Impact of Neurofibromatosis 2 on Quality of Life

Rachael Hornigold

UCL

Thesis submitted for the degree

MD (Res)

Declaration

I, Rachael Hornigold, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Specifically, all patient interviews, pilot group and questionnaire studies were undertaken by myself. The qualitative data analysis was undertaken independently by myself. Additional professional opinions were sought where methodologically appropriate, such as in item generation for the pilot study, and this is indicated in the text. I received specialised statistical advice and support during questionnaire development and validation from Professor John Golding (University of Westminster) and this is indicated within the thesis. Clinical imaging of NF2 patients with epilepsy were reviewed by Dr Steve Connor, Consultant Neuroradiologist, and histology by Dr Bodi Istvin, Consultant Histopathologist.

Rachael Hornigold

10/3/2015

Abstract

Objectives: To perform a case note review to describe unusual clinical manifestations of NF2 within the patient cohort. To describe quality of life (QOL) in individuals with Neurofibromatosis 2 (NF2) using qualitative and quantitative measures. To develop a reliable, validated disease-specific score to measure QOL in NF2.

Design: A case note review of 61 patients with NF2 was performed to identify trends or novel findings. The novel finding of hypertension in the cohort was investigated using a retrospective cohort study. The causes of epilepsy in NF2 were explored using imaging and histological findings. Qualitative interviews and a focus group session generated items for a pilot questionnaire. This was tested and refined. The final version (NFTI-QOL) was validated with two generic QOL questionnaires and the use of two control groups.

Results: Trends in cause of death and surgical intervention were described. In the hypertension study, 50 patients with NF2 were matched against 45 controls. Mean systolic and diastolic blood pressure (BP) was significantly higher in the NF2 group than the control group ($p=0.003$). Imaging of 5 individuals with epilepsy and NF2 was reviewed and cortical lesions were identified in all cases. NF2 impacts QOL in a number of areas, and these are described using framework analysis and quantitative measures. An 8-point disease-specific QOL score for NF2 patients was developed with good internal reliability. It correlated strongly with clinician rated disease severity in

NF2, with stronger correlation than the Short-form 36 (SF-36) in this regard, and was validated against both SF-36 and EuroQOL.

Conclusions: The primary aim of this project was to produce a disease-specific QOL score for NF2 and this has been achieved. There was a novel finding of hypertension in NF2, and if this is confirmed with a prospective study, it may lead to changes in assessment and management.

Acknowledgements

My first vote of thanks is to the Bernice Bibby Research Trust, whose generous support allowed me to take time out of my clinical work in order to complete this research project. I hope that the development of the NFTI-QOL and its continued use will go some way to accomplishing the aims of the trust to improve the lives of people with disabilities, in particular hearing loss. I couldn't have undertaken this work without the enthusiastic involvement of the fantastic patients and staff of the Guy's and St Thomas' Neurofibromatosis Unit. I must also pay tribute to an amazing young man, Tristan Gray who acted as my expert patient in the development of the NFTI-QOL, and who has since sadly passed away. I'd also like to acknowledge the support of the clinical teams of the Nationally Commissioned NF2 Specialised Service in Cambridge, Manchester, Oxford and Sheffield.

Professor John Golding was invaluable in providing specialist knowledge and advice in the field of quality of life research and access to his wide and varied experience both in Psychology and statistical analysis allowed me to be confident of the strong methodological integrity of this piece of work.

A number of significant life events occurred during the completion of this study, not least the birth of my two wonderful daughters, Daisy and Mirabelle and I must thank my husband, Simon Hogan, for his continued support.

The last word however must go to my inspirational supervisors: Professor Michael Gleeson and Professor Rosalie Ferner. Your continued enthusiasm, knowledge and hard-work have had a massive impact on my career to date, and I dedicate this thesis to you.

Table of Contents

Declaration 1
Abstract 3
Acknowledgements..... 5
Table of Contents 7
List of Abbreviations 9
Study Contributors..... 12
List of Figures and Tables 13
1. Introduction..... 15
1.1 Summary 177
1.2 Historical aspects of NF2..... 18
1.3 Diagnosis of NF2 222
1.4 NF2 Epidemiology 29
1.5 NF2 Genetics..... 29
1.6 Natural history and cause of death in NF2..... 38
1.7 Clinical manifestations of NF2 444
1.8 Imaging in NF2 755
1.9 Management of NF2..... 777
1.10 Quality of life (QOL) in NF2 944
1.11 Conclusion..... 98
2. Retrospective case note review of NF2 patients 99
2.1 Summary 1011
2.2 Aims..... 102
2.3 Methods..... 102
2.4 Results..... 106
2.5 Discussion 119
2.6 Conclusion..... 124
3. Quality of life in NF2..... 125
3.1 Summary 127
3.2 Aims..... 129
3.3 Methods..... 129
3.4 Results..... 136

3.5 Discussion 172
3.6 Conclusion 181
References 184
Appendix A 195
Appendix B 215

List of Abbreviations

ABI	Auditory brainstem implant
ABR	Auditory brainstem response
BP	Blood pressure
BVS	Bilateral vestibular schwannoma
CAL	Café au lait
CI	Cochlear implant
CN	Cranial nerve
CNAP	Cochlear nerve action potential
CPA	Cerebellopontine angle
CPERH	Combined pigment epithelial and retinal hamartoma
CROS	Contralateral routing of offside signal
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
EEG	Electroencephalography
EMG	Electromyography
ENT	Ears, nose throat
EQ-5D	Euro-QOL
ERM	Ezrin-radixin-moesin

FLAIR	Fluid-attenuated inversion recovery
GFAP	Glial fibrillary acidic protein
GSTT	Guy’s and St Thomas’ NHS Foundation Trust
HADS	Hospital anxiety and depression score
H&E	Hematoxylin and eosin
IAM	Internal auditory meatus
LINAC	Linear accelerator
MDM	Multi-disciplinary meeting
Merlin	Moesin-ezrin-radixin like protein
MRI	Magnetic resonance image
mTOR	Mammalian target of rapamycin
NCS	Nerve conduction study
NSCG	National Specialised Commissioning Group
NF1	Neurofibromatosis 1
NF2	Neurofibromatosis 2
NFTI-QOL	Neurofibromatosis 2 impact on quality of life questionnaire
NIH	National Institute of Health
NVS	Non-vestibular cranial nerve schwannoma
N/A	Not applicable

OAE	Oto-acoustic emission
ONSM	Optic nerve sheath meningioma
PDGF	Platelet derived growth factor
PTA	Pure tone audiogram
QOL	Quality of life
REC	Research and Ethics Committee
SDS	Speech discrimination score
SF-36	Short Form 36
SRT	Speech recognition threshold
SRS	Stereotactic radiosurgery
SVS	Solitary vestibular schwannoma
UVS	Unilateral vestibular schwannoma
UK	United Kingdom
US	United States
VAS	Visual analogue score
VEGF	Vascular endothelial growth factor
VS	Vestibular schwannoma
WHO	World Health Organisation

Study Contributors

BI Bodi Istvin, Consultant Histopathologist, King's College London

GL Guy Leschziner, Consultant Neurologist

JG John Golding, Professor of Psychology

MJG Michael Gleeson, Project Supervisor, Consultant Otolaryngologist

MVB Melissa Vann Blockley, NF2 Clinical Nurse Specialist

RH Rachael Hornigold, author

RF Ros Ferner, Project Supervisor, Consultant Neurologist

SC Steve Connor, Consultant Neuroradiologist

SH Simon Hogan, Pharmaceutical Physician

List of Tables

Table 1. Revised Manchester criteria for diagnosis of NF2 23
Table 2 Diagnostic criteria for NF1 25
Table 3. Diagnostic criteria for schwannomatosis 27
Table 4 High risk individuals 35
Table 5. Moderate risk individuals 36
Table 6. Cause of death in NF2 43
Table 7. Clinical manifestations of NF2 44
Table 8 Location of meningiomas 60
Table 9. NF2 specific eye findings 65
Table 10. NF2-associated eye findings 65
Table 11. Prevalence of cutaneous manifestations in NF2 69
Table 12 Surgical approaches to the CPA 82
Table 13 Cause of death in NF2 cohort (1997-2008) 107
Table 14 Surgical procedures performed on NF2 cohort 109
Table 15 NF2 specialist versus non-specialist surgeon 110
Table 16 Correlations between age and BP in both groups. 114
Table 17 Site of meningiomas in epilepsy and non-epilepsy groups 116
Table 18 Framework analysis of fifteen patient interviews 138
Table 19 Correlation between judges on severity score 152
Table 20 Pilot questionnaire sub-groups 159
Table 21 NFTI-QOL field test results 164
Table 22 SF-36 results, correlations with NFTI-QOL 166
Table 23 Comparison of NFTI-QOL scores 169
Table 24 Individual item loadings on the whole scale 170

List of Figures

Figure 1. Kaplan-Meier survival curve (log-rank test): age at diagnosis..... 39
Figure 2. Kaplan-Meier survival curve (log-rank test): intracranial meningiomas……40
Figure 3. Kaplan-Meier survival curve (log-rank test): type of constitutional *NF2* mutation 41
Figure 4. Kaplan-Meier survival curve (log-rank test): type of treatment centre 42
Figure 5 Number of patients undergoing vestibular schwannoma excision by specialist (NF2) and non-specialist (other) surgeons by year, compared to number of patients managed within the NF2 specialist clinic..... 112
Figure 6 Areas of high signal intensity (arrowed) thought to indicate cortical dysgenesis. 116
Figure 7 Meningioangiomatosis. 117
Figure 8 Glial microharmartomas. 118
Figure 9 Eligible patient group consensus severity score 153
Figure 10 EURO-QOL question 5 162
Figure 11 Proportion of responders who felt the symptom caused difficulty with or stopped their daily activities..... 165

1. Introduction

1.1 Summary

Neurofibromatosis 2 (NF2) is a rare, autosomal dominant, tumour suppressor disorder, with an incidence of approximately 1 in 25,000 - 33,000. NF2 is characterised by bilateral vestibular schwannomas (BVS) and schwannomas of other cranial, spinal and peripheral nerves. Cranial and spinal meningiomas, ependymomas and NF2 neuropathy also form part of the diagnostic criteria.

In adults, the initial symptom is usually unilateral or bilateral hearing loss, which may be associated with tinnitus and vertigo. Facial palsy may arise from tumour infiltration or compression, mononeuropathy or trauma following surgical excision of a vestibular schwannoma. Ophthalmic and peripheral nerve abnormalities may be the presenting features in children with NF2.

Controversy exists in the management of NF2, with regard to timing and completeness of excision of vestibular schwannomas; the role of hearing-preservation surgery; the indication for ‘sleeper’ auditory brainstem implant and the place of radiotherapy in the management of NF2 tumours. NF2 is a distressing disease and often has a negative impact on quality of life.

Advances in the molecular biology of NF2 have led to the identification of potential targets for medical therapies and the commencement of clinical trials. Current outcome measures include tumour size, hearing loss and quality of life As NF2 is such a rare condition, published outcomes are often small series, and meta-analysis of several studies may be required to

demonstrate real differences in treatment groups. There has previously been little data published on quality of life in NF2 and no consensus as to which method should be employed to measure quality of life in NF2.

1.2 Historical aspects of NF2

a. First published description of NF2

The first published description of NF2 was in the Edinburgh Medical and Surgical Journal in 1822. James Wishart was a Scottish surgeon and President of the Royal College of Surgeons of Edinburgh, and he described the case of Michael Blair, a twenty-two year old baker, who presented with a two year history of progressive bilateral hearing loss (Wishart, 1822).

The patient's father also reported that his son was noted to have right visual loss at the age of four months, had a 'peculiarly shaped head, being considerably longer than natural' and a tendency to fall over. Perhaps due to his balance problems, Michael Blair sustained two significant occupational head injuries. The first at the age of thirteen was sustained whilst apprentice to a gardener, when he was delivered a 'violent blow' on his head with a pitchfork to the left of the union of coronal and sagittal sutures.

The second occurred at the age of nineteen when he fell over on the street whilst carrying a basket of bread on his head, striking his occiput. Tumours were apparent at both sites of trauma within a short period of time of the injury, appearing to protrude from the cranial sutures, the occipital growth

being extremely tender. Mr Blair was offered a diagnostic biopsy of his occipital tumour, but declined.

Six months later the patient represented with worsening symptoms. His occipital tumour had increased in size, his hearing and vision had been completely lost and he was suffering from painful seizures, preceded by olfactory aura. Following consultation with his colleague, Mr Wishart made the decision to biopsy one of the lesions. The patient was sat on a chair and the smaller tumour was explored with an incision over the lesion. It was found to originate from the cranial cavity, protruding through a bony defect in the cranium, covered by an intact layer of dura. The dura was pierced and no further action was taken: the wound was dressed but not closed.

Post-operatively Mr Blair developed significant vomiting and hypotension. Three days later, the tumour ‘fungated’ through the dura and continued to grow, by 10 days post-operatively there was also drainage of ‘clear serum’ and a significant improvement in symptoms – the vomiting settled, his hearing and vision improved. It is likely that his worsening symptoms pre-operatively were due to increased intracranial pressure and the dural puncture allowed decompression of the cranial cavity, hence the clinical improvement.

Unfortunately he began to discharge pus from the incision and became systematically unwell two weeks post-operatively, with pain and rigors and died. A post-mortem was performed and revealed a thickened and irregular cranium; multiple tumours attached to the dura; enlarged lateral ventricles;

and multiple cranial nerve tumours, particularly affecting the 5th and 7th. The 'general tendency to the formation on tumours seemed to proceed also down the medulla spinalis'.

b. Demarcation of NF2 from NF1

It is likely that the first published description of Neurofibromatosis 1 (NF1) was in 1761, when a St Thomas' Hospital physician provided an account of a man of about thirty years, who 'had been accustomed during the greater part of his life to a constant succession of wens that shot out in several places on his head, trunks, arms and legs: which indisposition he inherited from his father' (Akenside, 1768).

Sixty years after Wishart's description of NF2, von Recklinghausen published his seminal review entitled 'On Multiple Cutaneous Fibroma and their Relationship to Multiple Neuromas' (von Recklinghausen, 1882) which included a literature review, reports of two new cases and concluded that neuromas and cutaneous fibromas were related structurally. Following this article, the eponymous name for NF1 became 'von Recklinghausen' disease.

Initially, NF1 and NF2 were treated as separate entities. In 1903, Henneberg and Koch described 'central neurofibromatosis', with tumours of the eighth cranial nerves bilaterally, but no cutaneous lesions, (Henneberg and Koch, 1903) and differentiated it from the more common von Recklinghausen 'peripheral neurofibromatosis'. However this correct assumption that the

conditions were distinct was sent awry by the publication of Harvey Cushing's paper which concluded that 'when the acoustic tumours are bilateral they are very apt to be merely a local expression of a more widespread process of the von Recklinghausen type' (Cushing, 1917). Following this, NF1 and NF2 were widely regarded as associated conditions.

c. Genetic Inheritance of NF2

In the early 1900s, many authors postulated that 'central neurofibromatosis' was an inherited condition, but the most detailed description was by Gardner and Frazier in 1930 (Gardner and Frazier, 1930) when they described the condition in 38 family members spread over five generations. They found that half of the family members at risk developed the condition and proposed that it was of autosomal dominant inheritance. Gardner's index family appeared to have a mild clinical course which led to the description of milder cases as having Gardner type NF2, with more severe cases having Wishart type NF2.

d. NF1 as a separate entity to NF2

The fact that neurofibromatosis 1 and 2 are two unrelated conditions was proven when the diseases were mapped to different chromosomes. NF1 maps to chromosome 17 and NF2 to chromosome 22. NF2 is inherited in an autosomal dominant manner; however 50% of cases arise from de novo mutations.

The defective gene causing NF2 was first localised to chromosome 22 in 1987 (Rouleau et al., 1987). Restriction fragment length polymorphisms (RFLPs) were used to show that loss of alleles on chromosome 22 was frequent both in unilateral vestibular schwannomas (UVS) and bilateral vestibular schwannomas in NF2. Genetic linkage analysis established that the defect was on the long arm of chromosome 22, in the immediate vicinity of D22S1 (Rouleau et al., 1987). The combined use of family studies and tumour deletion mapping narrowed the location of the *NF2* gene to within the q12 band of chromosome 22 (Wolff et al., 1992, Rouleau et al., 1990).

1.3 Diagnosis of NF2

A diagnosis of NF2 may be made on clinical and radiological findings, or more increasingly by the identification of an abnormality of the *NF2* gene on chromosome 22. In order to facilitate the accurate diagnosis of NF2 prior to, or in the absence of genetic markers of the disease, a number of clinical diagnostic criteria have been developed.

a. Clinical Diagnostic Criteria for NF2

A total of five sets of clinical diagnostic criteria for NF2 have been proposed. Three main sets have been devised; the first was devised by expert consensus (National Institute for Health - NIH), and was revised at a later date. The second (Manchester criteria) was a revision of the NIH criteria, taking into account the results of a large population study of NF2, the original was published in 1992 (Evans et al., 1992a), and the revised criteria

published in 1999, 2002 and 2012 (Evans et al., 1999c, Evans et al., 2012, Baser et al., 2002b). The third set was produced by an expert committee (National Neurofibromatosis Foundation Clinical Care Advisory Board) following review of the literature (Gutmann et al., 1997a).

All sets of criteria diagnosed NF2 in the presence of bilateral vestibular schwannomas and in people with a first-degree relative with NF2 plus either a vestibular schwannoma at less than 30 years or at least two other characteristic disease features of NF2. The most commonly used criteria in now the revised Manchester criteria (see below) and its most recent form may be found below. A further revision has been made, (Evans et al., 2012) the basic content has not changed, but there have been changes to format and wording:

Bilateral vestibular schwannoma of family history of NF2 plus 1) UVS or 2) Any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities Or Multiple meningioma (two or more) plus UVS or any two of: glioma, neurofibroma, schwannoma and cataract.

Table 1. Revised Manchester criteria for diagnosis of NF2 (Evans et al., 2012).

The authors also state that ‘individuals who meet Manchester criteria for NF2 or who have evidence of a germline or mosaic NF2 mutation on molecular testing should be considered to be affected by NF2’ (Evans et al., 2012).

The diagnostic efficacy of each set was evaluated in 2002, with reference to people that do not have bilateral vestibular schwannomas but who do have other signs of NF2 (Baser et al., 2002b). This study concluded that none of the existing sets of criteria was satisfactory in certain patient groups, and that a single, revised set of diagnostic criteria be devised to replace all the existing sets of criteria. It was thought that the addition of mononeuropathy and molecular data would improve the sensitivity. Specificity was not assessed but the paper states that there is considerable evidence that specificity is high (approaching 99%) and similar for each set of diagnostic criteria (Baser et al., 2002b).

b. Differential Diagnosis for NF2

i. Neurofibromatosis type 1

Neurofibromatosis 1 (NF1) is a clinically and genetically different disease from NF2, but there are a few overlapping clinical features that may occasionally cause confusion with NF2. NF1 is more common than NF2, with a birth incidence of 1 in 2500-3500 and a prevalence of 1 in 4000-5000 (Evans et al., 2010). It is an autosomal dominant condition, affecting the gene on chromosome 17q11.2. The protein product, neurofibromin, acts as a

tumour suppressor, and patients with NF1 have a tendency to develop benign and malignant tumours (Ferner, 2010).

The diagnostic criteria for NF1 are based on the presence of at least two of the following features:

- A first degree relative with NF1
- Six or more café au lait patches (may be present at birth or, if not, appear in the first few years of life)
- Axillary or groin freckling
- Two or more neurofibromas or one plexiform neurofibroma
- Lisch nodules (in iris)
- Optic pathway glioma
- Bony dysplasia of sphenoid wing
- Pseudoarthrosis of the long bones

Table 2 Diagnostic criteria for NF1 from NIH Consensus Development Conference (National Institutes of Health Consensus Development Committee, 1988).

ii. Schwannomatosis

Schwannomatosis has been described as the third major form of neurofibromatosis (MacCollin et al., 2005). In the past there has been speculation that schwannomatosis was an attenuated form of NF2, as there is an overlap in their presentation and phenotype. However clinical and genetic studies have shown that they are distinct conditions (MacCollin et al., 2003).

Molecular analysis at the *NF2* locus in schwannomatosis-derived tumours did reveal a number of alterations, however there was no evidence of *NF2* mutations in normal tissue, or of shared germline *NF2* locus alterations in the families studied (MacCollin et al., 2003). An inactivating germline mutation in exon 1 of the tumour suppressor gene *SMARCB1* (*INI1*) has been reported in patients with schwannomatosis. It is located on chromosome 22, close to the *NF2* gene (Hulsebos et al., 2007).

Schwannomatosis is characterised by the presence of multiple schwannomas, in the absence of vestibular tumours. Pain does appear to be the most significant feature of schwannomatosis (MacCollin et al., 2005). It is difficult to accurately predict the incidence and prevalence of schwannomatosis; however a Finnish study estimated the annual incidence of newly diagnosed cases as 1 in 1,700,000 (Antinheimo et al., 2000). Schwannomatosis is rarely familial, and when familial occurrence occurs, incomplete penetrance is common (Jacoby et al., 1997, Evans et al., 1997).

Diagnostic criteria for schwannomatosis have been developed and revised (MacCollin et al., 2005, Baser et al., 2006) and the most current criteria are below. An initial diagnosis of schwannomatosis may be re-classified to that of NF2 if vestibular tumours develop.

All patients with definite or possible schwannomatosis must not fulfil any of the existing sets of diagnostic criteria for NF2, and have no evidence of vestibular schwannoma on high-quality MRI scan, no first-degree relative with NF2 and no known constitutional NF2 mutation.

1. Definite Schwannomatosis

A. Age older than 30 years and two or more non-intradermal schwannomas, at least one with histological confirmation, or

B. One pathologically confirmed schwannoma plus a first degree relative who meets the above criteria.

2. Possible Schwannomatosis

A. Age younger than 30 years and two or more non-intradermal schwannomas, at least one with histological confirmation, or

B. Age older than 45 years and two or more non-intradermal schwannomas, at least one with histological confirmation, or

C. Radiographic evidence of a schwannoma and first degree relative meeting the criteria for definite schwannomatosis.

3. Segmental Schwannomatosis

Meets criteria for either definite or possible schwannomatosis but limited to one limb, or five or fewer contiguous segments of the spine.

Table 3. Diagnostic criteria for schwannomatosis (Baser et al., 2006).

iii. Other schwannoma syndromes

The Carney complex is a rare autosomal dominant condition characterised by melanotic schwannomas, spotty skin pigmentation, endocrine tumours, myxomas and endocrine tumours. There has been one report of a family of seven, who were affected by a new syndrome of multiple deep schwannomas, multiple nevi and multiple leiomyomas. The schwannomas and leiomyomas only manifest in adulthood and transmission appears to be autosomal dominant (Gorlin and Koutlas, 1998).

iv. Sporadic non-vestibular schwannomas

These tumours may occur in all age groups; however peak incidence is between the third and sixth decades. The most common sites for the development of sporadic schwannomas are the head and neck, and the flexor surfaces of the extremities (Schiethauer et al., 1999). There is no significant difference between the incidence in males and females, and it is unrelated to racial background. Sporadic schwannomas affect sensory roots more commonly than motor roots or sympathetic nerves (MacCollin et al., 2005).

1.4 NF2 Epidemiology

The most recent and detailed epidemiological data for NF2 are provided by the North West Regional family genetic register. The register covers a population of 4.1 million based around Manchester in the North West of England. In their most recent report, (Evans et al., 2010) data from the last five decades are presented, with data from the highest incidence decade (1974-1983) shown below:

Birth incidence: 1 in 33,206

Prevalence 1 in 56,161

De novo proportion: 56%

Mosaicism: 17%

Median age at diagnosis (de novo): 23 years (range 4-48)

Median age at diagnosis (familial): 20 years (range 3-39)

1.5 NF2 Genetics

NF2 is inherited in an autosomal dominant manner; however more than 50% of cases arise from de novo mutations (Evans et al., 2010).

a. The *NF2* gene

The defective gene causing NF2 was first localised to chromosome 22 in 1987 (Rouleau et al., 1987). Restriction fragment length polymorphisms

(RFLPs) were used to show that loss of alleles on chromosome 22 was frequent both in unilateral vestibular schwannomas and bilateral vestibular schwannomas in NF2. Genetic linkage analysis established that the defect was on the long arm of chromosome 22, in the immediate vicinity of D22S1 (Rouleau et al., 1987). The combined use of family studies and tumour deletion mapping narrowed the location of the *NF2* gene to within the q12 band of chromosome 22 (Rouleau et al., 1990, Wolff et al., 1992).

b. The *NF2* gene product

Merlin (moesin-ezrin-radixin like protein), also known as schwannomin, is a 66-69kDa protein encoded by the *NF2* gene (Rouleau et al., 1993, Trofatter et al., 1993). It contains 16 exons and 595 amino acids (Gutmann, 1997). Sequence alignment has demonstrated that merlin is homologous to the ezrin/radixin/moesin (ERM) protein family (Gutmann et al., 1999).

The ERM proteins are thought to function as general cross-linkers between actin based cytoskeletons and plasma membranes (Arpin et al., 1994). Merlin appears to have additional properties to those of the ERM proteins. In addition to functions of cellular remodelling and formation of membrane microvilli and ruffles, merlin has also been shown to suppress the growth of cells in vitro and in vivo (Gutmann et al., 1999).

c. Tumourigenesis in NF2

Schwannomas and meningiomas from individuals with NF2 have demonstrated inactivating mutations in both *NF2* alleles (Rouleau et al., 1993, Trofatter et al., 1993).

It has also been found that the *NF2* gene is implicated in the development of sporadic schwannomas and meningiomas without NF2. Significantly reduced or absent expression of merlin, using protein-specific antibodies has been found in sporadic meningiomas, ependymomas and schwannomas (Gutmann et al., 1997b).

d. Genotype/phenotype correlation

Historically, NF2 has been sub-grouped by the severity of its symptoms, initially into the Gardner (mild) and Wishart (severe) subtypes. In 1995, a genotype-phenotype was first described and this has been further confirmed and clarified (Merel et al., 1995, Selvanathan et al., 2010).

There are a variety of mutations that may affect the *NF2* gene, resulting in the condition NF2. Mutations can cause a loss of protein, reduced protein function, or a gain of protein function (abnormal allele leading to truncated protein product). Mutations leading to the production of a truncated protein, such as nonsense or frameshift mutations, tend to be linked to more severe disease than those caused by large deletions, missense mutations and in-frame deletions (Evans et al., 1998a).

A study comparing clinical presentation of mutations resulting in truncated protein versus loss of protein expression revealed that those with protein truncation had a significantly: younger age of diagnosis; higher prevalence/proportion of meningiomas, spinal tumours and other cranial nerve schwannomas (not VS). They presented earlier with VS and had a higher mean number of cutaneous lesions. Symptom-wise, those with truncating mutations had a younger age of onset of: hearing loss; tinnitus; paraesthesiae; wasting; weakness and headaches (Selvanathan et al., 2010).

e. Mosaicism

More than 50% of people with NF2 have no family history of the disease and have developed the mutation in a de novo manner. De novo mutations may occur at either the pre-zygotic or post-zygotic stage. Pre-zygotic mutations occur in the germline cells of either of the parents. Post-zygotic mutations can occur in any cell after fertilisation and cell division. If it occurs in the post-zygotic stage, mosaicism may develop.

Mosaicism means that the affected individual will have mixed cell populations with and without mutation. Leukocytes are often unaffected, or only a proportion are affected, (Kluwe and Mautner, 1998) so the mutation cannot be detected during blood tests for the NF2 mutation, only in tumour cells. The timing of the development of the post-zygotic mutation will affect the number

of cells affected and thus the severity of the disease. The individual may develop severe, mild or incomplete disease phenotypes depending on the type of tissue affected, particularly that of neural crest origin.

Mosaicism is likely to lead to milder phenotypes, as a result of a reduced population of mutation-bearing cells. Mosaicism may explain the phenomenon of the index case in a family having relatively mild disease, but children who inherit the mutation have typical phenotypes. If the mutation is present in the germ-line cells, there is a 50% chance of the child inheriting the disorder in an autosomal dominant manner, and developing the disease in a typical, non-mosaic fashion.

A presumed diagnosis of mosaicism may be made from when patients appear to have limited tumour formation within a specific anatomical area, or do not fulfil the criteria for a diagnosis of NF2 but do have many clinical characteristics. Mosaicism may also be diagnosed when no mutation of the NF2 gene is discovered in blood DNA. Using exon scanning techniques, mutations have been discovered in up to 66% of all affected subjects (Parry et al., 1994). It may be that current technology fails to detect certain mutations, such as large deletions, promoter and intronic mutations and locus heterogeneity may play a role (Kluwe et al., 2003). However, it has been proposed that somatic mosaicism may account for a high proportion of these cases (Kluwe and Mautner, 1998, Evans et al., 1998b).

f. Screening for NF2 in the ‘at-risk’ individual

Individuals are ‘at-risk’ of NF2 when they have a parent with features of NF2 or when they have some of the clinical features of the disease, but fall short of the Manchester criteria for diagnosis (Evans et al., 2012). It is advised that these individuals undergo screening until their residual risk is less than 1%.

Genetic analysis is often performed, but a mutation-negative blood test does not rule out NF2. This is due to the relatively high proportion of mosaicism within individuals with no family history of the disease – around 40% of those who do fill the criteria for ‘classical NF2’ will not have an identifiable mutation within their blood (Evans et al., 2012). It is therefore important to have further ways of screening those individuals whose presenting features could represent mosaic NF2 but may just be a chance association.

Screening of individuals at risk of NF2 can be divided into three groups, those at high-risk (≥20%), moderate risk (1-19%) and those with a parental family history of NF2. The risk of NF2 in an individual has been predicted by using genetic testing of over 1000 individuals through the Manchester NF2-testing service and tables of risk are available in the publication (Evans et al., 2012).

i. High risk individuals (Group A, ≥20% risk of NF2)

Examples include: Isolated unilateral vestibular schwannoma (UVS) in person <20 years old Isolated cranial meningioma in person <20 years old Childhood isolated schwannoma at another site *Childhood typical retinal hamartoma Individuals fulfilling two Manchester criteria <50yrs, with additional criterion of childhood mononeuropathy.

Table 4 High risk individuals (Evans et al., 2012, Evans et al., 1999b, Evans et al., 2007, Evans et al., 2008).

This group should undergo mutation testing for NF2 in blood and tumour (if available), as there is at least a 5% chance of finding a mutation in blood (Evans 2012).

If blood mutation testing is negative, these high risk individuals should undergo audiological assessment, imaging (brain and spine MRI), ophthalmic examination and cutaneous examination at presentation and again at 18-20 years of age. They should also undergo cranial MRI at age 25, 35 and 45 years (or 5, 10 and 20 years after first assessment). If no further features of NF2 are found they should be discharged (risk of NF2 will now be <1%). The exception is those within the group that have childhood typical retinal

hamartoma. If mutation testing is negative in these patients, a normal cranial and spinal MRI at age 18 years will be enough to reduce their risk to <1% and they can be discharged at this point.

ii. Moderate risk individuals (Group B, 1-19% risk of NF2)

Examples include: UVS aged 20-30years Individuals fulfilling two Manchester criteria at >50 years of age.

Table 5. Moderate risk individuals (Evans et al., 2012, Evans et al., 1999b).

Blood mutation analysis should be offered but only has a <5% chance of proving positive as most cases in this group are likely due to mosaicism. Cranial and spinal MRI, ophthalmic and cutaneous examination should be performed at presentation. If no further features of NF2 are found, then cranial MRI should be performed at 5, 10 and 20 years after first assessment. If these are normal then the risk is <1% and the individual may be discharged (Evans et al., 2012).

ii. Positive family history in parent

If a child has a parent with NF2, then they should be presumed to have a 50% risk of NF2 and screening can begin with ophthalmological assessment for cataracts soon after birth. If the previous two generations are affected

then the risk will be 50%. If the mutation has previously been identified within the family then mutation testing of blood DNA will provide an accurate answer as to whether the child has developed the disease. If, however, the affected parent was a de novo case and blood mutation testing in the child is negative, the risk of NF2 may be substantially less than 50% (Evans et al., 2012).

A table of risk of NF2 pre- and post-genetic testing in this scenario is available, and may be as low as 1.25% (Evans et al., 2012). In these cases, screening should commence with cranial and spinal MRI at the age of 10 years and continue until the risk of disease if <1%. Between 10 and 20 years, scans are performed every two years and over the age of 20 years, every 3-5 years. The risk of NF2 falls with negative screening and may fall below 1% at 15 years (if parent has mosaic disease and MRI at 15yrs is normal), 25 years or rarely 40 years if NF2 is multi-generational but no mutation has been identified. If at this point, there is no evidence of NF2, the individual can be discharged from further assessment.

1.6 Natural history and cause of death in NF2

a. Tumour growth

A study has assessed patterns of intra-cranial tumour growth in 17 patients with NF2 with a mean follow-up of 9.5 years (range 4-20.7 years) (Dirks et al., 2012). Overall, 59.2% displayed a saltatory growth pattern (alternating periods of growth and quiescence), 29.6% of tumours exhibited linear growth and 11.2% showed exponential growth. A younger age at the onset of NF2-related symptoms (p=0.01) and female sex (p=0.05) were associated with an increased growth rate in meningiomas (Dirks et al., 2012).

b. Life expectancy

In one study of the natural history of NF2, predictors of survival rate following diagnosis were: 5 year survival - 85%, 10 year survival - 67% and 20 year survival - 38% (Otsuka et al., 2003). The United Kingdom NF2 registry study (Baser et al., 2002a) found that of their study group of 368 people, 74 had died during follow-up (20%). In an earlier study of 150 patients, mean age at death in 40 cases was 36.25 years. Mean actuarial survival from diagnosis was 15 years. Over 40% would be expected to have died by 50 years and all cases by 70 years (Evans et al., 1992a).

c. Predictors of mortality

A large study using data from the United Kingdom NF2 registry found four covariates that predicted the risk of mortality in NF2. These were: age at diagnosis; presence of intracranial meningiomas; type of *NF2* mutation and type of treatment centre (specialist versus non-specialist) (Baser et al., 2002a). Kaplan-Meier survival curves are below (Figs 1-4). Relative risk of mortality increased 1.13 fold per year decrease in age of diagnosis, increased 2.51 fold in the presence of meningiomas and decreased by 0.34 fold when patients were treated in a specialist NF2 centre. The risk of mortality in those with NF2 missense mutations was very low compared to those with other types of mutations (Baser et al., 2002a).

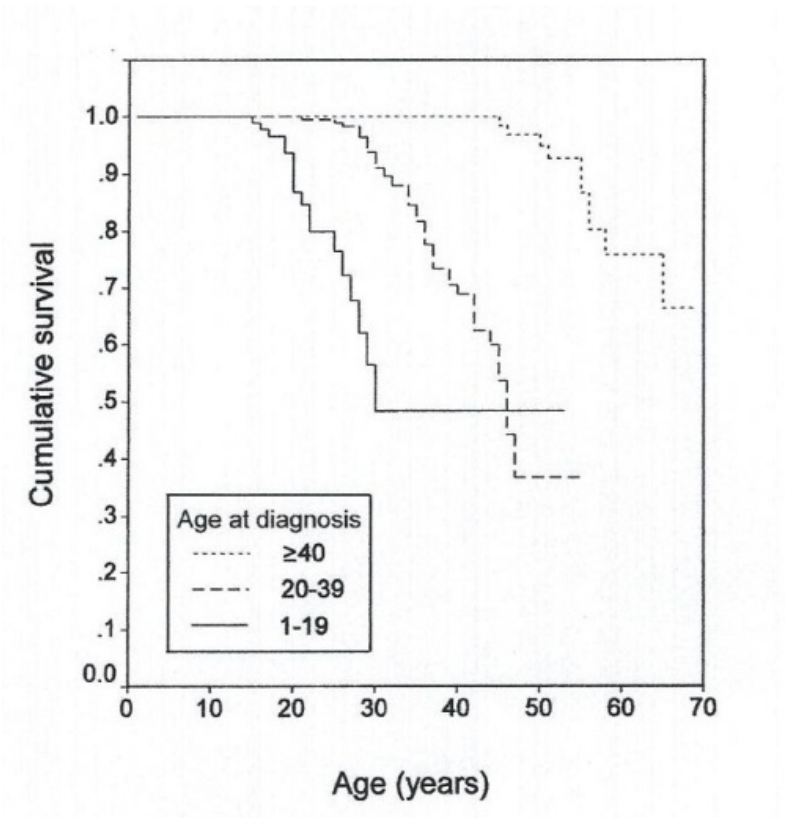


Figure 1. Kaplan-Meier survival curve (log-rank test): age at diagnosis ($p<0.0001$) (Baser et al., 2002a).

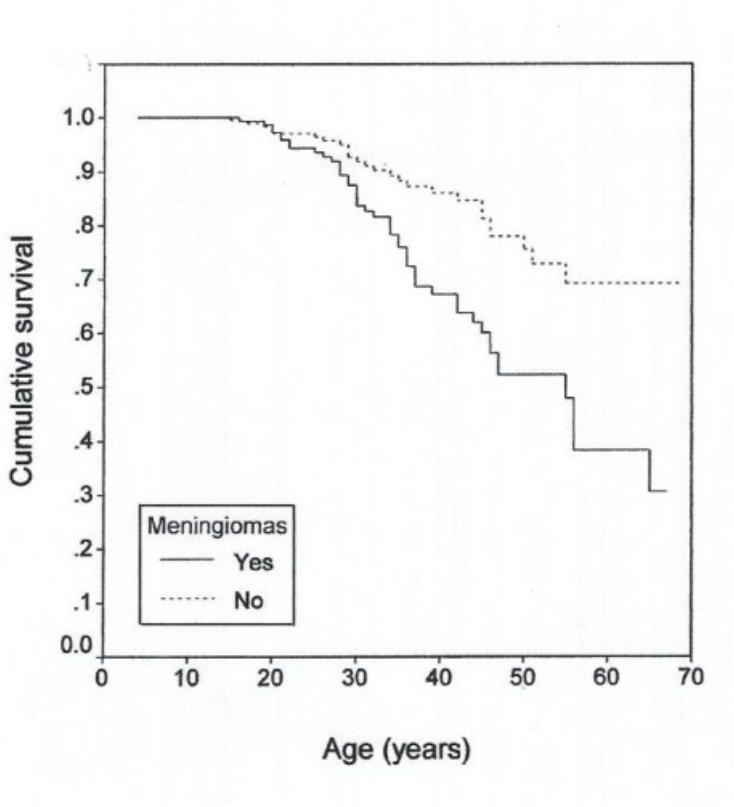


Figure 2. Kaplan-Meier survival curve (log-rank test): intracranial meningiomas (Baser et al., 2002a).

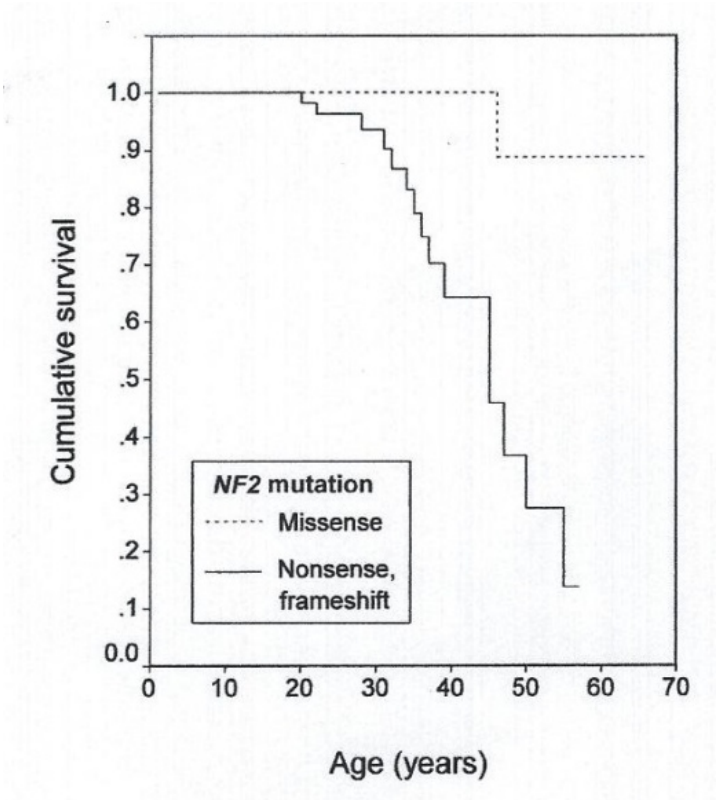


Figure 3. Kaplan-Meier survival curve (log-rank test): type of constitutional *NF2* mutation (p=0.002) (Baser et al., 2002a).

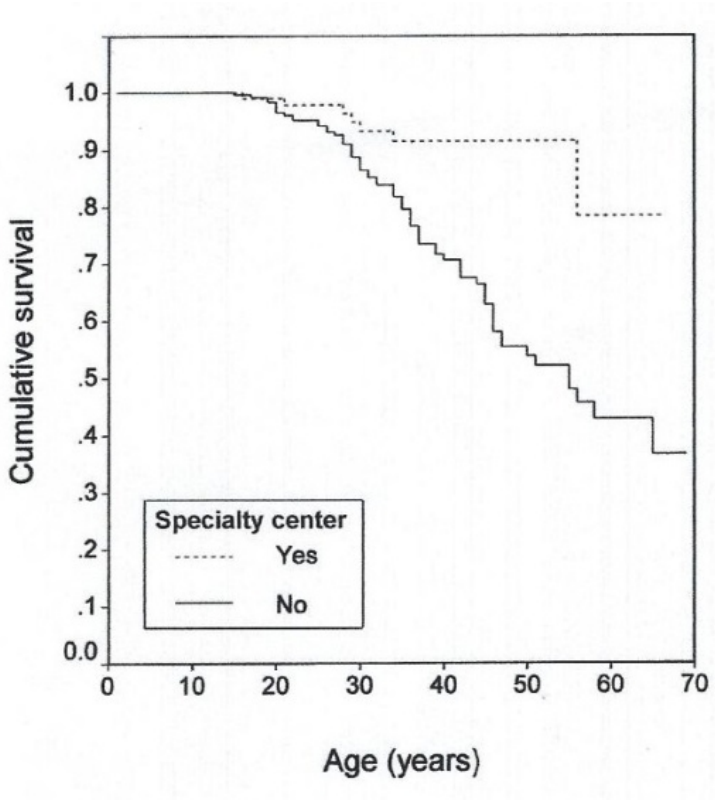


Figure 4. Kaplan-Meier survival curve (log-rank test): type of treatment centre (p=0.0001) (Baser et al., 2002a).

d. Cause of death

There are few reports of the cause of death in NF2. In the UK NF2 registry study (Baser et al., 2002a) the causes of 74 deaths during follow-up were reported, and are summarised below:

Cause of death	% (n)
'Tumour burden'	68.9 (51)
Post-operative complications	18.9 (14)
Malignancy associated with NF2-related tumour	4.0 (3)
Traffic accident	2.7 (2)
Suicide	2.7 (2)
Fall	1.4 (1)
Myocardial infarction	1.4 (1)

Table 6. Cause of death in NF2 (Baser et al., 2002a).

1.7 Clinical manifestations of NF2

The clinical manifestations of NF2 have been described in four major studies and their findings are summarised below: adapted from (Evans, 2009).

Characteristic	Study			
	Kanter et al. (1980)	Evans et al. (1992a)	Parry et al. (1994)	Mautner et al. (1996)
Number of cases	73	120	63	48
Sporadic cases	0	45	17	44
Mean age onset (years)	20 (n=59)	22	20	17
Intracranial meningiomas %	18	45	49	58
Spinal tumours %	n/a	26	67	90
Skin tumours %	32 (n=73)	68 (n=100)	67	64
Café-au lait macules %	42 (n=31)	43 (n=100)	47	n/a
Cataract %	n/a	38 (n=90)	81	62
Intracranial astrocytoma %	n/a	4.1	1.6	n/a
Ependymoma %	n/a	2.5	3.2	6
Optic sheath meningioma %	n/a	4.1	4.8	8

Table 7. Clinical manifestations of NF2 (Evans, 2009).

A large clinical study (n=100) found that the first presenting symptom was: hearing loss in 44%; weakness or wasting in 12%; tinnitus in 10%; balance disturbance in 8%; seizure in 8%; pain in 4%; dysthaesia in 2% and visual loss in 1%. Eleven percent were asymptomatic at diagnosis and were detected through screening with a positive family history (Evans et al., 1992a).

a. Vestibular schwannoma

Bilateral vestibular schwannomas (VS) are the main hallmark of neurofibromatosis 2, and the majority of individuals with NF2 will develop them within the course of their life. VS tend to present with symptoms related to the compression of the vestibular and cochlear nerves at the internal auditory meatus (IAM) and cerebellopontine angle (CPA). These include hearing loss, tinnitus and vertigo. VS can also cause compression of the facial nerve, leading to facial palsy, and trigeminal nerve, leading to facial dysthaesia and paraesthesia. Large tumours may also cause cerebellar and brainstem compression, impair drainage of cerebrospinal fluid (CSF) at the fourth ventricle, leading to non-communicating hydrocephalus and compress the lower cranial nerves leading to bulbar signs.

i. Hearing loss

Hearing loss is the presenting symptom of NF2 of 60% of patients and is most often due to bilateral vestibular schwannomas. The loss of sensory

perception is an extremely emotive feature of disease and many with NF2 face the likelihood of complete hearing loss. The nature of hearing loss in NF2 can be extremely variable and difficult to predict, it is not related to the size of the tumour and may gradually worsen, suddenly be lost and even worsen and then improve. Hearing loss in NF2 is functionally very significant and may be used as a trigger for intervention and an end-point in clinical trials. Patients with NF2 may also experience tinnitus and vertigo, which is discussed further in this section.

Natural history of hearing loss in NF2

A large study of the natural history of hearing loss following diagnosis of NF2 showed that if an individual had measurable hearing, they were unlikely to experience any worsening over the short-term (7 months to 2 years) following diagnosis. Many were diagnosed with NF2 before they had noticeable hearing loss, patients who were diagnosed at a younger age and had a positive family history for NF2 had better hearing at diagnosis. They also found that the rate and size of change is unlikely to be similar in both ears, even when untreated (Masuda et al., 2004). A significant decline in hearing occurred over long-term follow-up.

Mechanisms of hearing loss in NF2

It was initially presumed that hearing loss in NF2 was as a direct result of compression and stretching of the cochlear nerve by a vestibular

schwannoma. However a number of features of NF2-related hearing loss have questioned this explanation. The severity of hearing loss does not appear to be related to the size of the tumour, and may continue to progress during periods of tumour stability (Fisher et al., 2009). The onset of hearing loss is not predictable and may deteriorate gradually, or in a stepwise fashion, may suddenly be lost and can remit. Hearing loss may even predate radiological diagnosis of a vestibular schwannoma and the pattern of hearing loss in one ear will not predict that in the contra-lateral ear (Masuda et al., 2004).

A prospective natural history study of one hundred individuals with NF2 attempted to gain further insight into mechanisms of hearing loss in NF2 (Asthagiri et al., 2012). They found that although the presence of hearing loss was correlated with larger vestibular schwannoma volumes, there were also a large proportion of ears with hearing loss that had small tumour volumes (47% of ears with hearing loss had tumour size of <0.5 cm^3). They had hypothesised that alternative or additional mechanisms of hearing loss in NF2 may include: intralabyrinthine haemorrhage; endolymphatic hydrops; disruption of cochlear vascular supply and/or alteration in the biochemistry within the inner ear fluids. Inner ear MR imaging was performed, with FLAIR sequences to assess for the presence of elevated proteins within the labyrinth.

In this study, raised intralabyrinthine protein was found in 94% of ears with hearing loss and in 70% of normal hearing ears with an ipsilateral vestibular schwannoma (Asthagiri et al., 2012). The five normal hearing ears assessed in the absence of a vestibular schwannoma did not show any evidence of raised intralabyrinthine protein. The cochlear aperture appeared to be blocked by the vestibular schwannoma in 96% of the ears with raised protein and only in 14% of ears without raised protein. The authors therefore postulate that blockage of the cochlear aperture may underlay elevation of intralabyrinthine protein, possibly contributed to by: disruption of the blood-CSF-labyrinthine barrier by permeable tumour vessels (Yamazaki et al., 2009); impaired clearance by tumour compression or involvement of the cochlear nerve disrupting axonal transport; and/or increased protein production or deposition.

It is thought that increased protein may cause biochemical degradation of the cochlea, a study of the proteome within perilymph of ears with a vestibular schwannoma (non-NF2) using mass-spectrometry revealed fifteen potential protein bio-markers – some of which had known roles in hearing and deafness (Lysaght et al., 2011).

Assessment of hearing loss

Hearing loss in NF2 has conventionally been assessed with detection of sound (pure tone thresholds) and speech discrimination. The pure tone audiogram (PTA) is generally performed by a trained audiologist within a

sound booth and assesses levels of sound detection over a range of frequencies. The pure tone average is often used and can be calculated by taking the average in decibels of the thresholds for pure tones at 500, 1000 and 2000Hz. Additional measurements at 4kHz allow further differentiation around thresholds indicative of speech discrimination.

Speech audiometry is a more practical assessment of useful hearing, as it assesses the ability to hear and repeat standardised lists of words at different decibel levels. Various thresholds can be produced from this test, including speech-recognition threshold (SRT) - the minimum intensity at which 50% of disyllable words are correctly identified, and the maximum speech discrimination score (SDS), the percentage of single syllable words correctly identified at 40dB above the SRT. The American Association of Otolayngology hearing outcomes scale is a composite of the pure tone average and speech discrimination score, and has been used widely as an outcome following hearing preservation surgery for vestibular schwannoma (Committee on Hearing and Equilibrium, 1995). However the insensitivity within grade D – grouping all hearing ears with maximum SDS or less than 50dB together – means that it is likely to miss clinically relevant changes in hearing in NF2 patients with a single hearing ear, and do should not be used as a standardised endpoint in NF2 trials. Instead, maximum word recognition score has been endorsed as the preferred primary endpoint (Plotkin et al., 2013).

More detailed techniques have been used for assessment when implantation with a cochlear or auditory brainstem implant is considered. These include oto-acoustic emissions (OAE), auditory brainstem response (ABR), promontory stimulation and cochlear nerve action potential (CNAP).

Management of hearing loss in NF2

Hearing aids may be helpful in the early stages, but are often less effective in NF2-associated hearing loss. If there is reasonable hearing in one ear, and no hearing in the other, then a Contralateral Routing of Sound (CROS) or bone-anchored hearing aid may be beneficial. There are a number of additional aids that may be beneficial including induction loops and vibration pads. It is often helpful to learn to lip read whilst hearing is still preserved, but it may be challenging to provide motivation for this while hearing is still acceptable. A week-long residential course is run by the Hearing Link Foundation, which is specifically aimed at people with NF2 and their families (http://www.hearinglink.org/nf2programmes). It offers practical support and training and is fully funded for individuals with NF2 in England. Details of hearing preservation surgery can be found in the management section.

ii. Tinnitus

Tinnitus may be defined as ‘the conscious experience of a sound that originates in the head of its owner’ (McFadden, 1982). In NF2, in the majority of cases, tinnitus is due to vestibular schwannoma. It may occur prior to measurable hearing loss and as such may be the presenting symptom of the

disease. Tinnitus can itself cause and can also interfere in sound perception, amplifying any existing hearing loss.

It is difficult to assess the actual prevalence of tinnitus in NF2 as in the majority of clinical series it is grouped in with hearing loss. However in a large genotype-phenotype study (Selvanathan et al., 2010), tinnitus was taken as an individual symptom, and occurred in 52.9% of those with nonsense or frameshift mutations and 52% of those with large deletions. The age of onset of tinnitus was significantly different (p=0.002) between those with nonsense/frameshift mutations (mean 22 years, 95% CI 19-24yrs) and large deletions (mean 30 years, 95% CI 25-35yrs). This was also the case for hearing loss (p=0.010).

Tinnitus may also develop after treatment for vestibular schwannoma, and it is important that this issue is raised when consent is obtained. In a large surgical series of NF2 patients undergoing translabyrinthine surgery, 63% of patients had tinnitus pre-operatively. Of these, 61% noticed no change post-operatively, it resolved in 17% and in 21% it worsened. 22% of patients developed new-onset tinnitus post-operatively (Moffat et al., 2013). There are few data specifically relating to tinnitus following radiosurgery for vestibular schwannoma. 6% of patients had ‘non-specific vestibular symptoms’ which included tinnitus post-treatment in one retrospective review of 96 NF2 patients, but it is unclear if these were new symptoms following treatment (Rowe et al., 2003).

Management of tinnitus is symptomatic. Optimisation of hearing aids is often beneficial. A variety of devices, such as sound generators can help, particularly at night-time. Cognitive behavioural therapy has been effective in the general tinnitus population, and a systematic meta-analysis of the literature found ‘a significant improvement in the quality of life (decrease of global tinnitus severity) of the participants, thus suggesting that cognitive behavioural therapy has an effect on the qualitative aspects of tinnitus and contributes positively to the management of tinnitus (Martinez Devesa et al., 2007).

iii. Vertigo and balance problems

The maintenance of balance is complex with sensory inputs from the vestibular system, eyes and muscles and joints via proprioception, integration in the brainstem and outputs to the eyes and joints, with further input from the cerebellum and cerebral cortex. It is therefore not surprising that balance problems are an issue for many in NF2. Vertigo or dizziness was the first symptom of NF2 in 8% in Evans’ clinical study and balance problems were present in all of those with ‘established vestibular schwannoma’ (Evans et al., 1992a).

True rotatory vertigo is the sensation of rotatory movement which can be extremely disabling to those affected. Vertigo in NF2 is most likely due to VS, but other coincidental common causes need to be ruled out, such as benign

paroxysmal positional vertigo. Vertigo is generally diagnosed symptomatically, but clinical examination and formal vestibular testing may allow further characterisation and guide any rehabilitation.

Management of balance disturbance in NF2 can be challenging. Symptoms of unilateral vestibular failure are generally improved by compensation by the contralateral side, which can be enhanced by specific movements and exercises; however this is complicated in NF2 by the likely presence of a contralateral VS. Mobility aids, such as a stick, may be helpful, and visual acuity should be optimised.

iv. Facial palsy and paraesthesia

Facial palsy may be measured using the House Brackmann score where grade I indicates normal facial function in all areas and grade VI relates to total paralysis (House and Brackmann, 1985). Facial palsy in NF2 may be as a result of compression of the facial nerve at the CPA by VS, by direct involvement in the nerve by schwannoma, due to mononeuropathy or, most commonly, as a result of treatment of VS by surgery or radiotherapy.

Facial palsy is an uncommon presenting feature of NF2 in adults; however unilateral facial palsy was the presenting feature of NF2 in 20% of children in one study (Evans et al., 1999a). It is thought that in at least some of these cases the palsy was due to facial mononeuropathy.

The risk of facial palsy following surgery for VS can be reduced by careful timing of surgery. The likelihood of preserved facial nerve function decreases as the size of tumour increases, and this needs to be considered when decided a management plan (see section on Surgery in NF2). There may be a period of worsened palsy following surgery due to neuropraxia which will recover in time though not necessarily completely. It is therefore important that facial palsy outcomes following surgery should be reported following a period of recovery, usually 6 months to one year. Physiotherapy and muscular stimulation may be used for rehabilitation during this period.

The management of established facial palsy in NF2 can be divided into: management of eye symptoms; improvement of facial symmetry and facial reanimation. The cornea is at risk if eye closure is limited. Regular lubrication, ophthalmic review and occasionally tarsorrhaphy, eyelid weights or chains are required to prevent corneal ulceration. Facial symmetry may be improved by fillers, Botox and plastic surgical procedures, such as muscular slings, brow lifts and face lifts. The input of a specialist facial palsy multidisciplinary team is extremely useful. Facial reanimation may be attempted at the time of VS surgery if the facial nerve is divided, using a direct nerve graft to bridge the defect, or may be attempted as a second procedure using free muscle transfer or hypoglossal-facial nerve transfer. The presence of schwannoma on donor nerves needs to considered, but results are promising (Vakharia et al., 2012).

Facial paraesthesia may be due to compression of the trigeminal nerve by a VS or trigeminal schwannoma. Loss of corneal sensation is a good indicator of dysfunction, and, particularly when combined with incomplete eye closure does increase the risk of corneal damage. Trigeminal neuralgia may also occur.

v. Brainstem compression

Bilateral large VS may cause brainstem compression. Symptoms may include headache and visual disturbance and disk swelling may be noted on fundoscopy. Brainstem compression can become imminently life-threatening if obstructive hydrocephalus develops, which if unchecked leads to brain herniation and death. Decompression with a ventricular shunt is often performed in these incidences, most-commonly followed by staged surgical de-bulking of the tumours. For large tumours (>3cm diameter) causing brain-stem compression in the absence of hydrocephalus, surgical decompression is generally advocated as first line management (Blakeley et al., 2012). Radiosurgery is not recommended for large tumours (>3cm), particularly when causing brainstem compression, due to the potential for further compression by oedema at the treated site.

vi. Diagnosis

Imaging, preferably with gadolinium enhanced magnetic resonance, will lead to the detection of the majority of VS. Hearing may or may not be

compromised (see hearing section). Prediction of the size of the vestibular schwannoma by imaging may be by linear measurements or more increasingly by volumetric estimation (see imaging section).

vii. VS growth

A number of groups have studied vestibular schwannoma growth rate and patterns in people with NF2. In the four main longitudinal studies, discrepancies were found, with two studies revealing that VS growth rates decreased with increasing age, (Baser et al., 2002c, Mautner et al., 2002) one study revealing no change in growth rate with age (Slattery et al., 2004) and one revealing growth rate increased with age (Abaza et al., 1996). However reanalysis of the data from these studies combined with data from the UK NF2 Registry concluded that VS growth rates are highly variable but tend to decrease with increasing age (Baser et al., 2005). Ito et al performed multivariate analysis on factors that may influence growth in 27 patients and found no significant factors (Ito et al., 2009).

Dirks et al analysed growth patterns in NF2-associated intracranial tumours and found that the most frequent growth pattern was characterised by alternating periods of growth and quiescence – salutatory growth. 59.2% of intracranial tumours exhibited this pattern (46.7% of VS), 29.6% exhibited linear growth and 11.2% exhibited exponential growth (Dirks et al., 2012).

It does appear that treatment of a contralateral tumour may affect growth in some instances; Peyre et al found that when bilateral VS were threatening the brainstem, surgery on one side led to significant elevation in velocity of diametric expansion of the contralateral VS (Peyre et al., 2011).

b. Non-vestibular cranial nerve schwannoma

In the NF2 natural history study by Fisher (Fisher et al., 2007), 51% of patients (42/83) had at least one non-vestibular cranial nerve schwannoma (NVS). Of a total 64 NVS, 28% of patients had one, 19% had two and 3.6% had three NVS. The most common site was the trigeminal nerve (CN V) with 72% (46/64) of NVS occurring at this site, followed by oculomotor (15.6%, 10/64). There were few tumours on the remaining cranial nerves: 4.7% were vagal (3/64) and 1.5% (1/64) involved each of the trochlear; abducens; glossopharyngeal; accessory and hypoglossal nerves. There were no schwannomas affecting the optic or olfactory nerves in this series, and there are no reports of these in the literature. NVS do appear to be a marker for more severe disease, and are found to occur more frequently and at a younger age in those with nonsense/frameshift mutations compared to those with large deletions (Selvanathan et al., 2010).

NVS are often asymptomatic, but may cause impairment of the affected nerve (e.g. loss of corneal reflex by trigeminal schwannoma, ‘down and out’ eye position by oculomotor schwannoma) or compression of other local structures. Lower cranial nerve schwannomas have the potential to cause

more significant symptoms, such as swallowing problems and aspiration, which can cause significant morbidity, and growth of lower cranial nerve schwannomas should be monitored to avoid these life-threatening complications (Fisher et al., 2007).

NVS tend to be very slow-growing: in the natural history study, there were no significant changes in tumour volume from baseline to the first-year evaluation and from the first to second-year evaluation (Fisher et al., 2007). Four patients had a large NVS (>2cm^3) and one of these increased in size between the first and fourth-year evaluation, the other three large tumours remained stable.

c. Meningiomas in NF2

Meningiomas are the second most common tumour in NF2 and form part of the diagnostic criteria. They most commonly develop intracranially, but are also found in the spine and have been rarely reported in the lungs (Walter et al., 2009). Intracranial meningiomas occur in between 45-58% of people with NF2 (Asthagiri et al., 2009) and are both a marker of more severe genotype (Selvanathan et al., 2010) and a predictor of mortality (Baser et al., 2002a). By 70 years of age, nearly 80% of patients with NF2 will have one or more meningiomas (Smith et al., 2011). Eight percent of people with NF2 present with a meningioma prior to developing vestibular schwannoma, and 20% of children who present with a meningioma will go on to be diagnosed with NF2 (Evans et al., 2005). Meningiomas in NF2 do not appear to be more aggressive than sporadic meningiomas (Goutagny et al., 2012).

Meningiomas are best imaged with contrast-enhanced T1-weighted MRI, with T2 weighted-images used to demonstrate surrounding oedema or cysts. They enhance homogenously and typically have a dural tail. The presence of oedema indicates that the meningioma is likely to show more aggressive growth (Goutagny et al., 2012).

i. Intracranial meningiomas

Intracranial meningiomas are often multiple in NF2: the median number per patient is 3 and 28% of patients in one series had seven or more (Goutagny et al., 2013). Meningiomas are often asymptomatic and diagnosed on routine imaging, particularly those of the cerebral convexity. If they become large, they may lead to focal or generalised seizures. Intracranial meningiomas cause more serious neurological deficit when occurring in intracranial regions with bony margins, such as the optic canal or skull base, where they have the potential to cause cranial nerve defects at a relatively small size. Parafalcine meningiomas may encroach on the sagittal sinus, leading to chronic venous hypertension (Blakeley et al., 2012).

The most common intracranial locations from one large study (Goutagny et al., 2012) are shown below:

Meningioma location	Percentage of tumours
Convexity and falx	71.8%
Skull base	24.7%
Lateral ventricles	2.8%

Table 8 Location of meningiomas (Goutagny et al., 2012)

Meningiomas of the optic nerve sheath (ONSM) are found more frequently in NF2 than the general population, and a review of eight clinical studies showed that 14 out of 356 patients with NF2 had ONSM (3.9%) (Bosch et al., 2006b). In the early stages ONSM cause visual loss, optic atrophy and optociliary shunt vessels can be observed. At later stages intraorbital expansion may occur, leading to proptosis and strabismus. ONSM may be bilateral.

The majority of intracranial meningiomas in NF2 patients are stable and can be managed by a watch-and-wait policy. In a study of 74 NF2 patients with 287 meningiomas, 66% of tumours showed no or minimal growth, and only 7.3% of tumours had a growth rate of 20% or more per year (Goutagny et al., 2012). Only symptomatic or growing meningiomas require treatment. Surgery is currently the treatment of choice, and 45.9% of patients underwent surgical treatment for meningioma in the follow-up period (mean 110 months) in one study – although 12.5% were removed incidentally ‘en-route’ to removing another tumour (Goutagny et al., 2012). Radiosurgery has been used for meningioma in NF2 but there is no long-term follow-up data at present (Asthagiri et al., 2009).

ii. Spinal meningiomas

See spinal tumour section.

d. Spinal tumours

Spinal tumours occur in between 63 and 90% of people with NF2 (Asthagiri et al., 2009). Spinal tumours are either intra-medullary - usually ependymoma, or extra-medullary – typically schwannoma or meningioma. Schwannomas seem to be the most prolific, accounting for 57.5% (177/308) of spinal tumours in one series, followed by intra-medullary (34.7%) and then meningioma (7.8%) (Patronas et al., 2001). The presence of a protein-truncating mutation is significantly more likely to be associated with the presence of spinal tumours than any other mutation (Dow et al., 2005).

Spinal tumours are normally identified following imaging of the spine. Whole spine MRI is performed as a baseline in all patients diagnosed with NF2 and also at regular intervals. Surgery for spinal tumours require careful consideration and a meticulous pre-operative evaluation, as symptoms attributed to the spinal tumour may in fact be due to neuropathy and patients may be no better or worse following surgery.

i. Intra-medullary tumours

The majority of intra-medullary tumours are histologically ependymoma, accounting for 75% of this tumour type (Asthagiri et al., 2009).

Ependymomas are found in 18-53% of people with NF2 but are frequently asymptomatic – only causing symptoms in less than 20% (Asthagiri et al., 2009). Intra-medullary tumours appear to occur more commonly in those with nonsense and frameshift mutations (Patronas et al., 2001). They enhance uniformly with contrast MRI and may have multiple 'seedlings' along the brainstem and central canal of the spinal cord, usually in the cervical region. They may be associated with a syrinx. Other intra-medullary tumours have been reported in NF2, including astrocytomas and schwannomas (Patronas et al., 2001).

When symptomatic, intra-medullary tumours tend to cause back pain (56%), weakness (28%) and/or sensory disturbance (16%) (Asthagiri et al., 2009). The majority of those with intra-medullary tumours do not require intervention. In a follow-up study, only two patients out of eleven (18%) experienced any growth of their intramedullary tumour (mean follow-up 52 months) and these patients were all managed conservatively (Dow et al., 2005). Those who require treatment will generally undergo surgical excision of the tumour.

ii. Extra-medullary tumours

Extra-medullary tumours are usually meningiomas or schwannomas and can be present intra-durally or extra-durally. Spinal schwannomas tend to arise from sensory rather than motor nerve roots. Extra-medullary tumours tend to

occur most commonly in the lower lumbar/cauda equina (69% of patients) and cervical regions (52%) (Dow 2005).

Extra-medullary tumours are multiple in the majority of patients - 56% had multiple spinal tumours in the study by Mautner et al (Mautner et al., 1995). They may be divided into small (<5mm) and large (>5mm) tumours.

Patients tend to have multiple small tumours which may or not be associated with solitary or few large tumours. Small tumours seem to be relatively stable, and in one series, there was no growth of any small extra-medullary tumours during the follow-up period (n=13, mean follow-up 53 months). Large extra-medullary tumours by contrast seem to be more aggressive, with growth in 36% of patients (Dow et al., 2005). Large tumours may require intervention if the lesion can be predictably pinpointed as to causing a reversible neurological deficit, the risk of complications is acceptable and the tumour is large and showing growth. In patients with large tumours, intervention rate is high, with surgical excision required in 57% of those with such tumours (Dow et al., 2005).

e. Ophthalmologic Findings in NF2

Ophthalmic pathology is a well-known feature of NF2 and appears in the diagnostic criteria. Abnormalities may be found incidentally on screening or may present with visual loss or cosmetic eye changes. Many ophthalmic changes may be asymptomatic. Functional visual problems may result from

a primary NF2-specific eye pathology or may arise secondarily due to other NF2 pathology, such as disc changes due to raised intracranial pressure or corneal ulceration secondary to facial palsy. Patients with NF2 should undergo regular ophthalmological assessment as many lesions may only be detected on slit-lamp examination with pupillary dilatation by an experienced NF2 ophthalmologist. Dedicated MR imaging of the orbit may reveal previously undetected optic nerve sheath meningiomas.

i. Incidence

There are limited data available as to the incidence of ophthalmic pathology in NF2. Evans et al found that 38% of their 90 patients had lens opacities (Evans et al., 1992a). Bosch et al found NF2-specific ocular pathology in 83% within their 30 patient cohort, and the incidence of NF2-specific and NF2-associated eye findings in their cohort are in the two tables below (Bosch et al., 2006a). However, these patients had all been referred for ophthalmological assessment so there may be some selection bias, with an over-estimation of incidence.

NF2-specific eye finding	Incidence (n=30)
Cataract	67%
Epiretinal membranes	40%
Combined pigment epithelial and retinal hamartoma (CPERH)	3%
Disk glioma	13%
Optic nerve sheath meningioma	27%

Table 9. NF2 specific eye findings (Bosch et al., 2006a).

NF2-associated eye findings	Incidence (n=23)
Disk oedema	30%
Optic atrophy	17%
Motility disorder	52%
Pupil dysfunction	35%
Lid dysfunction	43%
Reduced corneal sensation	26%
Exophthalmos	17%
Keratopathy	22%

Table 10. NF2-associated eye findings (Bosch et al., 2006a)

f. Peripheral nerve involvement in NF2

Peripheral nerve involvement in NF2 may include distal symmetric sensorineural neuropathy, focal amyotrophy and mononeuropathy. It has been suggested that neuropathy be added to the diagnostic criteria for NF2 to improve its sensitivity (Baser 2002). Peripheral neuropathy in NF2 may have been underestimated in the past: it was found in only 6% of patients in a large clinical study (Evans et al., 1992a). However a study in 2002 revealed the incidence may be as high as 66.7% on electrophysiological testing (Sperfeld et al., 2002).

Children present with peripheral nerve involvement more commonly than adults and in one series at least 10% of children under 10 years old (n=3/30) presented with mononeuropathy: facial palsy in the absence of vestibular schwannoma or foot drop (Evans et al., 1999a).

Symptomatic focal amyotrophy was first described as a presenting feature of NF2 in 2000 (Trivedi et al., 2000), however the ‘wasting of a muscle group with no obvious antecedent cause’ was recorded in 4% (n=6/150) in a large clinical study (Evans et al., 1992a). Mononeuropathy most commonly affects the facial nerve, causing permanent lower motor neurone palsy, often before the detection of a vestibular schwannoma (Evans et al., 2005).

Histology of peripheral nerves in patients with NF2 neuropathy has revealed loss of myelinated and unmyelinated fibres and abnormal Schwann cell proliferation, some with an onion bulb appearance (Asthagiri et al., 2009). A number of underlying mechanisms have been proposed as the cause of peripheral neuropathy in NF2, including: compression by multiple tumourlets along the length of an adjacent nerve; Schwann cell proliferation with entangled axons (schwannosis); Schwann cell dysfunction or local toxic effects by pathological cells (Asthagiri et al., 2009). Merlin isoform 2 has been found to have a specific role in maintaining axonal integrity and the reduction of axonal *NF2* gene dosage may result in polyneuropathy (Schulz et al., 2013).

g. Cutaneous manifestations of NF2

Although cutaneous changes in NF2 are not as common or as prominent as in NF1, they are sometimes the first or presenting symptom. A number of cutaneous stigmata may be present in NF2, including café au lait (CAL) patches and skin tumours, including cutaneous plaque-like schwannomas, intra-dermal tumours and discrete subcutaneous peripheral nerve schwannomas. Skin tumours may be multiple (when present, average tumour number = 5.8) (Evans et al., 1992a) and appear to have a raised frequency in more severally affected people (Mautner et al., 1997). They usually occur above the waist (Ferner, 2007). Cutaneous lesions were the first clinical symptom of NF2 in 27.3% of patients in the series by Mautner et al (Mautner

et al., 1997). The prevalence of skin lesions in 5 major series of NF2 patients is summarised in the table below:

Series (S) Review (R)	Kanter et al. (1980) (S)	Evans et al. (1992a) (S)	Parry et al. (1994) (S)	Otsuka et al. (2003) (S)	Mautner et al. (1997) (S)	Asthagiri et al. (2009) (R)
Number of patients	73	100	63	74	88	n/a
Café-au-lait patches	42%	43%	47%	50%	33%	33-48%
Skin tumour/s	32%	68%	67%		59%	59-68%
>10 skin tumours		10%			27.4%	
Cutaneous schwannoma		48%			41%	41-48%
Subcutaneous schwannoma		43%		70%	48%	43-48%
Intra-dermal tumour		27%			8%	Rare
Neurofibroma/ mixed tumour					5 NF, 2 mixed from 29	Rare

Table 11. Prevalence of cutaneous manifestations in NF2

h. Café au lait (CAL) patches

Café au lait patches are areas of pigmentation of varying size and shape, although they characteristically have a smooth border. Their colour can vary from light to dark brown and they tend to have uniform pigmentation. Although multiple CALs are often present in NF1 (>6 is a diagnostic criterion) they tend to be less frequent in NF2. A review of clinical features in series of NF2 patients found that 33-48% of people with NF2 have CAL patches, and most only have one or two (Asthagiri et al., 2009). In a series of 48 patients, 20 patients had CAL patches and of these 6 only had one patch (30%) and 14 had multiple CAL (70%) with a mean of 2.6 patches. Two had six or more patches (10%) (Mautner et al., 1996).

ii. Cutaneous schwannomas

Cutaneous schwannomas were first described by Martuza in 1982 and are raised, well-circumscribed plaque-like lesions, often slightly hyperpigmented and typically smaller than 2cm (Martuza and Ojemann, 1982). They tend to have a roughened surface and hypertrichosis may occasionally be a feature (Mautner et al., 1997). Cutaneous schwannomas can occasionally cause discomfort and may be easily excised under local anaesthetic. Excision of cutaneous schwannoma and mutation analysis for the NF2 gene may be useful in the diagnosis of mosaic disease.

The prevalence of cutaneous schwannomas has been found to be significantly greater in patients with more severe disease than in patients with

mild disease (Mautner et al., 1997). In their series, cutaneous schwannomas were found in 8% of mild patients and 55% of severe patients ($p<0.001$).

iii. Subcutaneous schwannomas

These fusiform or nodular swellings develop along peripheral nerves and on examination can be demonstrated to be deep to the skin, which moves easily over them. They are often painful to pressure and may require excision for symptomatic control. Subcutaneous schwannomas may also be an indicator of disease severity, as they were found in 24% of patients with mild disease and 58% with severe disease ($p=0.004$) (Mautner et al., 1997).

iv. Intradermal tumours

These rare tumours are described as being epicutaneous and similar to NF1 dermal lesions. They sometimes have violaceous colouring and histological analysis has demonstrated schwannoma infiltration (Mautner et al., 1997).

v. Neurofibroma

NF2 patients have also developed cutaneous neurofibromas and mixed tumours; Mautner et al found that of 29 skin tumours biopsied, 5 were neurofibromas and 2 mixed tumours (Mautner et al., 1997).

vi. Genetic changes in NF2-related skin tumours

Kluwe et al (2000) studied 40 NF2-related skin tumours and found NF2 mutations in 5 (13%) and NF2 allelic loss in 18 (45%) of the tumours. In 17 (43%) of tumours, alterations were found on both NF2 alleles. They conclude that loss of functional NF2 gene product is the critical event in the development of skin tumours (Kluwe et al., 2000).

i. Seizures in NF2

Seizures have been reported in association with NF2, but only within the context of large clinical studies. There has been no systematic assessment of seizure frequency in NF2. In a genetic based study, 8% of adults with NF2 were reported to have epilepsy (Evans et al., 1992b). There have been no studies regarding the aetiology of seizures in NF2, but a number of associated abnormalities may be responsible.

Loss of *NF2* gene function predisposes to tumour formation, predominantly the development of meningiomas (frequently multiple) and gliomas that are potentially epileptogenic (Evans et al., 1992b, Ferner, 2007, Trofatter et al., 1993). Neuropathological studies have demonstrated a microdysgenesis including glial hamartomas that cluster in the grey matter of the cerebral cortex and the thalamus (Wiestler et al., 1989).

Meningioangiomatosis is rare and usually sporadic but has been associated with NF2 in 16 out of 100 cases in the literature, only a minority of these

patients presented with seizures (Omeis et al., 2006). In NF2 the site is predominantly in the frontal cortex, but lesions can be multiple. Meningioangiomatosis involves the leptomeninges and underlying cortex with meningiovascular proliferation and leptomeningeal calcification (Omeis et al., 2006, Wiestler et al., 1989).

Intracranial calcifications unrelated to tumour were described in the choroid plexus, cerebral and cerebellar hemispheres in 7 out of 11 patients imaged with brain computerised tomography (Mayfrank et al., 1990) but the frequency in large NF2 populations, aetiology and relationship with epilepsy is uncertain.

j. Vascular disease in NF2

There have been anecdotal reports of vascular pathology in patients with NF2. A 36 year old man had an un-ruptured middle meningeal artery aneurysm which was successfully managed with embolization (Lesley et al., 2004). Two strokes have occurred in children and young adults (Ryan et al., 2005, Ng et al., 2009) and bilateral renal vascular disease and resulting hypertension has been reported in a 21 month-old child (Cordeiro et al., 2006).

k. NF2 in children

At least 18% of people with NF2 present before the age of fifteen years, and 10-18% of children presenting with a meningioma or schwannoma are likely

to develop NF2 so will require screening (Evans et al., 1999a). Children under ten years of age tend to present very differently than adults: hearing loss or tinnitus as a presenting symptom is uncommon (<20%) and presentations with facial mononeuropathy, seizures and visual loss occur more frequently than in adults (Evans et al., 1999a). People who present with symptoms of NF2 at a younger age are more likely to have positive mutation testing for NF2 and are likely to have a more severe genetic mutation and therefore phenotype (Selvanathan et al., 2010).

The natural history of NF2 in very young children has been studied in three children who all developed bilateral VS in the first few months of life, and the authors postulate that this could be a congenital form (Ruggieri et al., 2013). All three children had bilateral VS as an incidental finding on MR imaging at the age of 4-5 months. They were asymptomatic for 10-14 years, then two had sudden and rapid progression (<12 months) at the age of 11 and 15 years. The authors also found atypical skin plaques and evidence of cortical dysplasia within these children.

l. NF2 in the elderly

Although the majority of patients with NF2 are diagnosed in their twenties or thirties, occasionally patients may be diagnosed at a much older age. There has been a recent description of seven patients diagnosed at seventy years or older. Only four of the seven had bilateral VS. There was little tumour growth during a mean follow up of 96 months – 8 of the 11 VS showed no

growth and only one required treatment. All other tumours (including other schwannomas and meningiomas) remained stable. No mutation was found in the blood of any of the patients, suggesting mosaic disease (Goutagny et al., 2013). The authors therefore advocated a watch-and-scan policy for people diagnosed with NF2 over the age of 70 years (Goutagny et al., 2013).

1.8 Imaging in NF2

The gold-standard method of imaging for NF2 patients is magnetic resonance imaging (MRI). Details of specific imaging techniques, screening and follow-up scans are discussed in other sections. There are specific factors relating to NF2 and imaging which are discussed below:

a. Measuring tumour size and growth: volumetrics

Tumour size was previously measured manually using standardised reference points. This method was often inaccurate, with errors introduced at many stages, and it was hard to accurately determine growth within a patient and between patients. Studies have shown that volumetric measurement of VS is more accurate than two-dimensional measurements (van de Langenberg et al., 2008). Linear measurement of VS on MRI underestimated volumetric growth by an average of 50% (Harris et al., 2008).

It is now possible to accurately obtain whole body tumour volumes measured with computerised volumetry and 3D segmentation of whole body MRI scans, reducing the time and resources required compared with manual measurement (Cai et al., 2009). It is likely that these methods will be used as end-points in studies of NF2 to allow accurate comparisons (Blakeley et al., 2012).

b. Coincidental findings on whole body MRI

Whole body MRI may be used more commonly in the future, both for assessment of tumours and treatment outcomes. However there are issues related to coincidental findings: in one study of whole body MRI in NF1 and NF2 patients, 42% had one or more incidental findings, 6.5% of which were clinically significant, including avascular necrosis in 9.3% of NF2 patients (Jaremko et al., 2012). Patients should be aware of the potential of coincidental findings prior to undergoing MRI and there should be a protocol to be followed if they occur.

c. Imaging with implants in situ

With increasing use of cochlear implants (CI) and auditory brainstem implants (ABI) in NF2, there are concerns as to the impact on follow-up imaging. In vitro and in vivo testing of CI and ABI revealed image distortion around the device but no measurable adverse effects for the patient or device (Heller et al., 1996, Vincent et al., 2008).

Twelve patients with NF2 and implants (10 ABI, 2 CI) underwent 77 MRI scans, 43 of the head, 27 of the spine and 7 of other areas. The magnet was not removed, but following displacement of a magnet, a credit-card sized piece of plastic was bandaged tightly to the head over the long axis of the receiver stimulator (Donnelly et al., 2012). Two scans had to be abandoned due to pain, but local anaesthetic infiltration allowed their completion. In all cases, the implant continued to function normally. The view of the ipsilateral internal auditory meatus (IAM) was unimpaired in 67% of the head; the contralateral IAM was unimpaired in all cases. The authors felt that it was always possible to view a vestibular schwannoma, even when the view was impaired (Donnelly et al., 2012).

1.9 Management of NF2

Once a diagnosis of NF2 is made, all patients should be offered baseline screening, including: spinal and brain MRI; pure tone and speech audiometry; blood mutation testing and ophthalmological assessment. Depending on signs and symptoms, they may also undergo nerve conduction studies (NCS) electromyography (EMG) and/or electroencephalography (EEG). Most patients are then seen at least annually if they remain asymptomatic or have no clinical change. The standard investigations in a stable patient include:

- Cranial MRI – annually (six monthly in adolescence – early twenties)

- MRI whole spine – every three years
- Pure tone audiometry and speech audiometry – annually
- Ophthalmological examination – annually for children and adults with abnormalities

If there is any change in symptoms or neurological examination, more frequent assessment and imaging will be organised as appropriate.

a. Specialist units for NF2

Studies of mortality in NF2 have revealed a survival benefit when patients are managed within a specialised unit (Baser et al., 2002a). Since April 2010, NF2 care within England has been nationally commissioned and is provided in one of four specialist units (Guy's and St Thomas' in London, Oxford, Cambridge and Manchester) with radiosurgery offered in Sheffield. As relatively few patients undergo highly specialised surgery, such as ABI insertion, it is currently recommended that this only takes place in two units (Cambridge and Manchester).

It is widely agreed that NF2 patients should be managed by a multi-disciplinary team, and this is the overriding principle of the majority, if not all NF2 specialist units. The multi-disciplinary team usually includes the following professional members: neurologist; geneticist; neurosurgeon; otolaryngologist; ophthalmologist; pathologist; radiologist; audiologist and experienced nursing staff. A psychiatrist and psychologist, paediatrician,

plastic surgeon, pain specialist and specialist physiotherapists may also be required for particular patients.

b. Surgery for NF2

The majority of patients with NF2 will undergo some form of surgical intervention during their lifespan. The timing of surgery, along with the procedure used and the surgical team involved is an extremely important aspect in the management of an individual with NF2. Developments in technology have allowed for surgical enhancement of hearing with cochlear and auditory brainstem implants and these are also discussed. Although VS often require some form of intervention, non-VS intracranial schwannoma rarely undergo excision, as their removal leads to loss of function of the affected nerve, which causes significant morbidity. Intracranial meningiomas and spinal tumours may be excised if they are causing reversible deficits.

i. Surgery for vestibular schwannoma

The decision to undertake surgery on VS in NF2 is very complex and indications still differ between individual patients and managing teams. Although the natural history of VS growth in NF2 is reasonably well described, its relation to hearing loss is much more variable and therefore cannot be used as an accurate predictor of future hearing ability. The ‘triggers’ for surgical intervention may include intervening when the tumour is small in an attempt to preserve hearing; when the VS is clearly growing but

still less than 3cm in diameter, and risk of facial palsy is reduced; when hearing is lost in small but growing tumours or when there is evidence of significant brainstem compression. In short, there is a wide dichotomy of opinion that is regularly debated but rarely with a universally accepted conclusion.

Early intervention may preserve hearing (see section below) but there are no predictors of when it may be successful and it may result in complications in a patient who would never have required surgery. Likewise, waiting until the tumour is large and causing brainstem compression often means that the tumour can only be de-bulked and has a high chance of recurrence. The decision of when to intervene must be tailored to each individual patient, taking into account patient preferences, the characteristics of that individual's disease (including mutation type and natural history in the family) and the previous experience and expertise within the department. Surgery for VS in NF2 tends to follow trends over time, cycling between early and late intervention, total, near total and subtotal resection, translabyrinthine, retrosigmoid and middle fossa approaches. It is likely to be normally distributed, with most departments generally falling into the middle of both extremes.

Surgical approach

There are three methods of approaching a vestibular schwannoma in the cerebellopontine angle (CPA). These are the translabyrinthine, middle fossa and retrosigmoid approaches. The translabyrinthine approach involves a mastoid approach in which the labyrinth is removed. In this way, the internal auditory canal is exposed together with the posterior fossa dura between the superior petrosal sinus and the jugular bulb. The middle ear structures and the cochlea are untouched. During the middle fossa approach, a small, temporal craniectomy is performed and the internal auditory meatus is approached from above. The retrosigmoid approach involves a craniectomy positioned behind the sigmoid sinus and below the transverse sinus thus accessing the posterior fossa immediately behind the temporal bone. Decompression by drainage of CSF and retraction of the cerebellum then provides excellent access to the CPA.

The advantages and disadvantages of each approach are summarised in the table on the following page:

Approach	Advantages	Disadvantages
Translabyrinthine	No cerebellar retraction Any size tumour can be removed Early identification of facial nerve Proximal and distal access to the facial should a nerve graft be required.	Destroys residual hearing Increased risk of CSF leak
Middle fossa	Possibility of hearing preservation	Cramped access to CPA Temporal lobe retraction Limit to size of tumour that can be removed Risk to facial nerve
Retrosigmoid	Possible hearing preservation No limit to size of tumour	Cerebellar retraction Incomplete view of fundus Immediate reconstruction of the facial nerve usually impossible. Increased risk of post-craniectomy headache

Table 12 Advantages and disadvantages of the surgical approaches to the cerebellopontine angle. From Scott-Brown's Otorhinolaryngology Vol 3 (Gleeson, 2008).

Facial palsy following VS surgery

An extremely significant risk of VS surgery is facial palsy due to damage to, or division of, the facial nerve at the CPA. Facial palsy may be partial or complete (see Section 6 a iv) and may be temporary or permanent. Intra-operative facial nerve monitoring allows for more accurate identification of the nerve and should improve outcomes (Blakeley et al., 2012). Even with facial nerve monitoring, facial nerve outcomes following vestibular schwannoma surgery in patients with NF2 are usually worse than in patients with solitary tumours.

It is clear that preservation of facial nerve function is achieved more frequently with small tumours than larger tumours. Meta-analysis of surgical data is difficult due to the large number of variables and reproducibility of results, but it does appear that facial palsy rates are reduced when the tumour is less than 2.5cm in diameter (Blakeley et al., 2012). In a study of early proactive management of VS in NF2 (Brackmann et al., 2001), 92% patients with normal facial function pre-operatively continued to have normally facial function at long-term follow-up (n=38, 92.5% of tumours less than 2cm in diameter). In another large series, which included non-NF2 patients, 100% of patients maintained facial function after surgery when the tumour was <2.5cm in diameter, compared to 83% when the tumour was greater than 2.5cm (Grey et al., 1996). However the use of non-NF2 data is misleading as the risk of facial palsy is much increased following VS surgery in NF2, possibly due to differing tumour biology and behaviour.

Hearing preservation surgery

Timing of surgery for vestibular schwannoma in NF2 is still a contentious area, and opinion varies from unit to unit. An ideal surgical outcome would be entire removal of the tumour with complete preservation of hearing and facial nerve function, however good results from certain units may be hard to replicate and there is always the risk of morbidity, such as complete hearing loss and facial palsy, from an operation that may not even be required.

Hearing preservation surgery is generally attempted with a tumour of less than 1.5cm in diameter and is undertaken by the middle fossa approach. Brackmann et al reported results from 40 procedures on 28 patients with NF2. Measurable hearing was preserved in 70%, 42.5% had hearing within 15dB of their pre-operative pure tone average and 15% of their pre-operative speech discrimination score. 87.5% had normal facial nerve function after one year (Brackmann et al., 2001).

Cochlear implantation (CI)

Cochlear implantation allows direct stimulation of auditory neurones within the cochlear by an electrode array. It can only be used where there is an intact cochlear nerve, and may be inserted at the time of vestibular schwannoma removal, or at a later date. Integrity of the cochlear nerve can be assessed pre-operatively using the technique of promontory stimulation,

and checked intra-operatively by recording the cochlear nerve action potential (CNAP) (Piccirillo et al., 2008).

Functional hearing outcomes from a cochlear implant in a patient with NF2 may be excellent, with 5/6 in one study able to use a telephone post-implantation, with open-set speech understanding scores in the range of 90-100% (Neff et al., 2007). This compares extremely favourably to the 3-7% open-set speech understanding in NF2 patients with an auditory brain stem implant. Long-term results in 5 patients with a mean follow-up period of 7.9 years showed no deterioration in hearing over the follow-up period (Neff et al., 2007). However, other authors report less promising results, with only 2/4 patients achieving open-set speech discrimination when a CI was used in NF2 patients with no hearing in the contralateral ear. All of these patients continued to use their implant every day thereby indicating the utility and importance of their implant (Lustig et al., 2006).

Auditory brain stem implant (ABI)

The auditory brain-stem implant allows auditory perception by bypassing the cochlear nerve and allowing direct stimulation of the cochlear nucleus, accessed via the lateral recess of the fourth ventricle. The first ABI was inserted at the House Ear Institute in 1979 and was a single channel device (Edgerton et al., 1982). Since then, technology has progressed rapidly, and current implants have a twelve electrode surface contact array.

An ABI may be inserted at the time of surgery for vestibular schwannoma, as an active device if all hearing is lost, or as a ‘sleeper’ device if hearing still persists, to be switched on at a later date when hearing is lost. ABI insertion may rarely be performed as a separate procedure, although placement is more difficult if performed at a second stage following vestibular schwannoma surgery, due to scarring and surgically-induced anatomical change. ABI cannot replicate results achieved with cochlear implantation, and although some users do get return to functionally significant hearing (Colleti et al., 2012), the majority find the ABI is a useful adjunct to lip-reading and can experience environmental background sound. A penetrating electrode has been used, as it was thought that design would improve contact with the cochlear nucleus itself and have an additional advantage in that the topographical representation of the frequency range within the cochlear nucleus is stacked from lateral to medial. However, it was found that penetrating electrodes offered no advantage and, in fact, proved to be inferior in terms of speech recognition (Otto et al., 2008).

Hearing outcomes with ABI in NF2 are significantly worse than those implanted in individuals without NF2. It is postulated that this is due to selective damage to specific pathways for modulated sound in NF2, either by surgery and/or tumour (Colleti and Shannon, 2005). Non-auditory stimulation by the ABI has also been experienced. This may be mild, such as vibro-tactile sensations or twitching, and can be minimised by the switching off of responsible electrodes during device programming. More serious non-auditory stimulation, such as twitching and pain, may result in non-use or

replacement of the implant. Non-use of the implant is not uncommonly reported as a result of poor results and/or non-auditory stimulation. A recent prospective study showed that 3/20 NF2 patients were non-users of their ABI (Patel et al., 2012).

ABI insertion can lead to difficulties in imaging using MRI, which is an issue in NF2 patients where regular assessment of tumours and screening for new tumours is required (see imaging section). It can cause difficulties in performing the scan and has necessitated magnet and even implant removal in the past or use of alternative imaging such as myelography (Ferner- personal communication 2013). It may also cause image distortion and difficulties in measuring tumour growth. These issues are particularly pertinent when a 'sleeper' device is inserted, as the drawbacks of the device are not balanced with benefits – after all, the implant may never be used. This needs to be carefully discussed with each patient and a joint decision made with the patient and their multi-disciplinary team.

iii. Surgery for meningioma

Many patients with NF2 have multiple meningiomas, and although less than a quarter of meninigiomas require surgical intervention during long term follow-up (23%), nearly half of patients with meningiomas required at least one surgical intervention for a meningioma (45.9%) (Goutagny et al., 2012). Indications for surgical excision of a meningioma in NF2 include symptoms such as seizures, intracranial hypertension or neurological deficit; significant growth on serial scanning; or for access to another tumour (Goutagny et al.,

2012). Complications may include worsening neurological function or recurrence.

iv. Spinal surgery

Surgery for spinal tumours is generally only performed when it is highly likely that the lesion is causing a reversible deficit and the risk of complications is outweighed by the benefits. It is again important that decisions to intervene surgically are made in a multidisciplinary setting, and performed by spinal surgeons with experience of NF2.

v. Other surgery for NF2

Surgery for cutaneous and subcutaneous lesions may be required for diagnosis and genetic diagnosis or for functional reasons or pain relief. Surgical excision of peripheral nerve lesions is difficult and rarely indicated. It may not provide symptom relief and has the potential to cause serious complications, such as loss of power. It should therefore only be performed after thorough neurological examination, investigation and multi-disciplinary and specialist peripheral nerve input.

c. Radiotherapy in NF2

Although a well-accepted form of treatment for sporadic vestibular schwannoma and other intracranial tumours, there are concerns with regard to the use of radiotherapy in NF2 due to the risk of radiation-induced

malignancy. The form of radiation most commonly used in NF2 is stereotactic radiosurgery (SRS), either gamma-knife or linear accelerator (LINAC). This involves a single or limited dose delivered accurately to the tumour following a formal dose plan, where various iso-centres of radiation deliver sufficient radiation to the tumour while limiting the exposure to surrounding structures. It is generally recommended that only VS less than 3cm in diameter are considered for radio-surgical treatment (Blakeley et al., 2012). The delivery of a therapeutic dose to larger tumours poses technical difficulties notwithstanding the risk of damaging adjacent structures. Furthermore, any post irradiation swelling of the tumour could cause critical brainstem compression.

A number of studies have assessed the effectiveness of radiotherapy in NF2 tumours and associated complications. Rowe et al published a retrospective consecutive series of their treatment of 122 vestibular schwannomas in 92 patients with NF2 (Rowe et al., 2008). They also provided extended follow-up data for 22 patients with 906 patient-years of follow-up. They predicted that 8 years after radiosurgery for NF2 VS, 20% will have required further treatment, 50% will be well controlled and 30% will have had some progression but still be managed conservatively. Risk of facial palsy after treatment was 5%. Hearing assessment revealed that three years after treatment, 40% retained functional hearing, 40% had deterioration and 20% lost hearing in the treated ear (Rowe et al., 2008).

Mathieu et al treated 74 VS in 62 patients with NF2. They found actuarial control rates were 85% at 5 years and 81% at ten and fifteen years. Facial nerve palsy developed in 8%, trigeminal neuropathy in 4% and vestibular dysfunction in 4%. There were no cases of malignancy at time of publication (Mathieu et al., 2007). A small study of four NF2 patients treated with LINAC has also revealed promising results (Kuo et al., 2008).

Care does need to be taken when selecting a treatment centre as local control and complications can vary massively – one centre reported the incidence of facial weakness in their cohort of 12 treated patients with NF2 was 42% (Wentworth et al., 2009). In the UK, all radiotherapy for patients with NF2 is undertaken at one specialist centre.

NF2 is a tumour-predisposition syndrome and there are concerns with regard to malignant transformation of existing tumours and the development of new malignancies. There have been more than 20 cases of malignancy in NF2 patients who have undergone radiotherapy; however this includes those who have undergone external beam radiation therapy, which is thought to offer a higher risk of malignant transformation (Blakeley et al., 2012). In Rowe's series of stereotactic radiosurgery for VS in NF2 there were only two cases of malignancy, one of which was pre-existing prior to treatment (Rowe et al., 2008).

The increased risk of malignant transformation has to be tempered with the reduced life-span of patients with NF2. A growing vestibular schwannoma can lead to hearing loss, facial palsy, brain-stem compression and death; therefore it is often necessary to provide some form of treatment. Like radiotherapy, surgery also offers worse outcomes in patients with NF2 than in those with solitary vestibular schwannoma. With surgery there are the added risks of a general anaesthetic and complications that may develop in the recovery period, such as deep vein thrombosis and hospital-acquired infections. Surgery for vestibular schwannoma commonly leads to permanent post-operative changes, such as hearing loss, facial weakness and occasionally swallowing difficulties, and at higher rates than those found following radiosurgery. It is therefore appropriate to consider SRS as an appropriate treatment for VS < 3cm in NF2.

SRS has been used as the primary treatment for sporadic intra-cranial meningioma, but there are no large series of its use in NF2-related meningiomas. Some authors have offered SRS to multiple tumour types in NF2 including meningioma, ependymoma and non-vestibular cranial nerve schwannoma (Wentworth et al., 2009), but patient numbers are very small and this treatment method is not currently recommended (Blakeley et al., 2012).

d. Novel therapies for NF2

Along with greater understanding of the molecular role of the *NF2* gene product comes the potential of targeted drug therapy. In normal cells, the *NF2* gene product Merlin (or Schwannomin) is a regulator of cell growth and cell-cell interactions. It also appears that Merlin may be a negative regulator of growth in other non-NF cancers (Blakeley et al., 2012). The following candidate drug targets have been identified:

- Epidermal growth factor family
- RAS-GTP pathway
- mTOR
- VEGF and PDGF
- Heat shock proteins (inhibition)
- DCAF1: ubiquitin ligase inhibitor

A number of drugs that have already been approved for clinical use in other conditions may be appropriate for targeted therapy in NF2. Several phase II clinical trials are underway, with promising results.

Bevacizumab is the most widely studied targeted therapy for NF2 to date. It is an IgG1 monoclonal antibody that binds biologically active vascular endothelial growth factor (VEGF). Bevacizumab has been used in over 30 patients with NF2, and has shown both significant reduction in tumour volume (<20%) and improvement in hearing function in a number of these patients (Plotkin et al., 2009, Mautner et al., 2010b). Further clinical trials are

now underway in many centres. Tumour shrinkage has been sustained with continuous use in two patients, but regressed when the drug was discontinued, and the authors postulated that bevacizumab does not seem to directly target the tumour cells but may induce reversible shrinkage of VS by increasing vascular permeability of the tumour cells and reducing intra-tumoural oedema (Mautner et al., 2010a). Bevacizumab does not appear to cause any persistent reduction in meningioma volume in NF2 (Nunes et al., 2013). The toxicity profile of bevacizumab is relatively well known and it appears to be well-tolerated. There are some concerns regarding its negative effect on wound-healing – surgery is not advised while the drug is being used (Blakeley et al., 2012).

Phase II studies are also underway for the following drugs:

- Lapatinib
- Sorafenib and nilotinib
- PTC299

1.10 Quality of life (QOL) in NF2

a. Definition

The World Health Organisation has defined health as ‘a state of complete physical, mental and social wellbeing, not merely the absence of disease’. The WHO quality of life group went on to define QOL as: ‘an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.’ They stated that: ‘it is a broad-ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment.’ They also comment that ‘this definition reflects the view that QOL refers to a subjective evaluation which is embedded in a cultural, social, and environmental context. As such, QOL cannot be simply equated with the terms "health status", "life-style", "life satisfaction", "mental state", or "well-being". Rather, it is a multidimensional concept incorporating the individual's perception of these and other aspects of life’ (World Health Organisation, 1995).

b. Health-related QOL

Health-related QOL has gained increased interest since the 1970s, and is now seen as an important indicator of the success of patient management. There are many reasons why QOL measures may be beneficial in the health-care setting. In the clinical environment they can aid medical decision making

and facilitate communication. They may act as a trigger for intervention and may be used as an additional marker of disease progress or treatment success. They may indicate factors that are of increased importance to patients and indicate concurrent problems such as anxiety and depression. They may ultimately improve symptom relief, care and rehabilitation. QOL has increasingly been used for political decision-making and financial 'rationing' where resources are limited.

Quantitative QOL measures or scores can also be used as a comparative marker between patients, treatment groups and units, and as such are an increasingly important end-point in audit and clinical trials of treatment with curative or palliative intent

c. Methods of measuring QOL

Quality of life is generally assessed by asking the patient their opinion. It can be assessed qualitatively by interviews which can vary from freeform to fully structured. QOL can also be quantitatively assessed using QOL instruments which may either be generic or disease or symptom specific.

i. Generic Measures

These instruments are intended for general use, irrespective of the patient's condition or disease process, and are often applicable for the healthy population. The most commonly used is the Medical Outcomes Study 36-Item Short Form (SF-36) (Ware et al., 1993). The SF-36 evaluates general

health status, its 36 questions address eight health concepts. There are two summary measures: physical health and mental health. Within physical health there are scales for physical functioning, role-physical, bodily pain and general health. Within mental health there are scales for vitality, social function, role-emotional and mental health. There is a general health transition question and a global question about health perception. Scoring of the SF-36 is complex, the questionnaire is not available freely for use and it does take some time to complete.

The EuroQol (EQ-5D) (See Appendix B) is another generic measure, which is generally freely available and is much shorter and simpler to use than the SF-36 (Brooks, 1996). It assesses five dimensions: mobility; self-care; usual activities; pain/discomfort and anxiety/depression. It also incorporates a visual analogue scale (VAS) for 'your own health state today'.

ii. Disease Specific Measures

Disease specific QOL measures are formulated for a particular medical condition or symptom. They tend to be more relevant to the particular patient group being assessed and can be shorter and less onerous to complete than generic measures. The method for construction and validation needs to be well structured and thorough in order to provide an alternative to generic measures. It has been advised that disease-specific scores should be used alongside the SF-36 (Brazier et al., 1992). Disease specific QOL measures

have been developed for a number of conditions, including lower-limb ischaemia (Morgan et al., 2001) and pressure ulcers (Gorecki et al., 2013).

d. Quality of life in NF2

There have to date been few published studies regarding QOL in NF2. Patel et al. undertook semi-structured interviews with six people with NF2 (Patel et al., 2011). They reported the negative impact of NF2 on daily activities, including work, and social isolation. They noted that patients expressed a range of negative emotional reactions in response to their diagnosis and the impact of the disease and that there was frustration at the limited awareness of NF2 among health professionals and within their local community.

Neary et al investigated QOL in 62 patients with NF2 (71% response rate) (Neary et al., 2010b). They posted out a questionnaire with 32 components and found that the greatest perceived problem was deafness, leading to communication problems with social contacts, close partners, family and friends. There appeared to be a relationship between general mood changes and hearing difficulties, social communication problems, balance difficulties and mobility problems. They found that self-confidence was only significantly related to social communication problems.

Neary et al also assessed QOL in 62 patients with NF2 (71% response rate) using the SF-36 (Neary et al., 2010a). They found that subjects with NF2

scored less than the standardised norm in both physical and mental component scores. They found that there were significant correlations between several components of the SF-36 and the following components from their questionnaire: perception of difficulty communicating with their significant other; social communication; balance; hearing difficulties and mood change.

1.11 Conclusion

NF2 is a rare genetic condition that has a variety of clinical manifestations affecting the brain, spine, eyes and skin. Disease severity is variable, both in the number and type of manifestation, and the impact that they may have on an individual's health and quality of life. It is therefore difficult to estimate the impact of the disease based purely on genotype, phenotype, imaging or clinical examination. Quality of life is fast becoming an invaluable asset in the holistic assessment of the patient. Generic tools to assess health-related QOL are already in wide use; however they can be time-consuming for the user, complex to analyse for the clinician and are not specific to the disease itself, particularly in the case of NF2. There have been a small number of studies investigating QOL in NF2, which confirm the variable and significant impact the condition can have on QOL. With the greater emphasis on evidence-based medicine and the identification of novel therapeutic targets, there is a clear need to measure QOL in NF2 patients, not only as a part of general clinical assessment, but also as an outcome measure in clinical trials.

2 Retrospective case note review of NF2 patients: interesting trends and novel findings

2.3 Summary

A comprehensive retrospective case note review of NF2 patients managed in the GSST NF2 clinic between 1998 and 2008 was performed and 61 patients' notes were reviewed. The data were analysed and four areas were selected for further study: cause of death; surgical intervention; hypertension and epilepsy. The retrospective case note review showed interesting trends in the management and outcome over a time of change in NF2 management. It emphasised the need for specialised care for this complex group, and over the course of this project, it has become policy in the UK. It revealed novel findings of a higher rate of hypertension in this NF2 patient cohort and of cortical dysplasia as a potential cause of epilepsy in NF2.

2.4 Aims

To describe interesting trends and novel clinical manifestations of NF2 identified within the patient cohort.

2.5 Methods

a. Study Approval

Approval was obtained for the retrospective case note review and the hypertension study by the GSTT Audit Department.

b. Target population and exclusions

All patients with a diagnosis of NF2 who had attended the GSTT NF2 clinic between 1997 and 2008 were identified using:

1. Database of NF2 patients managed within the department

2. Skull base database of all patients managed at GSTT and King's College Hospital since 1994 (MJG)

2. Review of case notes of NF2 patients in the Neurofibromatosis Unit

All patients with a diagnosis of NF2 were included in the case note review. Exclusions included patients whose clinical notes could not be traced.

c. Data collection

Case notes of twenty patients with NF2 in the target group were reviewed and used to develop potential fields for a database which were refined following discussion with the multidisciplinary team. The database was anonymised in line with Trust confidentiality guidance, each patient was identified on the database by a number, and identifiable patient details were kept on a central password protected computer.

The database was developed using a simple Microsoft Excel spread sheet and was divided into the following sections:

- Demographics (including age, gender, ethnicity, occupation and handedness)
- Route of referral to the service
- Clinical features (including presenting symptom, age at presentation, clinical features of NF2, other medical history)
- Clinical findings (including neurological examination, cutaneous and ophthalmological findings and blood pressure)
- Investigations (including scan results, tumours and genotype)
- Treatment (including surgery, radiotherapy, medication and clinical trial inclusion)

d. Data input

The data were retrieved by retrospective analysis of clinical case notes, and were inputted by the author (RH). Accuracy was confirmed by random validation of 10 fields in ten separate patients by an independent observer (SH).

e. Data analysis

The data were reviewed and the following areas were selected for further study:

i. Cause of death

Patients who had died whilst under the care of the Department were identified and cause of death was reviewed. This topic was selected as there was relatively little published data providing information on cause of death in NF2.

ii. Surgical intervention

The type, timing and number of surgical interventions in the cohort were analysed, and comparisons were made between those undertaken by specialist and non-specialist surgeons. This area was selected as being particularly topical, as at the time of study, NF2 services in the UK were being reorganised.

iii. Hypertension study

Following data input, it was noted that there may be an increased incidence of hypertension (BP > 140/90 mmHg) in NF2 patient compared to the general population, and the hypertension study was developed. Patients who had had their blood pressure measured within the GSTT NF2 outpatient clinic were identified from the database and were matched for age, ethnicity and gender, with controls using consecutive patient records from the general neurology clinic. Patients receiving anti-hypertensive medication and those who had died during the study period were excluded. The same measurement method, clinic setting and sphygmomanometer (Omron M6, automated) were used in all cases.

iv. Epilepsy study

Patients who had a history of seizures were identified from the database and clinical, histological and radiological characteristics were reviewed. Imaging of patients with seizures was case-matched and compared to NF2 patients with similar clinical and demographic characteristics who did not experience seizures. A retrospective case note review was performed. Inclusion criteria were those patients with a confirmed clinical diagnosis of NF2, attending the NF2 clinic between 1997 and 2008. Patients who had a history of seizures were identified and clinical, histological and radiological characteristics were reviewed with SC and BI. Differences between the total number and site of meningiomas were compared and tested for significance using a student t-test.

2.4 Results

a. Patient Demographics

Patients attending NF2 service at GSTT 1997-2008

Total number of patients eligible for inclusion with available notes = 61/88

Number of patients with unavailable case notes = 27/88

45 generalised NF2 (73.8%), 16 mosaic NF2 (26.2%).

32 males, 29 females

Mean age:

- at date of analysis = 40.0yrs (4 – 81yrs)
- at first symptom = 23.4yrs (1-50yrs)
-

b. Cause of death

6/61 patients died during follow-up (9.8%), one with mosaic NF2 and five with generalised NF2. The mean age at death was 43.7yrs, mean age at symptom onset was 19.5yrs and mean survival was 24.2 years.

Patient	Gender	Age at first symptom	Age at death	Cause of death
1	M	21	28	Haemorrhage following excision of VS
2	F	7	44	LRTI, secondary to radiation-associated encephalopathy
3	M	20	76	Myocardial infarction
4	M	44	76	LRTI (2° to COPD)
5	F	14	17	Malignant osteosarcoma
6	F	11	21	Cerebro-vascular accident (non-tumour related)

Table 13 Cause of death in NF2 cohort (1997-2008)

d. Surgical interventions

i. Demographics

Complete surgical data was available for 57/61 patients.

A total of 43 out of 57 patients had surgery relating to their NF2 at some time in their lifetime (75.4%)

- 30 out of 41 with generalised NF2 (73.2%)
- 13 out of 16 mosaic NF2 (81.3%)

ii. Timing of surgery

Age at first procedure:

- Mean age = 24.5yrs (range 1-63yrs)
    - Generalised NF2 = 26.1yrs
    - Mosaic NF2= 31.5yrs

Time from first symptom to surgery

- Mean = 5.9yrs

17 out of 43 patients had surgery before diagnosis (39.5%)

- Generalised = 8/30 (26.7%)
- Mosaic NF2 = 9/13 (69.2%)

32 out of 43 patients had surgery before specialist clinic referral (74.4%)

iii. Type of procedures

Of those patients that had surgery (n=43):

- Average number of procedures = 3 (range 1-8)
    - Generalised NF2 = 3.4
    - Mosaic NF2 = 2.3

Procedure Type	Number of procedures	Number of patients
Resection of vestibular schwannoma	34	25
Procedures for facial palsy	17	10
Shunt procedures (primary or revision)	17	11
Spinal surgery	16	12
Other intra-cranial resection	15	14
Resection of schwannoma involving major plexuses	12	4
Resection of sub/cutaneous schwannoma	8	5
Ophthalmology	4	3
Hearing rehabilitation	3	3
Other	4	4

Table 14 Surgical procedures performed on NF2 cohort

iv. Location of surgery

62/130 procedures were performed by specialist NF2 surgeons in a major centre (47.3%). Specialist NF2 surgeons were defined as those practising within a centre offering multi-disciplinary NF2 care (such as Guy's and St Thomas', Manchester, Oxford or Cambridge) or those who offered specialist services to or worked alongside a specialist unit (such as specialist facial nerve surgery offered by a specialist plastic surgery unit).

Procedure Type	Number performed by specialist NF2 surgeons	Number performed by other surgeons
Resection of vestibular schwannoma	22 (4 outside our unit)	12
Procedures for facial palsy	14	3
Shunt procedures (primary or revision)	7	10
Spinal surgery	5	11
Other intra-cranial resection	4	11
Resection of schwannoma involving major plexuses	0	12
Resection of sub/cutaneous schwannoma	7	1
Ophthalmology	0	4
Hearing rehabilitation	3	0
Other	2	2

Table 15 NF2 specialist versus non-specialist surgeon

v. Morbidity and mortality

One death in 130 procedures: post-op VS resection haemorrhage (our unit)

Documented complications:

- Facial nerve palsy = 18/34 (8/18 in our unit)

- Shunt infection/blockage = 8
- Swallowing problems (requiring NG/PEG feeding) = 3
- CSF leak = 2
- Spinal instability = 2
- Wound infection = 2
- Lower respiratory tract infection = 1
- Hydrocephalus = 1
- Arm weakness = 1
- Globe puncture (eye) = 1

vi. Impact of multi-disciplinary clinic

Multi-disciplinary clinic commenced 2000

- Patients seen in clinic prior to 2000 = 19

Total number of procedures:

- Pre-2000, 53 procedures performed
    - Of these 15 were in our unit – 28.3% of total
- Post-2000, 77 procedures performed
    - Of these 34 were in our unit – 44.2% of total

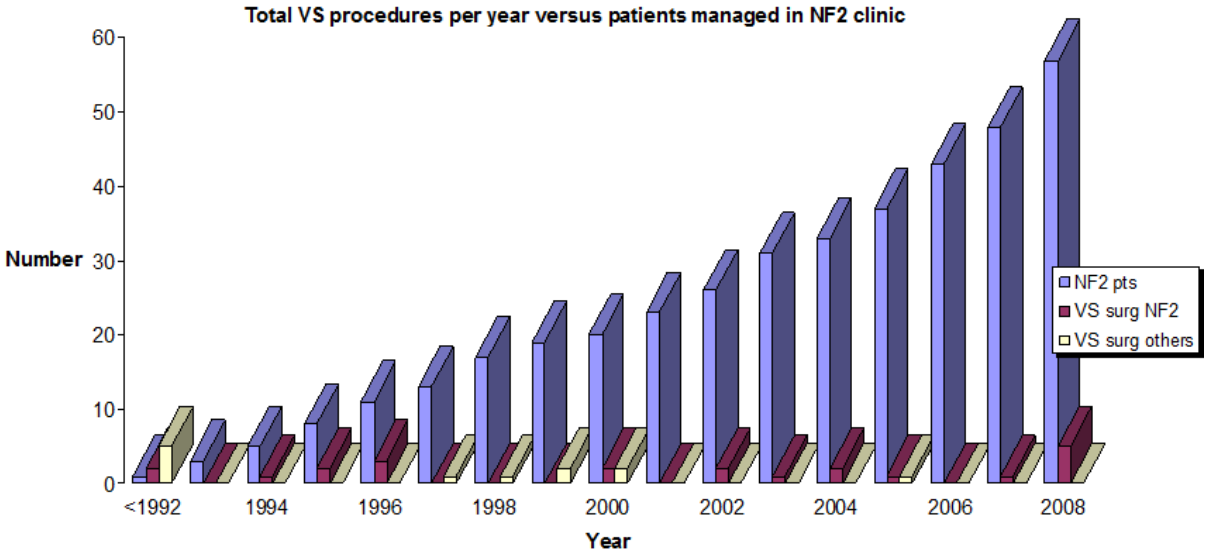


Figure 5 Number of patients undergoing vestibular schwannoma excision by specialist (NF2) and non-specialist (other) surgeons by year, compared to number of patients managed within the NF2 specialist clinic

VS surgery and facial palsy:

- Pre-2000, 12 out of 17 had palsy – 70.6%
    - 5 of 8 operated in our unit had post-op palsy – 62.5%
- Post-2000, 6 out of 17 palsy – 35.3%
    - 3 of 10 operated in our unit had post-op palsy – 30%

d. Hypertension

i. Demographics

Fifty patients within the NF2 database were eligible for this study. Age range at time of BP measurement was 1-81 years with a mean of 39.52 years, there were 27 males and 23 females.

It was possible to match 45 of these individuals for age (within two years), ethnicity and gender with patients who had attended the general neurology outpatients within the last month (for whom case notes were readily available).

ii. Blood pressure (BP) measurements

Mean systolic BP

- NF2 group, mean = 137mmHg (95% CI 133-143mmHg)
- Control group, mean = 128mmHg (95% CI 123-132mmHg)
- Paired t-test – means significantly different p=0.003 (2-tailed)

Mean diastolic BP

- NF2 group, mean = 84 mmHg (95% CI 81–88 mmHg)
- Control group, mean = 77 mmHg (95% CI 73–80 mmHg)
- Paired t-test - means significantly different p=0.003 (2-tailed)

The mean diastolic and systolic BP of patients with NF2 was therefore significantly higher than the matched control group (p=0.003)

Twenty-one NF2 patients (42%) were hypertensive according to the British Hypertension Society Guidelines (systolic > 140 mmHg or diastolic > 90 mmHg), compared with 22% within the general neurology group (p = 0.033 by Fisher's exact test).

There was no significant correlation between systolic or diastolic BP in either group dependent on gender, however both systolic and diastolic BP correlated positively with age over both groups:

		ageyrs	BPsyst	BPdiast
ageyrs	Pearson Correlation	1.000	.438**	.232*
	Sig. (2-tailed)		.000	.024
	N	95	95	95
BPsyst	Pearson Correlation	.438**	1.000	.704**
	Sig. (2-tailed)	.000		.000
	N	95	95	95
BPdiast	Pearson Correlation	.232*	.704**	1.000
	Sig. (2-tailed)	.024	.000	
	N	95	95	95

Table 16 Correlations between age and BP in both groups (**correlation is significant at the 0.01 level (2-tailed) *correlation is significant at the 0.05 level (2-tailed)).

e. Epilepsy

Sixty-one patients within the database had full clinical information available to confirm or deny a history of seizures. Six had a confirmed history of seizures (9.8%). Mean age of this group was 37.8 yrs, with a range of 27-52 years. 5 were male and 1 female. Seizure was the first presentation symptom of NF2 in two patients. All six patients had cranial meningiomas, compared to 22 patients in the cohort who had cranial meningiomas without seizures (40%).

The number and site of meningiomas within the group with epilepsy and meningiomas were compared to those in the group without epilepsy but with meningiomas. The mean number of meningiomas in the total cohort was 2.6, mean in the epilepsy group was 2.5 and in the non-epilepsy group was 2.6 (no significant difference, p=0.874). In the epilepsy group 43.75% of meningiomas were on the right (n=7), 37.5% were on the left (n=6) and 18.75% (n=3) were in the midline, compared to 35.4% on the right (n=18), 45% on the left (n=23) and 19.6% in the midline (n=10) in the non-epilepsy group. The position of the meningiomas within the cranial cavity appeared to be distributed in a similarly in both the epilepsy and non-epilepsy groups. (See table 24).

Site of meningioma	Epilepsy Group	Non-epilepsy group
Sphenoid wing	14.3% (2)	16.7% (9)
Posterior fossa	14.3% (2)	13.0% (7)
Anterior	21.4% (3)	26% (14)
Superior	36.4% (4)	31.5% (17)
Parietal	21.4% (3)	23.0% (7)

Table 17 Site of meningiomas in epilepsy and non-epilepsy groups

Imaging of five affected patients was reviewed (SC). In all cases, cortical lesions were discovered. In four of the five, these were likely to be secondary to surgery or radiotherapy, but in one case three lesions were present with no obvious underlying cause and appeared dysplastic in nature. (Figure 7)

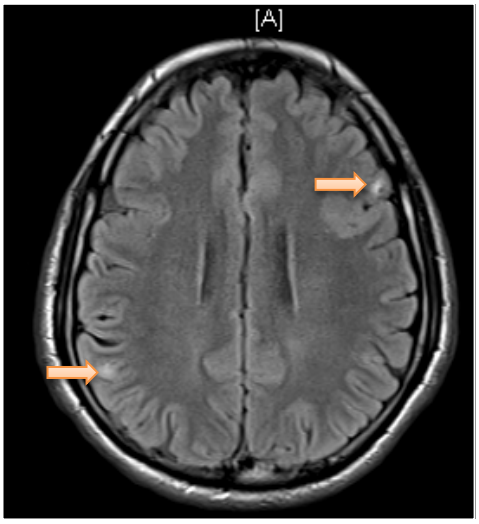


Figure 6 Areas of high signal intensity (arrowed) thought to indicate cortical dysgenesis.

One patient underwent a right temporal lobectomy for intractable epilepsy and the histology was reviewed (by BI). The specimen revealed evidence of glial microhamartomas and also meningioangiomatosis with associated neurofibrillary tangles and granulovacuolar degeneration in the surrounding cortex. (Fig 7 and 8)

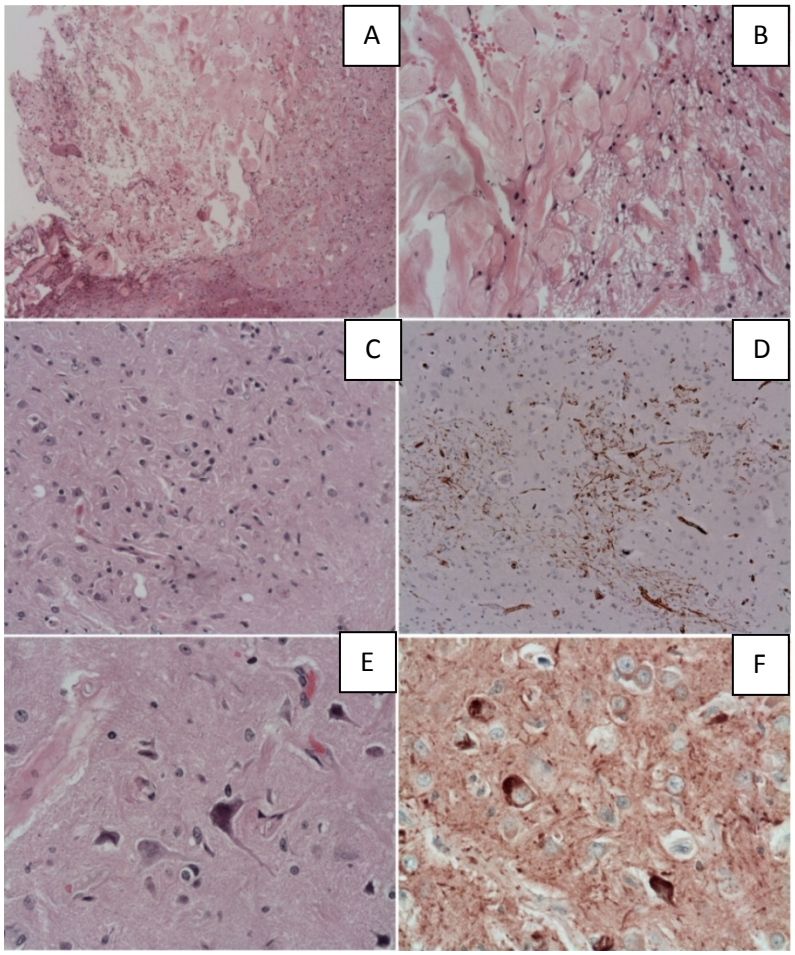


Figure 7 Meningioangiomatosis.

(A-B) The surgical site is surrounded by numerous hyalinised blood vessels which are densely packed and invade the surrounding cortex. (C) Distant cortical areas also show blood vessel proliferation, highlighted by CD34 immunorectivity (D), where the cortex also shows disturbance of the neuronal network. (E-F) Scattered neurofibrillary tangles are visible even by H&E and confirmed by tau immunohistochemistry.

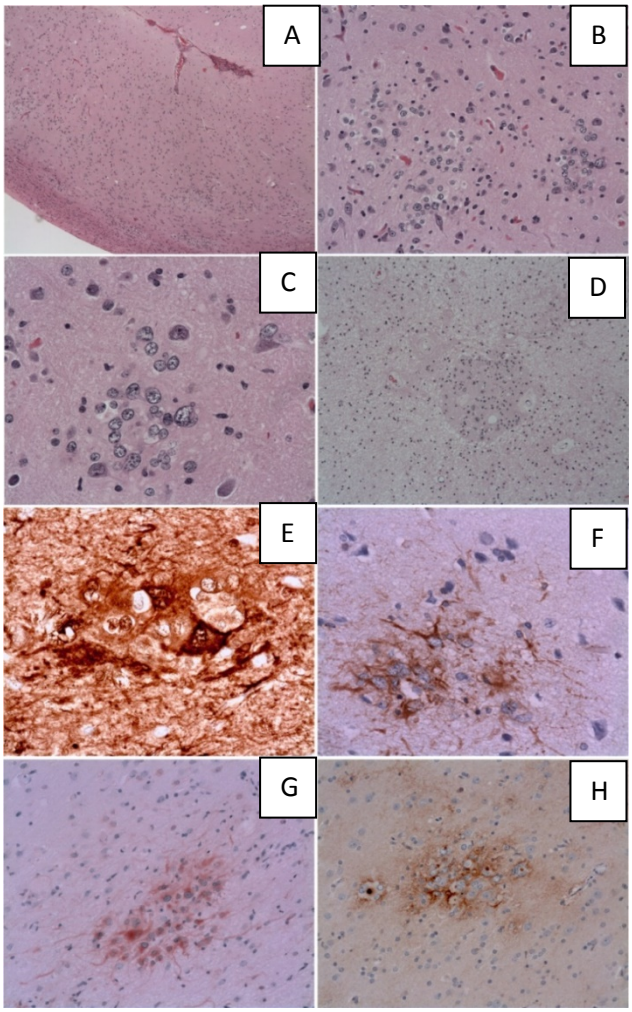


Figure 8 Glial microharmartomas.

(A) Cortical lamination is disturbed by glial microhamartomas, underlying white matter is thinned. (B) Glial microhamartomas consist of small clusters of round, small to large nuclei, with perinuclear halo formation. (C) Occasional large bizarre nuclei with irregular contour. (D) Glial microhamartoma in deep white matter. (E) Strongly positive with S100, few positive with GFAP (F-G) bcl-2. (H) Microhamartomas containing small round cells showed cytoplasmic paranuclear dot-like positivity.

2.5 Discussion

a. Cause of death

This retrospective descriptive study investigated deaths that had happened within the GSTT NF2 cohort. The mortality rate in our group was 9.8%, lower than the 20% in the UK NF2 registry study (Baser et al., 2002a), however in the UK study only 29.6% of cases had been managed in a specialist centre. No patients died directly 'due to tumour burden': two died secondary to elective treatment (similar to UK registry study findings); three died of conditions apparently unrelated to their NF2 and one died due to osteosarcoma.

The individual who developed radiation-related encephalopathy had undergone post-operative radiotherapy (most likely fractionated) in 1973 to residual meningioma in the right middle fossa, and then underwent stereotactic radiosurgery to the same area in 2007. An MRI scan in 2008 revealed 'radiation necrosis'. She became wheelchair and then bed-bound, eventually succumbing to a lower respiratory chest infection.

Osteosarcoma has not previously been reported in NF2, but the *NF2* gene product merlin has been implicated in osteosarcoma in mice (McClatchey et al., 1998) so this may warrant further investigation.

b. Surgical interventions

This retrospective descriptive study described surgical interventions within the GSTT NF2 cohort. In our cohort 75% of patients had a surgical procedure and of these 39.5% had surgery before diagnosis and 74% had surgery before specialist clinic referral.

There is now a clear consensus that all patients with a diagnosis of NF2 should be managed within a specialist clinic, and all surgery should be performed in a specialist unit.

Before the nationally commissioned NF2 service, our specialist unit performed more VS surgery than non-specialists in our patients, but less spinal, plexus and intra-cranial surgery. This may well reflect the fact that in most cases, a watch and wait policy is followed within the specialist unit, particularly with spinal and plexus surgery as neurological outcomes appear to be worse in NF2-related tumours than those sporadic ones.

There has been a reduced rate of facial nerve palsy after 2000, and this may reflect a local drive to more sub-total resection of VS, based on surgeon experience.

c. Hypertension

This study was a retrospective cohort study, with the exposure being NF2, and the outcome being hypertension. It is the first to show a significant difference in BP between NF2 individuals and a matched control group and is important for the management of patients with NF2, and in the differential diagnosis of secondary hypertension. There are however anecdotal reports of hypertension and vasculopathy in NF2.

This was a retrospective study and there is potential for bias. There may be misclassification, with overestimation of BP due to inaccuracy of measurement or recording BP. In this case the bias would be non-differential, with both groups affected, and so shouldn't influence the comparison. If the misclassification was associated with 'white coat hypertension', where patients attending the NF2 clinic were more anxious than those attending the general neurology clinic, the bias would be non-differential and could have magnified the true difference. There may be selection bias, as both the cases and controls were only included if they had attended their appointment and their BP had been measured and recorded. This will have excluded those who did not attend, those who did not need to attend, and those who may have refused measurement. This may mean that the study is not representative of the general NF2 population.

Numbers included in the study are small, due to the fact that NF2 is a rare disease. The power of this study is therefore low, but may be improved if more patients could be included, such as in a national or multi-national study.

The method of measurement of BP – a one-off measurement – is not adequate to diagnose persistent hypertension, and a further study, for example using 24 hour ambulatory BP measurement would be more appropriate to detect clinically important hypertension.

However, despite its limitations, we do recommend that BP is continued to be measured routinely in all NF2 patients, with initiation of appropriate treatment if required, as this is a minimally invasive measurement, which is currently already routinely undertaken in this department. Bevacizumab is being evaluated in NF2 to reduce vestibular schwannomas' growth (Plotkin 2009, Mautner 2010) and it may promote severe hypertension (Monsuez 2010): our study highlights the need for caution. There may be an underlying vasculopathy in NF2 patients, similar to NF1, and this requires further elucidation.

e. Epilepsy

This was a descriptive study of the prevalence of epilepsy in our NF2 patients. There are no published studies on the types of epilepsy in NF2. Our NF2 patients with epilepsy had varying severity of NF2 and a mixture of seizure types but complex partial seizure with secondary generalisation was predominant. Seizures were the presenting manifestation of severe NF2 in two of our patients aged 7 years and 19 years, but the age range of first seizure was from 7-52 years. A diagnosis of NF2 may therefore fall into the differential diagnosis for seizures in children and young adults.

The six patients with seizures all had meningiomas, but there was no difference in the site or number of meningiomas between patients with epilepsy and the 22 NF2 individuals without seizures. We detected imaging evidence of non-tumour related cortical changes in the majority of our patients with epilepsy, and evidence of cortical dysplasia in one. Histology of one patient also identified glial microhamartomas in a known area of epileptogenicity. This may indicate that an underlying non-tumour related dysplasia may lead to epilepsy in patients with NF2.

Dysplastic foci have previously been reported in patients with NF2 (Wiestler et al., 1989). Wiestler et al. observed immature neuroectodermal cells within the cerebral cortex and basal ganglia in the brains of all six deceased NF2 patients who underwent autopsy. On the basis of cytological and immunoreactive findings they designated these foci as glial micro-hamartomas, as was the case in our patient. These may therefore form the

epileptogenic foci in patients with NF2, with or without cranial meningiomas. Pre-operative investigation with EEG and MR imaging is essential to ensure the focus for seizure is a meningioma and not a dysplastic focus when surgical removal is planned to reduce seizures.

2.6 Conclusion

The retrospective case note review showed interesting trends in the management and outcome over a time of change in NF2 management. It emphasised the need for specialised care for this complex group, and over the course of this project, it has become policy in the UK. It revealed novel findings of a higher rate of hypertension in this NF2 patient cohort and of cortical dysplasia as a potential cause of epilepsy in NF2.

3 Quality of life in NF2

3.1 Summary

The aim of this part of the project was to describe the impact of NF2 on QOL, using both qualitative and quantitative methods, and to use this knowledge to develop a disease-specific quality of life measure for NF2. Although generic QOL measures exist, they were not particularly well suited for use in the NF2 population. This is largely due to the time they take to complete and the complexity of use and analysis for staff and patients. Furthermore, generic scores cannot differentiate between the multiple disease manifestations that may lead to the impact on domains of QOL. It was therefore beneficial to develop a new QOL tool.

The methodological approach both to the analysis of the qualitative and quantitative data and questionnaire development was robust and structured. Although NF2 is a rare condition, patient numbers were well within acceptable numbers for this type of project in other, more common groups, and questionnaire response rates were high.

Analysis of the NFTI-QOL showed it had good internal validity, with consistency across the questions, and strong correlation with physician-rated severity, SF-36 and EuroQOL. It also appeared to be testing what it was designed to test as scores were significantly different to the control groups. The NFTI-QOL was acceptable to patients, staff and relatives and has since been adopted into routine clinical assessment in the National NF2 units. It appears to be reliable and was validated against two widely used generic measures. It is thought that the NFTI-QOL should be applicable for use

between clinics within the UK and also overseas, but this will become clearer following future testing.

Potential sources of error include random error, due to differences in an individual's understanding and interpretation of a question, and systematic error, however the rigorous methodology employed should have minimised this source of error.

3.2 Aims

a. To assess the impact of NF2 on quality of life using qualitative and quantitative measures.
b. To develop and validate a disease-specific score to measure quality of life in NF2 for use as an assessment tool in clinical practice and as an outcome-measure for treatment.

3.3 Methods

a. Study approval

Ethical approval was obtained for the patient interviews and completion of questionnaires from the South East London 5 Research and Ethics Committee (REC reference 08/H0810/68) and by the Guy's and St Thomas's Research and Development Committee, London (Ref RJ109/N107). Potential participants were provided with an invitation letter and study information sheet and all gave written consent. Principles of patient confidentiality were followed, data was anonymised where appropriate and secure methods of data storage were followed.

b. Target population, sub-groups and exclusions

The target population was defined as all adults (16yrs or older) who fulfilled the diagnostic criteria for NF2 and attend the National Specialised Commissioning Team (NSCT) NF2 service at Guy's and St. Thomas' NHS Foundation Trust (GSTT). Exclusion criteria included: patients under 16yrs;

patients who could not give informed consent; patients for whom there was no up-to-date contact information. A total of 65 eligible patients were identified within the target group.

The whole cohort of 65 eligible patients were included in the field testing section of the study, however sub-groups were also formed from within this group to take part in additional parts of the study:

- All patients were invited to attend an NF2 information day. During this day, the attendees were invited to attend a focus group, along with their friends and relatives, and a total of thirty-two people attended.
- The first twenty patients to attend the GSTT NF2 clinic on commencement of the study were asked to take part, and all agreed. All twenty were asked to complete a pilot questionnaire – forming the questionnaire pilot group.
- The first fifteen from the above group were also asked to take part in an interview, forming the interview group.

c. Control groups

Control groups were individuals who did not have NF2 – and were used to assess the construct validity of the NFTI-QOL. For control group 1, it was decided to compare the NF2 cohort to individuals that had some clinical problems similar to NF2, but not all. It was therefore decided to use those with sporadic unilateral VS as they may have had unilateral hearing loss,

tinnitus, facial paralysis and vertigo, but not the visual or bilateral symptoms of NF2. Thirty patients who consecutively attended the GSTT Skull Base clinic with a sporadic vestibular schwannoma (SVS - non-NF2) were asked to take part and all agreed.

For control group 2, it was decided to compare the NF2 cohort to well individuals from the 'general population'; therefore thirty individuals were recruited from staff working within the Neurology and Ear, Nose and Throat (ENT) departments at GSTT. All agreed to take part.

d. Qualitative methods of assessing QOL

A focus group session and fifteen in-depth patient interviews used to obtain qualitative data on the impact of QOL in those with NF2. The focus group session took place on 15th January 2010 at Guy's Hospital, London. All patients attending the NSCT GSTT NF2 clinic were invited to attend an NF2 Open Day, along with their friends and families. All attending were invited to attend the focus group session, and all thirty-two people at the day attended. Participants were divided into four groups and discussed the impact of NF2 on their lives, with a moderator from the GSTT NF2 clinical team. There was then a discussion amongst the larger group which was transcribed.

The interviews were all conducted by RH in the Neurofibromatosis Unit. They underwent in-depth semi-structured interviews based on a schedule of main questioning areas which was produced following literature review of previous

QOL work in NF2 and discussion with experienced multi-disciplinary team members and an expert NF2 patient.

The schedule included questions exploring:

- initial presentation and diagnosis of NF2
- Emotional and psychological impact
- Physical impact
- Relationships
- Coping strategies.

The interview schedule was used as a guide; however the interviewees were allowed to direct the interview in their own chosen direction. All interviews were allowed to continue until they came to a natural end.

The interviews were recorded with written consent and then manually transcribed verbatim. Examples are included within appendix A, where they do not include patient identifiable data, and where the contributor gave explicit consent for verbatim inclusion. The accuracy of the transcripts was checked against the original recordings by SH.

The interviews were then analysed and the data described using Framework analysis. Framework analysis is a strategy to analyse qualitative data and involves the development of thematic framework which is used to classify and organise the data (Ritchie and Lewis, 2003). Data from the interviews were categorised into five main themes, with eighteen sub-themes and illustrative examples are given for each.

e. Development of the disease specific QOL questionnaire (NFTI-QOL)

The **NF T**wo **I**mpact on **QOL** (NFTI-QOL) questionnaire was developed using the following sequential stages to ensure robust construction.

f. Assessment of disease severity within the patient cohort

It was initially necessary to develop a method to assess current disease severity in order to allow assessment of the sensitivity of the new questionnaire. All 65 patients within the target population were eligible for inclusion in this part of the study.

Three clinicians (RH, RF and GL) independently gave a severity score to each eligible individual with 1 indicating mild disease, 2 moderate disease and 3 severe disease. Severity was assessed based on current patient wellbeing rather than potential for future disease progress, and was based on personal knowledge of the patient and review of current clinical case notes and imaging. The inter-observer scores were analysed. In an attempt to further understand the reasoning behind the decisions the clinicians made with regard to the severity score, correlation between the clinician severity score and a number of disease factors was undertaken. The severity scores were then discussed amongst the clinicians and where there were differing score, consensus was reached. A question within the pilot questionnaire asked patients to assess their disease severity, using the same scoring system (Q17) and the patient-rated severity score was compared to the

physician-rated score. The physician-rated scores were used for analysis of the field-test.

ii. Developing a conceptual framework (Item generation)

A comprehensive list of symptoms, social and emotional difficulties related to NF2 was produced using the following: 1. literature review (Medline 1966 – 2011, search terms: NF2); 2. the focus group session with 32 NF2 patients and relatives; 3. the fifteen in-depth semi-structured interviews with NF2 patients. A potential list of items to include was produced following review of these approaches, and this list was consolidated and rationalised following discussion by a multi-disciplinary panel of NF2 specialists. This consisted of three clinicians (RH, RF, GL) an NF2 specialist nurse (MVB) and a psychologist (JG).

ii. Developing the pre-test (pilot) questionnaire

The pilot questionnaire was developed from the item list to assess the impact of NF2 on QOL in all main areas of interest. It was further refined after review by members of the multi-disciplinary team and two ‘expert’ NF2 patients for ease of completion and acceptability. The 31-point pilot questionnaire was administered to 20 patients with NF2, along with the EuroQOL.

iii. Item reduction

The pilot questionnaire underwent factor analysis, to reduce it to 7 items. Statistical advice and support was given by JG. An extra item related to vision deemed to be clinically important (Q4) was added during testing to produce the final 8 item NFTI-QOL. This was again sense checked by the NF2 'expert patient' to ensure ease of completion and acceptability prior to field-testing.

iv. Field-testing

A questionnaire pack containing the final 8-item NFTI-QOL, a covering letter, information sheet, stamped addressed envelope and two generic QOL questionnaires, the SF-36 and EuroQOL were posted to each eligible patient. Patients were given 4 weeks to respond. Non-responders were reminded once by telephone after four weeks. A second pack containing the original material and a reminder letter was mailed if patients could not be reached by telephone or had lost their packs. The questionnaires were posted to each of the eligible 65 patients with NF2.

vi. Evaluation of NFTI-QOL

Methodological advice was provided by JG. The sensitivity of the NFTI-QOL was assessed by correlating NFTI-QOL score to the physician-rated disease severity score (Pearson correlation). Concurrent validity was assessed by correlating NFTI-QOL with SF-36 and EuroQOL. Construct validity was

confirmed by administrating the NFTI-QOL to control groups 1 and 2: patients with SVS (non-NF2) and the general population. Internal reliability across the NFTI-QOL was also assessed.

3.4 Results

a. Focus group session

All thirty-two people attending the NF2 information day took part in the focus group session. Individuals in attendance were divided into four groups, with a NF2 team member moderating each group. Each group was asked to share and discuss the impact of NF2 on their lives. There was an opportunity for free discussion, with individuals sharing their own experiences for around twenty minutes, observed by the group moderator. The findings of each group were then shared and discussed by the group as a whole and this part of the session was transcribed by a professional transcriber. (See appendix A)

Common themes that were raided included the impact of NF2 on physical activities, with balance impairment again being raised as an important issue. There was discussion on the impact of visible impairment on the general public's perception of people with NF2. Many examples were given of when people with NF2 had been mistaken as being drunk or otherwise incapable, which led to distress and potential harm, such as being denied access to public transport at night. There was also discussion of the role of loved ones as carers, and particularly of children as carers for parents with NF2.There

was discussion surrounding negative impact on work – having to change jobs or take time off for appointments. Many patients could no longer work.

b. Semi-structured Interviews

i. Patient demographics

Fifteen patients were recruited consecutively following their attendance at the NSCT GSTT NF2 clinic. Demographics were as follows:

- Nine males, six females
- Mean age = 42 years (range 18-74 years)
- Mean age at diagnosis = 33 years (range 11-72 years)
- Five patients had familial NF2, 10 sporadic
- Six patients were in employment, two were students and seven were not in employment

All interviews took place in a quiet environment in a clinic room within the Neurofibromatosis Unit at GSTT. Interviews were of a mean duration of 70 minutes (range 45 – 90 minutes). Interviews were either oral with communication aids as required or written/typed when patients were deaf and could not lip-read or could not speak. The interviews were transcribed verbatim by RH and samples of transcription were checked for accuracy by SH. For examples of transcription, see Appendix A.

c. Framework analysis

Each interview recording and transcription was analysed over time by RH. With repeated reviews, it became possible to categorise all data in the following themes: and sub-themes

Theme	Sub-theme	Theme discussed in interview (total patient number and patient IDs)
Emotional (E)	E1. Response to diagnosis	**15** (P1-15)
	E2. Feelings/mood	**10** (P1,2,5- 8, 11-14)
	E3. Personality change	**6** (P1,2, 5-8)
	E4. Role of 'fate'	**2** (P1,P8)
	E5. Coping strategies	**8** (P1,2,8,9,11-13,15)
	E6. Positive impact	**7** (P1,2,6-8,11,13)
Physical (P)	Ph1. Hearing	**11** (P1,2,5,6, 8-13,15)
	Ph2. Balance	**5** (P1,5, P10,11,15)
	Ph3. Facial palsy	**5** (P1,5-7,11)
	Ph4. Pain	**2** (P7,8,11)
	Ph5. Impact on activities of daily living	**12** (P1,2,5-13,15)
	Ph6. Impact on work	**8** (P1,6-9,11-13)
Relationships (R)	R1. Partner	**5** (P2,5,6,10,11)
	R2. Friends, family and colleagues	**7** (P1,2,5,6,11,13,14)
	R3. Children	**8** (P1,2,5-8,13,14)
	R4. NF2 in the family	**5** (P5,6,9,13,14)
Knowledge of NF2 (K)	K1. Personal	**5** (P1,8,9,14,15)
	K2. Healthcare professionals	**5** (P2,5,9,11,13)
	K3. General population	**3** (P5,11,13)
The future (F)		**15** (P1-15)

Table 18 Framework analysis of fifteen patient interviews

The following examples for each theme and sub-theme are given direct from interview transcription and are identified by patient number (P1-15).

i. Emotional impact of NF2

The emotional response to having NF2 was varied amongst patients, with some denying any emotional impact and others describing prolonged periods of emotional turmoil. On a number of occasions there was a consistent tone through the whole interview, for example a general strategy of positive thought (P1), cynicism (P2) or negativity (P5). The following sub-themes emerged during interview analysis:

E1. Emotional response to diagnosis

Diagnosis with NF2 appeared to elicit a strong emotional response in the majority of interviewees. In most it was negative:

“when I first found out I had to be sedated” (P4)

“I was in a state of shock. I made a will. It was like being told I had cancer.” (P3)

In some cases there were more initial positive feelings:

“it will sound stupid, but I was like quite excited… it was new and exciting and stuff” (P1)

“it was good to finally find out that there was something wrong with me” (P13)

Other reactions included:

“I went crazy, before I had £20k in the bank, now I’m £20k in debt” (P8)

“I just thought it was an inconvenience to be honest” (P10)

E2. Feelings/mood

It was clear that a number of individuals had a low mood and were likely to be suffering from features of depression:

“I’m never really happy” (P3)

“my children say ‘you’re a right moaner’” (P4)

“I do get down, not like before” (P7)

“there’s nothing to look forward to” (P14)

NF2 clearly has had a negative impact on confidence and has triggered a sense of vulnerability in a number of those interviewed, where the word ‘vulnerable’ was introduced with no prompting:

“I feel too vulnerable to fight.” (P7)

“I feel really vulnerable” (P3)

“the vulnerability makes you closer” (P1)

Three patients raised the subject of suicide, although all denied current ideation.

E3. Personality change

Some individuals thought that their general personality had ‘changed’ since diagnosis, some for the worse and some for the better:

“I’ve become a harder person” (P4)

“I’m more cynical” (P2)

Others thought that they hadn’t undergone any change

“there’s been no change in my mood” (P1)

“I think my personality has just changed with age, I don’t think I’d be any different if I didn’t have NF2” (P6)

E4. Role of ‘fate’

Two individuals believed that they were ‘fated’ to develop NF2 and they had always known that they would develop a disease:

“it sounds weird, but I always expected to get something” and

“I’m not religious or anything, but I think I was meant to get the whole NF2 thing” (P1)

“When I was a teenager I just knew that I wouldn’t live long and there would be something wrong with me. So when I found out about the NF2 it was just a confirmation, I wasn’t really surprised.” (P8)

E5. Coping strategies

When asked about their methods of coping with the NF2 diagnosis, eight interviewees discussed specific mechanisms of coping. These varied from taking a positive attitude to not thinking about the future.

“when I was in rehab after my spinal op I saw so many people worse off than me, I feel lucky that I got off so lightly” (P8)

“I don’t really think about the future, I shut it out” (P8)

E6. Positive impacts

Four individuals could see a positive emotional impact of NF2:

“I feel that I’m a nicer person. I think that I have better empathy” (P6)

“The NF2 pushes me to do things… I don’t want any regrets in life” (P8)

“ I’ve saved money… I’ve got nothing to spend it on now, I can’t go away” (P3)

“I can use my position to help others with NF2” (P14)

ii. Physical impact of NF2

NF2 had a varied impact on the physical status of the interviewees, due to the variety symptoms and their severity. Some interviewees reported little effect on the day-to-day functioning but many reported debilitating problems. Although hearing was the most common physical issue, the more ‘visible’ disabilities, such as balance disturbance and facial palsy appeared to elicit more negative reactions in patients than hearing loss when suffered in combination:

“I can cope with my hearing loss, the worst thing is my balance and face – it stops me going out and having a social life” (P4)

“I am worried about my hearing but not as worried as about my face and balance as then people can see that there’s something wrong with you.” (P7)

Ph1. Hearing

Both the loss of hearing and the idea of hearing loss were issues that many felt strongly about. The fact that hearing loss was unpredictable and unlikely to follow a set pattern did lead to uncertainty and distress. Hearing loss led to a sense of isolation in many and also impacted on communication with friends and family, strangers and health professionals. The sadness at the loss of music and nature sounds was particularly prevalent.

“When I lost my hearing it became really difficult… I feel like I’m missing out” (P5)

“I can’t listen to music anymore. I can hear it but it’s just sounds, it’s not the same” (P15)

“If I was in the garden I wouldn’t be able to hear the birds singing” (P9)

Ph2. Balance

For those who had a balance problem, it appeared to cause significant morbidity, significantly impacting on daily activities, work and even relationships. It was a common occurrence that the individual was mistakenly identified as being drunk with the social stigma attached to this.

“I can’t stand to look in the mirror, I hate my face” (P14)

“it’s the balance that’s the problem. That’s what stops me doing things. I can’t walk the dog, go shopping, cycle with my kids” (P5)

“If I fall over people think that I’m just a drunk” (P5)

“the worst thing is the balance problem, it’s a constant reminder that I have NF2” (P3)

Ph3. Facial palsy

Again, for those who had a facial palsy, it caused significant problems, with a visible ‘deformity’ leading to lack of confidence and social isolation. It also caused functional problems – with one individual refusing to eat in public. Facial palsy was also raised as an issue by those who didn’t have it but knew of someone who had.

“I used to work in Next childrenswear and I did get a lot of stares from the children” (P1)

“shouting or talking really fast are hard to do without it sounding weird” (P1)

“the worst thing would be to have a paralysed face like my mum” (P7)

Ph4. Pain

Pain was a significant issue for three of the interviewees, and did significantly impact on quality of life. It mainly consisted of headaches, with some bodily pain, particularly in the mornings.

“I find it hard to get going in the morning because my joints hurt, but once I take my headache pills and have some tea, it seems to help.” (P7)

Ph5. Activities of daily living

NF2 has had a negative impact on the physical activities of most interviewees. It has physically prevented them from taking part in a range of social, travel and day to day activities. Some feared further loss, such as having to use a wheelchair and not being able to manage their day to day care. Although one interviewee felt his general health had improved as he was taking better care of himself, others felt that their general health had deteriorated.

“I used to love travelling but now I can’t” (P2)

“I used to see myself as a young fit man. Now I can’t physically do the things I used to.” (P3)

“Now I’m not so fit, because I get stressed, I need to smoke, need something to distract me” (P7)

Ph6. Work

Although some individuals were still managing to work, all had had to make some changes and adaptations to allow them to do so. NF2 had led to a change in choice of career for a number of the younger interviewees.

“It’s stopped me from going in the army and that’s all I ever wanted to do” (P7)

“I’ve had to change the amount of time I spend in the classroom now, I do more paperwork” (P12)

iii. Impact on relationships

R1. Partner

Although some interviewees reported either no impact of the NF2 on their relationship, or improvement in the relationship, others reported relationship breakdown and distress. Some actively avoided relationships as they didn’t want to put a new partner through their suffering. The difficulties of meeting a new partner was discussed, two interviewees had successfully met new partners over the internet in specialised chat rooms. There were some issues of guilt over meeting a new partner with a pre-existing NF2 diagnosis.

“Poor X, he has to put up with a wreck of a wife” (P5)

“I was in a relationship for six years and had to end it because she wanted children” (P2)

“My fiancée is the only good thing that’s come from NF2, I would never have met her if not and she’s saved my life.” (P11)

“my wife is young and I’m worried that she doesn’t realise how bad it could get” (P6)

R2. Friends and family

Many interviewees felt that they had worse relationships with friends and family following the development of NF2 but it was generally felt that the relationships they now had were stronger, and they had found their ‘true friends’.

“it improves relationships… one to one personally with family and friends is more close” (P1)

“Lots of so-called friends disappeared… the few friends that I’ve got left are really good friends.” (P2)

There were some more subtle issues raised with regard to improved relationships – and the feeling that family may gain some benefit from the fact that the individual is unwell so they can take care of them:

“I’m not saying that she liked it… she just liked to care for me again, because I’m the youngest” (P1)

R3. Children

The impact of NF2 both on children and future children was obviously an issue. Those with children were worried about the impact of their condition on the child's upbringing and were concerned that they were missing out. There were some children who were acting as carers for their parent.

"my daughter does a lot for me, she's not had much of a childhood" (P5)

"I just wish I could cycle along with my daughter with our hair in the breeze" (P13)

For those who did not have children, many had given serious thought to whether they would have children due to the risk of passing on NF2. Some were aware of the potential for pre-implantation diagnosis and thought that this was a positive development.

R4. NF2 in the family

The discussion of NF2 in patients with familial NF2 revealed both the impact of growing up with an unwell parent, and the fear of passing on the condition to their child.

"I felt so guilty, like I'd killed my son… I do blame myself, if I'd known I had NF2 I would never have had children" (P4)

"I don't think my daughter has the condition… if she did have it, it's just bad luck, you can't do anything about it"

"my father never had a facial palsy so I wasn't expecting it" (P5)

iv. Knowledge of NF2

K1. Personal

Interviewees with familial NF2 generally had a good knowledge of the condition prior to their diagnosis, although some expressed surprise that their symptoms differed from those of their parents and fear that their condition might be as severe as their siblings.

All of the patients with sporadic disease had never heard of NF2 prior to their diagnosis and there was general consensus that an internet search was not a good idea.

“I put NF2 in Google and thought ‘oh my god!’ I wasn’t happy when I read that” (P9)

“You can’t help typing it into Google and there’s a lot of crap on the internet. There’s been some nights when I’ve spent hours looking through case studies” (P1)

Information given at diagnosis varied. A number of interviewees and their families had attended the LINK NF2 course and were highly positive as to the information they were given. Opinions on NF2 patient groups varied, with some highly engaged and others completely uninterested.

K2. Health professionals

All interviewees were very satisfied with the quality of care they had received at the GSTT NF2 clinic and the knowledge of the clinicians. There was a

divide with regard to their pre-referral care – some interviewees felt very strongly that their local doctors did not have a good knowledge or understanding of NF2 and they couldn't trust them with their care.

"I was seeing an ENT surgeon but they said it was a waste of time seeing me regularly" (P3)

"My ophthalmology appointments were terrible, they talk to my wife and not me, they treated me like I was stupid." (P6)

K3. General population

A key feature was the general disappointment in the lack of knowledge of NF2 in the general population, particularly compared to other life-threatening conditions:

"People with cancer can get treatment and support, MacMillan nurses. People with NF2 get no help, no one knows what it is, there's no treatment." (P4)

v. The future

All interviewees discussed their future hopes and plans. They had three different responses: those who were hopeful and optimistic about the future; those who were scared and had negative feelings about the future and those who didn't want to think about it at all.

"I think positive and look forward… a new chapter" (P9)

“I just don’t think about it. I try to take one day at a time” (P5)

“I do worry about the future and how much worse it’s going to get. I worry about who will look after me.” (P4)

c. Physician-rated severity score

All sixty-five patients within the eligible population had their disease severity rated. Correlation between judges was significant ($p<0.001$) – see table below. Concordance between the three judges was rated 'fair' (Pearson's correlation/Spearman's correlation coefficient).

		Judge 1	Judge 2	Judge 3	Severity
Judge 1	Pearson Correlation	1	0.441	0.801	0.842
	Sig. (2-tailed)		0.001	0.000	0.000
	N	65	65	65	65
Judge 2	Pearson Correlation	0.441	1	0.570	0.539
	Sig. (2-tailed)	0.001		.000	.000
	N	65	65	65	65
Judge 3	Pearson Correlation	0.801	0.570	1	0.862
	Sig. (2-tailed)	0.000	0.000		0.000
	N	65	65	65	65
Severity	Pearson Correlation	0.842	0.539	0.862	1
	Sig. (2-tailed)	0.000	0.000	0.000	
	N	65	65	65	65

Table 19 Correlation between judges on severity score (statistical support from JG)

Following the consensus meeting, the patient group had the following severity scorings:

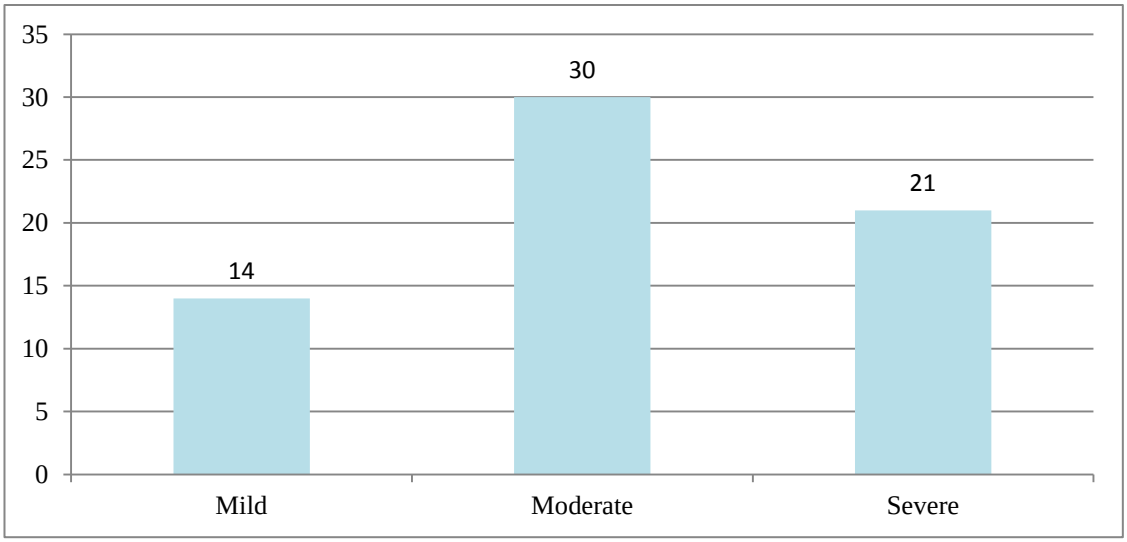


Figure 9 Eligible patient group consensus severity score

Correlations between physician-rated severity score and clinical variables

In order to further understand why the clinicians may have chosen their particular severity rating for each patient, the correlation between the severity score and 37 clinical variables was assessed, including:

- Age: at first symptom; at diagnosis and at first operation
- Gender
- Neurological signs: facial palsy; cranial nerve palsy; upper motor neurone signs; lower motor neurone signs; sensory signs; ataxia.
- Cutaneous manifestations
- Ophthalmological signs
- Seizures

- Positive family history for NF2
- Previous surgical intervention
- Emergency hospital admission
- Hearing loss
- Tumour load: VS; cranial schwannoma (non-VS); cranial meningioma; spinal schwannoma; spinal meningioma; ependymoma
- Genotype
- Peripheral neuropathy

Statistical analysis was performed using Spearman's Rank Correlation (significance 2-tailed) and the following items were found to strongly correlate with the severity score:

- Facial nerve palsy (0.701 $p<0.000$)
- Cranial nerve palsy (0.491 $p<0.000$)
- Upper motor neurone signs (0.410 $p=0.003$)
- Ataxia (0.488 $p<0.000$)
- Previous surgical procedures (0.586 $p<0.000$)
- Emergency admissions (0.428 $p=0.002$)
- Ependymoma (0.529 $p<0.000$)

d. Developing the NF2-specific quality of life questionnaire

i. Patient demographics

Pilot questionnaire group (n=20):

11 females, 9 males

Age range 17-82 (mean = 45 years)

Physician rated disease severity:

Mild: 6 (30%)

Moderate: 4 (20%)

Severe: 10 (50%)

Field testing group (final NFTI-QOL) (n=65):

Responders (n=50)

32 females, 18 males

Age range 16-82 years (mean = 44 years)

Physician rated disease severity:

Mild = 9 (18%)

Moderate = 22 (44%)

Severe = 19 (38%)

Non-responders (n=15)

8 females, 7 males

Age range 19 – 67 (mean = 40 years)

Physician rated disease severity:

Mild = 5 (33%)

Moderate = 8 (53%)

Severe = 2 (13%)

Control group 1 - SVS (n=30)

16 males, 14 females

Age range 28-80 years (mean = 56.5 years)

Control group 2 – healthy (n=30)

18 males, 12 females

Age range 17 – 65 years (mean – 41.6 years)

ii. Item generation

Following the literature review, in-depth interviews and focus group session, a list of relevant items was produced (see appendix). It consisted of a total of 149 items, with six common symptoms. They were divided into the following sub-groups:

Positives (n = 10)

Negatives (n = 101)

Worries and concerns (n = 14)

Coping strategies (n = 24)

The common NF2 symptoms identified were: balance problems; hearing loss; facial palsy and headaches/pain. Problems with eating and drinking and vision were apparent in the literature review but did not appear important in the interview and focus group.

iii. Developing the pilot questionnaire

The pilot questionnaire consisted of 31 questions (see appendix B). Q1-16 were NF2 specific and were developed from the item list. Q17 was a patient disease severity rating (mild, moderate or severe) and Q18-31 were reproduced from the Hospital Anxiety and Depression Score (HADS). The pilot was produced by RH then reviewed by a clinical nurse specialist (MVB) and psychologist (JG) for appropriateness and acceptability. It was also

reviewed by two NF2 ‘expert’ patients and after minor changes was tested by the pilot group.

iv. Pilot testing results

The pilot questionnaire was completed by all twenty members of the pilot group. Data was missing from Q1 (not answered by 3/20), Q5 (not answered by 4/20) and Q9 (not answered by 3/20). The pilot group also completed the EuroQOL questionnaire on the same occasion (see introduction and appendix B for further details of EuroQOL).

The results from the pilot questionnaire were correlated to physician-rated disease severity, age, gender and EuroQOL. Support in this analysis was provided by JG.

The pilot questions were divided into the following sub-groups for analysis:

Group name	Pilot questionnaire questions included	Description of group
NFTI-TOT	Q2+Q3+Q4+Q6+Q7+Q8+Q10+Q11+Q12+Q13+Q14+Q15+Q16	NFTI-QOL pilot questions excluding Q1, 5 and 9 due to missing data and anxiety and depression questions.
ANX	Q18+Q20+Q22+Q24+Q26+Q28+Q30	NFTI-QOL pilot questions: HADS, anxiety questions
DEP	Q19+Q21+Q23+Q25+Q27+Q29+Q31	NFTI-QOL pilot questions: HADS, depression questions
PAT-SEV	Q17	Patient-rated severity
EURO1-5	E1+E2+E3+E4+E5	Euro-QOL questions excluding visual analogue score
EUROVAS	E6	Euro-QOL visual analogue score

Table 20 Pilot questionnaire sub-groups

The sub-group correlations were analysed using Pearson Correlation.

There were no correlations between any of the pilot questionnaire sub-groups and age or gender.

The following strong correlations were found:

Physician-rated severity score.

Correlated strongly (Pearson correlation, 2-tailed significance) with:

- NFTI-TOT (0.563, p=0.015)
- EURO-VAS (-0.604, p=0.008)
- PAT-SEV (0.724, p=0.001)

There was no correlation between physician-rated severity score and the non-VAS questions from Euro-QOL (EURO1-5).

NFTI-TOT

NFTI-TOT correlated strongly with:

- EURO1-5 (0.708, p<0.000)
- EURO-VAS (-0.460, p=0.041)
- ANX (0.623, p=0.008)
- DEP (0.870, p<0.000)
- PAT-SEV (0.579, p=0.007)

Anxiety and Depression

Anxiety questions (ANX) correlated strongly with:

- DEP (0.684, p=0.002)
- NFTI-TOT (0.623, p=0.008)
- EURO1-5 (0.666, p=0.003)
- EURO-VAS (-0.615, p=0.009)

Depression questions (DEP) correlated strongly with:

- ANX (0.684, p=0.002)
- NFTI-TOT (0.870, p<0.000)
- EURO1-5 (0.806, p<0.000)
- EURO-VAS (-0.493, p=0.032)

d. Item reduction

Factor analysis was performed using the sub-groups NFTI-TOT and ANX and DEP. It showed clustering around the following areas:

Balance and dizziness

Hearing

Facial weakness

Travel and mobility

Life: outlook/role

Anxiety and depression

As there was strong correlation between the HADS anxiety and depression scores and EURO-QOL. It was therefore decided that a version of the EURO-QOL question 5 would be used to assess anxiety and depression in the NFTI-QOL (see figure 10).

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

Figure 10 EURO-QOL question 5

The shortened NFTI-QOL psychometric was produced by developing questions that would envelop the areas of clustering. All questions had four possible answers, scoring 0-3. Where there was no impact on QOL, a score of 0 was given, increasing to 3 for a large impact on QOL.

The NFTI-QOL initially consisted of seven questions, but an eighth question regarding visual problems was added (Q4) during the period of field testing as it was felt after reflection that although it wasn't a prominent feature in the pre-test group, visual problems were important in a minority of the wider NF2 population, particularly where visual impairment compounds hearing loss. Although speech and swallowing problems may be symptoms of NF2, they were not raised as issues impacting on QOL in our interviews or focus group, so were not included.

The format of the shortened NFTI-QOL was designed to allow it all to fit onto one A4 sheet. Scoring labels were added to each question part to allow for easier results input. No loading was thought necessary as the clustering and correlations around each area were not grossly different. The final version is in Appendix B.

e. Field testing

The questionnaire pack consisting of the NFTI questionnaire, Euro-QOL and the SF-36 was sent out to the 65 eligible participants. Fifty completed packs were returned (77% response rate). The additional question on vision (Q4) was added during field testing (see above) so was completed by 37 participants. All parts of the NFTI-QOL were fully completed by all respondents.

Each question was scored from 0-3, 0 indicating no or minimal impact on QOL and 3 indicating significant impact. The minimum total possible score from the NFTI-QOL was 0 (no or minimal impact on QOL) and the maximum total possible score was 24 (very large impact on QOL). The range of scores in the responder group who had completed the revised questionnaire including question 4 varied from 0-20, with a mean score of 9.4 (n=37, SD 5.57). The mean of the NFTI-QOL score without Q4 was 8.3 (n=50, max score=21, SD 4.80). Results from the NFTI-QOL field test are as follows:

Question	Subject	Number of individuals scoring:				Total
		0	1	2	3	
1	Balance	8	9	24	9	50
2	Hearing	8	3	31	8	50
3	Facial weakness	27	10	10	3	50
4	Vision	15	7	15	0	37
5	Mobility	19	21	8	2	50
6	Role/outlook	9	19	16	9	50
7	Pain	26	12	11	1	50
8	Anxiety/depression	21	15	9	5	50

Table 21 NFTI-QOL field test results

The following graph (figure 11) shows the percentage of responders who felt that the following symptoms caused difficulty with or stopped them from performing their usual activities (scored 2 or 3):

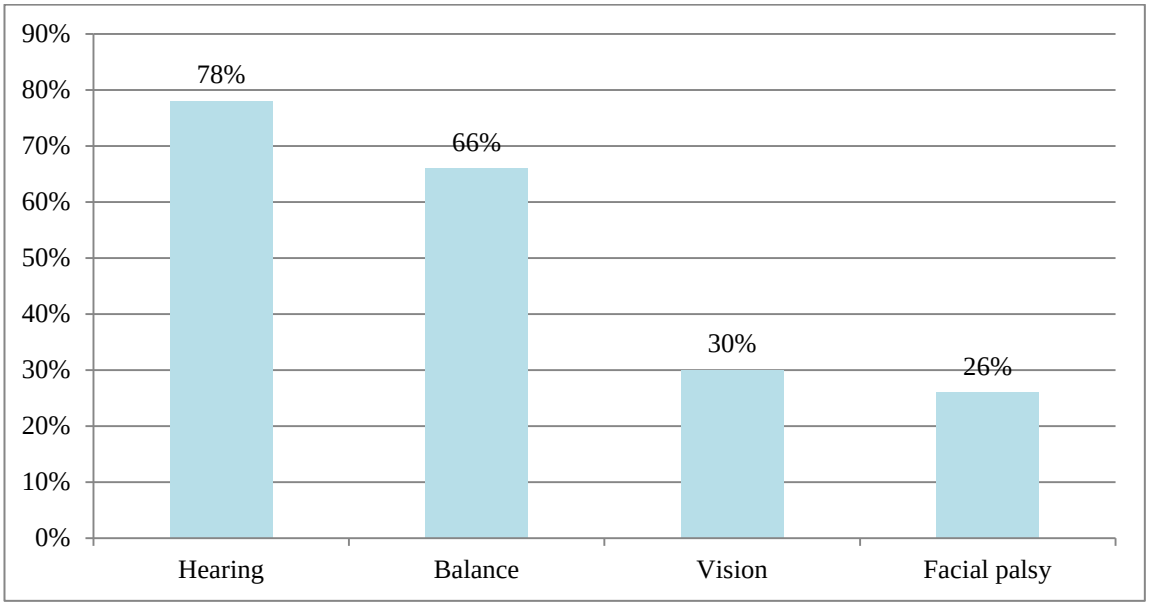


Figure 11 Proportion of responders who felt the symptom caused difficulty with or stopped their daily activities.

Other findings included:

- 20% were unable to walk without help
- 24% had moderate or severe pain
- 28% reported moderate or severe anxiety or depression
- 50% felt that NF2 had a moderate or large negative effect on their role or outlook on life.

The total NFTI-QOL score showed good sensitivity by strongly correlating with physician-rated disease severity (Pearson correlation=0.576, $p<0.000$).

f. Validation

i. NFTI-QOL versus SF-36

The SF-36 consists of eight scaled scores which are the weighted sums of the questions in their section, and are directly transformed to a 0-100 scale. UK population norms from Jenkinson et al. (1999) Results are as follows:

SF-36 domain	UK population norm	NF2 test group mean	Correlation with total NFTI-QOL score
Physical functioning score	87.99 (SD 19.65)	57.4 (SD 32.9)	-0.715 p<0.000
Role physical score	87.17 (SD 22.01)	51.5 (SD 45.3)	-0.510 p=0.001
Role emotional score	85.75 (SD 21.18)	59.3 (SD 45.8)	-0.564 p<0.000
Social functioning score	82.77 (SD 23.24)	64.7 (SD 33.3)	-0.798 p<0.000
Mental health score	71.92 (SD 18.15)	61.84 (SD 26.7)	-0.688 p<0.000
Energy/vitality score	58.04 (SD 19.60)	49.2 (SD 27.5)	-0.773 p<0.000
Pain score	78.80 (SD 23.01)	67.3 (SD 29.0)	-0.656 p<0.000
General health perception score	71.06 (SD 20.43)	48.7 (SD 31.1)	-0.651 p<0.000

Table 22 SF-36 results, correlations with NFTI-QOL (Pearson correlation sig 2-tailed, SD=standard deviation) and UK population norms

The total NFTI-QOL score correlated strongly with all eight scores of the SF-36 in the target population group. Although standard deviation around the NF2 means are large due to the relatively small number (n=50), it does appear that the NF2 means may lie outside the population norms in all domains.

There was strong correlation ($p<0.01$) between the physician-rated severity score and all SF-36 domain scores apart from role physical score and role emotional score.

There was no correlation between any of the SF-36 domain scores and age, gender or gene mutation type.

ii. NFTI-QOL versus EuroQoL

Both parts of the EuroQol (Q1-5 and visual analogue score) correlated strongly with each other (Pearson correlation = -0.660, $p<0.000$).

Physician-rated severity score also correlated with the EuroQol Q1-5 (0.343 $p=0.015$) and more strongly with the EuroQol VAS (-0.554 $p<0.000$).

The NFTI-QOL total score also correlated strongly to the sum of questions 1-5 of the EuroQoL (Pearson correlation=0.707, $p<0.000$) and the EuroQol visual analogue score (Pearson correlation=-0.584, $p<0.000$).

iii. Field group versus control groups

The mean NFTI-QOL total score was calculated for the following groups:

- NF2 group:
    - n=37
    - mean=9.4
    - SD=5.56
- Solitary vestibular schwannoma group:
    - n=30
    - mean=5.5
    - SD=3.79
- Normal population:
    - n=30
    - mean=0.4
    - SD=1.07

The NFTI-QOL total score was significantly different between the NF2 group and the solitary vestibular schwannoma group (independent t-test, $p<0.000$) and also between the NF2 group and the normal population group (independent t-test, $p<0.000$).

Item	Mean score			‡ANOVA between groups
	NF2	SVS	Healthy controls	
	n=50	n=30	n=30	
Q1. Hearing	1.68	1.13	0.13	<0.001
Q2. Dizziness and balance	1.78	1.43	0.00	<0.001
Q3. Facial palsy	0.78	0.20	0.00	<0.001
Q4. Sight†	1.0	0.37	0.03	<0.001
Q5. Mobility and walking	0.86	0.40	0.00	<0.001
Q6. Role and outlook on life	1.5	0.83	0.07	<0.001
Q7. Pain	0.74	0.60	0.03	<0.001
Q8. Anxiety and depression	0.96	0.47	0.17	<0.001
Total score [95% CI]	9.41 [7.55-11.26]	5.50 [4.09-6.91]	0.43 [0.03-0.83]	<0.001

Table 23 Comparison of NFTI-QOL scores between NF2 patients, solitary vestibular schwannoma (SVS) patients, and healthy controls. (†n=37 for Q4, ‡ Kruskal Wallis non-parametric ANOVA)

iv. Reliability and item loadings

The NFTI-QOL showed good internal reliability (Cronbach's alpha = 0.87).

Loadings of each item on the whole scale NFTI-QOL are shown below:

Item	Pearson Correlation	Significance (2 tailed)
Q1. Hearing	0.817	<0.001
Q2. Dizziness and balance	0.668	<0.001
Q3. Facial palsy	0.772	<0.001
Q4. Sight	0.662	<0.001
Q5. Mobility and walking	0.720	<0.001
Q6. Role and outlook on life	0.853	<0.001
Q7. Pain	0.605	<0.001
Q8. Anxiety and depression	0.706	<0.001

Table 24 Individual item loadings on the whole scale

g. Post-field testing adaptations

An optional blank A4 sheet was added to the back of the NFTI-QOL to allow for expansion of answers if felt necessary.

The NFTI-QOL was also altered for use in the US (by RH and AB. See appendix B) and is awaiting validation.

3.5 Discussion

The aims of this section were to assess the impact of NF2 on quality of life and to develop and validate a disease-specific score to measure QOL in NF2.The impact on quality of life from NF2 has been comprehensively evaluated within this study, in both qualitative and quantitative ways. It is clear that NF2 is a variable disease, both in terms of clinical manifestations and impact on activities and outlook. However, there are common themes that surfaced in the qualitative methods which informed the structure of the quantitative methods.

a. Focus group session and interviews

The initial part of this study consisted of qualitative research, a focus group session and fifteen interviews. The focus group was undertaken to obtain a sense of the impact of the condition, with free and unguided ‘conversation’ in an informal atmosphere. There was no recording of the smaller group breakouts, although the larger group discussion was transcribed. Although this may have led to some omissions, it was felt to be more important to allow free speech with no concerns from the participants that they were ‘saying the wrong thing’.

In contrast, the in-depth interviews were recorded. This had the obvious benefit of capturing the detail of the discussion but potentially limited responses or frank discussion. Steps were taken to ensure that participants

felt able to fully express their feelings and opinions. The interviewer (RH) was not a regular member of the treating team and the individual was reassured that his/her comments would not be shared without specific consent. The interviews were undertaken in a private room, with no interruptions.

The interviews were semi-structured, in order to introduce certain themes and offer cues if conversations faltered, but were generally a conversation between an individual who had undergone a certain life event and an engaged listener. The interviews were allowed to flow in directions mainly dictated by the interviewee. The main themes that were discussed in the interviews were the emotional impact of diagnosis, the physical impact of the disease, impact on relationships, knowledge of NF2, by both the individual, family and healthcare workers and the future.

There is no consensus as to how many interviews are ‘enough’ in qualitative research. (Baker and Edwards, 2012) The sample size of fifteen patient interviews was selected following guidance for best practice, taking in to account the small size of the NF2 population, the level of information saturation that would be likely to occur and the limited time of the investigator. There may have been selection bias, as although patients were asked to take part sequentially, they were selected from those attending the NF2 clinic. This excluded those who did not attend their hospital appointment, either through choice or circumstance. The selection window

was relatively small, so those who attended frequently had a greater ‘chance’ if being selected than those who attended less frequently.

Quality of life in NF2 has been assessed previously by Patel (Patel et al., 2011) who undertook six semi-structured interviews with people with NF2 and their findings were borne out by this study; however the positive impact of NF2 on life was new to this study, such as the individual who said “I feel that I’m a nicer person. I think that I have better empathy” (See Results p108). A positive response to life from NF2 was reported by four of the fifteen interviewees. The belief that NF2 diagnosis can be positive may already be a coping mechanism within the NF2 population and it could also potentially be utilised to provide psychological support to NF2 patients.

It was also clear from the interview process that a number of patients were exhibiting symptoms of depression. These patients were referred, with their permission, to the psychiatric team. Following the interview process, a specialised psychiatrist was introduced into the multi-disciplinary clinic and both medication and counselling therapy were offered where appropriate. This is a very important finding, as these symptoms had not arisen or been discussed in the usual multi-disciplinary clinic setting, where patients are seen and assessed by a number of health professionals.

b. Physician severity scoring

Physician severity scoring was undertaken as it was necessary to develop a method to assess current disease severity in order to allow assessment of the sensitivity of the new questionnaire. This could not be based on genotype or imaging findings as in NF2 these don't tend to be representative of the individuals clinical condition. During the scoring it became clear that the decisions were made on a 'gut-instinct' by the clinician with knowledge of the patient, taking into account the holistic wellness of the patient and their interaction with their environment. In order to try and better understand this, the score was correlated against a number of clinical factors.

The factors that correlated were those that may cause a functional disability to the patient – such as facial and other cranial nerve palsies, upper motor neurone weakness and ataxia. It could be that these more 'visual' disabilities were what stayed with the clinician as they recalled the patient in their mind for severity scoring. It is also interesting that the clinician score correlated strongly with the patient's rating of their own disease severity. It may be that these findings could be used in future work to develop a disease scoring system.

c. Assessment of QOL using generic measures

This is the first study to assess the QOL in NF2 using both the EuroQOL (EQ-5D) and SF-36 generic scores. Our patients scored significantly worse than the population norms in all domains of each score, confirming the

negative impact on many aspects of QOL by NF2. The SF-36 scores were comparable to those found by Neary in Manchester (Neary et al., 2010a) and this may reflect the fact that both units are National Specialised Centres for NF2 in England and include patients with similar disease severity.

The NF2 patients commented in their feedback that the SF-36 was too long, took too much time to complete, and was too complex. It was particularly troublesome for patients who have fatigue or who have visual problems, as found in NF2. Both EuroQOL and SF-36 assess QOL using general physical, emotional and vitality domains, but provide no differentiation as to the cause of the disability, such as hearing, balance or vision. This may lead to blunting of the instrument, for example, a change in balance that is worsening QOL may not be 'visible' in the generic questionnaires, due the presence of additional symptoms.

d. The NFTI-QOL

In this study a disease-specific questionnaire was developed to measure QOL in NF2, as an assessment tool in clinical practice and in clinical trials. It is quick and simple to complete, and took our patients around 3-5 minutes to complete. Difficulties may arise for patients who are both deaf and unable to read the questionnaire, but this could be overcome by using other communication tools, such as tactile signing. In our field-testing, all parts of each question were completed, implying high acceptability. This is in

comparison to the pilot questionnaire and also the SF36 and EuroQOL, which had missing questions when completed by the same group.

We chose to make the NFTI-QOL a self-report questionnaire rather than interview based questionnaire. It may be that the NFTI-QOL could be adapted as a tool for carers to complete in those more seriously affected if necessary, although this would require further validation.

The construction of the questionnaire followed a structured pathway in order to ensure maximum reliability and validity. The response rate of 77% to our postal questionnaires was high and should limit bias: there was no significant difference in age, gender or disease-severity in our non-responders. Potential sources of error in the NFTI-QOL may be due to systematic error in the completion of questions – for example by the respondent ticking all of the first boxes, or all of the last boxes, however the short length of the questionnaire and the lack of repetition in all of the questions should mitigate this. There is the possibility of the ‘halo effect’ where a negative response for one question leads to a falsely negative response for all, but there was no evidence of this in our field testing group. There is the potential for confusion with regard to the pain question, as it asks for pain symptoms over a different time frame (1 week) compared to one day for the other questions, but this was not raised as an issue by any of our responders.

The total NFTI-QOL score is higher in people with higher morbidity. Comparison with the control groups indicated that the healthy population scored significantly lower in all domains of the NFTI-QOL, confirming construct validity. Furthermore, patients with SVS scored highly on hearing, balance and pain, but scored lower on the other domains than NF2 patients and had a significantly lower total score.

Balance and dizziness problems had the largest negative impact on QOL in our patients. The symptoms were reported by 84% and it was disruptive to usual activities in 78% of individuals. Hearing problems were found in 84% and were disruptive in 66% of patients; visual problems were present in 60% and were disruptive in 41% of individuals; facial palsy was present in 46% and disruptive in 26% of patients. During the interview studies and focus group session NF2 manifestations that were obvious to the general public, such as balance disturbance and facial weakness, caused significant distress. Some patients had been ejected from public places as they were perceived erroneously to be under the influence of alcohol. We have developed an NF2 information card for use by our patients in public settings to try and increase public understanding and awareness.

The method of developing the NFTI-QOL included the use of a much longer questionnaire which then underwent factor analysis to determine representative questions, and it was seen that there was clustering around seven topics which were converted to the final NFTI-QOL questions. The

issues of sight, speech and swallowing did not appear to impact significantly on QOL in our focus group or interview patients, and therefore it was decided initially not to include them in the questionnaire.

The decision was made to encompass anxiety and depression questions into one question based on the EURO-QOL anxiety and depression question. The EURO-QOL is a well-respected and fully validated quality of life score. In our pilot study we found that the total of the numerous HADS anxiety and depression questions correlated strongly to the single EURO-QOL question. Although this may have led to some blunting of NFTI-QOL as a tool for the diagnosis of anxiety and depression, it is meant to be a screening tool, not a diagnostic tool, and the principle behind its development was to make a short questionnaire that is easy and quick to complete. This was discussed with our NF2 expert patient who felt that it was an acceptable question, as did the rest of the multi-disciplinary team. It may however lead to the underestimation of anxiety and depression in individuals who either lack insight into mental health issues or who do not wish to disclose their symptoms in this form.

As mentioned in the methods, the decision was made to add a sight question mid-testing. This was thought necessary to provide a more comprehensive assessment of QOL in NF2 as sight problems may occur in isolation from other symptoms. Sight was found to have a moderate to severe impact on QOL in 30% of those tested in the field-test. In contrast, in our cohort, speech

and swallowing problems occurred predominantly as a complication of VS or surgery for VS and manifested along with other tested symptoms.

Following discussion at a national meeting, a blank page was added at the end of the questionnaire for in depth comment that may be used by investigators. A further 30 NF2 patients have since used the additional page and their comments amplify their questionnaire answers rather than adding new information

Since its development, the NFTI-QOL has been used in other units in the UK and internationally and has been further tested in 288 patients in a longitudinal study, demonstrating its ability to detect changes over time. (Ferner et al., 2014)

3.6 Conclusion

The impact of NF2 on QOL has been analysed in this section of the thesis, and a new disease-specific QOL questionnaire has been developed, tested and validated. It has proven useful for everyday clinical assessment, and as an outcome measure for clinical care – it is now being used as an outcome measure in the national NF2 centres and in England and the USA to monitor response to novel therapy.

References

ABAZA, M. M., MAKRIOU, E., ARMSTRONG, M. & LALWANI, A. K. 1996. Growth rate characteristics of acoustic neuromas associated with neurofibromatosis type 2. *Laryngoscope,* 106**,** 694-699.

AKENSIDE, M. 1768. Observations on cancers. *Med Trans Coll Phys Lon,* 1**,** 64-92.

ANTINHEIMO, J., SANKILA, R., CARPEN, O., PUKKALA, E., SAINIO, M. & JAASKELAINEN, J. 2000. Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. *Neurology,* 54**,** 71-76.

ARPIN, M., ALGRAIN, M. & LOUVARD, D. 1994. Membrane-actin microfilament connections: an increasing diversity of players related to band 4.1. *Current Opinion in Cell Biology,* 6**,** 136-141.

ASTHAGIRI, A. R., PARRY, D., BUTMAN, J. A., KIM, H. J., TSILOU, E. T., ZHUANG, A. & LONSER, R. R. 2009. Neurofibromatosis type 2. *Lancet,* 373**,** 1974-1986.

ASTHAGIRI, A. R., VASQUEZ, R. A., BUTMAN, J. A., WU, T., MORGAN, K., BREWER, C. C., KING, K., ZALEWSKI, C., KIM, H. J. & LONSER, R. R. 2012. Mechanisms of Hearing Loss in Neurofibromatosis Type 2. *PLOS One,* 7**,** e46132.

BAKER, S. E. & EDWARDS, R. 2012. How many qualitative interviews is enough. *National Centre for Research Methods Review Paper*.

BASER, M. E., FRIEDMAN, J. M., AESCHLIMAN, D., JOE, H., WALLACE, A. J., RAMSDEN, R. T. & EVANS, D. G. 2002a. Predictors of the risk of mortality in neurofibromatosis 2. *Am J Hum Genet,* 71**,** 715-23.

BASER, M. E., FRIEDMAN, J. M. & EVANS, D. G. 2006. Increasing the specificity of diagnostic criteria for schwannomatosis. *Neurology,* 66**,** 730-2.

BASER, M. E., FRIEDMAN, J. M., WALLACE, A., RAMSDEN, R. T., JOE, H. & EVANS, D. G. 2002b. Evaluation of clinical diagnostic criteria for neurofibromatosis 2. *Neurology,* 59**,** 1759-1765.

BASER, M. E., MAKARIOU, E. V. & PARRY, D. M. 2002c. Predictors of vestibular schwannoma growth in patients with neurofibromatosis type 2. *J Neurosurg,* 96**,** 217-222.

BASER, M. E., MAUTNER, V. F., PARRY, D. M. & EVANS, D. G. R. 2005. Methodological issues in longitudinal studies: vestibular schwannoma growth rates in neurofibromatosis 2. *J Med Genet,* 42**,** 903-906.

BLAKELEY, J. O., EVANS, D. G., ADLER, J., BRACKMANN, D., CHEN, R., FERNER, R. E., HANEMANN, C. O., HARRIS, G., HUSON, S. M., JACOB, A., KALAMARIDES, M., KARAJANNIS, M. A., KORF, B. R., MAUTNER, V. F., MCCLATCHEY, A. I., MIAO, H., PLOTKIN, S. R., SLATTERY, W., 3RD, STEMMER-RACHAMIMOV, A. O., WELLING, D. B., WEN, P. Y., WIDEMANN, B., HUNTER-SCHAEDLE, K. & GIOVANNINI, M. 2012. Consensus recommendations for current treatments and accelerating clinical trials for patients with neurofibromatosis type 2. *Am J Med Genet A,* 158A**,** 24-41.

BOSCH, M. M., BOLTSHAUSER, E., HARPES, P. & LANDAU, K. 2006a. Ophthalmologic findings and long-term course in patients with neurofibromatosis type 2. *Am J Ophthalmol,* 141**,** 1068-1077.

BOSCH, M. M., WICHMANN, W. W., BOLTSHAUSER, E. & LANDAU, K. 2006b. Optic nerve sheath meningiomas in patients with neurofibromatosis type 2. *Arch Opthalmol,* 124**,** 379-385.

BRACKMANN, D. E., FAYAD, J. N., SLATTERY, W., 3RD, FRIEDMAN, R. A., DAY, J. D., HITSELBERGER, W. E. & OWENS, R. M. 2001. Early Proactive Management of Vestibular Schwannomas in Neurofibromatosis Type 2. *Neurosurgery,* 49**,** 274-283.

BRAZIER, J., JONES, N., O'CATHAIN, A., THOMAS, K., USHERWOOD, T. & WESTLAKE, L. 1992. Validating the SF 36 health survey questionnaire, a new outcome measure for primary care. *BMJ,* 3**,** 160-164.

BROOKS, R. 1996. EuroQol: the current state of play. *Health Policy,* 37**,** 53-72.

CAI, W., KASSARJIAN, A., BREDELLA, M. A., HARRIS, G. J., YOSHIDA, H., MAUTNER, V. F., WENZEL, R. & PLOTKIN, S. R. 2009. Tumor burden in patients with neurofibromatosis types 1 and 2 and schwannomatosis: determination on whole-body MR images. *Radiology,* 250**,** 665-673.

COLLETI, L., SHANNON, R. V. & COLLETI, V. 2012. Auditory brainstem implants for neurofibromatosis type 2. *Curr Opin Otolaryngol Head Neck Surg,* 20**,** 353-357.

COLLETI, V. & SHANNON, R. V. 2005. Open Set Speech Perception with Auditory Brainstem Implant. . *Laryngoscope,* 115**,** 1974-1978.

COMMITTEE ON HEARING AND EQUILIBRIUM 1995. Guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma): American Academy of Otolaryngology–Head Neck Surgery Foundation, Inc. *Otolaryngol Head Neck Surg,* 113**,** 179-180.

CORDEIRO, N. J., GARDNER, K. R., HUSON, S. M., STEWART, H., ELSTON, J. S., HOWARD, E. L., TULLUS, K. O. & PIKE, M. G. 2006. Renal vascular disease in neurofibromatosis type 2: association or coincidence? *Dev Med Child Neurol,* 48**,** 58-9.

CUSHING, H. 1917. *Bilateral tumors and generalized neurofibromatosis. Tumors of the nervus acusticus and the syndrome of the cerebellopontine angle.,* New York, Hafner Publishing Company.

DIRKS, M. S., BUTMAN, J. A., KIM, H. J., WU, T., MORGAN, K., TRAN, A. P., LONSER, R. R. & ASTHAGIRI, A. R. 2012. Long-term natural history of neurofibromatosis Type 2-associated intracranial tumors. *Neurosurgery,* 117**,** 109-117.

DONNELLY, N., JACKSON, C., TAM, Y., C., JOUBERT, I., TYSOME, J. R., PATEL, P., AXON, P. R., MANNION, R., DURIE-GAIR, J., MACFARLANE, R. & SCOFFINGS, D. 2012. MRI without magnet removal in NF2 patients with cochlear and auditory brainstem implants. Congress Abstract. *J Neurol Surg B,* 73**,** A285.

DOW, G., BIGGS, N., EVANS, D. G., GILLESPIE, J., RAMSDEN, R. T. & KING, A. 2005. Spinal tumours in neurofibromatosis type 2. Is emerging knowledge of genotype predictive of natural history? . *J Neurosurg: Spine,* 2**,** 574-579.

EDGERTON, B. J., HOUSE, W., F. & HITSELBERGER, W. E. 1982. Hearing by cochlear nucleus stimulation in humans. *Ann Otol Rhinol Laryngol (Suppl),* 91**,** 117-124.

EVANS, D., G, R. 2009. Neurofibromatosis type 2 (NF2): A clinical and molecular review. . *Orphanet J Rare Dis,* 4.

EVANS, D., G, R., BIRCH, J., M. & RAMSDEN, R. T. 1999a. Paediatric presentation of type 2 neurofibromatosis. *Arch Dis Child,* 81**,** 496-499.

EVANS, D., G, R., HOWARD, E. L., GIBLIN, C., SPENCER, H., HUSON, S. M. & LALLOO, F. 2010. Birth incidence and prevalence of tumor-prone syndromes. . *Am J Med Genet,* 152A**,** 327-332.

EVANS, D., G, R., HUSON, S. M., DONNAI, D., NEARY, W., BLAIR, V., NEWTON, V. & HARRIS, R. 1992a. A Clinical Study of Type 2 Neurofibromatosis. *Quarterly Journal of Medicine,* 84**,** 603-618.

EVANS, D., G, R., HUSON, S. M., DONNAI, D., NEARY, W., BLAIR, V., TEARE, D., NEWTON, V., STRACHAN, T., RAMSDEN, R. T. & HARRIS, R. 1992b. A genetic study of type 2 neurofibromatosis in the United Kingdom. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. . *J Med Genet,* 29**,** 841-846.

EVANS, D., G, R., LYE, R., NEARY, W., BLACK, G., STRACHAN, T., WALLACE, A. & RAMSDEN, R. T. 1999b. Probability of bilateral disease in people presenting with a unilateral vestibular schwannoma. *J Neurol Neurosurg Psych,* 66**,** 764-767.

EVANS, D., G, R., MASON, S., HUSON, S. M., PONDER, M., HARDING, A. E. & STRACHAN, T. 1997. Spinal and cutaneous schwannomatosis is a variant form of type 2

neurofibromatosis: a clinical and molecular study. *J Neurol Neurosurg Psych,* 62**,** 361-366.

EVANS, D., G, R., RAMSDEN, R., GOKHALE, C., BOWERS, N., HUSON, S. M. & WALLACE, A. 2007. Should NF2 mutation screening be undertaken in patients with an apparently isolated vestibular schwannoma? . *Clin Genet,* 71**,** 354-358.

EVANS, D., G, R., RAMSDEN, R., SHENTON, A., GOKHALE, C., BOWERS, N., HUSON, S. M. & WALLACE, A. 2008. What are the implications in individuals with unilateral vestibular schwannoma and other neurogenic tumours? . *J Neurosurg,* 108**,** 92-96.

EVANS, D., G, R., RAYMOND, F. L., BARWELL, J. G. & HALLIDAY, D. 2012. Genetic testing and screening of individuals at risk of NF2. *Clin Genet,* 82**,** 416-424.

EVANS, D., G, R., TRUEMAN, L., WALLACE, A., COLLINS, S. & STRACHAN, T. 1998a. Genotype/phenotype correlations in type 2 neurofibromatosis (NF2): evidence for more severe disease associated with truncating mutations. *J Med Genet,* 35**,** 450-455.

EVANS, D., G, R., WALLACE, A., WU, C. L., TRUEMAN, L., RAMSDEN, R. T. & STRACHAN, T. 1998b. Somatic mosaicism: a common cause of classic disease in tumour-prone syndromes? Lessons from type 2 neurofibromatosis. *Am J Hum Genet,* 63**,** 727-736.

EVANS, D. G. R., BASER, M. E., O'REILLY, B., ROWE, J., GLEESON, M. J., SAEED, S., KING, A., HUSON, S. M., KERR, R., THOMAS, N., IRVING, R., MACFARLANE, R., FERNER, R., MCLEOD, R., MOFFAT, D. A. & RAMSDEN, R. T. 2005. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. *Br J Neurosurg,* 19**,** 5-12.

EVANS, D. G. R., LYE, R., NEARY, W., BLACK, G., STRACHAN, T., WALLACE, A. & RAMSDEN, R. T. 1999c. Probability of bilateral disease in people presenting with a unilateral vestibular schwannoma. *Journal of Neurology, Neurosurgery & Psychiatry,* 66**,** 764-767.

FERNER, R. 2010. The neurofibromatoses. *Prac Neurol,* 10**,** 82-93.

FERNER, R. E. 2007. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. *The Lancet Neurology,* 6**,** 340-351.

FERNER, R. E., SHAW, A., EVANS, D. G., MCALEER, D., HALLIDAY, D., PARRY, A., RAYMOND, F. L., DURIE-GAIR, J., HANEMANN, C. O., HORNIGOLD, R., AXON, P. & GOLDING, J. F. 2014. Longitudinal evaluation of quality of life in 288 patients with neurofibromatosis 2. *J Neurol,* 261**,** 963-9.

FISHER, L. M., DOHERTY, J. K., LEV, M. & SLATTERY, W., 3RD 2007. Distribution of Nonvestibular Cranial Nerve Schwannomas in Neurofibromatosis 2. *Otol Neurotol,* 28**,** 1083-1090.

FISHER, L. M., DOHERTY, J. K., LEV, M. & SLATTERY, W., 3RD 2009. Concordance of bilateral vestibular schwannoma growth and hearing changes in neurofibromatosis 2 natural history consortium. . *Otol Neurotol*.

GARDNER, W., J. & FRAZIER, G. H. 1930. Bilateral acoustic neurofibroma: A clinical study and field survery of a family of five generations with bilateral deafness in 28 members. *Arch Neurol Psychiatry,* 23**,** 266-300.

GLEESON, M. J. 2008. *Scott-Brown's Otorhinolaryngology, Head and Neck Surgery*, Hodder Arnold.

GORECKI, C., BROWN, J. M., CANO, D., LAMPING, D. L., BRIGGS, M., COLEMAN, S., DEALEY, C., MCGINNIS, E., NELSON, A. E., STUBBS, N., WILSON, L. & NIXON, J. 2013. Development and validation of a new patient-reported outcome measure for patients with pressure ulcers: the PU-QOL instrument. . *Health Qual Life Outcomes,* 11**,** 95.

GORLIN, R. J. & KOUTLAS, I. G. 1998. Multiple schwannomas, multiple nevi and multiple vaginal leiomyomas: a new dominant syndrome. . *Am J Hum Genet,* 78**,** 76-81.

GOUTAGNY, S., BAH, A. B., PARFAIT, B., STERKERS, O. & KALAMARIDES, M. 2013. Neurofibromatosis type 2 in the elderly population: clinical and molecular features. *Am J Med Genet,* 161A**,** 667-670.

GOUTAGNY, S., BOUBACAR BAH, A., HENIN, D., PARFAIT, B., BOZORG GRAVELI, A., STERKERS, O. & KALAMARIDES, M. 2012. Long-term follow-up of 287 meningiomas in neurofibromatosis type 2 patients: clinical, radiological and molecular features. *Neuro Oncol,* 14**,** 1090-1096.

GREY, P. L., MOFFAT, D. A., PALMER, C. R., HARDY, D. G. & BAGULEY, D. M. 1996. Factors which influence the facial nerve outcome in vestibular schwannoma surgery. . *Clin Otolaryngol,* 21.

GUTMANN, D. H. 1997. Molecular insights into neurofibromatosis 2. *Neurobiol Dis,* 3**,** 247-261.

GUTMANN, D. H., AYLSWORTH, A., CAREY, J. C., KORF, B. R., MARKS, J., PYERITZ, R. E., RUBENSTEIN, A. & VISKOCHIL, D. 1997a. The Diagnostic Evaluation and Multidisciplinary Management of Neurofibromatosis 1 and Neurofibromatosis 2. *JAMA,* 278**,** 51-57.

GUTMANN, D. H., GIORDANO, M. J., FISHBACK, A. S. & GUHA, A. 1997b. Loss of merlin expression in sporadic meningiomas, ependymomas and schwannomas. . *Neurology,* 49**,** 267-270.

GUTMANN, D. H., SHERMAN, L., SEFTOR, L., HALPEK, C., HOANG LU, K. & HENDRIX, M. 1999. Increased expression of the NF2 suppressor gene product, merlin, impairs cell motility, adhesion and spreading. . *Hum Molec Genet,* 8**,** 267-275.

HARRIS, G. J., PLOTKIN, S. R., MACCOLLIN, M., BHAT, S., URBAN, T., LEV, M. & SLATTERY, W., 3RD 2008. Three-dimensional volumetrics for tracking vestibular schwannoma growth in neurofibromatosis type 2. *Neurosurgery,* 62**,** 1314-1320.

HELLER, J. W., BRACKMANN, D. E., TUCCI, D. L., NYENHUIS, J. A. & CHOU, C.-K. 1996. Evaluation of MRI Compatibility of the Modified Nucleus Multichannel Auditory Brainstem and Cochlear Implants. *Otology & Neurotology,* 17**,** 724-729.

HENNEBERG, K. & KOCH, M. 1903. Ueber "Centrale" neurofibromatose und id geschwulste des klein-hirnbruckenwinkels (acusticusneurome). *Arch Psy Nervenkr* 36**,** 251-304.

HOUSE, J. W. & BRACKMANN, D. 1985. Facial nerve grading system. *Otolaryngol Head Neck Surg,* 93**,** 146-147.

HULSEBOS, T. J. M., PLOMP, A. S., WOLTERMAN, R. A., ROBANUS-MAANDAG, E. C., BAAS, F. & WESSELING, P. 2007. Germline Mutation of INI1/SMARCB1 in Familial Schwannomatosis. *The American Journal of Human Genetics,* 80**,** 805-810.

ITO, E., SAITO, K., YATSUYA, H., NAGATANI, T. & OTSUKA, G. 2009. Factors predicting growth of vestibular schwannoma in neurofibromatosis type 2. *Neurosurg Rev,* 32**,** 425-433.

JACOBY, L. B., JONES, D. & DAVIS, K. 1997. Molecular analysis of the NF2 tumour-suppressor gene in schwannomatosis. . *Am J Hum Genet,* 61**,** 1293-1302.

JAREMKO, J. L., MACMAHON, P. J., TORRIANI, M., MERKER, V. L., MAUTNER, V. F., PLOTKIN, S. R. & BREDELLA, M. A. 2012. Whole-body MRI in neurofibromatosis: incidental findings and prevalence of scoliosis. . *Skeletal Radiol,* 41**,** 917-923.

JENKINSON, C., STEWART-BROWN, S., PETERSEN, S. & PAICE, C. 1999. Assessment of the SF-36 version 2 in the United Kingdom. . *J Epidermiol Community Health,* 53**,** 46-50.

KANTER, W. R., ELDRIDGE, R., FABRICANT, R., ALLEN, J. C. & KOERBER, T. 1980. Central neurofibromatosis with bilateral acoustic neuroma. Genetic, clinical and biochemical distinctions from peripheral neurofibromatosis. . *Neurology,* 30**,** 851-859.

KLUWE, L., FRIEDRICH, R. E., HAGEL, C., LINDENAU, M. & MAUTNER, V. F. 2000. Mutations and Allelic Loss of the *NF2* Gene in Neurofibromatosis 2-Associated Skin Tumors. *J Invest Dermatol,* 114**,** 1017-1021.

KLUWE, L. & MAUTNER, V. F. 1998. Mosacism in sporadic neurofibromatosis 2 patients. *Hum Molec Genet,* 7**,** 2051-2055.

KLUWE, L., MAUTNER, V. F., HEINRICH, B., DEZUBE, R., JACOBY, L. B., FRIEDRICH, R. E. & MACCOLLIN, M. 2003. Molecular study of frequency of mosaicism in neurofibromatosis 2 patients with bilateral vestibular schwannomas. *Journal of Medical Genetics,* 40**,** 109-114.

KUO, Y. H., ROOS, D. & BROPHY, B. P. 2008. Linear accelerator radiosurgery for treatment of vestibular schwannomas in neurofibromatosis 2. *J Clin Neurosci,* 15**,** 744-8.

LESLEY, W. S., THOMAS, M. R. & ABDULRAUF, S. I. 2004. N-Butylcyanoacrylate Embolization of a Middle Meningeal Artery Aneurysm in a Patient with Neurofibromatosis Type 2. *Am J Neuroradiol,* 25**,** 1414-1416.

LUSTIG, L. R., YEAGLE, J., DRISCOLL, C. L. W., BLEVINS, N., FRANCIS, H. & NIPARKO, J. K. 2006. Cochlear Implantation in Patients with Neurofibromatosis Type 2 and Bilateral Vestibular Schwannoma. *Otol Neurotol,* 27**,** 512-518.

LYSAGHT, A. C., KAO, S. Y., PAULO, J. A., MERCHANT, S. N., STEEN, H. & STANKOVIC, K. M. 2011. Proteome of human perilymph. *J Proteome Res,* 10**,** 3845-51.

MACCOLLIN, M., CHIOCCA, E. A., EVANS, D. G., FRIEDMAN, J. M., HORVITZ, R., JARAMILLO, D., LEV, M., MAUTNER, V. F., NIIMURA, M., PLOTKIN, S. R., SANG, C. N., STEMMER-RACHAMIMOV, A. & ROACH, E. S. 2005. Diagnostic criteria for schwannomatosis. *Neurology,* 64**,** 1838-45.

MACCOLLIN, M., WILLETT, C., HEINRICH, B., JACOBY, L. B., ACIERNO, J. S., PERRY, A. & LOUIS, D. N. 2003. Familial schwannomatosis: exclusion of the NF2 locus as the germline event. *Neurology,* 60**,** 1968-1974.

MARTINEZ DEVESA, P., WADDELL, A., PERERA, R. & THEODOULOU, M. 2007. Cognitive behavioural therapy for tinnitus. . *Cochrane Database Syst Rev,* 24**,** CD005233.

MARTUZA, R. L. & OJEMANN, R. J. 1982. Bilateral acoustic neuromas: clinical aspects; pathogenesis and treatment. *Neurosurgery,* 10**,** 1-12.

MASUDA, A., FISHER, L. M., OPPENHEIMER, M. L., IQBAL, Z. & SLATTERY, W., 3RD 2004. Hearing changes after diagnosis in neurofibromatosis type 2. . *Otol Neurotol,* 25**,** 150-154.

MATHIEU, D., KONDZIOLKA, D., FLICKINGER, J. C., NIRANJAN, A., WILLIAMSON, R., MARTIN, J. J. & LUNSFORD, L. D. 2007. Stereotactic radiosurgery for vestibular schwannomas in patients with neurofibromatosis type 2: an analysis of tumor control, complications and hearing preservation rate. *Neurosurgery,* 60**,** 460-470.

MAUTNER, V. F., BASER, M. E., THAKKER, N., FEIGEN, U., FRIEDMAN, J. M. & KLUWE, L. 2002. Vestibular schwannoma growth in patients with neurofibromatosis type 2: a longitudinal study. . *J Neurosurg,* 96**,** 223-228.

MAUTNER, V. F., LINDENAU, M., BASER, M. E., HAZIM, W., TATAGIBA, M., HAASE, W., SAMII, M., WAIS, R. & PULST, S. M. 1996. The neuroimaging and clinical spectrum of neurofibromatosis 2. *Neurosurgery,* 38**,** 880-885.

MAUTNER, V. F., LINDENAU, M., BASER, M. E., KLUWE, L. & GOTTSCHALK, J. 1997. Skin Abnormalities in Neurofibromatosis 2. *Arch Dermatol,* 133**,** 1539-1543.

MAUTNER, V. F., NGUYEN, R., KNECT, R. & BOKEMEYER, C. 2010a. Radiographic regression of vestibular schwannomas induced by bevacizumab treatment: sustain under continuous drug application and rebound after drug discontinuation. . *Ann Oncol,* 21**,** 2294-2295.

MAUTNER, V. F., NGUYEN, R., KUTTA, H., FUENSTERER, C., BOKEMEYER, C., HAGEL, C., FRIEDRICH, R. E. & PANSE, J. 2010b. Bevacizumab induces regression of vestibular schwannomas in patients with neurofibromatosis type 2. *Neuro Oncol,* 12**,** 14-8.

MAUTNER, V. F., TATAGIBA, M., LINDENAU, M., FUNSTERER, C., PULST, S. M., KLUWE, L. & ZANELLA, F. E. 1995. Spinal tumors in patients with neurofibromatosis type 2: MR imaging study of frequency, multiplicity and variety. . *AJR,* 165**,** 951-955.

MAYFRANK, L., MOHADJER, M. & WULLICH, B. 1990. Intracranial calcified deposits in neurofibromatosis type 2. A CT study of 11 cases. . *Neuroradiology,* 32**,** 33-37.

MCCLATCHEY, A. I., SAOTOME, I., MERCER, K., CROWLEY, D., GUSELLA, J. F., BRONSON, R. T. & JACKS, T. 1998. Mice heterozygous for a mutation at the Nf2 tumor suppressor locus develop a range of highly metastatic tumors. *Genes & Development,* 12**,** 1121-1133.

MCFADDEN, D. 1982. Tinnitus: treatments and research needs. *In:* PROCEEDINGS COMMITTEE ON HEARING, B. A. B. (ed.) *Overviews of Emerging Research Techniques in Hearing, Bioacoustics and Biomechanics.* Washington, D.C.: National Academy Press.

MEREL, P., HOANG-XUAN, K., SANSON, M., BIJLSMA, E., ROULEAU, G. A., LAURENT-PUIG, P., PULST, S. M., BASER, M. E., LENOIR, G., STERKERS, J. M., PHILIPPON, J., RESCHE, F., MAUTNER, V. F., FISHCHER, G., HULSEBOS, T. J. M., AURIAS, A., DELATTRE, O. & THOMAS, G. 1995. Screening for germline mutations in the NF2 gene. . *Genes Chromosomes Cancer,* 12**,** 117-127.

MOFFAT, D. A., LLOYD, S. K. W., MACFARLANE, R., MANNION, R., KING, A., RUTHERFORD, S., AXON, P., DONNELLY, N., FREEMAN, S., TYSOME, J. R., EVANS, D., G, R. & RAMSDEN, R. 2013. Outcome of translabyrinthine surgery for vestibular schwannoma in neurofibromatosis type 2. . *Br J Neurosurg,* 27**,** 446-453.

MORGAN, M. B., CRAYFORD, T., MURRIN, B. & FRASER, S. C. 2001. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg,* 33**,** 679-87.

NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT COMMITTEE 1988. National Institutes of Health Consensus Development Conference. Neurofibromatosis. Conference Statement. *Arch Neurol,* 45**,** 575-8.

NEARY, W., HILLIER, V. F., FLUTE, T., STEPHENS, S. D., RAMSDEN, R. & EVANS, D., G, R. 2010a. The relationship between patients' perception of the effects of neurofibromatosis type 2 and the domains of the Short Form-36. . *Clin Otolaryngol,* 35**,** 291-299.

NEARY, W., HILLIER, V. F., FLUTE, T., STEPHENS, S. D., RAMSDEN, R. & EVANS, D., G, R. 2010b. Use of a closed set questionnaire to measure primary and secondary effects of neurofibromatosis type 2. . *J Laryngol Otol,* 124**,** 720-728.

NEFF, B. A., WIET, R. M., LASAK, J. M., COHEN, N. L., PILLSBURY, H. C., RAMSDEN, R. T. & WELLING, D. B. 2007. Cochlear implantation in the neurofibromatosis type 2 patient: long-term follow-up. *Laryngoscope,* 117**,** 1069-72.

NG, J., MORDEKAR, S. R., CONNOLLY, D. J. & BAXTER, P. 2009. Stroke in a child with neurofibromatosis type 2. *Eur J Paediatr Neurol,* 13**,** 77-9.

NUNES, F. P., MERKER, V. L., JENNINGS, D., CARUSO, P. A., DI TOMASO, E., MUZIKANSKY, A., BARKER, F. G., STEMMER-RACHAMIMOV, A. & PLOTKIN, S. R. 2013. Bevacizumab Treatment for Meningiomas in NF2: A Retrospective Analysis of 15 Patients. *PLOS One,* 8**,** e59941.

OMEIS, I., HILLARD, V. H., BRAUN, A., BENZIL, D. L., MURALI, R. & HARTER, D. H. 2006. Meningioangiomatosis associated with neurofibromatosis: report of 2 cases in a single family and review of the literature. *Surg Neurol,* 65**,** 595-603.

OTSUKA, G., SAITO, K., NAGATANI, T. & YOSHIDA, J. 2003. Age at symptom onset and long-term survival in patients with neurofibromatosis type 2. *J Neurosurg,* 99**,** 480-483.

OTTO, S. R., SHANNON, R. V., WILKINSON, E. P., HITSELBERGER, W. E., MCCREERY, D. B., MOORE, J. K. & BRACKMANN, D. 2008. Audiologic Outcomes With the Penetrating Electrode Auditory Brainstem Implant. . *Otol Neurotol,* 29**,** 1147-1154.

PARRY, D. M., ELDRIDGE, R., KAISER-KUPFER, M. I., BOUZAS, E. A., PIKUS, A. & PATRONAS, N. 1994. Neurofibromatosis 2 (NF2): Clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. . *Am J Med Genet,* 52**,** 450-451.

PATEL, C., FERNER, R. & GRUNFELD, E. 2011. A qualitative study of the impact of living with neurofibromatosis type 2. . *Psych Health Med,* 16**,** 19-28.

PATEL, P. M., DURIE-GAIR, J., TAYLOR, S., TYSOME, J. R., DONNELLY, N., VANAT, Z. H., TAM, Y., C., HARRIS, F., KNIGHT, R., MANNION, R., AXON, P., MOFFAT, D. A. & MACFARLANE, R. 2012. Auditory Implantation in Neurofibromatosis Type 2: A Cambridge Experience (Congress Abstract). . *J Neurol Surg B,* 73.

PATRONAS, N., COURCOUTSAKIS, N., BROMLEY, C. M., KATZMAN, G. L., MACCOLLIN, M. & PARRY, D. M. 2001. Intramedullary and spinal canal tumors in patients with neurofibromatosis 2: MR imaging findings and correlation with genotype. *Radiology,* 218**,** 434-442.

PEYRE, M., GOUTAGNY, S., IMBEAUD, S., BOZORG GRAVELI, A., FELCE, M., STERKERS, O. & KALAMARIDES, M. 2011. Increased growth rate of vestibular schwannoma after resection of contralateral tumor in neurofibromatosis type 2. . *Neuro Oncol,* 13**,** 1125-1132.

PICCIRILLO, E., GUIDA, M., FLANAGAN, S., LAUDA, L., FOIS, P. & SANNA, M. 2008. CNAP to predict functional cochlear nerve preservation in NF-2: cochlear implant or auditory brainstem implant. . *Skull Base,* 18**,** 281-287.

PLOTKIN, S. R., ARDERN-HOLMES, S. L., BARKER, F. G., BLAKELEY, J. O., EVANS, D., G, R., FERNER, R., HADLOCK, T. A. & HALPIN, C. 2013. Hearing and facial function outcomes for neurofibromatosis 2 clinical trials. *Neurology,* 81**,** S25-32.

PLOTKIN, S. R., STEMMER-RACHAMIMOV, A., BARKER, F. G., HALPIN, C., PADERA, T. P., TYRRELL, A., SORENSEN, A. G., JAIN, R. K. & DI TOMASO, E. 2009. Hearing Improvement after Bevacizumab in Patients with Neurofibromatosis Type 2. *N Eng J Med,* 361**,** 358-367.

RITCHIE, J. & LEWIS, J. 2003. *Qualitative research practice: a guide for social science students and researchers.,* London, Sage.

ROULEAU, G. A., MEREL, P., LUTCHMAN, M., SANSON, M., ZUCMAN, J., MARINEAU, C., HOANG-XUAN, K., DEMCZUK, S., DESMAZE, C., PLOUGASTEL, B., PULST, S. M., LENOIR, G., BIJLSMA, E., FASHOLD, R., DUMANSKI, J., DE JONG, P., PARRY, D., ELDRIGE, R., AURIAS, A., DELATTRE, O. & THOMAS, G. 1993. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. *Nature,* 363**,** 515-521.

ROULEAU, G. A., SEIZINGER, B. R., WERTELECKI, W., HAINES, J. L., SUPERNEAU, D., MARTUZA, R. L. & GUSELLA, J. F. 1990. Flanking markers bracket the neurofibromatosis type 2 (NF2) gene on chromosome 22. *Am J Hum Genet,* 46**,** 323-328.

ROULEAU, G. A., WERTELECKI, W., HAINES, J. L., W., H., TROFATTER, J. A., SELIZINGER, B., MARTUZA, R. L., SUPERNEAU, D., CONNEALLY, P. & GUSELLA, J. F. 1987. Genetic linkage of bilateral acoustic neurofibromatosis to a DNA marker on chromosome 22. . *Nature,* 329**,** 246-248.

ROWE, J., RADATZ, M. W. R. & KEMENY, A. A. 2008. Radiosurgery for type II neurofibromatosis. *Prog Neurol Surg,* 21**,** 176-182.

ROWE, J., RADATZ, M. W. R., WALTON, L., SOANES, T., RODGERS, J. & KEMENY, A. A. 2003. Clinical experience with gamma knife stereotactic radiosurgery in the management of vestibular schwannomas secondary to type 2 neurofibromatosis. . *J Neurol Neurosurg Psych,* 74**,** 1288-1293.

RUGGIERI, M., GABRIELE, A. L., POLIZZI, A., SALPIETRO, V., NICITA, F., PAVONE, P., PLATANIA, N., MILONE, P., DISTEFANO, A., PRIVITERA, G., BELFIORE, G., GRANATA, F., CALTABIANO, R., ALBANESE, V., PAVONE, L. & QUATTRONE, A. 2013. Natural history of neurofibromatosis type 2 with onset before the age of 1 year. . *Neurogenetics,* 14**,** 89-98.

RYAN, A. M., HURLEY, M., BRENNAN, P. & MORONEY, J. T. 2005. Vascular dysplasia in neurofibromatosis type 2. *Neurology,* 65**,** 163-164.

SCHIETHAUER, B. W., WOODRUFF, J. M. & ERLANDSON, R. A. 1999. Schwannoma. *Atlas of tumor pathology, tumors of the peripheral nervous system.* . 3 ed.: Armed Forces Institute of Pathology.

SCHULZ, A., BAADER, S. L., NIWA-KAWAKITA, M., JUNG, M. J., BAUER, R., GARCIA, C., ZOCH, A., SCHACKE, S., HAGEL, C., MAUTNER, V. F., HANEMANN, C. O., DUN, X. P., PARKINSON, D. B., WEIS, J., SCHRODER, J. M., GUTMANN, D. H., GIOVANNINI, M. & MORRISON, H. 2013. Merlin isoform 2 in neurofibromatosis type 2-associated polyneuropathy. . *Nature Neuroscience,* 16**,** 426-433.

SELVANATHAN, S. K., SHENTON, A., FERNER, R., WALLACE, A. J., HUSON, S. M., RAMSDEN, R. T. & EVANS, D. G. 2010. Further genotype--phenotype correlations in neurofibromatosis 2. *Clin Genet,* 77**,** 163-70.

SLATTERY, W., 3RD, FISHER, L. M., IQBAL, Z. & OPPENHEIMER, M. L. 2004. Vestibular schwannoma growth rates in neurofibromatosis type 2 natural history consortium subjects. *Otol Neurotol,* 25**,** 811-817.

SMITH, M. J., E., H. J., BOWERS, N., HALLIDAY, D., PATERSON, J., GILLESPIE, J., HUSON, S. M., FREEMAN, S., LLOYD, S. K. W., RUTHERFORD, S., KING, A., WALLACE, A., RAMSDEN, R. & EVANS, D., G, R. 2011. Cranial meningiomas in 411 neurofibromatosis type 2 (NF2) patients with proven gene mutation: clear positional effect of mutations, absence of female severity effect on age at onset. . *J Med Genet,* 48**,** 261-265.

SPERFELD, A. D., HEIN, C., SCHRODER, J. M., LUDOLPH, A. C. & HANEMANN, C. O. 2002. Occurrence and characterization of peripheral nerve involvement in neurofibromatosis type 2. *Brain,* 125**,** 996-1004.

TRIVEDI, R., BYRNE, J., HUSON, S. M. & DONAGHY, M. 2000. Focal amyotrophy in neurofibromatosis 2. *J Neurol Neurosurg Psych,* 69**,** 257-261.

TROFATTER, J. A., MACCOLLIN, M., RUTTER, J. L., MURRELL, J. R., DUYAO, M. P., PARRY, D., ELDRIDGE, R., KLEY, N., MENON, A. G., PULASKI, K., HAASE, V. H., AMBROSE, C. M., MUNROE, D., BOVE, C., HAINES, J. L., MARTUZA, R. L., MACDONALD, M. E., SELZINGER, B. R., SHORT, M. P., BUCKLER, A. J. & GUSELLA, J. F. 1993. A Novel Moesin-, Ezrin-, Radixin-like Gene Is a Candidate for the Neurofibromatosis Tumor Suppressor. *Cell,* 72**,** 791-800.

VAKHARIA, K. T., HENSTROM, D., PLOTKIN, S. R., CHENEY, M. & HADLOCK, T. A. 2012. Facial reanimation of patients with neurofibromatosis type 2. . *Neurosurgery,* 70**,** 237-243.

VAN DE LANGENBERG, R., DE BONT, B. J., NELEMANS, P. J., BAUMERT, B. G. & STOKROOS, R. J. 2008. Follow-up assessment of vestibular schwannomas: volume quantification versus two-dimensional measurements. . *Neuroradiology,* 51**,** 517-524.

VINCENT, C., RUZZA, I., VANEECLOO, F. M. & DUBRULLE, F. 2008. Magnetic resonance imaging with the Digisonic SP Neurelec cochlear implant. . *Eur Arch Otorhinolaryngol,* 265**,** 1043-1046.

VON RECKLINGHAUSEN, F. D. 1882. *Uber die multiplen fibroma der haut und ihre Beziehung zu den multiplen neuromen. ,* Berlin, A Hirschwald.

WALTER, J., KUHN, S. A., BRODHUN, M., REICHART, R. & KALFF, R. 2009. Pulmonary meningioma and neurinoma associated with multiple CNS tumours in a patient with neurofibromatosis type 2. *Clin Neurol Neurosurg,* 111**,** 454-9.

WARE, J. E., SNOW, K. K., KOSINSKI, M. & GANDEK, B. 1993. *SF-36 Health Survey Manual and Interpretation Guide. ,* Boston, New England Medical Centre.

WENTWORTH, S., PINN, M., BOURLAND, J. D., ALLAN, F., EKSTRAND, K., ELLIS, T. L., GLAZIER, S. S., MCMULLEN, K. P., MUNLEY, M., STIEBER, V. W., TATTER, S. B. & SHAW, E. G. 2009. Clinical experience with radiation therapy in the management of neurofibromatosis-associated central nervous system tumors. . *Int J Rad Oncol,* 73**,** 208-213.

WIESTLER, O. D., VON SIEBENTHAL, K., SCHMITT, H. P., FEIDEN, W. & KLEIHUES, P. 1989. Distribution and immunoreactivity of cerebral micro-hamartomas in bilateral acoustic neurofibromatosis (neurofibromatosis 2). *Acta Neuropathol,* 79**,** 137-143.

WISHART, J. H. 1822. Case of tumours in the skull, dura mater and brain. . *Edinburgh Med Surg,* 18**,** 393-397.

WOLFF, R. K., FRAZER, K. A., JACKLER, R. K., LANSER, M. J., PITTS, L. H. & COX, D. R. 1992. Analysis of chromosome 22 deletions in neurofibromatosis type 2-related tumors. *Am J Hum Genet,* 51**,** 478-485.

WORLD HEALTH ORGANISATION 1995. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. . *Soc Sci Med,* 41**,** 1403-1409.

YAMAZAKI, M., NAGANAWA, S., KAWAI, H., NIHASHI, T. & FUKATSU, H. 2009. Increased signal intensity of the cochlear on pre- and post-contrast enhanced 3D-FLAIR in patients with vestibular schwannoma. *Neuroradiology,* 51**,** 855-863.

Appendix A

Transcription of focus group session

Date: 15.1.10
Venue: Guys Hospital
Subject: **NF2 - Information Day**

RH

Great to see you all here. Quality of Life is hard to define, can be different for all. I will shorten this to QOL.

[see screen] World Health Organisation [see screen] not sure if we all have that quality of life.
One person having a certain tumour, it may not bother them but for a tap dancer in the audience it may affect them. it depends how it will affect you. We want to help you improve your quality of life. We are looking not just at how big the tumour is but how it affects you.
Now, can we divide into groups to talk to each other and suggest ways NF2 can affect your quality of life.

[see screen] Now, spend some time talking to the people around you, about how NF2 has affected you.

Group discussions

If you are all ready, we will go around the room feel free to say whatever you like.

Comments

Main issues that affect her are balance weakness in leg, can't go for long walks and horse riding and walking the dark, quite difficult for her.

What things has it stopped you doing?

Walking down steps so if I want to go clubbing with mates, I have to go somewhere without too many steps, ensure I don't drop things, like in Tesco's. I need to hold my balance, I have my new son and picking him up and keeping my balance, very difficult. I used to go horse riding and just general stuff, I need friends with me most of the time. I can't always bend down to the pushchair.

How do people respond to you?

Everyone is very good. I am more conscious, in public places, I can get off the train but I am ok and then suddenly lose my balance. When drinking with my friends people think I am drunk.

After the operation, I didn't know where to put myself in the family group. I am sitting not in a good place. My family didn't realise that everything changes, they don't always remember. it has changed.

Has your role in the family changed?

Yes, because I can't hear them. They can be in another part of the house and I can't hear them. I have problem with coordination with my eye and my limbs. I see things on the floor but I still step on them I can't avoid it.

Hello. It has ruined my life. I can't do anything. I don't go out on my own. My little girl, 11, she is my carer: she does lots of things - the oven. I have a good family, lost most of my friends, they can't be bothered. People don't realise what it is like, but I have to get on with it.

Have you changed things that you do to make it easier, what did you do before that is different now?

Can't go to the funfair. Can't take them out but they get the hump if she can't go on a ride. The daughter does it all, the son is autistic and people on the outside world don't care about her.

When you say you have centres set up but you have to travel miles to get there. Worthing is useless - the physio departments don't do anything.

RF - Just recruited 2 other nurses so that should improve.

I am Paul's mum. He is recovering from a brain operation. He is still in hospital and says hello to all.
His balance and communication is bad but he is on computer and made great friends since having NF2. They are outside the family, nothing to do with NF2, it is through a Church. They are there 24/7 for him. He is the only one in the family with the problem but he still great. We get on with our lives and think positive.

Hello. Families with NF2, when I was younger I could do everything but I look fit, but sometimes I feel why is this happening, but I am living with it. My vision is going.

I used to do sport, I lost all my friends, I enjoy music and dancing and clubs. But, if I go there, I may fall down. People may think I fall over intentionally. If you look fine then people think you are not sick. But I am sick. In a club, you don't know where you are stepping. Sometimes I don't find my hand. My brain knows I have hands and a leg!

Do people agree, if you can't see something you think everything is fine.

Anyone have problems with members of the public?

I have experienced that in work.

People do stare and I did have problems with that. You do get over that. You say to friends and they are happy to look at me and it doesn't matter to them. You get used to a lot of things, things are always hard but be adaptable. I was a violinist when I lost my hearing so I sold it and went travelling to Australia. it is friends that you really need, they are so important. If you are without friends, there are ways of contacting people. Through our charity you can contact people. We can help you with that.

He is 7, he is usually happy and has good quality of life and we are grateful to that. It is inspiring listening to others and it is good to hear from Andrew. His balance is not always great and suffers weakness in legs. For us, it is the emotional side. You try to live in the moment there is that at the back of our minds, that hangs over us, what the future holds for him. When he has the scan, there will be a sleepless night.

The balance issues and people misinterpreting you, we used to do things with people with Huntingdon's disease. We gave them a credit size card for their wallet that says they have the disease and that they are not drunk. In NF2 people can be accosted by police, we could develop that. Would that be helpful?

I am a Speech therapist - I am Sue. We find people that have had strokes with language problems, the Stroke Assoc has produced the same sort of thing. Asking people to take their time.

Interview Transcriptions

Interviewer = I, Participant = P

Interview 1

I – I have 4 or 5 headings for this interview, if you want to talk about anything else, just let me know.

P- Yes

I – If we can just start with when you were diagnosed with NF2, can you tell me a little bit about that?

P – Ok, it was when I was 16, year 11, I had an i-pod and I always assumed the right earphone was broken. I couldn't hear from it. One day I was in the playground with one of my mates and he was like "can I listen to your i-pod" and I said "yep, but watch out, the right earphone is broken." He listened and said "no it isn't" and I was like "oh". I thought that was strange. And then I developed a little lump here [points to face] and another little lump here [points to face] and I was concerned. My mum said that they were just fatty lumps.

I – Did you tell your mum about your hearing loss as well?

P – Yes and I sort of connected them, I thought it was strange. We had a biopsy taken from that lump and he said it was a schwannoma. And he said "I reckon we should do an MRI scan"

I – And what did you think then?

P – I was like, it will sound stupid, but I was like quite excited, I'd never had anything wrong with me, I was fit and healthy and it was like, oh wow. I was missing lots of school which was quite nice. It was new and quite exciting and stuff. Anyway, I had the scan and I was about to play football. He rang us up, I could still hear in my left ear so I could speak to him, and he said, "the results are back". I was like, "I'm going to play football, can we re-arrange the time" and he goes "well I think you should come in", hinting at something, and I was like, "ok". That's when we found out obviously on the right side, like a big tangerine, 4cm and I was like 'whoah". And he said you know, "an operation to remove it". He said in 6 months or more you'd probably collapse or something like that you know. And I was like "Oh". It was really strange, it was just weird, because I couldn't have imagined all the events."

I – It's quite a lot to cope with at that age

P – I wasn't scared, because I was 16, I didn't know that much. I'd never had an operation and so it was like "bring it on". I was naive you know.

I – how upset were you when you first found out?

P – It was sort of like typical me, it sounds weird, but I always expected to get something. I could sort of feel that something wasn't write. The few months leading up to the operation, I was a bit, I developed shingles and was sleeping a lot. My mum noticed that and I was, like in the playground or in a film and stuff, I wasn't my usual chirpy self. So I was sort of expecting it but you obviously couldn't predict that.

I – Were you surprised when you found out?

P – I obviously missed loads of school, I didn't realise the severity. It was like, just do it and move on. I didn't realise the severity. It wasn't a question of not having the operation, I had to have it. So it like, yeah, I've got to do it.

I – So as the decision had been made, it was quite easy to face the next obstacle?

P – I didn't realise about NF2. I just thought, brain tumour, get it removed. I was in the last year of GCSEs and I knew I'd come back for my exams, exams in July, operation in February, it was quite a while. The school were alright about it, they said if you're too unwell you don't have to do them but you can still get into the sixth form because they knew I was a good student. I didn't really think about it that much, it was kind of like exciting because it was new.

I – Did you tell many of your friends?

P – Yes I did actually. They couldn't really believe it. When I said I had a brain tumour they were like "shit, you've got a brain tumour". It wasn't a joke. In school everyone heard about it and the last week leading up to the operation if I walked into a class I got a standing ovation. It was really nice. I got quite a few hugs.

I – Did that help or were you embarrassed by all the attention?

P – None of us had ever faced a situation like this. None of my mates had anything wrong so they were sort of like joking about it, the usual banter, like 'in hospital look out for the nurses'. We were 16, we weren't prepared for it.

I – Is joking something that you use to get through things?

P – Yes, I think that it takes off the pressure. It doesn't make it seem like such a big deal.

I – How long do you think it took before they made your diagnosis? Did it take a long time or was it quite quick?

P - Quite quickly. I'd always had, for as long as I can remember, a dull pain right there [points] where the tumour was and I always assumed, because I

always slept on my right side because there was a picture on my left wall that I was scared of, so I always slept facing away from it. I just assumed that the little pain was because I was sleeping on that side. The actual scan was in November time and the operation was in February, it was quite urgent. The hearing, that first went in the new term, I noticed it from October time. That's why no-one, me, my mates, we just couldn't, we weren't sure what to do with it as it happened so quickly.
I – What about your family? How do you think they coped with it all?

P – I think [pause] my mum was like, because I was the youngest son, the youngest in the family, she was like, I'm not saying she liked it, I don't mean that. She just liked to care for me again, because I'm the youngest and stuff. I think they're alright about it.

I – has your relationship changed with your mum and dad?

P – I think that its got better. Because my mum and dad are divorced. I saw my dad loads anyway. They got divorced when I was 8 yrs old and they've both got married again. Dad's got kids actually. I mean, definitely my mum. Because we've been through a lot, going to hospital and on the train, one-to-one time you know. With the deafness, it makes it one-to-one talking and I have to concentrate on what the person is saying and they do the same and speak slowly. The vulnerability makes you closer. I'd say we became closer because we spent more quality time together. It made me realise how much they cared, because they were upset and stuff.

I – do you think its changed your life? Are you the same person you were before you found out?

P – it has changed me a lot. I used to be, like, sit in the middle of the table and dictate the talk. But now, I can't do that. It's rare if I'm sitting in a group, for me to follow along. I've got to make the topic of conversation. If its just a random topic, I won't get it. And it has made me more, not like shy and withdrawn, but more like, not as outgoing. If somebody comes to talk to me, that's fine. It happened so quickly – you change a lot from 16 to 20, so who's to say I wouldn't have become like this anyway? I've kept the same friends, so in that respect I haven't really changed much because if I had changed I would have had different friends. My character is still pretty much the same. I think I'm handling it ok.

I – What about your relationships with your siblings?

P – We always got on really well, but now because they have to talk slower and speak to me one-on-one it shows how much you need each other. It made me realise that I needed them. Because they're older than me, they've always been really protective. So they probably feel even more protective, because there's something wrong with me. They probably feel more superior, which is good, they can look after me.

I- So do you think that they may like it in some way?

P – Yes, it's strange. Its just because it happened so quickly. I'm not religious or anything, but I think I was meant to get the whole NF2 thing. Because it hasn't really changed me. I don't know what I would be like without it, things might not be a lot different, you know.

I – Does it make you angry?

P – No, it's annoying. I just see it as if it was meant to happen. I'm still the same person. When I was ten, I'd say to myself, I want to pass my driving test first time – I did that last year. I want to go to a good university in a big city – Leicester is a big city. I'm on track you know. My goals haven't changed.

I – Is there anything you can't do, physically.

P – The balance is a problem. We went to Ibiza with my mates last summer and there was a beach with lots of rocks. They were all climbing them but I just knew I couldn't so that restricted me.

I – how did that make you feel

P – I never felt that I was missing out or anything. I can't do that, so I'll go and do something else, something better. On a train, standing up, that's tough. I always make sure I have something to hold on to. Sport, I've had to change. I still play football, that's a really big passion, I've noticed that I'm not the same player that I was. I do a lot of gym work now or running. It's a solo thing. I run a lot outside, I hate treadmill running. I like the whole scenery thing and being outside. I run maximum four miles. I keep a decent pace.

I – what do you think about when running?

P – I think about my life, but not really about NF2. I have a nice life at the moment, I have a lot to look forward to. Its not like I'm alone, I'm lucky in that respect. I wouldn't run with a friend, because I'd have to look at them the whole time. I do like being on my own sometimes. Like in the gym, I prefer it on my own – me time. I'd have been like that anyway. NF2 is part of me. I really don't think my life have changed that much. I only know of 3 guys with NF2. It sounds really insensitive, but they're my motivation of what not to become. It sounds bad, but they all work part-time, they're not that well-educated and they don't have a lot of friends. I sort of feel like I'm a new hope. I look at them and I think…

I – How did you meet them?

P- At LINK. I met two guys at that and one was one of their friends. When I tell my mum this, she says I shouldn't think like that, but its true, they're not an inspiration, they're an anti-inspiration.

I – What do you think the difference is between you and them?

P – They've got no aspiration. I understand that they have difficulties dealing with their condition, but I think we're on a level playing field. I think that some people jump the hurdle and carry on. Those guys have got NF2 and let it beat them. Sometimes when I'm at University reading and I'm tired, I think if I go to have a sleep, I've let NF2 beat me. When I was at LINK the person said that there would be an NF2 person joining us in the middle of the week and I was looking forward to it. It was the opposite and it made me think that maybe I should be inspirational to other people. The guys I've meant wouldn't be inspirational to me. If there was some new guy, a little kid with NF2, I'd hope that I could give them hope. That's one way NF2 has changed me. Like the Paralympics. Pre-NF2 I dismissed it but now I appreciate that it's really inspirational. I want to get this operation out of the way, but then… I'd like to give inspiration to other people and show them there's more to life than NF2.

I – Do you think about NF2 a lot, or does it not normally come up in everyday life?

P – Obviously now I'm thinking about it a lot because of my operation. I've always been one to think ahead. Even now I plan ahead. I asked the other NF2 bloke "what are you're hope" and he said "don't really have any" "what are your fears?" "Don't really have any." That's the complete opposite ethos to me. I do think about it a lot but I think of ways around it. I like to think about every scenario. Like the operation – I've always known it's a possibility so I what to think about it. I work out difference outcomes and work out how I'll deal with it. You do always think about it. It doesn't mean a bad thought – its like a normal person, if they're sitting by the sea, they'll always have in the back of their mind 'maybe I'm going to drown'. Subconsciously its always with you, but its not like you're sitting on a bus thinking 'I hate NF2'. Its not always a big deal.

I – What do you think about work in the future?

P – I had to change my career aspirations. Now I want to be a management accountant. When I had my first operation, my stepdad is a chartered surveyor, and I said to him 'what about being an accountant?' And he said that accountants were really boring, so I dismissed it. I wanted a career like law or economics and business. I got some advice from a man from LINK and he said that accountancy would suit a deaf person. As I was weighing it up I thought it was secure, good money. I think a job does define you and helps with your ego. It would be nice to help people that are deaf and with NF2. A lot of guys who have illness are the executive directors of charities. My mum always says 'it's going to be a struggle for you to work fulltime'. I use that as a motivational factor to prove her wrong. At university fatigue hasn't been an issue, I was always up-to-date with my work and if I can do that, then well not.

I – Do you think your family are pleased that you went to university?

P – My dad, definitely. He's quite successful in retail, so he's like 'achievement, achievement'. My mum, its because I'm the youngest and she does worry. But they're paying for my accommodation, so I guess they must be glad.

I – Do you think your mum is protective of you?

P – She was always like that, because I'm the youngest. Yesterday I had to text her to tell her where I was. I went travelling to Europe last summer. I still let her know and text her, I know she's worrying and its not a big deal to just text her and relieve her worries.

I – Does it ever annoy you?

P – Not really. It would annoy me if she wasn't a loving mum. Its nice. I've got a car, so I get a lot of freedom from that. She doesn't restrict what I do. My oldest two brothers: the oldest one was in jail, his friends aren't good people and he got involved in drugs. Then my second oldest brother has always been quite single minded and doesn't listen to anyone. I think its nice that mum has me who she can worry about and see as a more normal youngest child that she can worry about and 'baby'. She's never said that I can't do something. Deep down she must know that I've been through a lot.

I – Do you ever get moody, do you have a temper?

P – I am really mellow. My dad used to get really angry, when we were in the car he used to get road rage and stuff. My brothers have a bit of a temper. I've just always been really chilled out. I take everything in my stride. I can confidently say that NF2 has nothing to do with how laid back I am. If anything, its made me realise that life is too short to stay angry all the time.

I – Can you see any positive things that having NF2 has done for you and your family?

P – It improves relationships. It is a good thing. I can't think what my life would be like without it. I could have got in with the wrong crowd, my personality might have changed. The good stuff; one to one personally with family and friends is more close.

I – Do you have any other ways of coping with NF2/

P – I just plan, that's the best strategy. If you plan things, you can hope for the best and expect the worst.

I – Have you done any research into NF2?

P – Yes, you can't help typing it into google and there's a lot of crap on the internet. There's been some nights when I've spent hours looking through case studies, looking for inspiration I suppose. I remember when I first got diagnosed. The doctor said to my mum, 'don't look on the internet because

you'll read a lot of bad stuff.' And that same day she went home and looked it up and I remember seeing the stuff she'd printed off and I read it and was like 'shit'. They made it hit home that it was a bit more serious than I thought. I just accepted it. It is depressing when you see other guys working part-time, like I'm scared that's what I'll become but it acts as motivation.

I – Do you see that as a failure on their part?

P – I can't judge success or failure, but it's the same as those guys who work 9-5 in a factory. You've got to think of lots of factors in their life. But a young bloke – if it were me I would definitely see that as a failure. Going to a good university was a real confidence booster. There are lots of universities that aren't very good, but because Leicester is an established university. It makes me feel better.

I – would you like to have a family in the future, is it something you've thought about?

P – What like marriage and stuff? My dad and his new wife have got two young children and I get on well with them so it would be nice. I'm not one of those guys who wants to settle down when I'm 20. My stepdad married my mum when he was 36. They don't have any kids and I'd regret that if I didn't have any kids. I do think that I'd like a family life, it's the ingredients of a happy life. They're the risk of passing it on, but they can test.

I – would you not want a child with NF2?

P - If there was a developing fetus and they could say that its going to have NF2 then I would terminate it.

I – Some people with a genetic condition would want a child with that condition, what do you think?

P – Strange! I wouldn't want to impose NF2 on them.

I – Which of the problems: balance and hearing has the worst effect on your life?

P – the hearing. If I'm not looking at someone its really hard. The balance can be improved, handrails and things. The hearing is worse. After the operation, not hearing the music again will be bad. In Ibiza you see all these people loving the music and you think about that. Losing a sense is like losing a part of you and it is really annoying, but you just have to deal with it.

I – How do you think you're going to cope with it.

P – Well my hearing is pretty crap now but it will be different having no hearing, this implant, who knows what it will sound like. This is the most challenging chapter. You do worry what it will be like with no hearing. One saving grace is that it has got worse slowly. The good thing about it being

gradual is that I've had time to deal with it, my friends have had time to adjust, my family have had time to adjust. The fact that its been gradual over four years, its helped.

I – what do you think will be the worst thing about losing your hearing?

P – probably in group situations. Its just so hard to participate. If someone says something and you don't hear them, you lose what they've said. Text messaging and the internet helps. If mobile phones didn't exist, I might lose contact with my friends. I think its more than a coincidence that I've lost my hearing yet texting and the internet is really popular. Its funny how it works out. Losing the hearing is the whole package – there's not just element I'd miss, its all of it. Its like when you put toast in a toaster, you know you have to remember it because you won't hear it pop up.

I – Has your facial paralysis made much of a difference?

P – I walked into school as normal and told everyone the facts. It's a secondary school with 2000 pupils and word got around. I just said what the story was. I think – I've had a life saving operation and though its annoying, facial paralysis is not a bad end product from a life saving operation.

I – Does it bother you when you meet people for the first time.

I – There've been numerous occasions, like when I got on a bus, the driver said 'have you had a stroke?' and at the bank, this cashier kept asking me questions. That makes you feel vulnerable. I think that's why I go to the gym a lot, not to look meaner but to make myself less vulnerable. I used to work in Next childrenswear and I did get a lot of stares from the children, it is annoying.

P – Has it stopped you from doing anything?

I – Drinking through a straw or blowing up balloons! I hate eating in public, but quite a lot of people do. Its like moving your mouth. Photograph were an issue, but now I do a funny pose to attract attention. Shouting or talking really fast are hard to do without it sounding weird.

P – When you meet new people, does anyone ever ask about it?

I – I don't really explain it. I don't get asked much, I don't look too vulnerable, because I'm pretty normal, its not a big issue. When someone says – what's wrong with your face, I can't be bothered to explain it, I just walk away, I won't take time to explain my reasons. I don't get a lot of hassle. Maybe a new person, like a friend of a friend, their initial look might be a bit longer, like in fresher's week meeting lots of people, it was weird but it was fine. I settled in really well.

P – Does having to go to lots of hospitals annoy you.

I – After the first operation, any hospital when I walk down the corridor I see people in bed and feel sorry for them. But I do like it, meeting doctors and people, they're nice people and good company. When I was at school I could take time off and that was good! On my gap year I was working and had to take time off and that was fine. I do worry about my dad having to take time off in this financial climate. Me personally, I don't have lots of commitments at University so I can just get the train. At the moment its not a problem.

P – what about the scans, do you get nervous.

I – yes, its not the scan that's the hard part, it's the results! When I got the results before the University and I needed an operation, I was expecting it. I knew it because I'd had bad dreams and my balance was worse. Before then I always expected good news, I've always been the kind of person who liked getting a test back because I'd normally done quite well, so my normal reaction was to look forward to the results. But from now on, any scan I won't look forward to it.

P – What about the eye checks and those screening tests

I – Yes I've had that and it was fine.

P – would you rather have regular checks or would you rather just go if you had a problem?

I – what like ignorance is bliss? No, a test can go both ways and it may be good news. My dad is 50 now and I tell him to go to the GP to get checked but he'd rather not know. Its only a test, I don't exactly like them but its important to benchmark your progress.

P – have you joined any NF support groups?

I – I did look on the internet for a forum but couldn't find any groups.

P – did your experience at LINK put you off?

I – I'm going back to LINK in July and it would be good to talk to others about it. In the future I'd be interested.

P - is there anything we could do to improve our clinic?

Even though patients have severe hearing loss, some doctors talk really quietly and don't move their mouths enough so I can't understand. I don't know if its an ego thing? It may be that some doctors think they're the important one and patients should listen to me.

END

Interview 2

I - Can I just ask about when you were first diagnosed?

P - It was when I was teaching in 1993, we were learning to Morris dance and I found that I couldn't lift my feet up which was really strange, I hadn't noticed that before. By Christmas that year, my legs felt heavy and cold and I couldn't run, I started to fall over.

I - What did this make you think?

P - I was really scared, I thought I must have multiple sclerosis or motor neurone disease, I was terrified.

I - So what happened next?

P - Well I was living in xx at the time and I went to the hospital there. They transferred me to xx Hospital and I had lots of tests and an MRI scan. I had lots of medical students examining me and practising on me and that really upset me as I didn't know what was wrong with me. At the time I couldn't walk. I was then told that it was due to a spinal tumour – a spinal schwannoma and it was removed.

I - When was the diagnosis of NF2 made?

P - After my scans they realised what was going on. I'd never heard of it before, and I was initially pleased that it was that rather than MS or MND. I was seen by a geneticist and that really upset me, they said that 'most people with NF2 wouldn't have children' which was devastating. I was cross that doctors kept calling it a disease.

I - What about the NF2 clinic?

P - The first thing I felt when I walked in to the clinic was a massive sense of relief, that someone knew what was going on and could help me.

I - How did you find out more about NF2?

P - I joined the NF association and found it extremely helpful, I got most information on NF2 from there. I didn't look on the internet, I'm not sure why really.

I - How has NF2 changed your life?

P - Well initially I always wanted three children, but now I'll stick with two, I couldn't risk having another with NF2

I - What do you think about pre-conception testing?

P - I totally disagree with it. I would never have it. It's like it completely devalues mine and Harriet's lives – we wouldn't be here if it had been used. Actually the thought of it makes me really angry.

I - How do you cope with NF2

P- Prayer helps a great deal. I'm part of a prayer group with my church and it helps to know that God loves me unconditionally. People at church don't really know what NF2 is, but they pray for me whenever I have an appointment or a scan. It really helps to have a community supporting you.

I - How else has your life changed since your diagnosis?

P - I feel that the diagnosis has been strengthening, it has changed my personality, I'm more confident than I was before. It has also helped me to succeed in my job – I just have to get on with it now. The children at school are very good – I have no problems with them. I've explained about my hearing aid. My brother had hearing difficulties and I had a very good experience with him so that has helped me.

I - How has it changed you physically?

P -I can't run in a straight line, and I can't cycle. I wanted to do the Race for Life but I couldn't. Sometimes this makes me feel sorry for myself but my friends, family and prayer pull me out of it.

I - What kind of a person are you?

P - I see myself as a happy, bubbly person. I try to see the positive in everything and to have a positive attitude.

I - Do you have thoughts about the future?

P - I know that I'll have a restricted lifespan, so I'm keen to take all the opportunities I'm given. I do think about my own death. I worry that my children will not be as close to their cousins and extended family than I was as we seem to be growing apart. I try not to dwell on it.

I - How has your diagnosis affected your family?

P - I don't think that it has changed my husband. The worst time was when Harry was diagnosed. I knew that there was something wrong when she couldn't breast feed. During the pregnancy, I didn't really think about NF2, I was too busy worrying about other things. As I hadn't been affected until I was much older, I thought that it wouldn't give her any trouble. I thought that she wouldn't be affected until she was in her thirties and by that time technology would have advanced so much that she wouldn't really be affected. When she was born I was told that she was blind and I felt guilty that she had inherited NF2. Then I realised that she did have some vision and she was diagnosed with retinal hamartomas.

I - Do you have concerns about your daughter's future?

P - I do worry that she won't be able to drive – we live in a village, I worry that she'll rebel against the NF2 as a teenager. At the moment she is fantastic. Her sister really looks out for her and we just treat them the same.

I - Does the management of your condition bother you – appointments and scans?

P - Most of the year, I completely forget that I have NF2. It's when I have appointments and scans that I get reminded. I start worrying in the weeks running up to my appointments, particularly that things will have got worse and that I'll need an operation.

I - Do you have any suggestions on how we could improve our clinic?

P - Try to de-hospitalise the waiting room – books, coffee, magazines.

I - How do you find the number of people in the clinic?

P - I find it reassuring and I like it that the whole team is there – and that they are all experts.

I - Are you able to hear everyone well, do you feel happy asking questions?

P - No problems there at all.

I - What do you think about the NF association weekends/meetings

P - The weekends are too far away and last too long. You have to think about NF2 for the whole weekend. You're forced to socialise with people you have nothing in common with apart from the worst thing in your life – NF2. You're making false links with people with whom your only link in the condition – not something to celebrate!
When Harriet was first born, I wasn't interested, all of the NFA leaflets when straight in the bin. Now I am keen on meeting other mums with children with NF2.

I - What hopes do you have about the future?

P - I do have big hopes about further non-surgical treatment – drug treatment and gene therapy.

END

Interview 3

I – Can you tell me what happened when you first found out that you had NF2?

P – I was first told I had NF2 in 1993. In 1992 I had an epileptic fit, but nobody thought anything of it. I had another one and a scan was organised for me. I had no idea what NF2 was when I was first told. When they found out it was NF2 they transferred me to Southampton and the neurosurgeon there wanted to operate on me. I saw an NFA newsletter and got in touch with Dr Ferner.

I – Did you understand what NF2 was?

P – Nobody described it and no-one looking after me seemed to know what it was. This made me really frightened, but things have changed a lot since then, I'm not frightened anymore.

I – What impact did the diagnosis have on you?

P – Not much to start with, I could still play hockey, I could still here, things hadn't really changed. Then in 1996 I had another seizure and I had to have an operation to remove the tumour, I couldn't play hockey anymore after that. It was really hard even to walk. I tried to carry on working but then in 2000 I was having problems walking. I couldn't work. I'd wake up in the morning with no idea how I might feel so I couldn't keep working.

I – How did your friends and family cope with everything?

P – Well, after my first operation, I got about 70 get well cards, and after my third and fourth I only got about 12. Lots of so-called friends disappeared. That really upset me, I realised how shallow people were. The few friends that I've got left are really good friends. My dad couldn't cope with the fact that his little baby was ill. He goes to great lengths to tell people to behave to help me, e.g. so I can lip read. It really bothers him and makes me really sad but he can't change.

I – Has having NF2 changed you as a person?

P – I think so, I'm more cynical, I try not to bother about pathetic things. It really annoys me when people complain – I think 'if only that was my worst problem'. I do sometimes think about ending it all, but I don't think I ever would. It would be selfish and upset my family too much. I do feel that I've got things to live for. I play olf with a friend still. I have a friend in the US with NF2 and she's really helpful, we email each other.

I –What about your relationships?

P – I was in a relationship for six years and had to end it because she wanted children. I had to break up with her and found it really hard, I do still. She's

now got three children. I have met one other girl and I would be keen to meet up again and perhaps start a relationship.

I – What about having children?

P – I do really want to be a dad, but couldn't live with myself if they had NF2. I've decided that I'm not going to have children.

I – How else has having NF2 affected you?

P – I think that I've come to terms with having NF2, but I don't like it! The life I had before and the life that I have now are very different. I used to love travelling but now I can't. I can't be alone because of my epilepsy. I was really independent before, I travelled on my own, I find it really hard to be reliant on other people. I'm a private person – I don't want to burden anyone else. I talk to my dog about things and also to my friend Geoff. No-one else knows.

I – How do you cope with things?

P – I don't know, I just do! What else can you do? I can't do anything about it, worrying about it won't change anything. You just have to hope. I keep things to myself, I think it would be unfair to tell my parents, it must be awful to see your child being unwell.

I – What do you find hardest to deal with?

P – how debilitating NF2 is. If it was just one thing, fits, paralysis, being deaf then I could cope. Because its all of them, it just wears you down. I try not to worry about the future, ignorance is bliss.

I - Can you think of anything good that's come from having NF2?

P – Meeting Dr Ferner, Mel and other people with NF2. I used to have an NFA advisor when it was bigger but don't anymore, now I have a counsellor.

I – Would you like to be more involved in events for people with NF2/

P – I would like to come to meetings, particularly in the evenings, but lots of people won't – there's such a big range of illness severity – people who aren't badly affected might think – that could be me! I used to be the youngest at NFA events now I'm the oldest, everyone else has died.

I – How do you find dealing with hearing loss?

P – I miss listening to music every day. I can hear a tune in my head, I try to remember different songs and play them in my head. I do have days when that gets me down. I don't know how I pick myself up out of it. The biggest thing that I miss is the sound of the sea. Sounds like that you take for

granted. Birdsong. It takes a lot of getting used to. Going to football matches and they're silent.

I – how have you found the management of your NF2?

P – I feel in control of it, as much as I want to. I really like Guy's. My local hospital was a disaster. I don't mind seeing so many doctors in the clinic – and have no problems with communication and understanding what is going on. I don't think that it's a good idea having a whole day in the clinic, I find that really tiring.

END

Appendix B

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

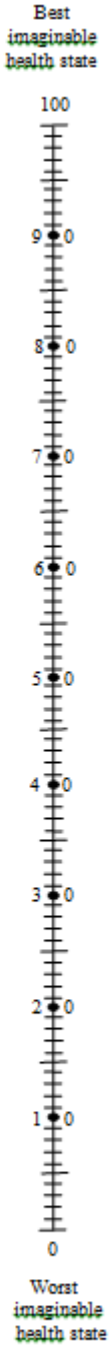
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



PILOT - The Guy's NF2 Impact – Quality of Life Score (NFTI-QOL)

It would be helpful to know some basic information about you:

Current age: (years)_____ Sex: Male / Female (please circle)

For the following questions, please circle the most appropriate answer for how you feel at this time.

Questions about work include paid and voluntary jobs and also housework. If you are retired or unemployed, please circle N/A (not appropriate).

Q1. Have balance/ dizziness problems caused you difficulty at work?

(e.g. stopped you performing your usual job, made you change what you wanted to do for a job)

YES 3 NO 0 N/A

Q2. Have balance/ dizziness problems caused difficulties in your social life?

(e.g. going out, planning holidays, etc)

YES 3 NO 0

Q3. Have balance/ dizziness problems caused difficulties in your family life?

(e.g. playing with your children, caring for others, doing housework, relationships)

YES 3 NO 0

Q4. Have balance/ dizziness problems restricted your ability to travel?

(e.g. cannot ride bike, travel by car, plane, public transport)

YES 3 NO 0

Q5. Have hearing problems caused you difficulty at work?

(e.g. answering the telephone, talking in a crowded room)

YES 3 NO 0 N/A

Q6. Have hearing problems caused difficulties in your social life?

(e.g. talking to friends, listening to music, meeting new people)

YES 3 NO 0

Q7. Have hearing problems caused difficulties in your family life?

(e.g. conversations with family, keeping in touch)

YES 3 NO 0

Q8. Have hearing problems restricted your ability to travel?

(e.g. cannot ride bike, travel by car, plane, public transport)

YES 3 NO 0

Q9. Have problems with your appearance (e.g. facial weakness) caused you difficulty at work?

YES 3 NO 0 N/A

Q10. Have problems with your appearance (e.g. facial weakness) caused difficulties in your social life? (e.g. meeting new people, going to the pub, going shopping)

YES 3 NO 0

Q11. Have problems with your appearance (e.g. facial weakness) caused difficulties in your family life?

YES 3 NO 0

Q12. Have problems with your appearance (e.g. facial weakness) restricted your ability to travel?

(e.g. cannot ride bike, travel by car, plane, public transport)

YES 3 NO 0

Q13. Has your medical condition changed your role in life?

(e.g. unable to care for family, be the breadwinner)

YES 3 NO 0

Q14. Has your medical condition prevented you from achieving what you wanted to do in life?

(e.g. job aspirations, education, sports, family)

YES 3 NO 0

Q15. Does your medical condition make you feel vulnerable?

(e.g. unsafe, loss of confidence, weak)

YES 3 NO 0

Q16. Do you worry about the possibility of passing your medical condition on to your children?

YES 3 NO 0

Q17. How severe would YOU say your medical condition is?

MILD 1 MODERATE 2 SEVERE 3

For the next section, circle the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer.

Q18. I feel tense or 'wound up':

Most of the time
A lot of the time
From time to time (occasionally)
Not at all

Q19. I still enjoy the things I used to enjoy:

Definitely as much
Not quite as much
Only a little
Hardly at all

Q20. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly
Yes, but not too badly
A little, but it doesn't worry me
Not at all

Q21. I can laugh and see the funny side of things:

As much as I always could
Not quite so much now
Definitely not so much now
Not at all

Q22. Worrying thoughts go through my head:

A great deal of the time
A lot of the time
From time to time, but not often
Only occasionally

Q23. I feel cheerful:

Not at all
Not often
Sometimes
Most of the time

Q24. I can sit at ease and feel relaxed:

Definitely
Usually

Not often
Not at all

Q25. I feel as if I am slowed down:
Nearly all the time
Very often
Sometimes
Not at all

Q26. I get a sort of frightened feeling like “butterflies” in the stomach:
Not at all
Occasionally
Quite often
Very often

Q27. I have lost interest in my appearance:
Definitely
I don’t take as much care as I should
I may not take quite as much care
I take just as much

Q28. I feel restless as if I have to be on the move:
Very much indeed
Quite a lot
Not very much
Not at all

Q29. I look forward with enjoyment to things:
As much as I ever did
Rather less than I used to
Definitely less than I used to
Hardly at all

Q30. I get sudden feelings of panic:
Very often indeed
Quite often
Not very often
Not at all

Q31. I can enjoy a good book or radio/TV program:
Often
Sometimes
Not often
Very seldom

This concludes the NFTI-QOL. Many thanks for your time.

NFTI-QOL

(Neurofibromatosis 2 impact on quality of life)

English version for the UK

INSTRUCTIONS FOR COMPLETING THE NFTI-QOL

Please complete the following information:

Age: _____ years

Gender: Male □ 1 Female □ 2 (please tick)

For each of the questions on the next page, please tick the one box that describes how you feel today

Usual activities include: work; housework; study; sport; social; family or leisure activities

Patient ID/Label:

Q1. Do balance or dizziness problems stop you performing your usual activities?

- No balance problems or dizziness ☐0
- Balance or dizziness problems but no difficulties ☐1
- Balance or dizziness problems cause me some difficulties ☐2
- Balance or dizziness problems stop my usual activities ☐3

Q2. Do hearing problems stop you performing your usual activities?

- No hearing problems ☐0
- Hearing problems but no difficulty ☐1
- Hearing problems cause me some difficulty ☐2
- Hearing problems stop my usual activities ☐3

Q3. Does facial weakness stop you performing your usual activities?

- No facial weakness ☐0
- Facial weakness, but no difficulty ☐1
- Facial weakness causes some difficulty ☐2
- Facial weakness stops my usual activities ☐3

Q4. Do problems with your sight stop you performing your usual activities?

- No problems with sight ☐0
- Sight problems, but no difficulty ☐1
- Sight problems cause me some difficulty ☐2
- Sight problems stop my usual activities ☐3

Q5. Do you have any problems in mobility and walking?

- No problems in mobility and walking ☐0
- Some difficulty but can manage on my own ☐1
- Unable to walk around without some help ☐2
- Unable to walk at all ☐3

Q6. Has your medical condition affected your role and outlook on life?
(e.g. confidence, vulnerability, relationships, caring for family, career, having children)

- No effect or positive effect ☐0
- Small negative effect ☐1
- Moderately negative effect ☐2
- Large negative effect ☐3

Q7. Pain; throughout our lives, most of us have had pain from time to time such as mild headaches, sprains and toothaches. Have you had pain *other than this* in the last week?

- None ☐0
- Mild pain ☐1
- Moderate pain ☐2
- Severe pain ☐3

Q8. Do you currently suffer from anxiety or depression?

- No ☐0
- Mild anxiety or depression ☐1
- Moderate anxiety or depression ☐2
- Extreme anxiety or depression ☐3

If you have any further comments regarding the impact of NF2 on your quality of life, please write them here:

You have now completed the NFTI-QOL. Thank you for your input.

NFTI-QOL

(Neurofibromatosis 2 impact on quality of life)

English version for the US

INSTRUCTIONS FOR COMPLETING THE NFTI-QOL

Please complete the following information:

Age: _____ years

Gender: Male 1 Female 2 (please circle one)

For each of the questions on the next page, please check the one box that best describes how you feel today

Usual activities include: work; housework; studying; sports; socializing; family life or leisure activities

Patient ID/Label:

Q1. Do balance or dizziness problems stop you performing your usual activities?

- No balance problems or dizziness ☐0
- Balance or dizziness problems but no difficulties ☐1
- Balance or dizziness problems cause me some difficulties ☐2
- Balance or dizziness problems stop my usual activities ☐3

Q2. Do hearing problems stop you performing your usual activities?

- No hearing problems ☐0
- Hearing problems but no difficulty ☐1
- Hearing problems cause me some difficulty ☐2
- Hearing problems stop my usual activities ☐3

Q3. Does facial weakness stop you performing your usual activities?

- No facial weakness ☐0
- Facial weakness, but no difficulty ☐1
- Facial weakness causes some difficulty ☐2
- Facial weakness stops my usual activities ☐3

Q4. Do problems with your sight stop you performing your usual activities?

- No problems with sight ☐0
- Sight problems, but no difficulty ☐1
- Sight problems cause me some difficulty ☐2
- Sight problems stop my usual activities ☐3

Q5. Do you have any problems in mobility and walking?

- No problems in mobility and walking ☐0
- Some difficulty but can manage on my own ☐1
- Unable to walk around without some help ☐2
- Unable to walk at all ☐3

Q6. Does your medical condition affect your outlook and participation in your life? (e.g. confidence, vulnerability, relationships, caring for family, career, having children)

- No effect or positive effect ☐0
- Small negative effect ☐1
- Moderately negative effect ☐2
- Large negative effect ☐3

Q7. Pain; throughout our lives, most of us have pain from time to time such as mild headaches, sprains and toothaches. Have you had pain *other than this* in the last week?

- None ☐0
- Mild pain ☐1
- Moderate pain ☐2
- Severe pain ☐3

Q8. Do you currently suffer from anxiety or depression?

- No ☐0
- Mild anxiety or depression ☐1
- Moderate anxiety or depression ☐2
- Extreme anxiety or depression ☐3