

### **Are there any benefits to taking part?**

We cannot promise the study will help you or your partner, family member or close friend personally, but we hope that the information we get from this study will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

### **Are there any disadvantages to taking part?**

Giving up your time to take part in this project has to be considered. We also recognise that the topic of this interview is sensitive and may cause some distress. Taking part in this study is voluntary and yourself and your partner, family member or close friend do not have to take part if you feel that it would be too upset discussing this topic. We will do our best to make yourself and your partner, family member or close friend feel as comfortable as possible. If your partner, family member or close friend feel on the day of the planned interview that they would like to rearrange, this would not be a problem. If they feel before or during the interview they would like to take some time out, or stop the interview that is completely acceptable to do so.

We would like to support your partner, family member or close friend as much as possible. Approximately 7-10 days following your interview the research team will contact them to make sure that they have not been left feeling upset or distressed. If they feel that after taking part in the interview (either immediately or in the weeks/months following) they would like to discuss things further, the research team can make a referral to their doctor or other appropriate NHS services and can also provide them with details of counselling services. This will only be done with their consent to do so.

The only time we will disclose personal information without your partner, family member or close friend or your prior consent would be if during the interview any information is disclosed that could be deemed related to the safety of you both or the safety of others. We would then contact their health care team or other appropriate services.

### **What happens at the end of the research study?**

We hope to interview 15 women from each group, a total of 30 women over 1- 2 years. At the end of the study, we will be able to inform your partner, family member or close friend of the outcomes of the study in a newsletter. Your partner, family member or close friend and yourself will not be made identifiable in the newsletter or any published work. You will be welcome to have a copy of the results once they are published.

### **Who has reviewed this project?**

All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your personal information in this project.

This research has been reviewed by NRES Committee xxxx xxxx who have decided they are happy for us to go ahead with the study.

### **Who has funded this project?**

The project is being funded by the Medical Research Council who has allocated funds to Newcastle team for research into Mitochondrial Diseases. None of the research team will receive any direct (or indirect) payment for entering your partner, family member or close friend or yourself into this study.

### **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you can contact either Julia Maddison on 0191 XXX XXXX (xxxx.xxxx@ncl.ac.uk) or the Principal Investigator XXXX XXXX on 0191 XXX XXXX

You may also contact the xxxx xxxx Patient Advice Liaison Services department on telephone xxx xxxx

If you feel that you have been treated unfairly throughout the research, or would like to make comment about the conduct of any aspect of this research, please contact the xxxx xxxx NHS Foundation Trust complaints department on 0191 XXX XXXX

Thank you for reading this information sheet



## To be on hospital headed paper

**Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation  
of Women's Experience**  
**Patient Information Sheet for**  
**Repeat Interview Arm**

You are being invited to take part in an extension to a study that you participated in, in the past. Before you accept or decline the invitation, it is important for you to understand why the extension to this research is being done and what it will involve. Please read the following information and discuss it with relatives, friends and your GP, if you wish. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

### Why are we asking you to take part?

You are being invited to take part in the extension of a previous project that you took part in, in the past. You were previously invited to take part in the past because you have mitochondrial disease or carry a mitochondrial DNA mutation and you had expressed an interest in discussing your reproductive options for the future with your doctor.

### Do I have to participate?

It is up to you to decide whether or not you want to participate in this extension. If you agree to take part, we will then ask you to complete another consent form. You are free

to withdraw at any time, without giving any reason. This would not affect the standard of care you receive.

### **What is the purpose of this study?**

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some women may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We have been conducting interviews in two groups of women, women who have made reproductive decision/decisions in the past 21 years (Retrospective Group) and those women who are making decisions now or in the future (Current/Prospective Group).

We are interested in learning about topics:

- what is important to women at this time,
- what information women have received or have not received at this time that would help them to make a decision
- and how women feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

### **What is the purpose of the extension to the study?**

A number of months or even years have elapsed since you were originally interviewed. Since the study was originally approved, changes in regulation have permitted the new reproductive technique, Mitochondrial Donation, to be considered by patients as a reproductive option. We have also been able to look at the data collected in interviews and we would like to gather more data on issues raised by patients. We would also like to see if your experiences or opinions on reproduction options are the same or different since your first interview.

## **What happens if I agree to take part?**

The study will involve another one to one interview with the researcher. Interviews will last between 30-45 minutes; they can be paused or stopped at any time. If you would prefer, a telephone interview can be arranged. There will be some areas we are keen to discuss but you are free to talk about anything you think is important about the decision you are making now, in future or may have made since your last interview.

If you are interested in taking part in the extension of this study, a member of the research team will contact you to arrange a time and date for your interview; you will be asked to sign a new consent form before the interview starts. If you have a telephone interview verbal consent will be taken over the phone and documented.

The interview will take place at a time convenient to you, usually coinciding with your planned clinic visit. If this is not possible, we will make an appointment at a time most convenient for you to attend the Clinical Research Facility at the xxxx xxxx or the researcher will visit you at your home or a location that you feel the most comfortable. If you wish to take part over the telephone the researcher will ring you at a time most convenient for you. If you prefer, someone else, like a partner, a member of your family or a close friend, can also take part in the interview with you. Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; you can decline to take part at any time. Not taking part in this study will not affect the standard of care you receive. If you decide after the interview has taken place that you would like collected data to be destroyed and not used, this will be done at your request.

## **Will information about me be kept confidential?**

All information we receive from you will be treated confidentially. Your personal details and replies will be kept safe and secure. The interview, like your last interview, will be audio-recorded so that the researcher can transcribe the information accurately. The audio-recording will be destroyed six months after we have finished analysing and writing up the data. Written information will be kept secure in a locked office and only members of XXXX XXXX team will be given permission to look at this information. Your

personal details will be converted into a code and stored on a secure computer located at Newcastle University. If we publish any research, we ask your permission to use direct quotes; this will not identify you in any way. Research records and data may also be inspected by regulatory bodies for audit purposes. This is a normal part of research and it is just to make sure that we are doing everything right.

### **Are there any benefits to taking part in the extension?**

We cannot promise that taking part in study and the extension to the study will help you personally, but we hope that the information we get from this study as a whole will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

### **Are there any disadvantages to taking part in the extension?**

Just like your first interview, giving up your time to take part in this project has to be considered. We also recognise that the topic of this repeat interview is sensitive and may cause some distress. Taking part in the study extension is voluntary and you do not have to take part if you feel that you would be too upset discussing this topic. We will do our best to make you feel as comfortable as possible. If you feel on the day of the planned interview that you would like to rearrange, this would not be a problem. If you feel before or during your interview you would like to take some time out, or stop the interview it is completely acceptable to do so.

We would like to support you as much as possible. Approximately 7-10 days following your interview the research team will contact you to make sure that you have not been left feeling upset or distressed. If you feel that after taking part in the interview (either immediately or in the weeks/months following) you would like to discuss things further, the research team can make a referral to your doctor or other appropriate NHS services and can also provide you with details of counselling services. This will only be done with your consent to do so. The only time we will disclose your personal information without your prior consent would be if during the interview you disclose any information that could be deemed related to your safety or safety of others. We would then contact your health care team or other appropriate services.

## **What happens at the end of the research study?**

We have been interviewing women from each group since August 2014 with a pause in conducting interviews to analyse data. At the end of the study (including the extension/repeated interviews), we will be able to inform you of the outcomes of the study in a newsletter. You will not be made identifiable in the newsletter or any published work. You will be welcome to have a copy of the results once they are published.

## **Who has reviewed this project?**

All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your personal information in this project. This research and the extension has been reviewed by NRES Committee xxxx xxxx who have decided they are happy for us to go ahead with the study.

## **Who has funded this project?**

The project is being funded by the Medical Research Council who has allocated funds to Newcastle team for research into Mitochondrial Diseases. None of the team will receive any direct (or indirect) payment for you entering this study.

## **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you can contact either Julia Maddison on 0191 XXX XXXX (xxxx xxxx@ncl.ac.uk) or the Principal Investigator XXXX XXXX on 0191 XXX XXXX You may also contact the xxx xxxx Patient Advice Liaison Services department on telephone xxxx XXXXX

If you feel that you have been treated unfairly throughout the research, or would like to make comment about the conduct of any aspect of this research, please contact the xxxx xxxx NHS Foundation Trust complaints department on 0191 XXX XXX

Thank you for reading this information sheet



**Reproductive Decision Making in Mitochondrial Patients: A Qualitative  
Investigation of Women's Experience**  
**Partner/Family Member/Close Friend Information Sheet for**  
**Repeat Interview Arm**

Your partner, family member or close friend has been invited to take part in the extension to a research study that they participated in the past. If you choose to accompany them it is important for you to understand why the extension to the research is being done and what it will involve. Please read the following information and discuss it with your partner, family member or close friend. If there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed on page 4).

**Why are we asking you to take part?**

Your partner, family member or close friend has been invited to take part in the extension to a previous research project that they took part in the past. They were invited to take part because they have mitochondrial disease or carry a mitochondrial DNA mutation and had expressed an interest in discussing their reproductive options for the future with their doctor.

**Do I have to participate?**

It is up to you to decide whether you want to participate in the extension study. If you agree to take part, we will then ask you to complete a consent form. You are free to

withdraw at any time, without giving any reason. This would not affect the standard of care your partner, family member or close friend receives.

### **What is the purpose of this study?**

Approximately 1 in 3,500 women are affected by a mitochondrial DNA mutation, many of whom are of childbearing age. The study aims to look at how women diagnosed with mitochondrial disease, or carrying a mitochondrial DNA mutation have made reproductive decisions in the past and how they make decisions now. Reproductive decisions to some women may mean, deciding to try to become pregnant or deciding not to become pregnant. Little is known about how patients with mitochondrial disease make these important and complex decisions.

We have been conducting interviews with two groups of women, women who have made reproductive decision/decisions in the past 21 years (Retrospective Group) and those women who are making decisions now or in the future (Current/ Prospective Group).

We are interested in learning about topics:

- what is important to them at this time,
- what information they have received or have not received at this time that would help them to make a decision
- and how they feel about new reproductive techniques.

This study is part of a PhD project for Julia Maddison, who is part of the Mitochondrial Research Group; results from this study will form part of her thesis.

### **What is the purpose of the extension to the study?**

A number of months or even years have elapsed since your partner/family member or close friend were originally interviewed. Since the study was originally approved, changes in regulation have permitted the new reproductive technique Mitochondrial Donation to be considered by patients as a reproductive option. We have also been able to look at the data collected in interviews and we would like to gather more data on issues raised by patients. We would also like to see if patient experiences or opinions on reproduction options are the same or different since they were first interviewed.

## What happens if I agree to take part?

The study will involve a one to one interview with the researcher and your partner, family member or close friend. Interviews will last between 30-45 minutes; they can be paused or stopped at any time. If they prefer, a telephone interview can be arranged. There will be some areas we are keen to discuss but your partner, family member or close friend is free to talk about anything they think is important about the decisions they are making now, in the future or may have made since their last interview. We will not be asking questions to you directly, but if you want to add anything that is fine

If your partner, family member or close friend is interested in taking part in the extension to this study, a member of the research team will contact them to arrange a time and date for their interview; if you choose to attend the interview both yourself and your partner, family member or close friend will be asked to sign a consent form before the interview starts. If your partner, family member or close friend takes part in a telephone interview verbal consent will be taken from you both over the phone and documented.

The interview will take place at a time convenient to your partner, family member or close friend, usually coinciding with their planned clinic visit. If this is not possible we will make an appointment at a time most convenient for them to attend the Clinical Research Facility at the xxx xxxx or the researcher will visit them at their home or a location that they feel the most comfortable. If your partner, family member or close friend wishes to take part over the telephone, the researcher will ring them at a time most convenient to them. Any travel / parking costs for helping with this research will be refunded.

Taking part in this study is voluntary; yourself and your partner, family member or close friend can decline to take part at any time. Not taking part in this study will not affect the standard of care your partner, family member or close friend will receive. If your partner, family member or close friend decide after the interview has taken place that they would like their collected data to be destroyed and not used, this will be done at their request. This is also the case if you wish that your collected data to be destroyed (if you choose to add anything to the interview).

### **Will information about me be kept confidential?**

All information we receive from your partner, family member or close friend and yourself will be treated confidentially. Your personal details and replies will be kept safe and secure. The interview will be audio-recorded so that the researcher can transcribe the information accurately. The audio-recording will be destroyed six months after we have finished analysing and writing up the data. Written information will be kept secure in a locked office and only members of XXXX XXXX team will be given permission to look at this information. Your personal details will be converted into a code and stored on a secure computer located at Newcastle University. If we publish any research, we ask your permission to use direct quotes; this will not identify you in any way.

Research records and data may also be inspected by regulatory bodies for audit purposes. This is a normal part of research and it is just to make sure that we are doing everything right.

### **Are there any benefits to taking part in the extension?**

We cannot promise the study and the extension will help you or your partner, family member or close friend personally, but we hope that the information we get from this study will help to improve the way we discuss and support patients who will be faced with making reproductive decisions in the future.

### **Are there any disadvantages to taking part?**

Just like in their first interview, giving up your time to take part in this project has to be considered. We also recognise that the topic of this repeat interview is sensitive and may cause some distress. Taking part in the study extension is voluntary and yourself and your partner, family member or close friend do not have to take part if you feel that it would be too upset discussing this topic. We will do our best to make yourself and your partner, family member or close friend feel as comfortable as possible. If your partner, family member or close friend feel on the day of the planned interview that they would like to rearrange, this would not be a problem. If they feel, before or during the interview, they would like to take some time out or stop the interview that is completely acceptable to do so.

We would like to support your partner, family member or close friend as much as possible. Approximately 7-10 days following their interview the research team will contact them to make sure that they have not been left feeling upset or distressed. If they feel that after taking part in the interview (either immediately or in the weeks/months following) they would like to discuss things further, the research team can make a referral to their doctor or other appropriate NHS services and can also provide them with details of counselling services. This will only be done with their consent to do so.

The only time we will disclose personal information without your partner, family member or close friend or your prior consent would be if during the interview any information is disclosed that could be deemed related to the safety of you both or the safety of others. We would then contact their health care team or other appropriate services.

### **What happens at the end of the research study?**

We have been interviewing women from each group since August 2014 with a pause in conducting interviews to analyse data. At the end of the study (including the extension/repeated interviews), we will be able to inform your partner, family member or close friend of the outcomes of the study in a newsletter. Your partner, family member or close friend and yourself will not be made identifiable in the newsletter or any published work. You will be welcome to have a copy of the results once they are published.

### **Who has reviewed this project?**

All research conducted within the NHS has to be reviewed by an ethics committee to make sure we are not doing anything harmful to you or your personal information in this project. This research and extension has been reviewed by NRES Committee xxx xxxx who have decided they are happy for us to go ahead with the study.

## **Who has funded this project?**

The project is being funded by the Medical Research Council who has allocated funds to Newcastle team for research into Mitochondrial Diseases. None of the research team will receive any direct (or indirect) payment for entering your partner, family member or close friend or yourself into this study.

## **What if I have any concerns?**

If you have any concerns or other questions about this study or the way it has been carried out, you can contact either Julia Maddison on 0191 XXX XXXX (xxxx xxxx @ncl.ac.uk) or the Principal Investigator XXXX XXXX on 0191 XXX XXXX

You may also contact the xxxx xxxx Patient Advice Liaison Services department on telephone xxx xxxx If you feel that you have been treated unfairly throughout the research, or would like to make comment about the conduct of any aspect of this research, please contact the xxxx xxxx NHS Foundation Trust complaints department on 0191 XXX XXXX .

Thank you for reading this information sheet

***A.3 Participant and Attendee Informed Consent Forms***

## To be on Hospital Headed Paper

**REC reference number:** 14/NE/0144

**Committee:** NRES Committee XXXX XXXXX

**Chief Investigator:** XXXX XXXX Mitochondrial Research Group, Newcastle University, NE2 4HH

**Sponsor:** Newcastle Upon Tyne Hospitals NHS Foundation Trust

### Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of Women's Experience

#### Consent Form

**Please write your initials in the box**

1. I confirm that I have read and understand the information sheet dated ..... (version ..... ) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. By signing this document, I understand that I give consent for the study interview to be audio recorded and transcribed.
4. I understand that direct quotations from my interview may be used in published results, but that I will remain non identifiable.

5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from: the study team; the Sponsor (Newcastle Upon Tyne Hospitals NHS Foundation Trust) or their representatives; and from regulatory authorities, where it's relevant to taking part in this research. I give permission for these individuals to have access to the records and I understand that the records will only be reviewed for information related to my participation in the study.

6. I understand that any information will be stored confidentially and identified by code rather than by name.

7. I understand that the results from this research will not have any direct implications for me or my family.

8. I agree to participate in this research.

---

Name of Patient

---

Date

---

Signature

---

Name of Researcher

---

Date

---

Signature

Original to be kept in medical notes;  1 copy for the researcher;  1 copy to be given to the patient



## To be on Hospital Headed Paper

**REC reference number:** 14/NE/0144

**Committee:** NRES Committee XXXX XXXXX

**Chief Investigator:** XXXX XXXX Mitochondrial Research Group, Newcastle University, NE2 4HH

**Sponsor:** Newcastle Upon Tyne Hospitals NHS Foundation Trust

**Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of  
Women's Experience**

**Partner/ Family Member / Close Friend**

**Consent Form**

**Please write your initials in the box**

1. I confirm that I have read and understand the information sheet dated ..... (version ..... ) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. By signing this document, I understand that I give consent for the study interview to be audio recorded and transcribed.

4. I understand that direct quotations from my interview may be used in published results, but that I will remain non identifiable.

5. I understand that relevant sections of data collected during the study may be looked at by individuals from: the study team; the Sponsor (Newcastle Upon Tyne Hospitals NHS Foundation Trust) or their representatives; and from regulatory authorities, where it's relevant to taking part in this research. I give permission for these individuals to have access to the records and I understand that the records will only be reviewed for information related to my participation in the study.

6. I understand that any information will be stored confidentially and identified by code rather than by name.

7. I understand that the results from this research will not have any direct implications for me or my family.

8. I agree to participate in this research.

---

Name of Participant

---

Date

---

Signature

---

Name of Researcher

---

Date

---

Signature

Original to be kept in medical notes of patient interviewed; 1 copy for the researcher; 1 copy to be given to the participant

## **Appendix B Interview Documentation**

***B.1 Interview Topic Guides (Retrospective and Current & Prospective Groups)***

## **Semi Scheduled Interview Schedule**

### **Reproductive Decision Making in Mitochondrial Patients: A Qualitative Investigation of Women's Experience**

#### **Women who may be faced with a decision**

*Note: The interview schedule is developmental. The questions will need to be tailored to the specific answers of each interviewee. It is designed to facilitate the addition of emerging topics and so is subject to change throughout the lifetime of the study*

\*Thanks will be given to participants before the interview commences, the purpose, intended duration and the voluntary nature of the study will be reiterated, along with the option to suspend or terminate the interview at any time. A general information gathering set of questions will be asked at the start

Can you tell me a bit about yourself?

- Age, work life, education, religion relationship status etcetera.
- Do you know if you have a nuclear or mitochondrial mutation?

#### **First learning about risks:**

Do you remember the time when you were first told about the potential risk of passing on your condition to a child?

- Was this by a doctor, nurse or genetic counsellor?
- Was this person someone you had regular contact with?
- Can you remember what it was that they told you?
- How did it feel at the time?

### **Talking about risks with others:**

Did you talk about these risks with your family/ close friends?

- What members of family/close friends did you discuss this with?
- How did they take the news?
- Was there anyone close who you did *not* tell?
- Why was this?

Do you think the people you chose to tell or not to tell could possibly influence any decision you are facing currently or in the future?

### **Impact of diagnosis**

How do you feel your diagnosis has affected your life and reproductive decisions?

- How important is becoming pregnant to you at this time?
- If relevant, how important is becoming pregnant to your partner?
- What are your thoughts about becoming or not becoming pregnant?
- What are your reasons for becoming pregnant or reasons for not becoming pregnant?

### **Family History:**

Does anyone else in your family suffer from mitochondrial disease?

If relevant, what was your mother's or siblings (or other) experiences of pregnancy?

- Did you discuss their experiences at any great length?
- Do you think their experiences have affected you and the decisions you are facing?

### **Relationships with healthcare team:**

Do you feel that the risk of complications of pregnancy with mitochondrial disease have been explained to you enough?

- Have you had enough on-going support from your health care professional at this time?
- What support have they offered?
- What has worked well?
- Is there anything you feel could be said or done differently?
- Do you feel you have a good relationship with your doctors (or others)

Do you feel that you are able to play an active role in your current decision-making or will do in the future?

**Information:**

Has information given to you so far impacted on any decision you may make to become or not to become pregnant?

- Have you had enough information each stage so far?
- What sort of information do you think would be helpful to you at this time?
  - Would any specific format, leaflets, information days, someone to talk to face-to-face help?

Have things like the media, social media and the internet had any influence?

**New techniques:**

Do you know anything about the new techniques available to women with mitochondrial disease?

- How did you learn about these techniques?
- How do you feel about these techniques?
- Do you feel that these techniques may be of any benefit to you?
- Would you choose any of these techniques if they had been available/ suitable to you?

**Closing questions:**

Finally, we need to understand whether the kinds of questions we are asking actually relate to the issues that you think are important?

- Are we asking the right questions?
- Did these questions allow you to talk about what was important for you?
- Is there anything else you would like to say?

Thank you for taking part

Remind them that you will be contacting them in 7-10 days

## **Semi Scheduled Interview Schedule**

### **Reproductive Decision Making in Mitochondrial Patients: A qualitative investigation of women's experiences**

#### **Patient Information Sheet for**

#### **Women who have made a decision**

*Note: The interview schedule is developmental. The questions will need to be tailored to the specific answers of each interviewee. It is designed to facilitate the addition of emerging topics and so is subject to change throughout the lifetime of the study*

\*Thanks will be given to participants before the interview commences, the purpose, intended duration and the voluntary nature of the study will be reiterated, along with the option to suspend or terminate the interview at any time. A general information gathering set of questions will be asked at the start

Can you tell me a bit about yourself?

- Age, work life, education, religion relationship status etcetera.
- Do you know if you have a nuclear or mitochondrial mutation?

#### **First learning about risks:**

Do you remember where you were when you were told about the potential risk of passing on your condition to a child?

- Were you told by a doctor, nurse or genetic counsellor?
- Was this person someone you have had a regular contact with?
- Can you remember exactly what it was that they told you?
- How did it feel at the time?

#### **Talking about risks with others:**

Did you talk about these results with your family/ close friends?

- What members of family/ close friends did you discuss this with?
- How did they take the news?

- Was there anyone close you did not tell?
- Why was this?

Do you think the people you chose to tell or not to tell influenced your decision?

### **Impact of diagnosis:**

How do you feel your diagnosis has affected your life and reproductive decisions?

- How important was becoming pregnant to you when you were making your reproductive choices?
  - If relevant, how important is becoming pregnant to your partner?
- What were your thoughts about becoming or not becoming pregnant?
- What was your reason for becoming pregnant or reasons for not becoming pregnant?

### **Family History:**

Does anyone else in your family suffer from mitochondrial disease?

If relevant, what was your mother's or siblings (or other) experiences of pregnancy?

- Did you discuss their experiences at any great length?
- Do you think their experiences affected you and your decisions about pregnancy? **(All)**

### **Relationships with healthcare team:**

Do you feel that the risk of complications of pregnancy with mitochondrial disease was explained to you enough?

- Have you had enough on-going support from health care professional at this time?
- What support have they offered?
- What has worked well?
- Is there anything you feel could be said or done differently?
- Do you feel you have a good relationship with your doctors (or others)

Do you feel that you are able to play an active role in your decision-making or will do in the future?

### **Information:**

Did the information given to you at the time impact any decision you made to become or not to become pregnant?

- Did you feel you had enough information at each stage?
- What sort of information do you think would have been helpful to you at that time?
- Would any specific format, leaflets, information days, someone to talk to face to face helped?

Have things like the media, social media and the internet had any influences?

### **New techniques:**

Do you know anything about the new techniques available to women with mitochondrial disease?

- How did you learn about these techniques?
- How do you feel about these techniques?
- Do you feel that these techniques may have been of any benefit to you?
- Would you choose any of these techniques if they had been available/ suitable for you?

### **Closing Question**

Finally, we need to understand whether the kinds of questions we are asking relate to the issue that you think are important?

- Are we asking the right questions?
- Did these questions allow you to talk about what was important for you?
- Is there anything else you would like to say?

Thank you for taking part

Remind them that you will be contacting them in 7-10 days

***B.2 Interview Aid (Version 1 and 2)***

## **Reproductive Decision Making – Topic Guide /Interview Aid**

### **1. Genetic Counselling**

Healthcare professionals who have been specifically trained in human genetics provide information, advice and support to individuals and families.

### **2. Conception without medical intervention**

### **3. Adoption**

### **4. Surrogacy and Ovum Donation**

**Surrogacy** – When a woman carries a baby for a woman who is unable carry a child. Using the woman's egg or an egg donated by another women

**Ovum Donation**- Using an egg donated by another woman (known or unknown) for IVF treatment

## 5. Prenatal Diagnosis Testing

There are two commonly offered prenatal tests. They can assess the level of risk to the unborn baby.

**Chorionic villus sampling** -involves removing and testing a sample of cells from the placenta (the organ linking the mother's blood supply with her unborn baby's)

**Amniocentesis** – involves removing and testing a sample of the amniotic fluid that surrounds the unborn baby in the womb.

## 6. Pre-Implantation Genetic Diagnosis (PGD)

Involves checking the genes and/or chromosomes of embryos created through IVF. After a discussion with the clinical team and the family the embryo that is least affected can then be transferred to the womb to allow it to develop.

## 7. Mitochondrial Donation

Faulty mitochondrial DNA from a mother's egg can be replaced with healthy mitochondrial DNA from a donor egg

## **Reproductive Decision Making – Topic Guide /Interview Aid**

### **1. Genetic Counselling**

Healthcare professionals who have been specifically trained in human genetics provide information, advice and support to individuals and families.

### **2. Conception without medical intervention**

### **3. Adoption**

### **4. Surrogacy and Ovum Donation**

**Surrogacy** – When a woman carries a baby for a woman who is unable carry a child. Using the woman's egg or an egg donated by another women

**Ovum Donation**- Using an egg donated by another woman (known or unknown) for IVF treatment

## **5. Prenatal Diagnosis Testing**

There are two commonly offered prenatal tests. They can assess the level of risk to the unborn baby.

**Chorionic Villus Sampling** -involves removing and testing a sample of cells from the placenta (the organ linking the mother's blood supply with her unborn baby's)

**Amniocentesis** – involves removing and testing a sample of the amniotic fluid that surrounds the unborn baby in the womb.

## **6. Pre-Implantation Genetic Diagnosis (PGD)**

Involves checking the genes and/or chromosomes of embryos created through IVF. After a discussion with the clinical team and the family the embryo that is least affected can then be transferred to the womb to allow it to develop.

## **7. Mitochondrial Donation**

Faulty mitochondrial DNA from a mother's egg can be replaced with healthy mitochondrial DNA from a donor egg

## **8. Decision not to have a family**

## **Appendix C – Conference Proceedings and Presentations**

- **Invited Speaker**

Tonge,J. (2017). 'The Implication of Clinical Relationships in Making Reproductive Decisions'. MitoSoc Symposium 2017. London, May 5<sup>th</sup>

- **Selected Abstract**

Tonge,J. (2016). 'Making Sense' of Reproductive Options: A Qualitative Examination of Reproductive Decision Making in Maternally Inherited Mitochondrial Disease'. British Sociological Association Medical Sociology 48<sup>th</sup> Annual Conference, Aston University, September 9<sup>th</sup>

Tonge,J. (2016). 'Exploring Factors Influencing Reproductive Decision Making in Women with Maternally Inherited Mitochondrial Disease'. British Sociological Association Annual Human Reproduction Conference 2016. De Montfort University, June 10<sup>th</sup>

- **Poster Presentations**

Tonge,J. (2017). 'Making Sense' of Reproductive Options: A Qualitative Examination of Reproductive Decision Making in Maternally Inherited Mitochondrial Disease'. Neuromuscular Translational Research Conference 10<sup>th</sup> Annual Conference, University College London, March 22<sup>nd</sup>-23<sup>rd</sup>

Tonge,J. (2016). 'Reproductive Decision Making in Mitochondrial Disease. A Qualitative Examination of Women's Experiences'. Neuromuscular Translational Research Conference 9<sup>th</sup> Annual Conference, Oxford University, March 22<sup>nd</sup>-23<sup>rd</sup>

Tonge, J. (2015). 'Reproductive Decision Making in Mitochondrial Disease. A Qualitative Examination of Women's Experiences'. Neuromuscular Translational Research Conference 8<sup>th</sup> Annual Conference, Newcastle University, March 19<sup>th</sup>-20<sup>th</sup>

- **Internal Presentations**

Tonge, J. (2017). 'Making Sense' of Reproductive Options: A Qualitative Examination of Reproductive Decision Making in Maternally Inherited Mitochondrial Disease'. Mitochondrial Research Group Journal Club, Newcastle University Feb 15<sup>th</sup>

Tonge, J. (2015). 'Reproductive Decision Making in Mitochondrial Disease'. Mitochondrial Research Group Journal Club, Newcastle University Nov 11<sup>th</sup>

Tonge, J. (2015). 'Reproductive Decision Making in Mitochondrial Disease. A Qualitative Examination of Women's Experiences'. Institute of Neuroscience Postgraduate Poster Session, Newcastle University, Nov 5<sup>th</sup>

Tonge, J. (2015). 'Reproductive Decision Making in Mitochondrial Disease. A Qualitative Examination of Women's Experiences'. Applied Qualitative Health Research Session, Newcastle University, March 11<sup>th</sup>

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