



The University of Liverpool

Doctorate in Clinical Psychology

**Emotional distress in Motor Neurone Disease:**

**The role of metacognitive beliefs and repetitive negative thinking**

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Navigation

Search document

HEADINGS PAGES RESULTS

- Measures
  - Demographics questionnaire...
  - Hospital Anxiety and Depressi...
  - Metacognitions Questionnaire...
  - Repetitive Thinking Questions...
  - Self-administered ALS Function...
- Procedure
  - Statistical Analysis
- Results
  - Association of Metacognitive Bel...
  - Mediation of the Relationship bet...
- Discussion
  - Limitations
  - Clinical Implications
  - Future Research
- References
  - Appendix A – Author Guidelines
  - Appendix B – Systematic review p...
  - Appendix C – Data extraction sheet
  - Appendix D – Quality Assessment...
  - Appendix E – Participant Flow
  - Appendix F – Power Calculation a...
  - Appendix G – Research Review C...
  - Appendix H – Research Review C...
  - Appendix I – Research Review Co...
  - Appendix J – University of Livep...
  - Appendix K – Research and Ethics...
  - Appendix L – Research and Ethics...
  - Appendix M – Site Permission Let...
  - Appendix N – Site Permission Let...
  - Appendix O – Health and Researc...
  - Appendix P – Participant Informa...
  - Appendix Q – Participant Consen...
  - Appendix R – Questionnaire Book...
  - Appendix S – Exploration of No...

Figure S10. Histogram of HADS-T scores. Dependent Variable: HADS total score (adjusted for MND) (Items removed: A1 & D1 & D2)

Figure S10. P-Plot of HADS-T. Dependent Variable: HADS total score (adjusted for MND) (Items removed: A1 & D1 & D2)

Figure S11. HADS-T scatterplot. Dependent Variable: HADS total score (adjusted for MND) (Items removed: A1 & D1 & D2)

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## Contents

Acknowledgements .....	iii
Contents .....	iv
List of Tables .....	v
Chapter 2 .....	v
Chapter 3 .....	v
List of Figures .....	v
Chapter 2 .....	v
Chapter 3 .....	v
List of Appendices .....	vi
Chapter 1: General Overview .....	1
References .....	5
Chapter 2: A Systematic Review of the Predictors of Distress in Motor Neurone Disease .....	7
Abstract .....	7
Introduction .....	9
Method .....	12
Search Strategy .....	12
Inclusion Criteria .....	12
Data Extraction .....	13
Assessment of Risk of Bias .....	13
Data Synthesis .....	14
Results .....	14
Risk of Bias Assessment .....	19
Demographic and Clinical Predictors .....	21
Social Predictors .....	28
Psychological Predictors .....	28
Discussion .....	29
Limitations of Included Studies .....	31
Implications for Future Research .....	32
Strengths and Limitations .....	33
References .....	35
Chapter 3: The role of metacognitive beliefs and processes in distress in people living with Motor Neurone Disease .....	44
Abstract .....	44
Introduction .....	46
Method .....	50
Participants .....	50

Design .....	51
Sample Size.....	51
Measures .....	51
Ethical Considerations .....	53
Procedure .....	54
Statistical Analysis.....	55
Results.....	56
Association of Metacognitive Beliefs and Distress .....	57
Mediation of the Relationship between Metacognitive Beliefs and Distress by Repetitive Negative Thinking .....	59
Discussion .....	61
Limitations .....	63
Clinical Implications .....	64
Future Research .....	65
References.....	67

### List of Tables

#### Chapter 2

Table 1. Sample characteristics of included papers.....	17
Table 2. Quality assessment of included papers using adapted tool from William et al., (2010).....	20
Table 3. Glossary of distress measures (DVs) used in included papers.....	22
Table 4. Summary of study design and significant findings from included papers grouped by outcome (DV) .....	24

#### Chapter 3

Table 1. Descriptive statistics and Spearman's rho correlations between study variables.....	57
Table 2. Statistics for the final regression model predicting distress (adapted HADS-T).....	58

### List of Figures

#### Chapter 2

Figure 1. A flow chart outlining article selection process.....	15
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#### Chapter 3

Figure 1. Mediation of Positive Metacognitive Beliefs on Distress, via Repetitive Negative Thinking.....	60
Figure 2. Mediation of Negative Metacognitive Beliefs on Distress, via Repetitive Negative Thinking.....	60

### List of Appendices

Appendix A. Author Guidelines for the Journal of Social Science & Medicine.....	78
Appendix B. Systematic review protocol.....	81
Appendix C. Data extraction sheet.....	93
Appendix D. Quality Assessment Tool adapted from Williams et al. (2010).....	96
Appendix E. Participant Flow.....	100
Appendix F. Power Calculation and sample size.....	101
Appendix G. Research Review Committee Approval.....	102
Appendix H. Research Review Committee Amendment Approval.....	103
Appendix I. Research Review Committee Amendment Approval.....	104
Appendix J. University of Liverpool Sponsorship Approval.....	105
Appendix K. Research and Ethics Committee Approval.....	107
Appendix L. Research and Ethics Committee Approval Amendment Approval.....	109
Appendix M. Site Permission Letter (Walton Centre).....	111
Appendix N. Site Permission Letter (Preston).....	112
Appendix O. Health and Research Authority Approval.....	114
Appendix P. Participant Information Sheet.....	117
Appendix Q. Participant Consent Form.....	121
Appendix R. Questionnaire Booklet.....	122
Appendix S. Exploration of Normality and Parametric Assumptions.....	141

## **Chapter 1: General Overview**

The overall aim of this thesis was to increase the understanding of distress in people living with Motor Neurone Disease (plwMND). Effective medical treatments for Motor Neurone Disease (MND) do not currently exist and treatment tends to focus on enhancing quality of life by managing physical symptoms. However, there is a limited understanding of the factors that are associated with emotional distress and quality of life in MND. Minimal investigation has been conducted into the psychological processes underlying distress and the potential utility of psychological interventions to alleviate distress in plwMND, despite recognition of the potential value of psychological support for plwMND. Increased understanding of the psychological processes underlying distress in plwMND will help to guide the development of evidence-based, MND-specific psychological interventions to reduce distress and improve quality of life.

The first question this thesis attempts to answer is: what is the current evidence for clinical, demographic, social, and psychological predictors of distress in MND? Chapter 2 systematically reviews current evidence for prospective predictors of distress in MND. Predictors are grouped into clinical and demographic, social, and psychological factors. There are few psychologists working with plwMND, thus by considering a variety of predictors, rather than psychological factors alone, it was hoped that the paper would attract the interest of a range of professionals involved in the care of plwMND. It was anticipated that this would raise awareness of distress in plwMND and the value of considering wider factors in supporting people to live well with MND. Current evidence is summarised, along with the strengths and limitations of both the studies included and the review itself. Findings indicated that there were limited prospective studies considering predictors of distress. Of the 11 included studies, there was very limited evidence that demographic, clinical, social, or psychological factors predicted distress.

There was scarce evidence that any demographic factors predicted distress. There was no evidence that overall physical functioning or bulbar functioning predicted distress, but there was some mixed evidence for specific clinical factors. For social factors there was consistent evidence that lower social support predicted distress. In single studies of psychological predictors, mindfulness and cognitive appraisals were significant predictors and warrant further investigation. Recommendations for future research are provided, with more studies, with longer follow-up periods, and larger sample sizes required to consider conflicting findings and to further understand distress in MND.

Another question this thesis attempts to answer is: Does the transdiagnostic Self-Regulatory Executive Functioning (S-REF) model of emotional distress have clinical utility in plwMND? The S-REF model is one theory of the psychological processes underlying distress. It informs metacognitive therapy (MCT) and proposes that repeated information processing in response to thoughts, rather than thought content, leads to distress (Wells & Matthews, 1994). This processing is termed the cognitive attentional syndrome (CAS; Wells & Matthews, 1994). Selection of the CAS is guided by beliefs about thinking, metacognitive beliefs, which can be categorised into positive and negative beliefs (Wells & Matthews, 1994). Holding these metacognitive beliefs can result in increased attention to thinking, and therefore lead to the CAS which results in distress (Wells, 2009).

There were a number of reasons for testing the S-REF model in plwMND. Firstly, MCT is a transdiagnostic and time-limited therapy, which could address a variety of mental health difficulties efficiently (Wells, 2013). This is a key consideration for people with a terminal condition whereby time is valuable. The S-REF model also posits that it is the process rather than the content of thinking that maintains distress, in contrast to traditional cognitive



behavioural therapy (Wells & Matthews, 1994). Therefore, MCT could be more suited to plwMND as the content of thoughts is often accurate and reflective of the nature of the disease, and therefore difficult to challenge. Finally, the S-REF model has demonstrated utility in other physical health populations (e.g. Maher-Edwards, Fernie, Murphy, Nikcevic & Spada, 2012; Cook et al., 2015; Brown & Fernie, 2015), therefore, the S-REF model warrants exploration in plwMND.

Chapter 3 leads into the empirical paper, which provides a detailed account of a research study which aims to test the S-REF model in plwMND. The relationship between metacognitive beliefs and distress was assessed, with the mediational role of the CAS considered. Metacognitive beliefs were measured by the Metacognitions Questionnaire (MCQ-30; Wells & Cartwright-Hatton, 2004), the CAS was assessed by the Repetitive Thinking Questionnaire (RTQ-10; McEvoy, Thibodeau, & Asmundson, 2014), and distress was measured by the Hospital Anxiety and Depression Scale total score (HADS-T; Zigmond & Snaith, 1983), adapted for plwMND. These measures were selected to give a general overview of the model, and its applicability to plwMND rather than focusing specifically on a type of distress such as depression, or anxiety; or aspect of the CAS such as worry or rumination. This allowed consideration of the relationship between metacognitive beliefs and distress, and whether metacognitive beliefs influence distress via the theorised pathway by activating the CAS. Findings indicated that the key prediction of the S-REF model was supported; the relationship between negative metacognitive beliefs and distress was mediated by repetitive negative thinking. Findings and implications are described in Chapter 3. The research is discussed in the context of previous research, methodological limitations, and directions for future research.

It is planned that both chapters of the thesis will be submitted to the journal of Social Science & Medicine subject to the author guidelines in Appendix A.

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**Chapter 2: A Systematic Review of the Predictors of Distress in Motor Neurone Disease****Abstract**

Understanding of the factors that predict emotional distress in Motor Neurone Disease (MND) is limited. This systematic review aimed to appraise currently available data to understand the clinical and demographic, social, and psychological factors that predict distress over time. A systematic search was conducted in three online databases (Medline, PsychINFO and CINAHL Plus) up to November 2016. Studies were included if they were prospective studies assessing if clinical and demographic, psychological, or social factors at baseline predicted distress at follow-up at least one month later in adults with a diagnosis of MND. Only studies written in the English language, using validated measures of distress or quality of life psychological subscales were included. The methodological quality of the articles was also assessed. In total 11 studies were included. Demographic or clinical factors were investigated in all 11 studies, social factors in two studies, and psychological factors in three studies. No conclusive predictors were identified due to the limited number of studies assessing the same predictors, and null or contradictory findings. There was scarce evidence that baseline demographic factors predicted distress. For clinical factors, there was minimal evidence that percutaneous endoscopic gastrostomy use reduced distress. For social factors, there was consistent evidence that lower social support predicted increased distress. Psychological factors were considered only in individual studies, not allowing for comparison of findings. Cognitive appraisals of coping potential, mindfulness, and psychological quality of life were predictors in single studies indicating a need for further research. Findings support previous research that there is no simple or consistent relationship between physical factors and distress. Findings also highlight the lack of prospective research considering potential predictors of distress in MND. Further research is

needed to investigate the mechanisms underlying distress, particularly modifiable factors such as psychological factors, to reduce distress in people living with MND.

Review Registration Number: PROSPERO ID:CRD42017050036

*Keywords:* Motor Neurone Disease, Amyotrophic Lateral Sclerosis, Psychology, Distress, Predictors, Social, Demographic, Clinical

## Introduction

Motor Neurone Disease (MND) is a neurological disorder which leads to the progressive degeneration and death of motor neurones (Brooks, Miller, Swash & Munsat, 2000). There are different variants of MND, including Amyotrophic Lateral Sclerosis (ALS), which can cause a range of physical symptoms (Talbot, 2009). This progressive muscular weakness has a variety of physical consequences that can affect limb, bulbar, and respiratory muscle (Hobson, Harwood, McDermott & Shaw, 2016). This can result in paralysis, swallowing difficulties, speech difficulties, and breathing difficulties (Brooks et al., 2000). Cognitive and behavioural changes occur in some cases, specifically alterations in social cognition and executive functioning difficulties (Bora, 2017). An estimated 10-15% of people living with MND (plwMND) meet the diagnostic criteria for frontotemporal dementia (Gordon et al., 2011; Lillo, Mioshi, Zoing, Kiernan & Hodges, 2011). MND affects slightly more males than females (ratio 1.5:1; Goldstein & Leigh, 1999) and usually occurs sporadically, although there is a familial vulnerability in 5-10% of cases (Leigh & Ray-Chaudhuri, 1994). MND has a prevalence rate of 7 per 100,000, with the average age of onset being 65 years, however, younger (10% under 45 years) and older (20% over 70 years) onset are observed (Talbot, 2009). A cure has not been identified and the life expectancy for approximately 50% of plwMND is three years from symptom onset (Ilse et al., 2015), although 5-10% survive for 10 years or more (Chiò et al., 2013). Riluzole is the only treatment option available; a medication that increases survival time by 2-4 months (Lacomblez, Bensimon, Leigh, Guillet & Meninger, 1996; Miller, Mitchell, Lyon & Moore, 2012). Given the limited treatment options, intervention currently focuses on symptom management and improving quality of life (QoL; Van den Berg et al., 2005). While the key components of QoL are generally agreed to include physical, psychological, spiritual, and social factors, QoL is a

complex concept with no universal definition (van Groenestijn, Kruitwagen-van Reenen, Visser-Meily, Van den Berg & Schroder, 2016) and the factors can vary in importance according to an individual's values (Ferrans, 1990).

There is increasing recognition that plwMND experience clinically significant psychological distress (Felgoise et al., 2010). Distress levels in plwMND are comparable to those living with other motor conditions (Taylor, Wicks, Leigh & Goldstein, 2010), and to psychiatric outpatients (Felgoise et al., 2010). Distress is more prevalent in plwMND than in healthy controls; 20.8% of plwMND compared with 6% of healthy controls were depressed and 85.7% compared with 24% were anxious (Cui et al., 2015). Distress in this population has a number of negative consequences including increased interest in hastened death (Ganzini, Johnston, McFarland, Tolle & Lee, 1998), reduced QoL (Johnston et al., 1999), and reduced survival rates (McDonald, Wiedenfeld, Hillel, Carpenter & Walter, 1994). Therefore, interventions to reduce distress should be a key priority within the treatment goal of improving QoL in plwMND (Pagnini, Simmons, Corbo & Molinari, 2012).

Given the physical nature of MND, research to date has primarily focused on clinical factors. However, an exclusive medical focus is insufficient to provide full support for plwMND (Matuz, Birbaumer, Hautzinger & Kübler, 2010) given the multifactorial nature of QoL and limited treatments available (van Groenestijn et al., 2016). Furthermore, a simple or consistent relationship between physical functioning and distress does not exist (McLeod & Clarke, 2007), with growing evidence that psychological QoL remains stable despite disease progression (Cupp et al., 2011; Ilse et al., 2015). Physical treatment alone neglects other aspects of QoL; accordingly, research has begun to explore other factors associated with distress. Religiosity and social support are associated with improved QoL (Cupp et al., 2011; Matuz et al., 2010).



Conversely, social withdrawal is associated with depression (Gibbons et al., 2013).

Psychological factors are also associated with distress, including negative, threatening, and fixed illness perceptions, for example; “MND has serious consequences on my life,” or “MND is largely due to my own behaviour,” (Matuz et al., 2010; Miglioretti, Mazzini, Oggioni, Testa & Monaco, 2008; Plahuta et al., 2002). Furthermore, repetitive negative thinking about the past, or rumination, is associated with depression (Hecht et al., 2002).

Despite increased research into factors beyond clinical predictors, distress in MND remains poorly understood and there are no effective psychological or pharmacological treatments for distress in this population (Gould et al., 2015). The majority of studies consider the prevalence of distress or clinical factors, or are cross-sectional. In order to identify those at risk of becoming distressed and highlight targets for intervention, it is important to explore other potential contributors to distress, including demographic factors, psychological processes, and social factors. Cross-sectional studies identifying correlates of distress are, however, of limited value in identifying potential causal factors. For this, prospective research is more informative. However, prospective research identifying factors that predict distress over time is yet to be synthesised. This systematic review aims to appraise currently available data to understand the clinical and demographic, social, and psychological factors that predict distress over time. The present review will outline the review methodology, then summarise and critically appraise the research findings concerning the predictors of distress. A discussion of the main findings will be summarised and concluded with recommendations regarding future research and clinical practice.

## **Method**

The methodology used in this review broadly followed the PRISMA statement for conducting and reporting systematic reviews (Moher, Liberati, Tetzlaff & Altman, 2009).

### **Search Strategy**

A review of the literature was conducted to identify published, prospective studies of adults with a diagnosis of MND that measured predictors of distress over time using a validated measure. Three electronic databases were used to identify relevant articles: Medline (1946 - November 2016), PsychINFO (EBSCOhost; 1806 - November 2016), and CINAHL Plus (EBSCOhost; 1937 – November 2016). Key words used included “Amyotrophic Lateral Sclerosis,” “Motor Neurone Disease,” “Motor Neuron Disease,” “Progressive Muscular Atrophy,” “Primary Lateral Sclerosis,” “Progressive Bulbar Palsy,” “Lou Gehrigs Disease,” and descriptors or potential predictors of distress including “Depress\*,” “Anxiety,” “Distress,” “Worry,” “Ruminat\*,” “Emotion\*,” “Psych\*,” “Mood,” “Affect\*,” “Psychosocial,” “Coping,” “Adapt\*,” “Quality of life,” “Adjustment,” “Illness cognition\*,” “Fear\*,” or “Belief\*.” Thesaurus and MeSH terms were utilised for specific databases. Full details of the search strategy can be found in the protocol (PROSPERO ID:CRD42017050036; see Appendix B). Searches were limited to those published in the English language with no restrictions on the date. A second reviewer repeated the searches on 30<sup>th</sup> November 2016. Reference lists of included studies were examined and experts in the field were contacted to identify additional relevant studies.

### **Inclusion Criteria**

Studies eligible for inclusion met the following criteria: a) adults aged 18 years or older; b) participants with a diagnosis of MND; c) written in the English language; d) included a

validated measure of distress or subscale of a QoL measure relevant to distress; e) measured associated clinical, demographic, psychological, or social factors; f) prospective studies assessing if factors at baseline predict distress at follow-up; g) minimum follow-up duration of one month.

### **Data Extraction**

Duplicate articles were removed using EndNote X7 software. Study titles and, where necessary, abstracts of all papers identified by the search were screened according to the inclusion criteria using a screening and selection tool (see Appendix B). Full-text articles of remaining studies were obtained and screened according to the same criteria. A second reviewer independently screened a random subset of the articles (25%), any discrepancies were resolved by consensus. Data from eligible studies was extracted using a standardised protocol (see Appendix C). A second reviewer reviewed a random subset of the extracted data (25%).

### **Assessment of Risk of Bias**

The risk of bias in the included studies was independently assessed at the study level by the author and a second reviewer using a tool adapted from the Agency for Healthcare Research and Quality (Williams, Plassman, Burke, Holsinger & Benjamin, 2010). This tool proposes nine areas of potential bias that enables the included studies to be compared across these dimensions (see Appendix D). Discrepancies in reviewer ratings were resolved through discussion with a third reviewer. Studies were not excluded based on the results of the quality assessment, in line with guidance from the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2009).

### **Data Synthesis**

A meta-analytic review was inappropriate due to the heterogeneity of included studies with respect to time since diagnosis, predictors, and distress outcomes assessed. Therefore, a narrative synthesis is provided. Findings for each type of distress outcome (anxiety or depression case, anxiety or depression severity, emotional distress severity, QoL psychological subscale) are discussed within three broad categories of predictor variable: clinical and demographic, social, and psychological.

### **Results**

Figure 1 outlines the search results and article selection process. The search yielded 1,924 results, with a total of 1,499 unique articles after removing duplicates. Of these articles, 1,337 were excluded based on title and abstract. Full-text articles for the remaining 162 records were accessed, with 151 excluded, resulting in 11 papers included in the systematic review.

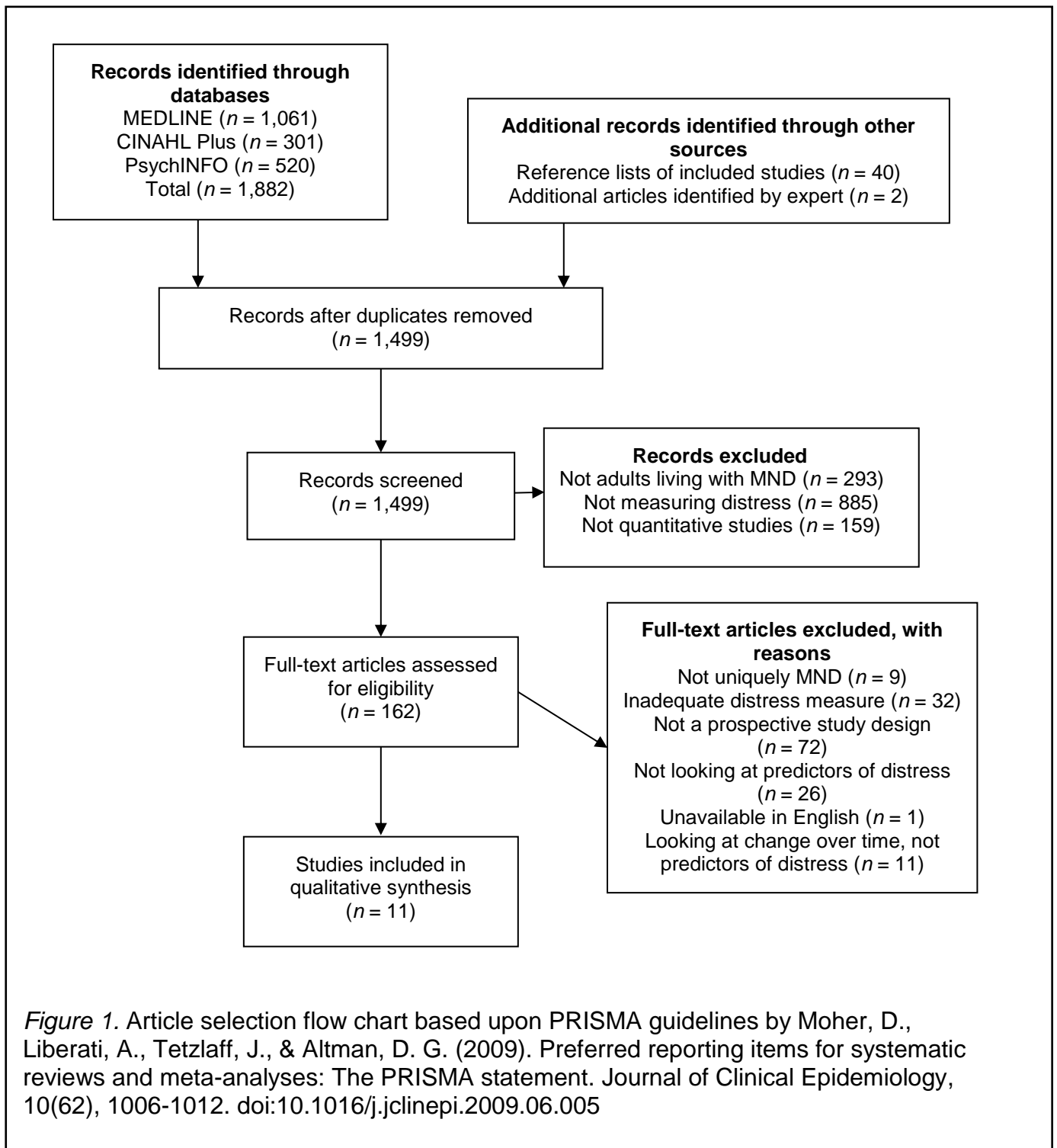


Table 1 describes study sample characteristics, Table 2 summarises quality assessment outcomes, and Table 3 provides a glossary of measures used to assess distress. Finally, Table 4 summarises study design and findings, grouped by type of distress outcome.

The majority of studies (eight studies, 72.73%) were conducted in Europe, with a further three studies conducted in America (27.27%). One study limited analyses to those commencing non-invasive ventilation (NIV) with orthopnoea symptoms (Bourke, Bullock, Williams, Shaw & Gibson, 2003), while another study limited time since diagnosis to less than 15 months (Goldstein, Atkins, Landau, Brown & Leigh, 2006). Mean sample ages ranged from 55 to 63 years.

Several measures were used to assess distress; most studies reported distress through psychological subscales from QoL measures (five studies). Three studies reported depression severity and two papers reported depression caseness. Two studies used distress measures designed for plwMND. Overall emotional distress was the primary outcome in one study. Only one study also reported the severity of anxiety in addition to depression. No papers reported on anxiety alone. Self-report measures were used to assess outcomes of interest across clinical and demographic, social, and psychological factors. Two studies used physical measurements including forced vital capacity and muscle scores.

Nine studies utilised multivariate analyses of predictors using regression analysis, although there was considerable variation in the method of entry and order of included predictors. Two studies utilised modelling methods and one study did not conduct inferential statistics. Nine papers used  $p < 0.05$  and one study used  $p < 0.01$  to indicate a significant association.

Table 1

*Sample characteristics of included papers*

Article	Sample size at each time point								Attrition (%)	Time since diagnosis (D) or onset (O) Mean $\pm$ SD	% Bulbar onset	% Female	Age in years Mean $\pm$ SD or Median (range)	Country		
	T1 (n =)	T2 (n =)	T3 (n =)	T4 (n =)	T5 (n =)	T6 (n =)	T7 (n =)									
Bourke et al., (2003)	Time points variable according to when met criteria for NIV.  Baseline = 22 T1 = 21 Met criteria = 17 Accepted trial = 15 Continued trial = 10							-	-	-	54.54%	<i>Recent diagnosis group =</i> 15.2 $\pm$ 9.9 (O) <i>Referred with RMW group =</i> 54.0 $\pm$ 35.0 (O) <i>Before NIV =</i> 32.6 $\pm$ 29.0 (O)	NR	<i>Recent diagnosis group =</i> 33.33% <i>Referred with RMW group =</i> 28.57% <i>Before NIV =</i> 29.4%	<i>Recent diagnosis group =</i> 57.8 (32-74) <i>Referred with RMW group =</i> 59.3 (48-73) <i>Before NIV =</i> 61.8 (48-74)	UK
Cupp et al., (2011)	72	72	48	-	-	-	-	33.33%	37 $\pm$ 44 (O)	24%	40%	55 $\pm$ 12	America			
Goldstein et al., (2006)	50	32	26	-	-	-	-	48.00%	28.79 $\pm$ 17.21 (O) 9.24 $\pm$ 4.26 (D)	28%	82%	63.14 $\pm$ 10.33	UK			
Hillemacher et al., (2004)	41	31	-	-	-	-	-	24.39%	24.0 $\pm$ 25.8 (D)	NR	34.15%	59.9 $\pm$ 11.4	Germany			
Lyall et al., (2001)	<i>NIV group</i> 16 16 10 7 4 3 2 <i>Control group</i> 11 11 6 4 4 - -							<i>NIV</i> 87.5% <i>Control</i> 100%	NR	NR	11.11%	<i>NIV group =</i> 61.3 $\pm$ 6.8 <i>Control group =</i> 61.2 $\pm$ 7.6	UK			
Matuz, Birbaumer, Hautsinger & Kübler (2015)	27	22	19	16	-	-	-	40.75%	NR	7.4%	44%	55.3 $\pm$ 11.1	Germany			

Article	Sample size at each time point								Attrition (%)	Time since diagnosis (D) or onset (O) (months) Mean $\pm$ SD	% Bulbar onset	% Female	Age in years Mean $\pm$ SD or Median (range)	Country
	T1 (n =)	T2 (n =)	T3 (n =)	T4 (n =)	T5 (n =)	T6 (n =)	T7 (n =)							
McElhiney, Rabkin, Gordon, Goetz & Mitsumoto (2009)	223	113	65	-	-	-	-	70.85%	Fatigue group = 33 $\pm$ 28 (O) Depression group = 33 $\pm$ 25 (O) Fatigue & depression group = 35 $\pm$ 31 (O) Neither group = 37 $\pm$ 31 (O)	Fatigue group = 15% Depression group = 50% Fatigue & depression group = 12% Neither group = 25%	44%	61 $\pm$ 12	America	
Norquist, Jenkinson, Fitzpatrick, Swash & ALS-HPS steering group (2003)	918	439	123	-	-	-	-	86.66%	1.29 $\pm$ 1.77 (D)	NR	42.16%	59.97 $\pm$ 11.54	UK multi-country	
Pagnini, Phillips, Bozma, Reece & Langer (2015)	197	102	-	-	-	-	-	48.22%	1-8m 40.1% 9-16m 24.1% 17-28m 24.6% $\geq$ 29m 11.7%	NR	41.1%	58 $\pm$ 9.9	Italy	
Roach, Averill, Segerstrom & Kasarskis (2009)	55	NR						NR	11.76 $\pm$ 20.16 (D)	NR	36%	58.4 $\pm$ 11.5	America	
Rodriguez de Rivera et al., (2011)	42	NR						NR	NR	33%	28.57%	57.97 $\pm$ 4.56	Spain	

Note. NIV = non-invasive ventilation; NR = not clearly reported; RMW = respiratory muscular weakness.



### **Risk of Bias Assessment**

The results from the assessment of the risk of bias are presented in Table 2. The most common methodological limitations were related to the selection of participants, assessment of distress and other predictors, justification for sample size, management of missing data, length of the follow-up period, and controlling for potential confounders. The majority of studies selected participants appropriately, however, two studies lacked detail about how participants were recruited. Many studies did not adequately describe the measures used to assess distress and other predictors, often not reporting appropriate reliability, internal consistency, or validity statistics. The majority of studies measured distress using subscales from larger QoL measures, rather than utilising specifically validated measures. This was also the case for some physical functioning measures with individual items or subgroups of items used, which were not clearly validated for use in this way.

Sample size was not justified in any of the included studies, resulting in a lack of clarity about whether the studies have sufficient power to draw conclusions about the results reported. This results in increased potential for inflated Type I error rate. Missing data is expected given the terminal nature of MND, however, a number of studies failed to discuss attrition rates, or account for missing data in the analysis. Subgroups of participants were often analysed due to missing data, which could result in a biased sample. For example, those with shortness of breath when lying down, defined as orthopnoea, or those attending repeated assessments. Similarly, many studies had follow-up periods that were shorter than Williams et al.'s (2010) suggested 12 month period, which makes it difficult to conclude that predictors are reliable over time. Some studies failed to control for potential confounding variables in analyses, despite reporting these when describing the sample.

Table 2

*Quality assessment of included papers using adapted tool from William et al., (2010)*

<b>Article</b>	<b>Unbiased selection of the cohort?</b>	<b>Sample size calculated?</b>	<b>Adequate description of the cohort?</b>	<b>Validated method for ascertaining distress?</b>	<b>Validated method for ascertaining other predictors?</b>	<b>Adequate follow-up period?</b>	<b>Missing data?</b>	<b>Analysis controls for confounders?</b>	<b>Analytic methods appropriate?</b>
Bourke et al., (2003)	Partially	Unclear	Partially	Partially	Partially	Partially	Yes	Yes	Unclear
Cupp et al., (2011)	Yes	Unclear	Partially	Partially	Partially	Partially	Partially	Partially	Yes
Goldstein et al., (2006)	Partially	Unclear	Yes	Partially	Partially	Yes	Partially	Partially	Yes
Hillemacher et al., (2004)	Yes	Unclear	Yes	Partially	Partially	Partially	Partially	Yes	Yes
Lyall et al., (2001)	Unclear	Unclear	Partially	Partially	Partially	Partially	Partially	Partially	Yes
Matuz et al., (2015)	Yes	Unclear	Yes	Yes	Partially	Yes	Partially	Partially	Yes
McElhiney et al., (2009)	Yes	Unclear	Yes	Partially	Partially	Partially	No	Partially	Yes
Norquist et al., (2003)	Yes	Unclear	Yes	Partially	Partially	No	No	Yes	Yes
Pagnini, Phillips et al., (2015)	Partially	Unclear	Partially	Partially	Partially	No	Partially	Yes	Yes
Roach et al., (2009)	Unclear	Unclear	Partially	Yes	Yes	Yes	Yes	Yes	Yes
Rodriguez de Rivera et al., (2011)	Partially	Unclear	Yes	Partially	Partially	Yes	No	No	Partially

A variety of predictors were considered across the studies included in the review. Of the 11 included studies, 10 considered at least one clinical or demographic predictor, two considered social predictors, and three considered psychological predictors of distress.

### **Demographic and Clinical Predictors**

**Age, gender, and education level.** Age was a significant predictor of distress in two out of six studies. Younger age predicted worse mental health (Norquist et al., 2003) however, this effect was not sustained at an 8 month follow up (Norquist et al., 2003). Younger age predicted increased anxiety (Pagnini, Phillips et al., 2015). The two studies that found significant effects had larger sample sizes than studies that did not find a significant effect, although both studies were limited by relatively short follow up periods of up to eight months compared with the other studies considering age as a predictor of distress.

Gender predicted distress in one of the five studies, with males reporting greater psychological wellbeing than females (Roach et al., 2009). This study managed missing data well, but was limited by a relatively small sample size for multilevel modelling and lack of clarity in reporting of attrition rates, therefore results may be due to inflated Type I error. Only one study examined education level and found it did not predict distress (Pagnini, Phillips et al., 2015).

**Clinical characteristics.** Physical functioning was considered in five studies, using a variety of physical and self-report measures. In five studies overall physical functioning did not predict distress. This appears to be a relatively robust finding over a number of studies. For specific aspects of physical functioning, bulbar functioning did not predict distress (Goldstein et al., 2006), QoL (Bourke et al., 2003), or depression (Hillemacher et al., 2004) in three studies. The methodological strengths and limitation of these studies varied, two studies had good length

Table 3

*Glossary of distress measures (DVs) used in included papers*

Measure	Abbreviation	Outcome assessed
ALS Depression Inventory	ADI-12	Depression
ALS Specific Quality of Life Instrument-Revised	ALSQoL-R	Quality of life, Negative emotion scale (NES)
Beck's Depression Inventory	BDI	Depression
Hospital Anxiety and Depression Scale	HADS	Depression (HADS-D, Anxiety (HADS-A), Distress (HADS-T))
Patient Health Questionnaire	PHQ-9	Depression
Short Form-36	SF-36	Quality of life (Mental Health (MH), Mental component summary score (MCS))
Depression Score of von Zerssen	D-S	Depression
The McGill Quality of Life Questionnaire	MQoL	Quality of life, psychological wellbeing domain (PWB)

**Note.** Kübler A., Winter S., Kaiser J., Birbaumer N., Hautzinger M. (2005). Das ALS-Depressionsinventar (ADI): Ein Fragebogen zur Messung von Depression bei degenerativen neurologischen Erkrankungen (amyotrophe Lateralsklerose). *Zeitschrift Fur Klinische Psychologie Und Psychotherapie*, 34(1), 19-26. doi:10.1026/1616-3443.34.1.19

Simmons, Z., Felgoise, S. H., Bremer, B. A., Walsh, S. M., Hufford, D. J., Bromberg, M. B., ... McCluskey, L. (2006). The ALSSQOL: Balancing physical and nonphysical factors in assessing quality of life in ALS. *Neurology*, 67(9), 1659-1664. doi:10.1212/01.wnl.0000242887.79115.19

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561-571.

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression scale. *Acta Psychiatrica Scandinavica*, 67(6), 361-370. doi:10.1111/j.1600-0447.1983.tb09716.x

Spitzer, R. L., Kroenke, K., Williams, J. B. W. (1999). Validation and utility of a self-report version of PRIME-MD: The PHQ Primary Care Study. *Journal of the American Medical Association*, 282(18), 1737-1744. doi:10.1001/jama.282.18.1737

Ware, J. E. & Sherbourne, C. D. (1992). The MOS 36-item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Medical Care*, 30, 473-83.

Von Zerssen, D., & Koeller, D. M. (1976). *Paranoid-Depressivitäts-Skala und Depressivitäts-Skala: Manual*. Beltz Test: Weinheim.

Cohen, S. R., Mount, B. M., Strobel, M. G., & Bui, F. (1995). The McGill Quality of Life Questionnaire: A measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. *Palliative Medicine*, 9(3), 207-219.

of follow up (Goldstein et al., 2006; Bourke et al., 2003), yet one of these studies analysed only people with respiratory muscular weakness (Bourke et al., 2003). The study by Hillemacher et al. (2004) recruited an unbiased sample but was limited by length of follow up and sample size. When considered in single studies limb functioning did not predict depression (Hillemacher et al., 2004); spinal functioning did not predict distress (Goldstein et al., 2006); and muscular scores, partial pressure of carbon dioxide, and maximum inspiratory pressure did not predict psychological QoL (Bourke et al., 2003). Although swallowing and breathing impairment did independently predict higher depression scores as examined in one study (Hillemacher et al., 2004). However, this study had a relatively small sample and utilised single items from larger measures of physical functioning to determine these effects.

Three studies assessed the site of symptom onset, categorised as bulbar or non-bulbar (spinal or limb). Findings were mixed; higher percentages of depression caseness were reported in the bulbar group, followed by the lower limb, and upper limb onset groups (Rodriguez de Rivera et al., 2011). This study recruited regular clinic attenders only which led to a strength in length of follow up, but may have resulted in a biased sample. Furthermore, inferential statistics were not utilised and therefore confounders were not controlled for. Conversely, non-bulbar site of onset predicted depression caseness in one study but this effect was accounted for by fatigue (McElhiney et al., 2009). The third study found that site of onset was not a predictor of negative emotion (Cupp et al., 2011). Studies that did not find an association between site of onset and distress had larger samples, although the length of follow up was shorter. One study with a large sample size and relatively adequate follow up period found that fatigue predicted depression caseness (McElhiney et al., 2009).

Table 4

Summary of study design and significant findings from included papers grouped by outcome (DV)

Article	Sample size	T2, T3, T4, T5, T6 ( <i>n</i> months later)	Dependant Variable (DV)	Analysis	Clinical /demographic	Social	Psychological	Significant Findings ( $p < .05$ )
<b>DV - ANXIETY/DEPRESSION CASE</b>								
McElhiney et al., (2009)	223	3	PHQ-9 (major/minor/absent)	Stepwise and multinomial regression	Fatigue, physical functioning, FVC, progression rate, site of onset (Bulbar/ non-bulbar)	-	-	Fatigue ( $\beta=0.073$ ) Non-bulbar onset ( $\beta=-1.41$ ) (accounted for by fatigue)
Rodriguez de Rivera et al., (2011)	42	3	BDI >21	Descriptive	Site of onset (Bulbar/Upper Limb/Lower Limb)			Bulbar = 78.57%, Upper Limb = 35.71%, Lower Limb= 64.28%
<b>DV ANXIETY/DEPRESSION</b>								
Hillemacher et al., (2004)	41	6	D-S	Logistic regression	Physical functioning (total, limb, bulbar, swallowing, breathing), time since diagnosis, age, gender	-	-	Swallowing impairment ( $r = -0.453$ ) (Odds ratio (OR) = 0.36; 95% CI 0.14-0.96), Breathing impairment (Odds ratio (OR) = 0.39; 95% CI 0.16-0.96)
Matuz et al., (2015)	27	3-6	ADI-12	Multiple regression	-	Berlin Social Support Scales Perceived social support	Cognitive appraisal (coping potential), MND coping scale	T2: $R^2=55\%$ Perceived social support ( $\beta = -0.44$ ) Appraisal of coping potential ( $\beta = -0.57$ )

Article	Sample size	T2, T3, T4, T5, T6 ( <i>n</i> months later)	Dependant Variable (DV)	Analysis	Clinical /demographic	Social	Psychological	Significant Findings ( $p < .05$ )
Pagnini, Phillips et al., (2015)	197	4	HADS-A  HADS-D	Mixed-effects models	Age, gender, years of education, time since diagnosis	-	Mindfulness, McGill Quality of Life Scale	Mindfulness ( $b = -0.12$ , $t(187) = -6.83$ ) Age ( $b = -0.73$ , $t(187) = -3.21$ )  Mindfulness ( $b = -0.14$ , $t(187) = -8.20$ )
<b>DV – QUALITY OF LIFE PSYCHOLOGICAL SUBSCALE</b>								
Bourke et al., (2003)	22	2	SF-36 (MCS)	Efficacy Analysis, Multivariate analysis	NIV, age, gender, NIV compliance, physical functioning (P <sub>1</sub> max, P <sub>a</sub> CO <sub>2</sub> , limb and axial muscle scores, bulbar score)	-	-	NIV (effect size > 0.8) NIV compliance predicts duration of benefit on MCS (only $p$ value reported)
Cupp et al., (2011)	72	3	ALSQoL-R (NES) fraction of baseline	Linear regression (fraction of baseline)	Visit number, PEG antidepressant use, NIV, time between intervention and scoring, age, site of onset (Bulbar/ Non-bulbar)	-	-	Antidepressant PEG (only $p$ values reported)
Lyall et al., (2001)	27	1 wk, 1, 6, 9, 12, 15	SF-36 (MH)	Repeated Measures ANOVA	NIV	-	-	NS

Article	Sample size	T2, T3, T4, T5, T6 ( <i>n</i> months later)	Dependant Variable (DV)	Analysis	Clinical /demographic	Social	Psychological	Significant Findings ( $p < .05$ )
Norquist et al., (2003)	918	4	SF-36 (MCS)	Stepwise regression	Physical functioning, age, gender, time since onset, time since diagnosis	-	SF-36 MCS baseline	T2 $R^2 = 49.8\%$ , Age ( $\beta = -.0133$ ), MCS baseline ( $\beta = 0.682$ ) T3 $R^2 = 53.6\%$ , MCS baseline ( $\beta = 0.735$ )
Roach et al., (2009)	55	6	MQoL (PWB)	Multi-level modelling,	Time since diagnosis, gender, age	-	-	Gender (male) $\Upsilon = -1.04$ $F(1,61) = 3.99$ $\eta = 0.06$
<b>DV – EMOTIONAL DISTRESS</b>								
Goldstein et al., (2006)	50	6	HADS-T	Linear regression, best combined predictor,	Physical functioning (bulbar, spinal), PEG	Marital intimacy, social support, psycho-social impact of illness,	Emotional lability, executive functioning, self-esteem, cognitive dysfunction, attention/concentration,	T2: Negative social support at T1 ( $R^2 = 27\%$ , $t = 2.91$ )

*Note.* ANOVA = Analysis of Variance; FVC = forced vital capacity; NIV = non-invasive ventilation; NS = non-significant; P<sub>1</sub> max = maximum static inspiratory pressure; P<sub>a</sub>CO<sub>2</sub> = partial pressure of carbon dioxide in arterial blood; PEG = percutaneous endoscopic gastrostomy; RMW = respiratory muscular weakness; (see Table 3 for details of measures).



Time since diagnosis did not predict depression (Hillemacher et al., 2004; Pagnini, Phillips et al., 2015), anxiety (Pagnini, Phillips et al., 2015), or mental health (Norquist et al., 2003; Roach et al., 2009) in four studies. When considered in single studies, time since onset of symptoms did not predict mental health (Norquist et al., 2003), progression rate did not predict depression caseness (McElhiney et al., 2009), and visit number did not predict mental health (Bourke et al., 2003). It appears to be a relatively robust finding over a number of studies that time since diagnosis or onset does not influence distress.

**Treatments.** Use of non-invasive ventilation (NIV) did not predict mental health in two studies with relatively small sample sizes but good length of follow up (Cupp et al., 2011; Lyall et al., 2001). However, compliance with NIV treatment did predict the duration of improvement in mental health (Bourke et al., 2003). Although this study was limited by a small sample size, and demanding two month follow ups may have biased the sample. Of the two papers assessing the provision of nutrition via percutaneous endoscopic gastrostomy (PEG), findings were mixed. In one study PEG predicted improvement in negative emotions (Cupp et al., 2011). This study had a relatively large sample size, and length of follow up period, however was limited by management of missing data. In another study PEG did not predict distress (Goldstein et al., 2006). This study's strengths were length of follow up period, recruitment of participants close to diagnosis, and considering potential reasons for attrition; however, it was limited by a smaller sample size.

**Antidepressant medication.** Antidepressant use predicted an improvement in negative emotion ratings as considered in one study (Cupp et al., 2011).

### **Social Predictors**

Social factors were considered in two of the 11 studies included in the review. Lower levels of social support predicted greater overall distress (Goldstein et al., 2006) and depression (Matuz et al., 2015). Neither the psychosocial impact of illness nor physical and interpersonal marital intimacy predicted distress in one study (Goldstein et al., 2006). These studies were relatively robust with both studies demonstrating good follow up periods, although the study by Matuz et al., (2015) was limited by a relatively small sample size.

### **Psychological Predictors**

Psychological factors were considered individually in three studies. Cognitive appraisals of coping potential predicted depression (Matuz et al., 2015), in a study with a relatively small sample size. Mindfulness predicted depression and anxiety over time, with lower trait mindfulness predicting greater depression and anxiety (Pagnini, Phillips et al., 2015). This study had a large sample size but was limited by an eight month follow up period. One study found that self-esteem, neuropsychological factors (executive functioning, cognitive dysfunction and attention) and emotional lability did not predict distress (Goldstein et al., 2006). This study had a relatively small sample size, but was unbiased in selection of participants and had an adequate follow up period. Coping strategies (emotion management, emotion avoidance and problem management) did not predict depression (Matuz et al., 2015). Overall QoL did not predict depression (Pagnini, Phillips et al., 2015), although a mental health subscale of QoL did predict later mental health (Norquist et al., 2003). These studies had large sample sizes, however were limited by the length of follow up.

## Discussion

This is the first review to systematically examine, collect, and appraise current data on the demographic, clinical, social, and psychological prospective predictors of distress in plwMND. Across the 11 studies included in the review, there was very limited evidence that demographic, clinical, social, or psychological factors predict distress.

Narrative synthesis indicated scarce consistent evidence that any baseline demographic factors reliably predict longer-term distress after MND diagnosis. This fits with previous findings that gender and age in plwMND are not differentially associated with distress (Goldstein & Leigh, 1999; Hogg, Goldstein & Leigh, 1994). For clinical factors, evidence was mixed. There was no evidence that overall physical functioning or bulbar functioning predicted distress. This appears to be a relatively robust finding over a number of studies. However specific swallowing and breathing impairments predicted depression in one study. Although this study was limited by a relatively small sample size and the use of single items from larger measures of physical functioning to assess specific impairments. These findings are consistent with previous reviews that have failed to identify a straightforward or consistent role for physical factors in distress (McLeod & Clarke, 2007). This highlights a need to consider more specific symptoms that may be associated with distress, or perhaps to focus on the cognitive appraisals associated with clinical factors which have demonstrated utility in other health conditions (Dempster et al., 2012). There was minimal evidence that PEG reduced negative emotions, which had equal numbers of null and significant findings across a small number of studies. The study that did not find an effect of PEG was limited by a small sample size thus may have lacked power to detect an effect. More studies with longer follow-up periods and larger sample sizes are required to consider conflicting findings. In single studies fatigue, compliance with NIV

intervention, and antidepressant use predicted distress. However, further detailed investigation of these factors is required to clarify their role in distress, given that studies were limited by small sample size and inadequate length of follow up respectively.

There were limited studies on social factors. Nonetheless, there was consistent evidence that lower social support predicted distress and depression in two studies. These studies were relatively robust with both studies demonstrating good follow up periods, although one study was limited by a small sample size. The subjective experience and quality of social support appears to act as a buffer to distress, fitting with longstanding views about the value of social support for plwMND (Hogg et al., 1994; Rabkin, Wagner & Del Bene, 2000). This is consistent with the protective role of social support against distress in other neurological conditions (Elliott, Charyton, Sprangers, Lu & Moore, 2011; Simpson, Haines, Lekwuwa, Wardle, Crawford, 2006). This also fits with cross-sectional studies of plwMND, finding that increased social support was associated with better mental health (Chiò et al., 2004). The remaining social factors considered, the psychosocial impact of illness, and marital intimacy were assessed only in single studies and did not predict distress. Given the limited number of studies, and lack of clarity about the power of studies, research to further evaluate the role of social and relational factors would help to clarify their role in distress for plwMND.

There was limited research into psychological predictors of distress over time. Despite this, there were some significant predictors identified by single studies with mindfulness, cognitive appraisal of potential to cope, and psychological QoL predicting distress over time. This is consistent with cross-sectional research relating a variety of cognitive appraisals to distress in plwMND (Matuz et al., 2010; Miglioretti et al., 2008). It is impossible to draw conclusions from single studies, yet we can consider the quality of the evidence. Studies

investigating mindfulness and psychological QoL both had good sample sizes, but were limited by length of follow up period (Pagnini, Phillips et al., 2015; Norquist et al., 2003). Whereas Matuz et al.'s (2015) study considering cognitive appraisal of coping potential, had a good follow up period but was limited by small sample size. However, further investigation of psychological predictors and underlying mechanisms required to understand their role in distress for plwMND.

### **Limitations of Included Studies**

Caution should be taken when interpreting findings. The studies included were limited most commonly by a lack of power calculation increasing the risk of Type I error. Many studies also failed to control for confounding factors, for example the majority of studies did not consider time since diagnosis or onset in the analysis. Even fewer studies considered time since diagnosis as part of their inclusion criteria. This fails to consider how distress evolves over time and whether different factors influence distress dependent on symptom severity or time since onset. In addition, many studies had inadequate follow-up periods, or insufficient numbers of participants at later time points to analyse data, with analyses and conclusions often based upon earlier time points. This may not provide enough time between assessments to conclude that factors predict distress over time. Additionally, despite the co-morbidity between depression and anxiety, the majority of studies failed to consider anxiety focussing instead on depression, mental health, or distress. This again highlights the neglect of assessment of distress in plwMND, particularly distress other than depression, fitting with the view that medical interventions are prioritised in MND treatment (Felgoise et al., 2010). Moreover, there was a wide range of measures used to assess distress, with psychological subscales of QoL measures often used rather

than more specifically designed and validated tools. This could result in studies measuring different conceptual ideas, reducing the utility of comparisons between current studies.

### **Implications for Future Research**

The methodological limitations that restrict our understanding of the predictors of distress in MND have important implications for future research. Future research should focus on increasing the understanding of predictors of distress by conducting adequately powered studies with large sample sizes to manage the risk of Type I error. More longitudinal studies are required, despite the challenges in this population, to infer causality between baseline level of various predictors and subsequent distress. It would also be useful to separate plwMND into groups based upon the time since diagnosis and consider differences based upon the severity of symptoms or rate of progression. This will provide greater insight into the role of physical factors in distress. As distress measures can be influenced by physical functioning, adapted MND-specific measures of distress that are validated in an MND population should be utilised (Pagnini, Manzoni, Tagliaferri & Gibbons, 2015). This will ensure valid assessment of the concept of distress. Distress should be considered more broadly outside of depression alone. Structured diagnostic interviews could also be used as a more valid method of ascertaining caseness of depression and anxiety should this be appropriate. Data analysis should control for potential confounding factors.

Clinical and demographic predictors have been considered in the largest number of studies and have not demonstrated clear predictive value, with the exception of minimal evidence for PEG. These factors are generally unmodifiable, particularly given the lack of treatment options available in MND. Therefore, a focus on understanding modifiable factors such as psychological predictors should be prioritised in future research. Further research should be

theory driven and focus on exploring and testing the specific mechanisms underlying psychological predictors. This would inform the development of appropriate psychological interventions for plwMND. Evaluation of the effectiveness of these interventions would allow health services to direct resources into evidence-based therapies to support plwMND to manage distress.

### **Strengths and Limitations**

This is the first systematic review to consider clinical and demographic, social, and psychological predictors of distress in MND. It addresses an important, under-researched area and makes the first steps to understanding more about psychological distress in plwMND to guide effective intervention. Limited conclusions can be drawn given that many predictors were only assessed by one study, and several studies reported null and contradictory findings. Many factors require further investigation to replicate preliminary findings from single studies. Publication bias should be considered, with significant results more likely to be published than non-significant findings. Furthermore, although a comprehensive search strategy was utilised, it is possible that relevant research studies were not included in the review. Adaptation of inclusion criteria to consider cross-sectional studies could have resulted in a larger number of studies, and therefore resulted in firmer, more informative conclusions. A useful direction for future research could be to include cross-sectional studies to answer the question: What are the psychological factors associated with distress in MND? Inclusion criteria could be amended to select only studies that assessed psychological factors, and used specific measures of distress. This would provide a more specific understanding of the psychological predictors of distress and lead to conclusions that could guide research into the development of psychological theories and interventions. Despite these limitations the conclusions drawn from several studies, rather than

based upon individual studies, are likely to be robust. This review highlights the need for further research into psychological distress in MND.



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### **Chapter 3: The role of metacognitive beliefs and processes in distress in people living with Motor Neurone Disease**

#### **Abstract**

Emotional distress following a diagnosis of Motor Neurone Disease (MND) is common and many people living with MND experience persistent or recurrent distress. This cross-sectional study explored, for the first time, the predictions of the Self-Regulatory Executive Functioning (S-REF) model. The S-REF model, an information-processing model of distress, specifies that metacognitive beliefs and processes play a fundamental role in the development and maintenance of emotional distress. This study explored whether metacognitive beliefs would explain additional variance in emotional distress after accounting for major demographics, time since diagnosis, and physical functioning. The mediational relationships between metacognitive beliefs, repetitive negative thinking, and emotional distress as predicted by the S-REF model were also explored. Seventy-seven adults with a diagnosis of MND in the United Kingdom (recruited from Preston MND Care Centre, The Walton Centre, the MND Association, and MND Scotland) completed self-report questionnaire measures assessing distress, physical functioning, repetitive negative thinking, and metacognitive beliefs. Correlational analysis, hierarchical linear regression, and mediational analysis were used to test experimental hypotheses. Regression analysis showed that metacognitive beliefs were associated with distress and explained additional variance in distress after controlling for age, gender, time since diagnosis, physical functioning, and repetitive negative thinking. The key prediction of the S-REF model was supported; the relationship between negative metacognitive beliefs about the uncontrollability and danger of worry and distress was partially mediated by repetitive negative thinking. This is the first study to demonstrate that metacognitive beliefs and processes contribute to emotional

distress beyond demographic variables, the time since diagnosis, and severity of MND symptoms. Prospective research is required to test the causal role of metacognitive beliefs in emotional distress in people living with MND, as well as testing if metacognitive therapy is effective at reducing distress in MND.

*Key words:* Motor Neurone Disease, Amyotrophic Lateral Sclerosis, Distress, Psychology, Metacognition, Repetitive Negative Thinking

## Introduction

Motor Neurone Disease (MND) is a progressive, fatal neurodegenerative disorder affecting the motor neurones (Brooks, Miller, Swash & Munsat, 2000). Common symptoms include muscular weakness, atrophy, fasciculations, spasticity, and brisk reflexes (Talbot, 2009). The cause is unknown and the majority of cases occur sporadically, although there is a familial vulnerability in 5-10% of cases (Hobson, Harwood, McDermott & Shaw, 2016). The clinical presentation of MND varies depending on the areas affected, for example, bulbar symptoms include speech and swallowing difficulties, whereas non-bulbar symptoms include limb weakness and falls (Brooks et al., 2000). Cognitive changes can occur, particularly in executive functioning and social cognition (Bora, 2017) and approximately 10-15% of plwMND (people living with MND) are also diagnosed with co-morbid frontotemporal dementia (Gordon et al., 2011; Lillo, Mioshi, Zoing, Kiernan & Hodges, 2011). The course of the disease is variable, with disease progression resulting in increased paralysis and breathing difficulties, eventually leading to respiratory failure and death (Chiò et al., 2013; Goldstein & Leigh, 1999). A cure does not exist and the median life expectancy is 2-4 years from onset (Chiò et al., 2009), although 15-20% survive beyond 5 years (Talbot, 2009). Riluzole, a glutamate release antagonist, is the only treatment available which increases survival time by 2-4 months (Lacomblez, Bensimon, Leigh, Guillet & Meninger, 1996; Miller, Mitchell, Lyon & Moore, 2012). The prevalence of MND in Europe ranges from 1.1/100,000 to 8.2/100,000 (Chiò et al., 2013). The incidence is highest in 55-75 year olds (Hobson et al., 2016), although 10% are younger than 45 years, and 20% are older than 70 years (Talbot, 2009). MND affects more males than females, with a lifetime risk of 1 in 350 for males compared with 1 in 472 for females in the United Kingdom (Hobson et al., 2016).

Many plwMND experience psychological distress including hopelessness, anxiety, depression, fear of death, phobic anxiety, and somatization (Felgoise et al., 2010; Pagnini, Manzoni, Tagliaferri & Gibbons, 2015). The exact prevalence of distress in plwMND remains unclear (McLeod & Clarke, 2007). Estimates suggest approximately 50% of plwMND experience clinically relevant levels of anxiety and/or depression that warrant intervention (Ganzini, Johnston & Silveira, 2002; Kübler, Winter, Ludolph, Hautzinger & Birbaumer, 2005; McDonald, Hillel & Wiedenfeld, 1996). Furthermore, distress in plwMND is more common than in the general population (Felgoise et al., 2010) and comparable to those living with other motor conditions (Taylor, Wicks, Leigh & Goldstein, 2010). Emotional distress in plwMND is associated with a poorer quality of life (Johnston et al., 1999), increased interest in hastened death (Fang et al., 2008), and elevated suicide risk (Ganzini, Silveira & Johnston, 2002). Given limited medical treatment options, MND care currently focuses on improving quality of life through management of physical symptoms (Van den Berg et al., 2005). The development of psychological treatment offers an additional route to reduce distress and improve quality of life for plwMND.

However, to date, there is no evidenced MND-specific psychological or pharmacological therapy for distress (Gould et al., 2015; Kurt, Nijboer, Matuz & Kübler, 2007). Moreover, the psychological mechanisms that underlie distress in MND remain poorly understood. Further investigation of these mechanisms is required to inform the development of appropriate therapeutic interventions (Matuz, Birbaumer, Hautzinger & Kübler, 2010). Some positive outcomes have been demonstrated in preliminary studies of traditional cognitive behavioural therapy in plwMND (Díaz et al., 2016). However, this therapy is of limited utility in plwMND as appraisals may be accurate, and therefore not amenable to challenge (for example: “There’s no

cure for MND, I'm not going to get better," or "I can't control my symptoms"). The Self-Regulatory Executive Function (S-REF) model (Wells & Matthews, 1994) may offer a more suitable framework for understanding the processes underlying distress experienced by plwMND. The S-REF model forms the theoretical basis of metacognitive therapy (MCT; Wells & Matthews, 1994), proposing that it is not the content of thoughts, but a pattern of responding to thoughts that results in psychological distress (Wells, 2009). This pattern of responding is termed the "Cognitive Attentional Syndrome" (CAS). The CAS consists of perseverative thinking (e.g. worrying, overanalysing), attentional strategies (e.g. monitoring for negative thoughts and feelings), and unhelpful coping strategies (e.g. resting excessively, avoidance of activities). Continuation of the CAS is fundamental to the development and persistence of emotional distress and is guided by metacognitive beliefs that can be categorised into two domains: 1) Positive metacognitive beliefs (for example: "Worrying about MND helps me to prepare for the future"); and 2) Negative metacognitive beliefs about the uncontrollability and danger of worry (for example: "I can't control my worry about MND;" Wells & Matthews, 1994). Holding these metacognitive beliefs can result in increased attention to thinking, and therefore lead to the CAS which sustains emotional responses and strengthens negative ideas (Wells, 2009). Specifically, positive metacognitive beliefs increase the likelihood of selection of repetitive negative thinking as a strategy, therefore acting indirectly to increase distress (Wells, 2009). Negative metacognitive beliefs about the uncontrollability and danger of worry decrease the likelihood of disengaging from repetitive negative thinking due to beliefs that thinking cannot be controlled, therefore increasing distress (Wells, 2013). These negative metacognitive beliefs also act directly to increase distress due to their content (Wells, 2013). MCT thereby aims to challenge metacognitive beliefs (Wells, 2009). MCT has effectively reduced levels of distress

in people with a variety of mental health difficulties, such as anxiety and depression (Wells, 2009).

In a population where there is little understanding of the processes underlying distress the S-REF model is a useful theoretical framework to explore in plwMND for a number of reasons. Firstly, MCT is a transdiagnostic and time-limited therapy that could address a variety of mental health difficulties efficiently (Wells, 2013). This is a key consideration for people with a terminal condition. Furthermore, the S-REF model focuses on the process rather than the content of thinking, in contrast to traditional cognitive behavioural theory. This could be more suited to plwMND as the content of thoughts is often accurate and reflective of the devastating nature of the disease. The S-REF model has also demonstrated utility in other physical health populations including Parkinson's disease (Brown & Fernie, 2015), cancer (Cook et al., 2015), and chronic fatigue (Maher-Edwards, Fernie, Murphy, Nikcevic & Spada, 2012). Therefore, supporting research to consider whether the S-REF model generalises to plwMND. Findings from research with plwMND also support exploration of the S-REF model, since repetitive negative thinking, a core component of the S-REF model, is a common coping strategy in MND that has been associated with depression (Hecht et al., 2002). Therefore, the S-REF model offers a potential framework for understanding distress in MND. Consideration of the S-REF model in MND will increase understanding of distress in MND, and encourage a clinical focus on psychological wellbeing. This study offers a starting point to guide future research and theory into the generalisation and adaptation of psychological models to plwMND. The outcome will aid the development of clinical interventions to reduce distress, whether this be through further testing of the S-REF model or consideration of alternative theoretical approaches.

This study aims to consider the contribution of metacognitive beliefs to understanding of distress. And to consider the specific predictions of the S-REF model by considering metacognitive beliefs and distress in plwMND, specifically the mediational role of repetitive negative thinking. It is hypothesised that:

1) Metacognitive beliefs will make a significant contribution to emotional distress, over and above basic demographic and clinical factors.

2) Positive metacognitive beliefs will cause emotional distress by activating repetitive negative thinking, and will not directly cause or maintain distress.

3) Negative metacognitive beliefs will cause emotional distress both by activating repetitive negative thinking and by triggering a direct emotional response due to their negative content.

## **Method**

### **Participants**

All participants reported a diagnosis of MND that had been given by a neurologist, and demonstrated sufficient English language to complete the questionnaires. They also reported they did not have a diagnosis of Frontotemporal Dementia that had been given by a neurologist as this can affect emotional responses (Kumfor & Piguet, 2012). A total of 98 participants were assessed for eligibility according to these criteria, either verbally or via online questionnaire. Participants with a diagnosis of Frontotemporal Dementia were excluded ( $n = 6$ ). A total of 77 plwMND were recruited over a seven-month period to complete a set of self-report questionnaires on one occasion. Of the 77 participants, 58 took part online. A further 14 participants, who took part online, withdrew from the study before completing the questionnaires, and 1 participant failed to return the questionnaire pack. Two participants did not



provide a full date of diagnosis and were not included in the final analysis, resulting in a final sample size of 75 (See Appendix E for participant flow).

### **Design**

This study used a cross sectional design using both paper-based and online survey methods.

### **Sample Size**

A power calculation using G\*Power (Faul, Erdfelder, Buchner & Lang, 2009) indicated that a sample size of 65 would have 80% power to identify an effect size of 0.25, with seven predictors at the  $p < 0.05$  significance level (see Appendix F).

### **Measures**

Service user consultation was undertaken to ensure that the materials were appropriately presented, sensitive, and understandable.

**Demographics questionnaire.** A self-report questionnaire was created to collect the following data: participant age, gender, date of diagnosis, date of symptom onset, current medications, co-morbid health conditions, and if participants required support to complete the questionnaires.

**Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983).** The HADS is a 14-item self-report scale designed to assess depression and anxiety in a medical population. Items are rated on a 4-item Likert scale. The scale can be separated into anxiety (HADS-A), depression (HADS-D), or an overall distress score (HADS-T). Meta-regression analysis demonstrated that some items from the HADS were related to physical functioning and time since symptom onset in plwMND (Pagnini, Manzoni, et al., 2015). Accordingly, the 11-item adapted HADS for plwMND was utilised in the current study, with three items related to

physical rather than emotional wellbeing removed (Gibbons et al., 2011). In an MND population, the HADS demonstrates acceptable internal consistency ( $\text{PSI} = 0.86$ ; Gibbons et al., 2011), which was maintained in the current study ( $\alpha = 0.91$ ). Scores range from 0-33, with higher scores indicating higher levels of distress. Cut-offs of 7 and 5 for the adapted HADS-A and HADS-D respectively are recommended (Gibbons et al., 2011).

**Metacognitions Questionnaire (MCQ-30; Wells & Cartwright-Hatton, 2004).** The MCQ-30 is a 30-item short form of the Metacognitions Questionnaire (Cartwright-Hatton & Wells, 1997). Items are rated on a 4-point Likert scale. The MCQ-30 consists of five subscales of positive metacognitive beliefs about worry, negative metacognitive beliefs about the danger and uncontrollability of worry, cognitive confidence, need for control, and cognitive self-consciousness. The subscales demonstrate adequate internal consistency ranging from ( $\alpha = 0.72$ - $0.89$ ; Wells & Cartwright-Hatton, 2004). This was maintained in the current study for an MND population ( $\alpha = 0.88$ ). The subscales also exhibit acceptable test-retest reliability and convergent validity in a general population (Wells & Cartwright-Hatton, 2004).

**Repetitive Thinking Questionnaire (RTQ-10; McEvoy, Thibodeau, & Asmundson, 2014).** The RTQ-10 is a 10-item self-report measure that assesses repetitive negative thinking, consisting of a subset of items from the full RTQ. Items were originally modified from other measures including the Penn State Worry Questionnaire (Meyer, Miller, Metzger & Borkovec, 1990), the Rumination Response Scale (Nolen-Hoeksema & Morrow, 1991), and the Post-Event Processing Questionnaire (Rachman, Grüter-Andrew & Shafran, 2000). The RTQ-10 demonstrates acceptable internal consistency ( $\alpha \geq 0.89$ ) and convergent validity through significant associations with a range of emotions (McEvoy, Mahoney & Moulds, 2010). Acceptable internal consistency was maintained in the current study for an MND population ( $\alpha =$

0. 92). The trait version was used in the current study, with participants rating items about their general responses when distressed, rather than in relation to a specific event. Each item is rated on a 5-point Likert scale.

**Self-administered ALS Functional Rating Scale-Revised (ALSFRS-R; Cedarbaum et al., 1999).** The ALSFRS-R is a 12-item self-report measure designed to assess physical functioning including bulbar, limb, and respiratory function related to activities of daily living for plwMND. Each activity is rated on a 4-item Likert scale with well-defined response points for each item (range 0-4). The total score ranges from 0-48, with a higher score indicating better physical functioning. The scale has satisfactory internal consistency ( $\alpha = 0.73$ ; Cedarbaum et al., 1999), which was maintained in the current study ( $\alpha = 0.87$ ). It is widely used, and has been validated for online administration (Maier et al., 2012).

### **Ethical Considerations**

Ethical approval was obtained from the Liverpool Central Health Research Authority research and ethics committee (16/NW/0073). A number of ethical considerations were made in the design of the study. Multiple methods of participation were offered, including online and paper, to ensure the study was accessible to individuals with varying levels of physical ability. Participants could be assisted to complete the questionnaires by either the researcher in clinic or another chosen person; this was reflected in the consent form by requiring a witness to confirm consent should the person be unable to write. Given the demands of attending clinic, it was agreed that plwMND would not be approached by the researcher but asked if they would like to speak to the researcher by their clinician. Some questions may have been difficult to respond to or causes some distress or worry, thus contact details for support and the researcher were provided to link with appropriate services if required. Confidentiality and safe storage of data

across multiple sites was managed by assigning unique identification codes and storing consent forms separately from questionnaire data in locked storage cupboards, with access only available to the research team. The ethical requirements of all host sites were met (See Appendices G, H, I, J, K, L, M, N, and O).

### **Procedure**

All participants provided informed consent for their data to be used for research purposes. Participants were presented with an information sheet (see Appendix P), followed by a consent form (see Appendix Q), and finally the questionnaire measures detailed above in a random order to prevent order effects (see Appendix R). For online data collection, the order of questionnaires was automatically randomised using Qualtrics software. For paper data collection [www.randomizer.org](http://www.randomizer.org) was used to generate the order of measure presentation.

Participants were identified through multiple sources. PlwMND were invited to participate in the study by a clinician during visits with posters placed in clinics to advertise the study at The Walton Centre (a specialist neurology and neurosurgery NHS trust) and Preston MND Care Centre, UK. Participants were recruited from branch meetings of the Motor Neurone Disease Association (MND Association), a UK charity for plwMND. The study was advertised online and via social media by the MND Association and MND Scotland, a Scottish charity for plwMND. Participants could complete the study online, in a clinic, or at home. A variety of participation methods were offered to increase accessibility and therefore maximise the range of individuals who could participate. Participants chose whether to complete measures alone, with researcher support, or with support from another trusted person.

### Statistical Analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS version 22). Data was deemed to be missing at random, with one missing value from the MCQ-30 managed using mean imputation (Raymond, 1986) which has demonstrated superiority in estimating parameters (Dodeen, 2003). Pair-wise deletion was implemented for two participants who did not provide a date of diagnosis. *P* values of  $< 0.05$  were used to indicate significance. First, a preliminary correlational analysis was reviewed to consider relationships between distress and metacognitive beliefs generally as they had not yet been explored before in this population and different type of metacognitive beliefs can be more important in different groups (Wells, 2013). Mann-Whitney U tests explored if there were gender differences between the study variables. A hierarchical linear regression analysis tested the first hypothesis that metacognitive beliefs would explain additional variance in distress over and above basic demographic and clinical factors, as measured by the adapted HADS-T. This analysis controlled for major demographic variables, physical functioning, and repetitive negative thinking. Predictor variables were entered in the following order: step 1; age, gender, step 2; time since diagnosis, physical functioning, step 3; repetitive negative thinking, step 4; metacognitive beliefs (all subscales).

To test the second and third hypotheses that repetitive negative thinking would mediate the hypothesised relationship between metacognitive beliefs (positive metacognitive beliefs and negative metacognitive beliefs about the danger and uncontrollability of worry) and distress (adapted HADS-T) two mediational analyses were conducted. Age, gender, physical functioning, and time since diagnosis were controlled for in both analyses. A custom dialog was installed using the Hayes (2013) PROCESS macro to conduct mediational analyses (Hayes, 2013).

Bootstrapped, bias-corrected, and accelerated (BCa) estimates, and 95% confidence intervals are reported for the indirect effect. BCa estimates adjust for potential bias and skew in the bootstrap distribution to produce more reliable parameter estimation (Preacher & Hayes, 2004, 2008). Following Preacher and Hayes (2004, 2008) recommendation, 5,000 bootstrap samples were used in mediation and regression analyses.

### **Results**

Participant ages ranged from 29 to 86, with a median of 61.0 (IQR = 54.00 - 68.50). There were 42 males (54.50%). Two participants were receiving nutrition via percutaneous endoscopic gastrostomy. Two required intubation or tracheotomy, sixteen required non-invasive ventilation: eight during the day and night, six during the night only, and two intermittently. The median ALSFRS-R score was 30 (IQR = 22.50 - 38.00). Time since diagnosis ranged from 1 to 258 months. Of the sample, 22.10% met the criteria for severe depression and 19.48% for severe anxiety (scores of 8 and above on adapted HADS-D and 9 and above on adapted HADS-A respectively; Gibbons et al., 2011). There were 37 participants treated with Riluzole and 27 were prescribed an antidepressant, however it was unclear whether this was to treat depression or to manage symptoms of MND such as hypersalivation through its side effects.

Non-parametric tests were used to assess bivariate correlations (see Appendix S for exploration of assumptions). The medians, interquartile ranges, and Spearman's rho correlations between distress scores, repetitive negative thinking scores, and metacognitive beliefs are presented in Table 1. There were significant positive correlations with distress for negative metacognitive beliefs about the uncontrollability and danger of worry, cognitive confidence, cognitive self-consciousness, and repetitive negative thinking from 0.26 to 0.69. Repetitive negative thinking was also significantly positively correlated with the majority of the MCQ

subscales, apart from cognitive confidence. Age significantly correlated with cognitive confidence ( $r = 0.28$ ). As expected time since diagnosis significantly negatively correlated with ALSFRS-R score ( $r = -0.36$ ). There was a significant effect of gender on cognitive confidence, with males ( $Mdn = 9.50$ ) scoring higher than females ( $Mdn = 7.00$ ),  $U = 524.50$ ,  $z = -2.20$ ,  $p = 0.03$ ,  $r = -0.25$ .

### Association of Metacognitive Beliefs and Distress

Results of the regression analyses are shown in Table 2. There was no evidence of multicollinearity; variance inflation factors were all less than 10, tolerance statistics were greater

Table 1

*Descriptive statistics and Spearman's rho correlations between study variables*

	2	3	4	5	6	7	<i>Mdn</i>	<i>IQR</i>
i) HADS-T	0.69***	0.14	0.68***	0.26*	0.06	0.36**	9.00	5.00-14.00
ii) RTQ-10	-	0.37**	0.75***	0.19	0.24*	0.49***	24.00	16.00-33.00
iii) MCQ-PB		-	0.31**	0.14	0.29*	0.28*	7.00	6.00-11.00
iv) MCQ-NB			-	0.12	0.21	0.57***	10.00	6.50-14.00
v) MCQ-CC				-	0.26*	0.01	8.00	6.00-11.00
vi) MCQ-NC					-	0.36**	9.00	8.00-12.00
vii) MCQ-CSC						-	14.00	11.00-16.50

*Note.* HADS-T = total adapted Hospital Anxiety and Depression scale score; RTQ-10 = repetitive thinking questionnaire; MCQ-PB = metacognitions questionnaire positive beliefs about worry subscale; MCQ-NB = metacognitions questionnaire negative beliefs about the uncontrollability and danger of worry subscale; MCQ-CC = metacognitions questionnaire cognitive confidence subscale; MCQ-NC = metacognitions questionnaire need for control subscale; MCQ-CSC = metacognitions questionnaire cognitive self-consciousness subscale.

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Table 2

*Statistics for the final regression model predicting distress (adapted HADS-T)*

Variable	$\Delta R^2$	$\Delta F$	$p$	$b$	95% BCa CIs	$\beta$	$P$
Step 1	0.08	0.30	0.74				
Constant				11.53	2.25, 19.24		0.03
Age				-0.04	-0.16, 0.08	-0.07	0.55
Gender				0.59	-2.43, 3.86	0.05	0.70
Step 2	0.03	1.01	0.63				
Constant				15.03	5.10, 23.20		0.01
Age				-0.05	-0.17, -0.75	-0.08	0.51
Gender				0.60	-2.46, 3.81	0.05	0.70
ALSFERS-R				-0.11	-0.28, 0.05	-0.17	0.18
Time since dx				-0.01	-0.03, 0.03	-0.01	0.97
Step 3	0.43	56.24	<0.001				
Constant				-4.55	-14.61, 4.73		0.37
Age				0.04	-0.06, 0.14	0.06	0.49
Gender				2.12	-0.22, 4.33	0.16	0.08
ALSFERS-R				-0.06	-0.17, 0.04	-0.09	0.93
Time since dx				<-0.01	-0.02, 0.02	-0.01	0.33
RTQ-10				0.43	0.29, 0.57	0.69	<0.001
Step 4	0.12	3.72	<0.001				
Constant				-0.43	-10.97, 8.96		0.93
Age				0.02	-0.08, 0.13	0.25	0.78
Gender				1.27	-0.93, 3.28	0.97	0.27
ALSFERS-R				-0.04	-0.16, 0.07	-0.07	0.43
Time since dx				<0.01	-0.02, 0.03	0.02	0.85
RTQ-10				0.30	0.12, 0.50	0.48	<0.001
MCQ-PB				-0.33	-0.64, 0.03	-0.20	0.03
MCQ-NB				0.55	0.14, 0.92	0.38	<0.01
MCQ-CC				0.11	-0.26, 0.61	0.06	0.54
MCQ-NC				-0.35	-0.69, 0.14	-0.17	0.06
MCQ-CSC				0.06	-0.29, 0.32	0.04	0.70

Adjusted  $R^2 = 0.59$ 

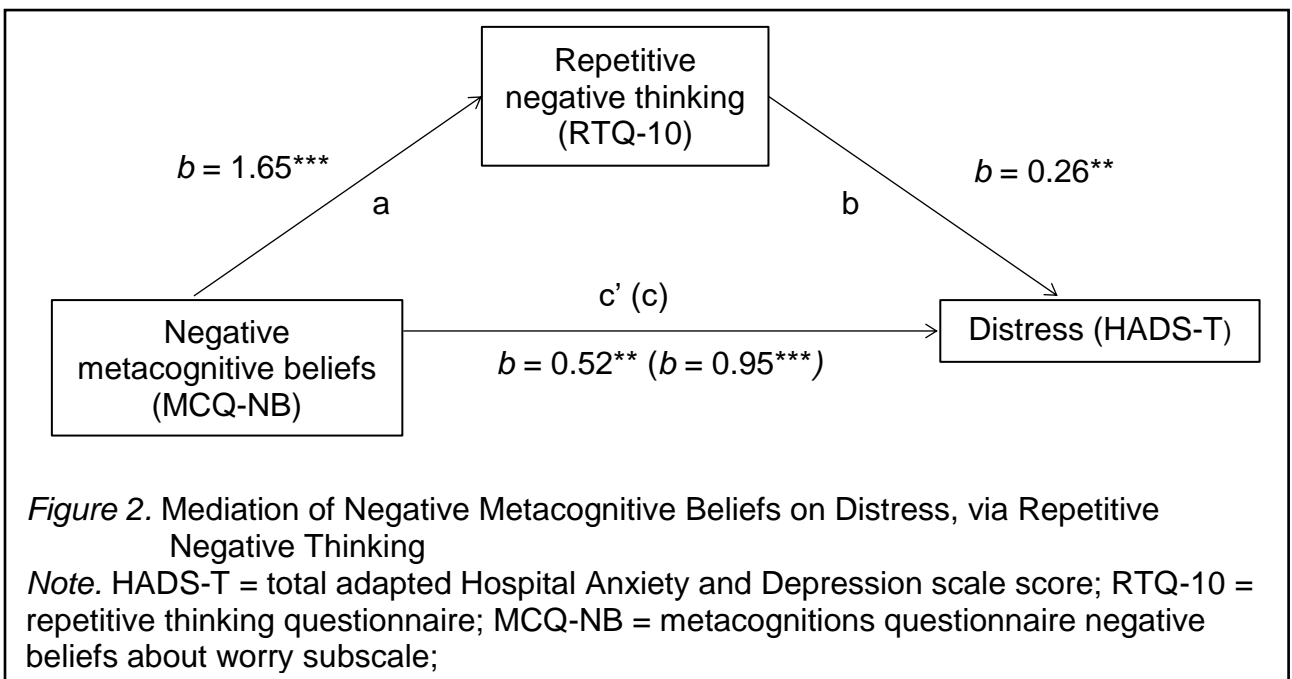
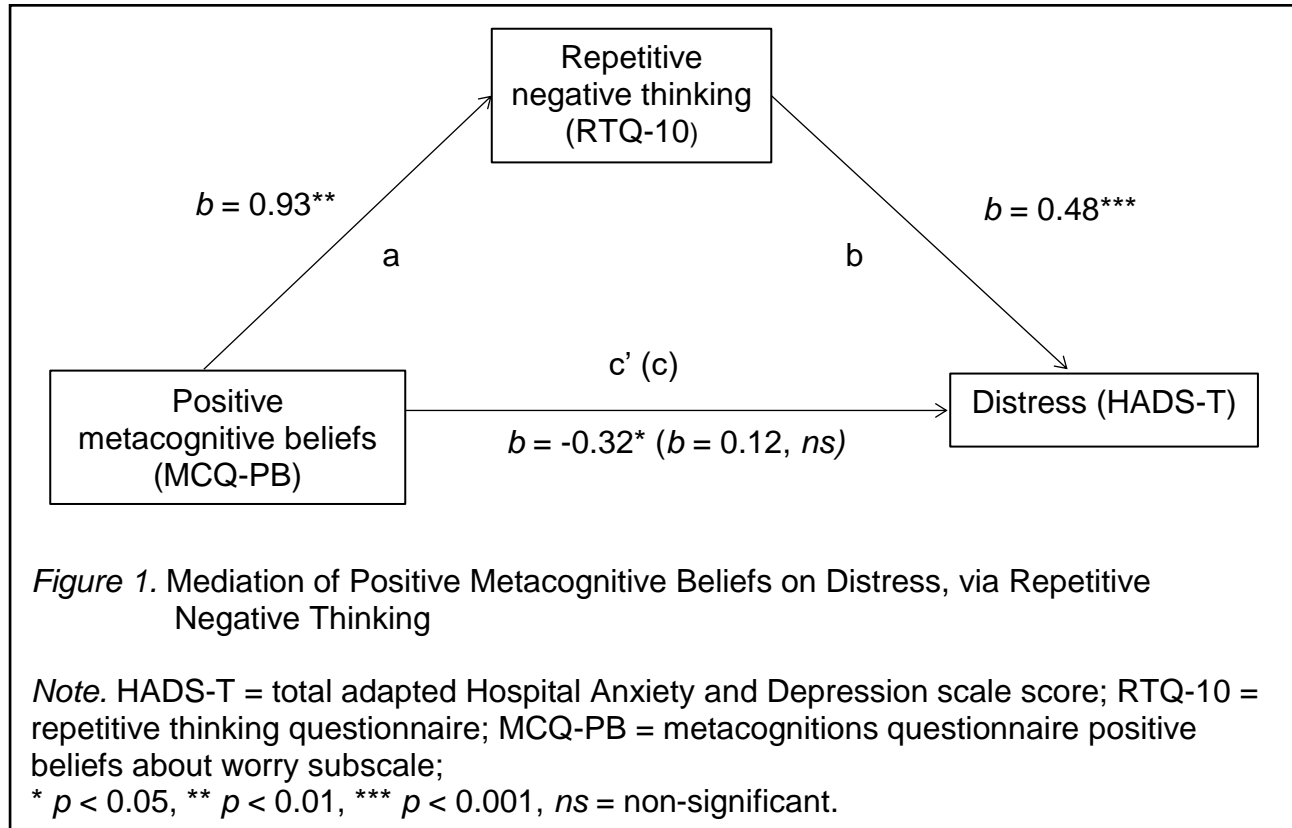
*Note.* ALSFRS-R = Amyotrophic Lateral Sclerosis functional rating scale-revised; dx = diagnosis, RTQ-10 = repetitive thinking questionnaire; MCQ-PB = metacognitions questionnaire positive beliefs about worry subscale; MCQ-NB = metacognitions questionnaire negative beliefs about the uncontrollability and danger of worry subscale; MCQ-CC = metacognitions questionnaire cognitive confidence subscale; MCQ-NC = metacognitions questionnaire need for control subscale; MCQ-CSC = metacognitions questionnaire cognitive self-consciousness subscale.



than 0.2, and correlations between the study variables were less than 0.8. There was no evidence of autocorrelation as indicated by a Durbin-Watson test statistic of 2.18. There were no outliers outside of 3 standard deviations. After controlling for age and gender, factors associated with MND severity explained an additional 3% of the variance in distress in step 2. Repetitive negative thinking explained a further 43% of the variance in step 3, and in the final step metacognitive beliefs explained a further 12% of the variance in distress. The final model accounted for 59% of the variance with repetitive negative thinking, positive beliefs about worry and, negative beliefs about the uncontrollability and danger of worry making independent contributions to the model.

### **Mediation of the Relationship between Metacognitive Beliefs and Distress by Repetitive Negative Thinking**

Results of the mediation analyses are shown in Figures 1 and 2. Age, gender, time since diagnosis, and physical functioning (ALSFRS-R) were controlled for in both mediation analyses. For positive metacognitive beliefs, there was a significant indirect effect ( $ab = 0.44$ , BCa 95% CIs = 0.19 - 0.81) on distress mediated by repetitive negative thinking, the direct effect remained significant. It should be noted that there was a negative relationship between positive metacognitive beliefs and distress. For negative metacognitive beliefs about the uncontrollability and danger of worry, there was a significant indirect effect ( $ab = 0.42$ , BCa 95% CIs = 0.10 - 0.82), mediated by repetitive negative thinking, on distress. The direct effect remained significant indicating partial mediation.



### Discussion

This was the first study to explore the utility of the S-REF model in an MND population. After controlling for age, gender, time since diagnosis, physical functioning, and repetitive negative thinking, metacognitive beliefs accounted for an additional 12% of the variance in distress. In the final model, three variables made independent contributions to distress. In descending order of magnitude these were repetitive negative thinking, negative metacognitive beliefs about the danger and uncontrollability of worry, and positive metacognitive beliefs about worry. In line with the S-REF model, the results indicate that metacognitive beliefs are associated with distress in plwMND.

Mediational analyses largely supported hypothesised relationships between metacognitive beliefs, repetitive negative thinking, and distress. The relationship between negative metacognitive beliefs about the danger and uncontrollability of worry and distress was partially mediated by repetitive negative thinking. This is consistent with the S-REF prediction that negative metacognitive beliefs will act, both indirectly via the CAS and directly due to their content, to influence distress. The relationship between positive metacognitive beliefs and distress was inconsistently mediated by repetitive negative thinking. This fits with the S-REF prediction that positive metacognitive beliefs guide the selection of the CAS as a coping strategy resulting in distress, and do not directly cause or maintain distress. The negative relationship between positive metacognitive beliefs and distress is not clearly understood. It could be explained by the nature of positive metacognitive beliefs, whereby the perceived helpfulness of thinking about difficulties provides a sense of control and ability to cope in the short-term, therefore reducing distress. However, when positive metacognitive beliefs lead to the selection of

persistent repetitive negative thinking as a coping strategy this results in distress. Nonetheless, this study provides support for the utility of the S-REF model in plwMND.

These findings are fitting with research testing the S-REF model in mental health populations (Wells, 2009, 2013), within the general population (Spada, Mohiyeddini & Wells, 2008), and other physical health populations (Allott, Wells, Morrison & Walker, 2005; Cook et al., 2015; Maher-Edwards et al., 2012) which have found that negative metacognitive beliefs were a predominant contributor to explaining distress. It could be hypothesised that the relationship between metacognitive beliefs and rumination becomes more toxic for plwMND who are often unable to effectively communicate their thoughts, perhaps resulting in increased repetitive negative thinking. Results also reflect previous findings that physical functioning, time since diagnosis, and demographic factors are unable to consistently or satisfactorily explain distress in MND (Cupp et al., 2011; De groot, Post, van Heuveln, Van den berg & Lindeman, 2007; Gauthier et al., 2007; Matuz, Birbaumer, Hautzinger & Kübler, 2015; McElhiney, Rabkin, Gordon, Goetz & Mitsumoto, 2009; Montel, Albertini, Desnuelle & Spitz, 2012; Mustfa et al., 2006; Pagnini, Phillips, Bosma, Reece & Langer, 2015; Rabkin, Wagner & Del Bene, 2000; Rabkin et al., 2005). This is also fitting with research noting the role of cognitions in distress (Matuz et al., 2010; Miglioretti, Mazzini, Oggioni, Testa & Monaco, 2008; Plahuta et al., 2002), which could be explained by the influence of metacognitive beliefs. It would be useful to consider whether the S-REF model is better able to account for distress than traditional cognitive models. MCT infers the advantage over traditional cognitive therapy of not requiring the individual to engage with the content of negative thoughts related to illness, which has been reported as distressing in other physical health populations (Baker et al., 2013). Furthermore,

MCT is not limited by reality-testing of potentially accurate thoughts associated with MND such as “I’m not going to get better.”

### **Limitations**

Although the findings of this study appear to be relatively robust there are a number of limitations that must be taken into account. Firstly, the study was cross-sectional and therefore causality cannot be assumed. In addition, there remains a large proportion of variance that cannot be explained by the model thus additional factors that could contribute to distress should be considered. Social factors were not measured in the current study, but have been associated with distress in plwMND in previous studies (Goldstein, Atkins, Landau, Brown & Leigh, 2006; Matuz et al., 2015). Considering social factors, such as quality of perceived social support, may result in a more robust model that is able to account for a larger proportion of the variance. Furthermore, the study used self-report measures, which rely on the individual to accurately assess each domain they are responding to. These measures are prone to response bias, which was not accounted for. Additionally, the RTQ-10 is a relatively short measure of repetitive negative thinking, which was selected to minimise the time required to complete the study given the prevalence of physical limitations and fatigue in this population. A more detailed measure of repetitive negative thinking that considers the CAS more widely may be useful to confirm findings in future studies. Furthermore, the site of onset was not recorded or controlled for in the analysis, although several studies have failed to demonstrate a relationship between site of onset and distress (McElhiney et al., 2009; Mora, Salas, Fajardo, Iváñez & Rodríguez-Santos, 2013; Vrijssen et al., 2015). This study utilised a relatively small sample of plwMND, which did not contain many individuals who were receiving nutrition via percutaneous endoscopic gastrostomy or required assisted ventilation. Scrutiny of the model in a larger sample of plwMND would lead

to the inclusion of a broader population and allow for grouping of individuals based upon time since diagnosis or site of onset to consider any differences between groups. A larger, more representative sample would likely strengthen findings and permit the use of alternative statistical methods, such as structural equation modelling, which may further the understanding of the utility of the S-REF model in plwMND. However, it should be recognised that recruiting and retaining plwMND with severe symptoms in research studies can be challenging given poor health and prioritisation of end of life needs (Albert et al., 2005). In terminal illness populations staff can fear that research is a further burden, given the MND prognosis and the number of professionals already involved in their care, and therefore may be reluctant to offer research opportunities (Mody et al., 2008). This contrasts with patient's perspectives, who often wish to advance knowledge and improve care for others whilst providing meaning for their own experience (Ross & Cornbleet, 2003). Training for staff to increase awareness of the patient perspective on research and to feel comfortable discussing research opportunities in plwMND could improve access to this population and therefore the representativeness of MND samples in research.

### **Clinical Implications**

Clinically, this research increases awareness of the prevalence of distress in plwMND and the need to recognise and provide psychological support for plwMND. It also provides evidence for further investigation of the utility of MCT in reducing distress for plwMND. In a population where there is little understanding of the psychological processes underlying distress, this study enhances our knowledge. It provides a stepping stone for further research to support plwMND who are experiencing distress. Assessing metacognitive beliefs also offers a potential method to identify those at risk of developing distress and provide early intervention.

### **Future Research**

Given the limited knowledge of psychological processes underlying distress in plwMND, this study significantly adds to the theoretical understanding of the experience of distress for plwMND. Future research to further assess the model could utilise a prospective design to consider the role of metacognitive beliefs in the development of distress over time. Consideration of MND specific factors, such as the relationship of perceived ability to communicate effectively with the level of repetitive negative thinking or the influence of social cognition changes on thinking processes, could further the understanding of the S-REF model in this population. This could potentially support identification and implementation of support for those at risk of developing distress. Case studies could be used to consider the effectiveness of MCT at challenging metacognitive beliefs, reducing repetitive negative thinking, and therefore distress for plwMND. This would help to understand if theoretical knowledge transfers to clinical outcomes for plwMND. This has already been demonstrated in a cancer population, with theoretical support for the S-REF model (Cook et al., 2015) supported by clinically significant effects of MCT in a case study (McNicol, Salmon, Young & Fisher, 2013), and an ongoing open trial of MCT for depression and anxiety to consider its effectiveness at alleviating distress (Fisher, 2016). Although for plwMND research is earlier in the research cycle, the current study offers significant insight into the knowledge of psychological processes in a relatively understudied group and provides direction for future research.

It would also be useful to compare the S-REF model with other psychological models, such as the traditional cognitive model, acceptance and commitment therapy (ACT), and mindfulness-based cognitive therapy (MBCT) to consider which of these models is most effective at explaining and managing distress in plwMND. MBCT and ACT also emphasise the

importance of attentional processes underlying emotional distress. MBCT aims to foster the ability to pay attention consciously to the present moment in a non-judgemental manner (Kabat-Zinn, 1994). MBCT intervention includes learning to return attention back to the anchor of the breath or body and away from distressing thoughts (Kabat-Zinn, 1994). Whilst ACT aims to create a meaningful life while accepting the pain that comes with it using a variety of intervention methods which aim to promote mindfulness, including cognitive diffusion and contacting the present moment through use of metaphor (Hayes, Strosahl & Wilson, 2016). Both of these therapeutic attentional methods differ from MCT as they involve responding to thoughts and therefore lead to continued processing, which is hypothesised to maintain metacognitive beliefs and activate the CAS (Fisher & Wells, 2009). MCT attentional exercises would instead focus on discontinuing further processing thoughts of thoughts, with the specific goal of modifying metacognitive beliefs about the uncontrollability of thinking (Wells, 2009). The current study provides evidence for the importance of metacognitive beliefs in maintaining distress; therefore MCT would be suggested for plwMND over and above other therapies as ACT and MCBT act to maintain the CAS, metacognitive beliefs and therefore distress. However further research to understand and compare these models in plwMND will ensure the best treatment efficacy and allow choice in intervention for plwMND who are experiencing distress. Future studies should utilise more robust methods than previous therapy trials, which are limited by inadequate follow-up, no control for differences between groups, no report of whether individuals experienced significant distress, and lack of active control conditions (Gould et al., 2015). Consistent use of validated measures that are designed to measure distress in plwMND will allow comparison of the effectiveness of psychological interventions to develop the best therapies for plwMND who are experiencing distress.



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## Appendix A – Author Guidelines for the Journal of Social Science & Medicine

Social Science & Medicine provides an international and interdisciplinary forum for the dissemination of social science research on health. We publish original research articles (both empirical and theoretical), reviews, position papers and commentaries on health issues, to inform current research, policy and practice in all areas of common interest to social scientists, health practitioners, and policy makers. The journal publishes material relevant to any aspect of health and healthcare from a wide range of social science disciplines (anthropology, economics, epidemiology, geography, policy, psychology, and sociology), and material relevant to the social sciences from any of the professions concerned with physical and mental health, health care, clinical practice, and health policy and the organization of healthcare. We encourage material which is of general interest to an international readership.

### Journal Policies

The journal publishes the following types of contribution:

- 1) Peer-reviewed original research articles and critical analytical reviews in any area of social science research relevant to health and healthcare. These papers may be up to 8000 words including abstract, tables, figures, references and (printed) appendices as well as the main text. Papers below this limit are preferred.
- 2) Peer-reviewed short communications of findings on topical issues or published articles of between 2000 and 4000 words.
- 3) Submitted or invited commentaries and responses debating, and published alongside, selected articles (please select the article type 'Discussion' when submitting a Commentary).
- 4) Special Issues bringing together collections of papers on a particular theme, and usually guest edited.

### *Manuscript:*

- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print

*Graphical Abstracts / Highlights files* (where applicable)

*Supplemental files* (where applicable)

Further considerations

- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa
- Manuscript does not exceed the word limit
- All identifying information has been removed from the manuscript, including the file name itself
- Permission has been obtained for use of copyrighted material from other sources (including the Internet)
- Relevant declarations of interest have been made
- Journal policies detailed in this guide have been reviewed
- Referee suggestions and contact details provided, based on journal requirements

### *References*

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.

### *Formatting Requirements*

The journal operates a double blind peer review policy. For guidelines on how to prepare your paper to meet these criteria please see the attached guidelines. The journal requires that your manuscript is submitted with double spacing applied. There are no other strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.

If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.  
Divide the article into clearly defined sections.

### ***Essential cover page information***

The Cover Page should **only** include the following information:

- **Title.** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible and make clear the article's aim and health relevance.
- **Author names and affiliations in the correct order.** Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that telephone and fax numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address. Contact details must be kept up to date by the corresponding author.**
- **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

### ***Title***

Please consider the title very carefully, as these are often used in information-retrieval systems. Please use a concise and informative title (avoiding abbreviations where possible). Make sure that the health or healthcare focus is clear.

### ***Abstract***

An abstract of up to 300 words must be included in the submitted manuscript. An abstract is often presented separately from the article, so it must be able to stand alone. It should state briefly and clearly the purpose and setting of the research, the principal findings and major conclusions, and the paper's contribution to knowledge. For empirical papers the country/countries/locations of the study should be clearly stated, as should the methods and nature of the sample, the dates, and a summary of the findings/conclusion. Please note that excessive statistical details should be avoided, abbreviations/acronyms used only if essential or firmly established, and that the abstract should not be structured into subsections. Any references cited in the abstract must be given in full at the end of the abstract.

### ***Keywords***

Up to 8 keywords are entered separately into the online editorial system during submission, and should accurately reflect the content of the article. Again abbreviations/acronyms should be used only if essential or firmly established. For empirical papers the country/countries/locations of the research should be included. The keywords will be used for indexing purposes.

Systematic reviews and meta-analyses must be reported according to PRISMA guidelines.

### ***Footnotes***

There should be no footnotes or endnotes in the manuscript.

### ***Tables***

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

## **References**

### *Citation in text*

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full at the end of the abstract. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal (see below) and should include a substitution of the publication date with either "Unpublished results" or "Personal communication". Citation of a reference as "in press" implies that the item has been accepted for publication.

### *Web references*

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

### *Data references*

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

### *Reference formatting*

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:

### *Reference style*

*Text:* All citations in the text should refer to:

1. *Single author:* the author's name (without initials, unless there is ambiguity) and the year of publication;
2. *Two authors:* both authors' names and the year of publication;
3. *Three or more authors:* first author's name followed by 'et al.' and the year of publication.

Citations may be made directly (or parenthetically). Groups of references should be listed first alphabetically, then chronologically.

Examples: 'as demonstrated (Allan, 2000a, 2000b, 1999; Allan and Jones, 1999). Kramer et al. (2010) have recently shown ....'

*List:* References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters 'a', 'b', 'c', etc., placed after the year of publication.

## **Appendix B – Systematic review protocol**

### **Systematic Review Protocol**

#### **Predictors of distress in Motor Neuron Disease**

##### **Background**

Motor neurone disease (MND) is a neurological disorder which involves the progressive degeneration and death of motor neurones. There are a variety of physical consequences depending on the neurones affected including progressive muscular weakness and paralysis, difficulties with swallowing, speech and breathing (Talbot & Marsden, 2008). Unfortunately no cure has yet been identified. Life expectancy for approximately 50% of people diagnosed with MND is three years from symptom onset (Ilse et al., 2015). Therefore treatment is focused upon symptom management. However, managing physical symptoms alone is insufficient to alleviate emotional distress since physical functioning and disease progression are not consistently associated with emotional distress (McLeod & Clarke, 2007).

Other potential contributors to distress need to be explored including demographic factors, psychological processes and social factors. This may help to identify those at risk of becoming distressed and highlight targets for intervention to reduce emotional distress. To date research that considers correlates of distress following diagnosis of MND has not been synthesized. Prospective research identifying factors that predict of distress over time, which are therefore causally related, is also yet to be synthesized. This systematic review aims to review current available data to understand the demographic, social and psychological factors associated with distress and also the factors which are predictive of distress over time.

##### **Review Questions**

- *Do any psychological, disease, or social factors predict distress over time in MND?*

## Methods

### Search Strategy

The search strategy will be designed to access published materials. The PROSPERO database has been searched to ensure that a similar review is not currently in progress.

Population	Variable	Study Design
Adults with a diagnosis of Motor Neurone Disease.	Studies measuring distress with established measures (e.g. anxiety, depression, hopelessness)  Studies measuring associated psychological, social or disease factors	Prospective

### Electronic databases:

The following electronic databases will be searched: Medline, PsychINFO (EBSCOhost) and CINAHL Plus (EBSCOhost). Searches will be limited to those published in English, human adults, with no restrictions on date. The basic search terms are presented below, with searches adapted across databases to utilise thesaurus terms.

### Basic search terms:

Connector	Search Terms	Search fields
	“Motor Neuron Disease” OR “Motor Neurone Disease” OR “Motor Neurone Diseases” OR “Motor Neuron Diseases” OR “Amyotrophic Lateral Sclerosis” OR “Progressive Bulbar Palsy” OR “Lou Gehrigs Disease” OR “Progressive Muscular Atrophy” OR “Primary Lateral Sclerosis”	All Fields
AND	“Depress*” OR “Anxiety” OR “Distress” OR “Worry” OR “Ruminat*” OR “Emotion*” OR “Psych*” OR “Mood” OR “Affect*” OR “Psychosocial” OR “Coping” OR “Adapt*” OR “Quality of life” OR	All Fields



	“Adjustment” OR “Illness cognition*” OR “Fear*” OR “Belief*”	
AND NOT	“Paediatric*” OR “Child*” OR “infant*” OR “Adolescent*”	Abstract
AND NOT	“Gene*” OR “Mutation*”	Abstract
AND NOT	“Mice” OR “Mouse” OR “Rat*” OR “Animal*”	Abstract

### **Other search strategies**

Reference lists and bibliographies of the articles collected from those identified will be manually searched. Key authors in the area will be contacted to check that relevant studies have not been missed.

### **Screening and selecting studies to include in the review**

All references identified by the search will be imported into the EndNote reference manager. Duplicate references will be identified and removed using EndNote referencing software. Titles and abstracts will be screened for relevance. Full copies of articles identified by the search, and considered to meet the inclusion criteria, based on their title, abstract and subject descriptors, will be obtained for further consideration. The reviewer will select articles against the inclusion criteria using a screening and selection tool (see Appendix). Another reviewer will also re-run the search and review a subset of the references for comparison purposes. Discrepancies in reviewer selections will be resolved through discussion with a third party and comparison with the search inclusion and exclusion criteria. Articles identified through reference lists and bibliographic searches will also be considered for data collection based upon their title.

### **Reporting results of searches**

Results of searches will be detailed and documented according to PRISMA guidelines

(Moher, Liberati, Tetzlaff, & Altman, 2009).

### **Data Extraction**

Data will be extracted from relevant studies including: general study details (author, date, country of origin, recruitment method); participant demographics (age, gender, time since diagnosis, time since onset of symptoms, onset of symptoms - bulbar or limb); study design and methodology (sample size, attrition if prospective studies, correlated factors, analysis method); and a summary of the reported findings (reported distress levels, any relevant correlations and/or predictors). A subset of the extracted data will also be checked by another reviewer. If required data is missing the authors will be contacted to request relevant data.

### **Quality Assessment**

Selected studies will be assessed for quality using a tool adapted from Williams et al., (2010). This quality assessment will also be completed by another reviewer. Discrepancies in reviewer ratings will be resolved through discussion with a third party.

### **Data synthesis**

A narrative synthesis of the findings will be presented. Factors that correlate with or predict distress will be grouped and findings synthesised within three broad categories of factors: demographic or clinical; social; and psychological. If there are sufficient high quality papers using established measures of distress a meta-analysis may be conducted.

### **Dissemination**

Findings will be submitted to a journal in the field for publication.

### References

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## Appendix

### Search Strategies

#### PsycINFO

	<b>PsychINFO</b> <b>Thesaurus terms in italics</b>	
	<i>Amyotrophic Lateral Sclerosis</i> OR “Motor Neuron Disease” OR “Motor Neurone Disease” OR “Motor Neurone Diseases” OR “Motor Neuron Diseases” OR “Amyotrophic Lateral Sclerosis” OR “Progressive Bulbar Palsy” OR “Lou Gehrigs Disease” OR “Progressive Muscular Atrophy” OR “Primary Lateral Sclerosis”	All Fields
AND	<i>Major Depression (explode) OR Depression (emotion) OR Rumination (cognitive process) OR Anxiety Disorders (explode) OR Emotional Adjustment (explode) OR Adjustment (explode) OR Adjustment Disorders OR Coping Behavior OR Distress OR Post-Traumatic Stress OR Posttraumatic Stress Disorder (explode) OR “Depress*” OR “Anxiety” OR “Distress” OR “Worry” OR “Ruminat*” OR “Emotion*” OR “Psych*” OR “Mood” OR “Affect*” OR “Psychosocial” OR “Coping” OR “Adapt*” OR “Quality of life” OR “Adjustment” OR “Illness cognition*” OR “Fear*” OR “Belief*”</i>	All Fields
AND NOT	<i>Cells (biology) (explode)</i>	All fields
AND NOT	OR “Gene*” OR “Mutation*”	Abstract
AND NOT	“Paediatric*” OR “Child*” OR “infant*” OR “Adolescent*”	Abstract
AND NOT	“Mice” OR “Mouse” OR “Rat*” OR “Animal*”	Abstract

#### PsycINFO limiters:

Publication Type: All Journals; Language: English; Age Groups: Adulthood (18 yrs & older), Young Adulthood (18-29 yrs), Thirties (30-39 yrs), Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older); Population Group: All

("Motor Neuron Disease" OR "Motor Neurone Disease" OR "Motor Neurone Diseases" OR "Motor Neuron Diseases" OR "Amyotrophic Lateral Sclerosis" OR "Progressive Bulbar Palsy" OR "Lou Gehrigs Disease" OR "Progressive Muscular Atrophy" OR "Primary Lateral Sclerosis") OR (DE "Amyotrophic Lateral Sclerosis")

AND (DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR DE "Depression (Emotion)" OR DE "Rumination (Cognitive Process)" OR DE "Anxiety Disorders" OR DE "Acute Stress Disorder" OR DE "Castration Anxiety" OR DE "Death Anxiety" OR DE "Generalized Anxiety Disorder" OR DE "Obsessive Compulsive Disorder" OR DE "Panic Disorder" OR DE "Phobias" OR DE "Post-Traumatic Stress" OR DE "Posttraumatic Stress Disorder" OR DE "Separation Anxiety Disorder" OR (((DE "Emotional Adjustment" OR DE "Emotional Control" OR DE "Identity Crisis") OR (DE "Adjustment" OR DE "Emotional Adjustment" OR DE "Occupational Adjustment" OR DE "School Adjustment" OR DE "Social Adjustment"))) OR (DE "Adjustment Disorders")) OR (DE "Coping Behavior")) OR (DE "Distress")) OR (DE "Post-Traumatic Stress" OR DE "Posttraumatic Stress Disorder" OR DE "Complex PTSD" OR DE "DESNOS")

OR "Depress\*" OR "Anxiety" OR "Distress" OR "Worry" OR "Ruminat\*" OR "Emotion\*" OR "Psych\*" OR "Mood" OR "Affect\*" OR "Psychosocial" OR "Coping" OR "Adapt\*" OR "Quality of life" OR "Adjustment" OR "Illness cognition\*" OR "Fear\*" OR "Belief\*"

NOT (AB "Paediatric\*" OR "Child\*" OR "infant\*" OR "Adolescent\*")

NOT (AB "Gene\*" OR "Mutation\*")

NOT (AB "Mice" OR "Mouse" OR "Rat\*" OR "Animal\*")

NOT ("Cells (Biology)" OR DE "Adipocytes" OR DE "Astrocytes" OR DE "Autophagy" OR DE "Blood Cells" OR DE "Cell Membrane" OR DE "Cell Migration" OR DE "Cell Nucleus" OR DE "Chromosomes" OR DE "Cones (Eye)" OR DE "Connective Tissue Cells" OR DE "Cytoplasm" OR DE "Cytoskeleton" OR DE "Endoplasmic Reticulum" OR DE "Epithelial Cells" OR DE "Golgi Apparatus" OR DE "Granule Cells" OR DE "Mast Cells" OR DE "Mitochondria" OR DE "Neuroglia" OR DE "Neurons" OR DE "Oligodendrocytes" OR DE "Progenitor Cells" OR DE "Ribosomes" OR DE "Sperm" OR DE "Stem Cells")

**MEDLINE**

	<b>Medline Thesaurus terms in italics</b>	
	<i>Amyotrophic Lateral Sclerosis [Psychology] (Explode) OR Motor Neuron Disease [Psychology] (explode) OR Progressive Bulbar Palsy [Psychology] (Explode) OR Spinal Muscular Atrophy [Psychology] (Explode) OR "Motor Neuron Disease" OR "Motor Neurone Disease" OR "Motor Neurone Diseases" OR "Motor Neuron Diseases" OR "Amyotrophic Lateral Sclerosis" OR "Progressive Bulbar Palsy" OR "Lou Gehrigs Disease" OR "Progressive Muscular Atrophy" OR "Primary Lateral Sclerosis"</i>	All Fields
AND	<i>Depression [Psychology &amp; epidemiology] (explode) OR Depressive Disorder [Psychology &amp; Epidemiology] (explode) OR Affective Symptoms [Psychology &amp; epidemiology] (explode) OR Anxiety Disorders [Psychology &amp; epidemiology] (explode) OR Anxiety [Psychology &amp; epidemiology] (explode) OR Metacognition (Explode) OR Thinking (explode) Or Psychology (explode) OR Emotions (explode) OR Affect (explode) OR Adaptation Psychological (Explode) Or Emotional Adjustment (explode) Or Quality of Life [psychology] (Explode) OR Fear [Psychology] (explode) OR "Depress*" OR "Anxiety" OR "Distress" OR "Worry" OR "Ruminat*" OR "Emotion*" OR "Psych*" OR "Mood" OR "Affect*" OR "Psychosocial" OR "Coping" OR "Adapt*" OR "Quality of life" OR "Adjustment" OR "Illness cognition*" OR "Fear*" OR "Belief"</i>	All Fields
NOT	<i>Biological science disciplines (explode)</i>	All Fields
AND NOT	"Paediatric*" OR "Child*" OR "infant*" OR "Adolescent*"	Abstract
AND NOT	"Gene*" OR "Mutation*"	Abstract
AND NOT	"Mice" OR "Mouse" OR "Rat*" OR "Animal*"	Abstract

**MEDLINE Limiters:**

Language: English; Humans, female, male; Age group: All adult

((Amyotrophic Lateral Sclerosis or Motor Neuron Disease or Bulbar Palsy, Progressive or Muscular Atrophy, Spinal or ('Motor Neuron Disease' or 'Motor Neurone Disease' or 'Motor

Neurone Diseases' or 'Motor Neuron Diseases' or 'Amyotrophic Lateral Sclerosis' or 'Progressive Bulbar Palsy' or 'Lou Gehrigs Disease' or 'Progressive Muscular Atrophy' or 'Primary Lateral Sclerosis')) and (Depressive Disorder or Depression or Affective Symptoms or Anxiety Disorders or Anxiety or Metacognition or Thinking or Psychology or Emotions or Affect or Adaptation, Psychological or Emotional Adjustment or "Quality of Life" or Fear or ('Depress\*' or 'Anxiety' or 'Distress' or 'Worry' or 'Ruminat\*' or 'Emotion\*' or 'Psych\*' or 'Mood' or 'Affect\*' or 'Psychosocial' or 'Coping' or 'Adapt\*' or 'Quality of life' or 'Adjustment' or 'Illness cognition\*' or 'Fear\*' or 'Belief\*')).af. not Biological Science Disciplines.ab. not ('Mice' or 'Mouse' or 'Rat\*' or 'Animal\*').ab. not ('Gene\*' or 'Mutation\*').ab. not ('Paediatric\*' or 'Child\*' or 'infant\*' or 'Adolescent\*').ab.

limit 30 to (english language and male and female and humans and "all adult (19 plus years)")

**CINAHL**

No thesaurus

Connector	Search Terms	Search fields
	“Motor Neuron Disease” OR “Motor Neurone Disease” OR “Motor Neurone Diseases” OR “Motor Neuron Diseases” OR “Amyotrophic Lateral Sclerosis” OR “Progressive Bulbar Palsy” OR “Lou Gehrigs Disease” OR “Progressive Muscular Atrophy” OR “Primary Lateral Sclerosis”	All Fields
AND	“Depress*” OR “Anxiety” OR “Distress” OR “Worry” OR “Metacog*” OR “Ruminat*” OR “Emotion*” OR “Psych*” OR “Mood” OR “Affect*” OR “Psychosocial” OR “Coping” OR “Adapt*” OR “Quality of life” OR “Adjustment” OR “Illness cognition*” OR “Fear*” OR “Belief*”	All Fields
AND NOT	“Paediatric*” OR “Child*” OR “infant*” OR “Adolescent*”	Abstract
AND NOT	“Gene*” OR “Mutation*”	Abstract
AND NOT	“Mice” OR “Mouse” OR “Rat*” OR “Animal*”	Abstract

**CINAHL limiters**

Language: English; Age group: All Adult; Publication Type: All

( "Motor Neuron Disease" OR "Motor Neurone Disease" OR "Motor Neurone Diseases" OR "Motor Neuron Diseases" OR "Amyotrophic Lateral Sclerosis" OR "Progressive Bulbar Palsy" OR "Lou Gehrigs Disease" OR "Progressive Muscular Atrophy" OR "Primary Lateral Sclerosis" ) AND ( "Depress\*" OR "Anxiety" OR "Distress" OR "Worry" OR "Metacog\*" OR "Ruminat\*" OR "Emotion\*" OR "Psych\*" OR "Mood" OR "Affect\*" OR "Psychosocial" OR "Coping" OR "Adapt\*" OR "Quality of life" OR "Adjustment" OR "Illness cognition\*" OR "Fear\*" OR "Belief\*" ) NOT AB ( "Paediatric\*" OR "Child\*" OR "infant\*" OR "Adolescent\*" ) NOT AB ( "Gene\*" OR "Mutation\*" ) NOT AB ( "Mice" OR "Mouse" OR "Rat\*" OR "Animal\*" )



### Screening and Selection Tool

#### Review Questions

- What are the psychological, social and disease factors associated with distress in Motor Neuron Disease?
  - What are the factors identified at diagnosis that predict later distress in Motor Neuron Disease?

#### Inclusion Criteria

Population	Variable	Study Design
Adults with a diagnosis of Motor Neurone Disease.	<p>Studies measuring distress with established measures (e.g. anxiety, depression, hopelessness)</p> <p>Studies measuring associated psychological, social or disease factors</p>	Prospective

**Reviewer:**

**Date:**

**Author:**

**Year:**

**Title:**

**Journal:**

#### Patient population

#### Include

- Adults with:
- Motor Neuron Disease
  - Amyotrophic Lateral Sclerosis
  - Spinal Muscular Atrophy
  - Primary Lateral Sclerosis
  - Progressive Bulbar Palsy
  - Lou Gehrig's Disease
  - Progressive Muscular Atrophy
  - Machedo Joseph Disease
  - Kennedy's disease
  - Monomelic Amyotrophy

#### Exclude

- Children
- Staff
- Carers
- Frontotemporal Dementia
- Sarcopenia
- Multifocal Motor Neuropathy
- Neuropathy
- Camptocormia
- Guillain-Barre syndrome
- Charcot Marie Tooth
- Hirayama disease
- Corticobasal degeneration
- Progressive Supranuclear Palsy
- Diseases that mimic MND
- Postpolio syndrome
- Werdnig-Hoffman disease
- Other diseases

<b>Measures</b>	<b>Include</b> <ul style="list-style-type: none"> <li>• Established measures of distress (depression, anxiety, hopelessness, Quality of life measure with mental health scale)</li> </ul>	<b>Exclude</b> <ul style="list-style-type: none"> <li>• No measure of distress e.g.</li> <li>• Biological or genetics studies</li> <li>• Other therapies (physiotherapy, speech and language, dietician, neuropsychology)</li> <li>• Quality of life measure without mental health scale, or inadequate assessment of mental health e.g. one question only</li> </ul>
<b>Study type</b>	<b>Include</b> <ul style="list-style-type: none"> <li>• Prospective studies</li> </ul>	<b>Exclude</b> <ul style="list-style-type: none"> <li>• Cross-sectional studies</li> <li>• Case reports</li> <li>• Reviews</li> <li>• Personal commentaries</li> <li>• Legal proceedings</li> <li>• Interviews</li> <li>• Focus groups</li> <li>• Memoriams</li> <li>• Obituaries</li> <li>• Magazine articles</li> </ul>
<b>Population</b>	<b>Include</b> <ul style="list-style-type: none"> <li>• MND only</li> <li>• Analysis considers MND separately from other conditions</li> </ul>	<b>Exclude</b> <ul style="list-style-type: none"> <li>• MND with other neurological or terminal conditions</li> </ul>
<b>Predictors</b>	<b>Include</b> Considers predictors of distress such as <ul style="list-style-type: none"> <li>• Age</li> <li>• Gender</li> <li>• Onset of symptoms</li> <li>• Date of diagnosis</li> <li>• SES</li> <li>• Psychological factors</li> <li>• Time</li> </ul>	<b>Exclude</b> <ul style="list-style-type: none"> <li>• Does not consider any predictors of distress</li> </ul>

**Appendix C – Data extraction sheet****Data Extraction Sheet****Form for the extraction of information from primary studies:****Predictors of distress in MND****Study**

Author(s):

Title:

Date:

Research Question:

**Study Sample**

Target population:

Country:

Ethnicity:

Gender:

Age:

Employment/Educ Status:

Diagnosis:

Treatment:

**Data collection**Setting: Home / Clinic / other (*specify*)

Method: Interview / Questionnaires

Outcome Variables Assessed (*Measures used*):

Anxiety Y/N

Depression Y/N

QoL(mental health scale) Y/N

Other (*specify*)                      Y/N

Adequacy of measures:

Predictor Variables Assessed:

Medical                                      Y/N

Social/environmental                      Y/N

Psychological                                Y/N

### **Design**

Prospective cohort

Other:

Timing:                      Baseline assessment:

Follow-up assessments:

Sampling Method:

Entry and exclusion criteria:

Is sample representative of study population                      Y/N

Sample size:

Was a prior estimate made for sample size                      Y/N

*If yes*, what was the power of the study:

Baseline response rate:

Follow-up response rate:

**Results**

Were the basic data adequately described?      Y/N

Quantitative:

Analysis used:

Statistical findings reported (*list*)

Statistical information omitted

**Discussion**

Author's conclusion:

Attrition:      not discussed / inadequately treated / treated well

**Reviewers comments**

Include / Exclude

Reason:

**Appendix D – Quality Assessment Tool adapted from Williams et al. (2010)****Quality Assessment – Observational Studies (adapted from William et al., 2010)**

General instructions: Grade each criterion as “Yes,” “No,” “Partially,” or “Unclear.”

Factors to consider when making an assessment are listed under each criterion. Note that some criteria will only apply to specify types of study.

**1) Unbiased selection of the cohort?**

Factors that help reduce selection bias:

- Prospective study design
- Inclusion/exclusion criteria
  - Clearly described
  - Diagnosis of MND or ALS reported and by which criteria e.g. El Escorial probable or definite,
- Recruitment strategy
  - Clearly described
  - Relatively free from bias (selection bias might be introduced, e.g., by recruitment via advertisement)
  - If a comparison group was used, was the sample and selection appropriate? And did the study investigators ensure groups were comparable by matching, etc.

**2) Sample size calculated?**

Factors to consider:

- Did the authors report conducting a power analysis or describe some other basis for determining the adequacy of study group sizes for the primary outcome(s) of interest?
- Did the eventual sample size deviate by  $\leq 10\%$  of the sample size suggested by the power calculation? (only applicable if power calculation conducted)

**3) Adequate description of the cohort?**

Factors to consider:

- Age

- Gender
- Time since diagnosis / onset of symptoms
- Site of onset
- Treatment
- Physical impairment

#### **4) Validated method for ascertaining distress?**

Factors to consider:

- Was the method used to ascertain distress clearly described? (Details should be sufficient to permit replication in new studies.)
- Was a valid and reliable measure used to ascertain exposure? (standardised measure, Cronbach's Alpha reported etc, self-report measures tend to have lower reliability and validity than clinical interview, single items of scales taken from larger measures are likely to lack content validity and reliability)
- Were these measures implemented consistently across all study participants?

#### **5) Validated method for ascertaining other predictors?**

Factors to consider:

- Were predictors assessed using valid and reliable measures? (standardised measure, Cronbach's Alpha reported etc, self-report measures tend to have lower reliability and validity than clinical interview, single items of scales taken from larger measures are likely to lack content validity and reliability)
- Were these measures implemented consistently across all study participants?

#### **6) Adequate follow-up period?**

Factors to consider:

- Minimum adequate follow-up period 1 year, shorter follow-up period may be appropriate for individuals in advanced stage of disease
- A justification for the follow period length is preferable
- Follow-up period should be the same for all groups
  - In cohort studies, length of follow-up should be the same across all groups

- OK if differences in follow-up time were adjusted for using statistical techniques, e.g., survival analysis.

### **7) Missing data?**

Factors to consider:

- Did attrition from any group exceed 30%? (Attrition is measured in relation to the time between baseline/allocation and outcome measurement. Where different numbers of patients are followed up for different outcomes, use the number followed up for the primary outcome for this calculation.) Note criteria of <30% may be unrealistic over longer follow-up periods given the nature of MND
- Did attrition differ between groups by more than 10% percent?
- If missing data is present and substantial, were steps taken to minimize bias (e.g. sensitivity analysis or imputation)

### **8) Analysis controls for confounding?**

Factors to consider:

Did the analysis control for any baseline differences between groups?

- Does the study identify and control for important confounding variables and effect modifiers? (Confounding variables are risk factors that are correlated with MND and distress and may therefore bias the estimation of the effect of predictors on distress if unmeasured. These may include demographic and clinical variables (e.g., using demographics or clinical factors likely to be correlated with predictor and outcome)

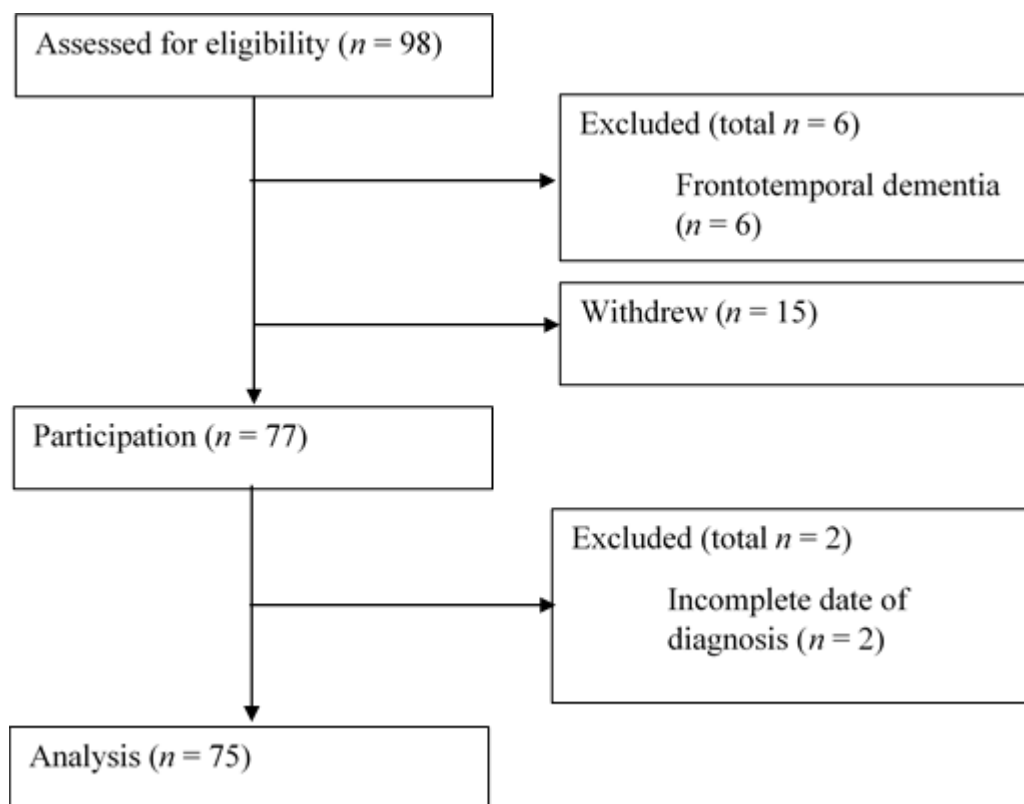
### **9) Analytic methods appropriate?**

Factors to consider:

- Was the kind of analysis done appropriate for the kind of outcome data?
  - Dichotomous – logistic regression, survival
  - Categorical – mixed model for categorical outcomes
  - Continuous – ANCOVA, mixed model



- Was the analysis done on an intention-to-treat basis? (That is, was the impact of loss to follow-up [or differential loss to follow-up] assessed, e.g., through sensitivity analysis or another intent-to-treat adjustment method?)
- Was the number of variables used in the analysis appropriate for the sample size? (The statistical techniques used must be appropriate to the data and take into account issues such as controlling for small sample size, clustering, rare outcomes, multiple comparison, and number of covariates for a given sample size)

**Appendix E – Participant Flow**

*Figure E1.* Flow of participants through the study

## Appendix F – Power Calculation and sample size

A power calculation using G\*Power (Faul, Erddelfer, Buchner & Lang, 2009) indicated that a sample size of 65 would have 80% power to identify an effect size of 0.25, with seven predictors at the  $p < 0.05$  significance level. Planned predictors were age, gender, time since diagnosis, physical functioning, repetitive negative thinking, positive metacognitive beliefs and negative metacognitive beliefs. Although comparable studies have found a large effect size ( $f^2 = 0.49$ ) (Allott, Wells, Morrison, & Walker, 2005) a conservative estimate of  $f^2 = 0.25$  was adopted to ensure the study was sufficiently powered to detect an effect.

## References

- Allott, R., Wells, A., Morrison, A. P., & Walker, R. (2005). Distress in Parkinson's disease: Contributions of disease factors and metacognitive style. *The British Journal of Psychiatry, 187*(2), 182-183. doi:10.1192/bjp.187.2.182
- Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analysis using G\*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160. doi:10.3758/BRM.41.4.1149

**Appendix G – Research Review Committee Approval**

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 Whelan Building, Quadrangle  
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[www.liv.ac.uk/dclinpsychol](http://www.liv.ac.uk/dclinpsychol)

22/07/15

Rachel Dodd  
 Clinical Psychology Trainee  
 Doctorate of Clinical Psychology Doctorate Programme  
 University of Liverpool  
 L69 3GB

**RE: Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)**

**Trainee:** Rachel Dodd

**Supervisors:** Dr Peter Fisher, Dr Selina Makin

Dear Rachel,

Thank you for your response to the reviewers' comments of your research proposal submitted to the D.Clin.Psychol. Research Review Committee (letter not dated, submitted 21/07/15).

I can now confirm that your amended proposal (Version 3, dated 22/07/15) and revised budget (Version 3, dated 22/07/15) meet the requirements of the committee and have been approved by the Committee Chair.

Please take this Chairs Action decision as **final** approval from the committee.

You may now progress to the next stages of your research.

I wish you well with your research project.

A handwritten signature in black ink, appearing to read 'Catrin Eames'.

Dr Catrin Eames  
 Vice-Chair D.Clin.Psychol. Research Review Committee.  
 cc. Dr J Dickson, Chair Dclin RRC

A member of the  
 Russell Group

Professor Peter Kinderman  
 Acting Programme Director  
[p.kinderman@liv.ac.uk](mailto:p.kinderman@liv.ac.uk)

Dr Jim Williams  
 Clinical Director  
[j.r.williams@liv.ac.uk](mailto:j.r.williams@liv.ac.uk)

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Dr Laura Golding  
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Mrs Sue Knight  
 Programme Co-ordinator  
[sknight@liv.ac.uk](mailto:sknight@liv.ac.uk)

**Appendix H – Research Review Committee Amendment Approval**

Rachel Dodd  
 Clinical Psychology Trainee  
 Doctorate of Clinical Psychology Doctorate Programme  
 University of Liverpool  
 L69 3GB

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14/09/2015

**RE: Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)**

**Trainee: Rachel Dodd**

**Supervisors: Peter Fisher and Selina Makin**

Dear Rachel,

Thank you for your notification of minor amendment to your proposal submitted to the Chair of the D.Clin.Psychol. Research Review Committee (dated 08/09/2015).

Your proposed amendment to your recruitment strategy has been approved on Chair's Action.

I wish you all the very best with the next stage of your research project.

A handwritten signature in black ink, appearing to read 'Joanne'.

Joanne Dickson  
 Chair D.Clin.Psychol. Research Review Committee.

A member of the  
 Russell Group

Professor Peter Kinderman  
 Acting Programme Director  
[p.kinderman@liv.ac.uk](mailto:p.kinderman@liv.ac.uk)

Dr Jim Williams  
 Clinical Director  
[j.r.williams@liv.ac.uk](mailto:j.r.williams@liv.ac.uk)

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Mrs Sue Knight  
 Programme Co-ordinator  
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**Appendix I – Research Review Committee Amendment Approval**

Rachel Dodd  
 Clinical Psychology Trainee  
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2<sup>nd</sup> February 2017

**RE: Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)**  
 Trainee: Rachel Dodds  
 Supervisors: Dr Peter Fisher

Dear Rachel,

Thank you for your notification of minor amendment to your proposal submitted to the Chair of the D.Clin.Psychol. Research Review Committee (dated 31/01/17).

I can now confirm that your amended proposal (version number 6, dated 31/01/17) and revised budget (dated 25/04/15) meet the requirements of the committee and have been approved by the Committee Chair.

Please take this Chairs Action decision as *final* approval from the committee.

You may now progress to the next stages of your research and associated amendments to ethics and R&D approvals.

I wish you well with your research project.

A handwritten signature in blue ink, appearing to read 'Ross White'.

Dr Ross White  
 Chair D.Clin.Psychol. Research Review Committee.

A member of the  
 Russell Group

Dr Laura Golding  
 Programme Director  
[l.golding@liv.ac.uk](mailto:l.golding@liv.ac.uk)

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Mrs Sue Knight  
 Programme Co-ordinator  
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**Appendix J – University of Liverpool Sponsorship Approval**

Dr Fisher  
University of Liverpool  
Whelan Building  
Brownlow Hill  
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**Mr Alex Astor**  
**Head of Liverpool Joint Research**  
**Office**

University of Liverpool  
Research Support Office  
2nd Floor Block D Waterhouse  
Building  
3 Brownlow Street  
Liverpool  
L69 3GL

01 October 2015

Sponsor Ref: UoL001169

Tel: 0151 794 8739  
Email: [sponsor@liv.ac.uk](mailto:sponsor@liv.ac.uk)

**Re: Sponsorship Approval**

**“Exploring the relationship between beliefs, worry and distress in Motor Neurone Disease (MND) - Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)”**

Dear Dr Fisher

After consideration at the JRO Non Interventional Sponsorship Sub Committee on 29<sup>th</sup> September 2015 I am pleased to confirm that the University of Liverpool is prepared to act as Sponsor under the Department of Health’s Research Governance Framework for Health and Social Care 2<sup>nd</sup> Edition (2005) for the above study.

The following documents have been received by the Joint Research Office

Document title	Version	Date
Protocol	Version 4	8 <sup>th</sup> September 2015
Invitation Letter	Version 2	No date
Participant Information Sheet	Version 3	No date
Participant Consent Form	Version 3	No date
Assistance Information Sheet	Version 2	No date
Demographic questionnaire	Version 4	No date

Please note this letter does **NOT** allow you to commence recruitment to your study. A notification of Sponsor Permission to Proceed will be issued when governance and regulatory requirements have been met. Please see Appendix 1 to this letter for a list of the documents required.

If you have not already applied for regulatory approvals through IRAS you may now do so at <https://www.myresearchproject.org.uk/Home.aspx>.

In order to meet the requirements of the Research Governance Framework 2<sup>nd</sup> Ed 2005, the University requires you to agree to the following Chief Investigator responsibilities:

1. Comply with the Research Governance Framework 2<sup>nd</sup> Ed 2005 and all relevant legislation, including but not limited to the Data Protection Act 1998, the Mental Capacity Act 2005 and the Human Tissue Act 2004;
2. Inform the Research Support Office as soon as possible of any adverse events especially SUSARs and SAE's, Serious Breaches to protocol or relevant legislation or any concerns regarding research conduct;
3. Approval must be gained from the Research Support Office for any amendments to, or changes of status in the study prior to submission to REC and any other regulatory authorities;
4. It is a requirement that Annual Progress Reports are sent to the NHS Research Ethics Committee (REC) annually following the date of Favourable Ethical Approval. You must provide copies of any reports submitted to REC and other regulatory authorities to the Research Support Office;
5. Maintain the study master file;
6. Make available for review any study documentation when requested by the sponsors and regulatory authorities;
7. Upon the completion of the study it is a requirement to submit and an End of Study Declaration (within 90 days of the end of the study) and End of Study Report to REC (within 12 months of the end of the study). You must provide copies of this to the Research Support Office;

The University also requires you to comply with the following:

1. University professional indemnity and clinical trials insurances will apply to the study as appropriate. This is on the assumption that no part of the clinical trial will take place outside of the UK. If you wish to conduct any part of the study in a site outside the UK or you wish to sub-contract any part of the study to a third party specific approvals and consideration of appropriate indemnity would be required.

If you have any queries regarding the sponsorship of the study or the above conditions please do not hesitate to contact the Joint Research Office governance team on 0151 794 8373 (email [sponsor@liv.ac.uk](mailto:sponsor@liv.ac.uk)).

Yours sincerely



Mr Alex Astor  
Head of Liverpool Joint Research Office



**Appendix K – Research and Ethics Committee Approval**

Page 1

**Health Research Authority**

North West - Liverpool Central Research Ethics Committee

3rd Floor  
Barlow House  
4 Minshull Street  
Manchester  
M1 3DZ

Telephone: 020 71048008

18 February 2016

Dr Peter Fisher  
University of Liverpool  
Whelan Building  
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L69 3GB

Dear Dr Fisher

**Study title:** Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)

**REC reference:** 16/NW/0073

**Protocol number:** UoL001169

**IRAS project ID:** 189296

Thank you for your email. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 08 February 2016

**Documents received**

The documents received were as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Other [response to favourable opinion with conditions]		16 February 2016
Other [questionnaire booklet]	3	11 February 2016
Participant consent form	4	11 February 2016
Participant information sheet (PIS) [online]	3	11 February 2016
Participant information sheet (PIS) [preston]	6	11 February 2016
Participant information sheet (PIS) [walton]	6	11 February 2016
Participant information sheet (PIS) [assistance]	3	18 February 2016

**Approved documents**

The final list of approved documentation for the study is therefore as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Copies of advertisement materials for research participants [Poster]	V2	30 November 2015
Copies of advertisement materials for research participants [MNDA Advert]	2	10 December 2015

Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Cover]	1	05 October 2015
Letter from sponsor [Sponsorship approval]	1	05 October 2015
Non-validated questionnaire [Questionnaire Booklet]	1	07 December 2015
Other [Letter of support MND]		20 November 2015
Other [response to favourable opinion with conditions]		16 February 2016
Other [questionnaire booklet]	3	11 February 2016
Participant consent form	4	11 February 2016
Participant information sheet (PIS) [walton]	6	11 February 2016
Participant information sheet (PIS) [assistance]	3	18 February 2016
Participant information sheet (PIS) [online]	3	11 February 2016
Participant information sheet (PIS) [preston]	6	11 February 2016
REC Application Form [REC_Form_10122015]		10 December 2015
Referee's report or other scientific critique report [Comments from RRC]		22 June 2015
Referee's report or other scientific critique report [Response to Comments]		22 July 2015
Referee's report or other scientific critique report [RRC Approval]		22 July 2015
Referee's report or other scientific critique report [Amendments Letter]		14 September 2015
Referee's report or other scientific critique report [Amendments approval]		14 September 2015
Research protocol or project proposal [Research Protocol]	4.2	11 December 2015
Summary CV for Chief Investigator (CI) [P FISHER CV]	1	27 September 2015
Summary CV for student [RDODDCV]	1	05 October 2015
Summary CV for supervisor (student research) [SMAKINCV]		06 October 2015
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary]	3	12 November 2015

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

16/NW/0073	Please quote this number on all correspondence
------------	--

Yours sincerely



**Carol Ebenezer**  
REC Manager

E-mail: nrescommittee.northwest-liverpoolcentral@nhs.net

Copy to: *Dr Peter Fisher, University of Liverpool*  
*Mr Alex Astor, University of Liverpool*  
*Mr David Watling, The Walton Centre NHS Foundation Trust*

**Appendix L – Research and Ethics Committee Approval Amendment Approval**

Page 1

**North West - Liverpool Central Research Ethics Committee**

3rd Floor  
Barlow House  
4 Minshull Street  
Manchester  
M1 3DZ

Tel: 020 71048008

25 April 2016

Dr Peter Fisher  
University of Liverpool  
Whelan Building  
Brownlow Hill  
Liverpool  
L69 3GB

Dear Dr Fisher

**Study title:** Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)  
**REC reference:** 16/NW/0073  
**Protocol number:** UoL001169  
**Amendment number:** 1  
**Amendment date:** 19 April 2016  
**IRAS project ID:** 189296

Add debrief sheet, copyright added to HADS, update to information sheets, randomisation order for questionnaires

The above amendment was reviewed by the Sub-Committee in correspondence.

**Ethical opinion**

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The members had no issues with this amendment.

**Approved documents**

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Notice of Substantial Amendment (non-CTIMP)	1	19 April 2016
Other [Debrief Sheet]	2	30 March 2016
Other [Questionnaire Booklet]	4	30 March 2016
Participant information sheet (PIS) [Preston]	7	04 April 2016

Participant information sheet (PIS) [Walton]	7	04 April 2016
Participant information sheet (PIS) [Online]	4	04 April 2016
Research protocol or project proposal	5	07 April 2016

#### Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

#### R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

#### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

16/NW/0073:	Please quote this number on all correspondence
-------------	--

Yours sincerely



**Mrs Julie Brake**  
Chair

E-mail: [nrescommittee.northwest-liverpoolcentral@nhs.net](mailto:nrescommittee.northwest-liverpoolcentral@nhs.net)

*Enclosures:*                      *List of names and professions of members who took part in the review*

*Copy to:*                              *Mr David Watling, The Walton Centre NHS Foundation Trust*  
   *Mr Alex Astor, University of Liverpool*

**Appendix M – Site Permission Letter (Walton Centre)**

Non-CTIMP Permission

F.A.O:

Principal Investigator - Dr S. Makin  
Student – Ms R. DoddThe Walton Centre   
NHS Foundation Trust

Excellence in Neuroscience

**Date: 10<sup>th</sup> March 2016**

Dear Dr Makin / Ms Dodd,

**Study Title:** Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)**REC Reference: 16/NW/0073    R&D Reference: RG180-16    IRAS/CSP ID: 189296**

Thank you for providing all of the documentation for the above study.

I am pleased to inform you that the above study has been given full R&amp;D permission and you may begin this at the Walton Centre NHS Foundation Trust. This has been granted for the duration of the REC approval for your study.

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, Trust policies and procedures, and all applicable legislation including, but not limited to, the Data Protection Act, the Health and Safety at Work Act, Human Tissue Act. As Principal Investigator you retain overall responsibility for compliance with these requirements by all members of the research team. The recruitment target is 65 patients for this study.

**You must ensure that you read and understand the enclosed conditions of approval**

Should you have any queries, or feel that we can be of assistance, please do not hesitate to contact a member of the R&amp;D office on 0151 529 5446.

I would like to take this opportunity to wish you well with your research

Yours Sincerely,


  
 Dr M. Steiger
   
 Director of Research, Development & Innovation

PP
   
 DAVID WATKINS
   
 R+D Manager



A SMOKE FREE SITE

[www.thewaltoncentre.nhs.uk](http://www.thewaltoncentre.nhs.uk)

## Appendix N – Site Permission Letter (Preston)

Excellent care with compassion

**Centre for Health Research  
and Innovation**  
Lancashire Teaching Hospitals   
NHS Foundation Trust

Royal Preston Hospital  
Sharoe Green Lane  
Fulwood  
Preston  
PR2 9HT

Tel: 01772 52(8268)

Our Ref: GW/HAA

20 May 2016

Dr T Majeed  
Consultant Neurologist  
Lancashire Teaching Hospitals NHS Foundation Trust  
Royal Preston Hospital

Dear Dr Majeed

R&amp;I Ref 2061

<b>Study title:</b>	Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)
<b>REC reference:</b>	16/NW/0073
<b>Protocol number:</b>	UoL001169
<b>IRAS project ID:</b>	189296

Thank you for submitting the above study for NHS R&I permission. Lancashire Teaching Hospitals NHS Foundation Trust is the host site for this [non-NIHR](#) portfolio study.

I am pleased to confirm that the Research Office has now received all necessary documentation, and the appropriate governance checks have been undertaken. This letter is issued subject to the research team complying with the attached 'conditions of permission', Trust SOPs, the DH Research Governance Framework, and any other applicable regulatory requirements.

## List of documents reviewed as part of the Trust permission process:

Document	Version	Date
Advertisement materials for research participants (MNDA Advert)	2	10 December 2015
Advertisement materials for research participants (poster)	2	30 November 2015
Debrief Sheet	2	30 March 2016
Questionnaire Booklet	4	30 March 2016
Participant information sheet (PIS) [Preston]	7	04 April 2016
Participant information sheet (PIS) [Online PIS]	2	11 December 2015
Participant information sheet (PIS) [Assistance IS]	2	30 November 2015
Research protocol	5	07 April 2016
NRES Favourable Opinion Letter		08 February 2016
NRES Favourable Opinion Letter	AM1	25 April 2016

Our agreed recruitment target for this study is 12, to be achieved by 30/11/2016.

To meet Department of Health benchmarks for patient recruitment you will be expected to recruit your first patient within 30 days of a valid study application i.e. 19 June 2016. Please inform the Research Office with the date when the first patient is recruited.

I would like to take this opportunity to wish you well with your research.

Excellent care with compassion

**Centre for Health Research  
and Innovation**

Lancashire Teaching Hospitals **NHS**  
NHS Foundation Trust

Yours sincerely



Mrs Gemma Whiteley  
Head of Research and Innovation

Cc

Rachel Dodd  
Trainee Clinical Psychologist  
University of Liverpool  
Whelan Building  
Brownlow Hill  
Liverpool  
L69 3GB  
Email: [Rachel.Dodd@liverpool.ac.uk](mailto:Rachel.Dodd@liverpool.ac.uk)

Dr Peter Fisher  
Senior Lecturer in Clinical Psychology  
University of Liverpool  
Whelan Building  
Brownlow Hill  
Liverpool  
L69 3GB  
E-mail [plfisher@liverpool.ac.uk](mailto:plfisher@liverpool.ac.uk)

Dr Selina Makin  
The Walton Centre NHS Foundation Trust  
Neuropsychology Department  
Sid Watkins Building, Lower Lane  
L9 7LJ  
E-mail [selina.makin@thewaltoncentre.nhs.uk](mailto:selina.makin@thewaltoncentre.nhs.uk)

Pauline Callagher / Marianne Hare

.....  
**Important:** Please read and sign the Conditions of Trust Permission overleaf, and return to:

Heather Adams  
RM & G Coordinator  
The Centre for Health Research and Innovation  
Royal Preston Hospital  
Sharoe Green Lane  
Fulwood  
PRESTON  
PR2 9HT

**Appendix O – Health and Research Authority Approval****Health Research Authority**

Dr Peter Fisher  
University of Liverpool  
Whelan Building  
Brownlow Hill  
Liverpool  
L69 3GB

Email: [hra.approval@nhs.net](mailto:hra.approval@nhs.net)

10 August 2016

Dear Dr Fisher

**Letter of HRA Approval for a study processed  
through pre-HRA Approval systems**

**Study title:** Investigating the role of metacognitive beliefs and processes in distress (depression and anxiety) in individuals with Motor Neurone Disease (MND)

**IRAS project ID:** 189296

**Sponsor:** University of Liverpool

Thank you for your request for HRA Approval to be issued for the above referenced study.

I am pleased to confirm that the study has been given **HRA Approval**. This has been issued on the basis of an existing assessment of regulatory compliance, which has confirmed that the study is compliant with the UK wide standards for research in the NHS.

The extension of HRA Approval to this study on this basis allows the sponsor and participating NHS organisations in England to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

If you have submitted an amendment to the HRA between 23 March 2016 and the date of this letter, this letter incorporates the HRA Approval for that amendment, which may be implemented in accordance with the amendment categorisation email (e.g. not prior to REC Favourable Opinion, MHRA Clinical Trial Authorisation etc., as applicable). If the submitted amendment included the addition of a new NHS organisation in England, the addition of the new NHS organisation is also approved and should be set up in accordance with HRA Approval processes (e.g. the organisation should be invited to assess and arrange its capacity and capability to deliver the study and confirm once it is ready to do so).



IRAS project ID	189296
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#### Participation of NHS Organisations in England

Please note that full information to enable set up of participating NHS organisations in England is not provided in this letter, on the basis that activities to set up these NHS organisations is likely to be underway already.

The sponsor should provide a copy of this letter, together with the local document package and a list of the documents provided, to participating NHS organisations in England that are being set up in accordance with [HRA Approval Processes](#). It is for the sponsor to ensure that any documents provided to participating organisations are the current, approved documents.

For non-commercial studies the local document package should include an appropriate [Statement of Activities and HRA Schedule of Events](#). The sponsor should also provide the template agreement to be used in the study, where the sponsor is using an agreement in addition to the Statement of Activities. Participating NHS organisations in England should be aware that the Statement of Activities and HRA Schedule of Events for this study have not been assessed and validated by the HRA. Any changes that are appropriate to the content of the Statement of Activities and HRA Schedule of Events should be agreed in a pragmatic fashion as part of the process of assessing, arranging and confirming capacity and capability to deliver the study. If subsequent NHS organisations in England are added, an amendment should be submitted to the HRA..

For commercial studies the local document package should include a validated industry costing template and the template agreement to be used with participating NHS organisations in England.

It is critical that you involve both the research management function (e.g. R&D office and, if the study is on the NIHR portfolio, the LCRN) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from [www.hra.nhs.uk/hra-approval](http://www.hra.nhs.uk/hra-approval).

#### After HRA Approval

In addition to the document, "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](#), and emailed to [hra.amendments@nhs.net](mailto:hra.amendments@nhs.net).
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](#).

IRAS project ID	189296
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The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

### Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/>.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

### User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at [hra.approval@nhs.net](mailto:hra.approval@nhs.net). Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

### HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>.

If you have any queries about the issue of this letter please, in the first instance, see the further information provided in the question and answer document on the [HRA website](#).

Your IRAS project ID is 189296. Please quote this on all correspondence.

Yours sincerely

*HRA Approvals Team*

Email: [hra.approval@nhs.net](mailto:hra.approval@nhs.net)

Copy to: *Mr Alex Astor, University of Liverpool*  
*Mr David Watling, The Walton Centre NHS Foundation Trust*

**Appendix P – Participant Information Sheet**

Lancashire Teaching Hospitals   
NHS Foundation Trust

The Walton Centre   
NHS Foundation Trust  
*Excellence in Neuroscience* 

**Participant Information Sheet– IRAS Ref – 189296****Study Title: Exploring the relationship between beliefs, worry and distress in Motor Neurone Disease (MND)**

We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Please take some time to read the following information carefully. Ask others what they think about the study and perhaps share this information sheet with them if you wish. You can contact the researcher with any questions that you may have about the study. Please let us know if there is anything that is not clear.

**What is the purpose of the study?**

There is very little research about psychological support in MND. This study aims to understand some of the factors that may impact on a person's wellbeing in MND. This includes looking at factors such as the role of metacognitive beliefs (our beliefs about our thoughts) and thinking patterns. It is hoped that findings from this research will help better guide future research, interventions, and support for people with MND.

**Why have I been invited?**

You have been invited because you have a diagnosis of MND.

**Do I have to take part?**

No - It is up to you whether you decide to take part. If you decide to take part, you will be asked to tick a checkbox on a consent form. If you are unable to do this, it would not prevent you from taking part. Instead the person assisting you to complete the study will tick a checkbox to confirm that you have consented to take part. You are free to withdraw at any time, without giving a reason. If you decide to withdraw from the study, you can have the data you provide destroyed up to 48 hours after completing the study. After this point it will not be possible to destroy the data, as it will be made anonymous and so we would not be able to identify specific participants. If you are currently receiving care, this would not be affected in any way. You will not have to respond to any questions you do not wish to.

**What will happen to me if I take part and what will I have to do?**

You will be asked to complete some questionnaires. This should take no longer than 40 minutes and you will only be asked to do this once. You will complete the questionnaires on a computer, with or without the support of a person close to you.

**What if I have trouble communicating?**

We understand that some people with MND may have difficulties with writing or speaking. We would like to ensure that this would not prevent you from taking part. It is very important that the perspectives of people who have difficulties with communicating are represented in the study. You can complete the questionnaires with a relative/friend/carer or other person that you feel comfortable with.

**What are the possible risks of taking part?**

There is little risk in taking part in the study. It could be that you find some questions difficult to respond to as they may cause some level of upset or worry. You can contact the researcher about this (details below), the **Motor Neurone Disease Association** helpline (**0808 802 6262**) or **Samaritans (08457 90 90 90)** should you experience any distress following the study.

You can be referred to see a psychologist in your local area for support via any member of your local MND team or your GP if you feel this would be helpful. You should contact a member of the research team for more local support services should you require them (details below).

**What are the possible benefits of taking part?**

Although we cannot promise the study will help you directly, the information we collect will help us to understand distress in MND and could help to shape psychological treatment for people with MND in the future.

**What happens when the research study stops?**

When you have completed all the study questions, you will not be asked to take any further part in the study.

The findings will be written up as part of the researcher's thesis that will form part of their doctoral training to become a clinical psychologist. No confidential information will be used in these reports. The researchers hope to publish papers in academic journals and to present the findings at conferences. With your consent, the researchers also hope to further analyse your anonymous data in future studies, which have been given ethical approval.

**How can I access the study findings?**

The study will last for about two years. Therefore a summary of the overall findings will not be available until after this time period. The summary will be available on the MND Association's website ([www.mndassociation.org/research](http://www.mndassociation.org/research)) and on the MND Association's research blog ([www.mndresearch.wordpress.com](http://www.mndresearch.wordpress.com)) when the study is complete. Alternatively you can contact the researcher to obtain a copy via email, telephone or post using the details at the end of the information sheet.

**What if there is a problem?**

If you have a concern about any aspect of this study, you should contact the researchers who will do their best to answer your questions. If you remain unhappy or have a complaint which you feel you cannot come to the researchers with, then you should contact the Research Governance Officer at the University of Liverpool at [ethics@liv.ac.uk](mailto:ethics@liv.ac.uk) or on 0151 794 8290. When contacting the Research Governance Officer, please provide details of the name or description of the study (so that it can be identified), the researchers involved, and the details of the complaint you wish to make.

### **Will my taking part in the study be kept confidential?**

No information will be passed onto any other person without your permission. The only exception will be if there is a direct risk of harm to you or another person. In these cases it may be necessary to talk to another health professional, such as a GP or therapist. If this happens this would normally be discussed with you first.

All information collected about you during the study will be kept strictly confidential, and any information about you that has your name and address will be removed so that you cannot be recognised. You will not be named or identified in any reports of the study.

All data collected from the study will be kept safely and securely on a password protected computer. Your data will be anonymised and stored securely at the University of Liverpool and The Walton Centre. Dr Peter Fisher (supervising this study) will be the custodian of the study data. Dr Selina Makin will be responsible for the archiving of data stored at The Walton Centre. With your permission, the data will be archived and stored for up to 10 years after the end of this study. If you consent, your anonymised data may also be used in future studies that have been given ethical approval.

### **Who is organising and funding the study?**

The University of Liverpool have provided the funding for the researcher to carry out this study and the University of Liverpool is the study sponsor.

### **Who has reviewed the study?**

This study was given a favourable ethical opinion for conduct in the NHS and other sectors by the Doctorate in Clinical Psychology Research Ethics Committee. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study was reviewed and given a favourable ethical opinion for conduct in the NHS by The North West Liverpool Central Research Ethics Committee (Reference Number: 16/NW/0073).

### **Who can I contact for further information about this study?**

If you have any questions at all, please contact the researcher:

**Miss Rachel Dodd** (tel: 0151 794 5102, email: [doddr@liv.ac.uk](mailto:doddr@liv.ac.uk)) who is based at the Division of Clinical Psychology, Whelan Building, University of Liverpool, Liverpool, L69 3GB.

Alternatively, you may prefer to contact:


**Dr Peter Fisher** (tel: 0151 794 5102, email: [plfisher@liverpool.ac.uk](mailto:plfisher@liverpool.ac.uk)) who is based at the Division of Clinical Psychology, Whelan Building, University of Liverpool, Liverpool, L69 3GB  
Or **Dr Selina Makin** (tel: 0151 556 3183, email: [selina.makin@thewaltoncentre.nhs.uk](mailto:selina.makin@thewaltoncentre.nhs.uk)) who is based at The Walton Centre, Sid Watkins Building, Lower Lane, Liverpool, L9 7LJ.

**Thank you very much for taking the time to read this information sheet.**

**Appendix Q – Participant Consent Form**

Lancashire Teaching Hospitals **NHS**  
NHS Foundation Trust

The Walton Centre **NHS**  
NHS Foundation Trust

Excellence in Neuroscience 

**Participant Consent Form - IRAS Ref - 189296**

**Title of Project:** Exploring the relationship between beliefs, worry and distress in Motor Neurone Disease (MND)

**Name of Researcher:** Rachel Dodd

		Please <b>initial</b> the box
1	I confirm that I have read and understand the information sheet dated 4 <sup>th</sup> April 2016 (Version 7) for the above study. I have had the chance to think about the information, ask questions and have my questions answered.	
2	I understand that taking part is voluntary and that I can change my mind at any time without giving any reason, without my medical care or legal rights being affected.	
3	I agree to take part in the above study	
4	I agree that anonymised data from the study may be used in future studies, which have been given ethical approval.	
5	I understand that relevant sections of my medical notes and data collected from the study may be looked at by regulatory authorities or by persons from the Trust where it is relevant to my taking part in this study. I give permission for these persons to have access to this information.	

\_\_\_\_\_  
Name of participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of person taking consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

*If participant is unable to sign: I confirm that I am completing these questionnaires with the participant's permission and under their direction.*

\_\_\_\_\_  
*Name of witness / person assisting  
with questionnaires*

\_\_\_\_\_  
*Date*

\_\_\_\_\_  
*Signature*

**Appendix R – Questionnaire Booklet**

## **Questionnaire Booklet**

# **Beliefs, worry and distress in MND**

IRAS Ref - 189296

### **Includes:**

1. Demographic Questionnaire
2. Self-Administered ALS Functional Rating Scale Revised
3. Metacognitions Questionnaire
4. Repetitive Thinking Questionnaire
5. Hospital Anxiety and Depression Scale





## Demographics Questionnaire

Please complete the following questions by entering numbers into the boxes or circling as appropriate.

1. Age:

--	--

Years

2. Gender (Please Circle):

Male

Female

3. Date of onset of MND symptoms *(This may be difficult to pinpoint - your best estimate is fine):*

--	--

Month

--	--	--	--

Year

4. Date of diagnosis of MND:

--	--

Month

--	--	--	--

Year

**5. Who is completing this questionnaire with you (Please Circle):**

No-one    Researcher    Family    Friend    Carer    Other

If Other Please State.....

**6. Please list any other health conditions: *(continue on the next page if required)***

**7. Please list any current medications: *(continue on the next page if required)***



### **SA-ALSFRS-R (Cedarbaum et al., 1999)**

These questions are about how you are currently functioning at home. Please read each item carefully and base your answers on your functioning **today** compared to the time **before** you had any symptoms of Motor Neurone Disease (MND). Please choose the answer that best fits your functional status today by placing a tick next to your answer.

## **Compared to the time before you had symptoms of Motor Neuron Disease:**

### **1. Have you noticed any changes in your speech?**

- No change
- Noticeable speech differences
- Speech has changed; often asked to repeat words or phrases
- Speech has changed; sometimes need the use of alternative communicative methods (i.e. computer, writing pad, letter board or eye chart)
- Unable to communicate verbally

### **2. Have you noticed any changes (increases) in the amount of saliva in your mouth (regardless of medication use)**

- No change

- Slight but definite excess of saliva, with or without night time drooling
- Moderate amounts of excessive saliva, with or without minimal day time drooling
- Marked amount of excessive saliva, with some day time drooling
- Marked excessive saliva with marked drooling requiring a constant tissue or handkerchief

**3. Have there been any changes in your ability to swallow?**

- No change (all foods and liquids)
- Some changes in swallowing or occasional choking episodes (including coughing during swallowing)
- Unable to eat all consistencies of food and have modified the consistency of foods eaten
- Use a feeding tube (PEG) to supplement what is eaten by mouth
- Do not eat anything by mouth and receive all nutrition through a feeding tube (PEG)

**4. Has your handwriting changed? Please choose the best answer that describes your handwriting with your dominant (usual) hand without a cuff or brace.**

- No change
- Slower and/or sloppier but all the words are legible
- Not all words are legible
- Able to grip pen but unable to write
- Unable to hold pen

**5. The following question refers to your ability to cut foods and handle utensils (feed yourself). If PEG, skip to part b. *EITHER***

***5a. Cutting and handling utensils:***

- No change
- Somewhat slow and clumsy (or different than before), but no assistance or adaptive equipment
- Sometimes need help with cutting more difficult foods
- Food must be cut by someone else but can feed slowly with assistance
- Need to be fed

***OR 5b. Using a feeding tube (PEG).***

- Use PEG without assistance or difficulty
- Use PEG without assistance however may be slow and/or clumsy
- Require assistance with closure and fasteners
- Provide minimal assistance to caregiver
- Unable to perform any of the manipulations

**6. Has your ability to dress and perform self-care activities (i.e. bathing, teeth brushing, shaving, combing your hair, other hygienic activities changed?)**

- No change
- Perform self-care activities without assistance but with increased effort or decreased efficiency
- Require intermittent assistance or use different methods (i.e. sit down to get dressed, fasten buttons with a fastener or your non-dominant hand)
- Require daily assistance
- Do not perform self-care activities and completely dependent on caregiver

**7. Has your ability to turn in bed and adjust the bed clothes (i.e. cover yourself with the sheet or blanket) changed?**

- No change
- Can turn in bed and adjust the bed clothes without assistance but it is slower or more clumsy
- Can turn in bed OR adjust the bed clothes without assistance but with great difficulty
- Can initiate turning in bed or adjusting the bed clothes but require assistance to complete the task
- Helpless in bed

**8. Has your ability to walk changed?**

- No change
- Walking has changed but do not require any assistance or devices (i.e. foot brace, stick, walker)
- Require assistance to walk (i.e. cane, walker, foot brace, hand-held assistance)
- Can move legs or stand up but unable to walk from room to room
- Cannot walk or move my legs

**9. Has your ability to climb stairs changed?**

- No change
- Slower
- Unsteady and need to hold the handrail
- Require 2 handrails or 1 rail and a stick/person
- Cannot climb stairs

**10. Do you experience shortness of breath or have difficulty breathing?**

- No change
- Shortness of breath only with walking
- Shortness of breath with minimal exertion (i.e. Talking, eating, bathing or dressing)
- Shortness of breath at rest while either sitting or lying down
- Significant shortness of breath (all of the time) and considering using mechanical ventilation



**11. Do you experience shortness of breath or have difficulty breathing while lying down on your back?**

- No change
- Occasional shortness of breath while lying on back but don't routinely use more than two pillows to sleep
- Shortness of breath while lying on back and require more than two pillows (or an equivalent) to sleep
- Can only sleep sitting up due to shortness of breath
- Require the use of respiratory (breathing) support (BiPAP® or invasive ventilation via tracheostomy) to sleep and do not sleep without it

**12. Do you require respiratory (breathing) support?**

- No respiratory support
- Intermittent use of BiPAP®
- Continuous use of BiPAP® at night
- Continuous use of BiPAP® at night and during the day (Nearly 24 hours per day)
- Mechanical ventilation by intubation or tracheotomy

*(BiPAP® is commonly used to describe non-invasive pressure ventilation and its use here in no way endorses or promotes a particular product)*

**Please ensure that you have responded to all items. Thank you**



### **Metacognitions Questionnaire (MCQ) – Sam Cartwright & Adrian Wells.**

This questionnaire is concerned with beliefs people have about their thinking. Listed below are a number of beliefs that people have expressed. Please read each item and say how much you generally agree with it by circling the appropriate number. Please respond to all the items, there are no right or wrong answers.

	Do not agree	Agree slightly	Agree moderately	Agree very much
1. Worrying helps me to avoid problems in the future	1	2	3	4
2. My worrying is dangerous for me	1	2	3	4
3. I think a lot about my thoughts	1	2	3	4
4. I could make myself sick with worrying	1	2	3	4
5. I am aware of the way my mind works when I am thinking through a problem	1	2	3	4

	Do not agree	Agree slightly	Agree moderately	Agree very much
6. If I did not control a worrying thought, and then it happened, it would be my fault	1	2	3	4
7. I need to worry in order to remain organized	1	2	3	4
8. I have little confidence in my memory for words and names	1	2	3	4
9. My worrying thoughts persist, no matter how I try to stop them	1	2	3	4
10. Worrying helps me to get things sorted out in my mind	1	2	3	4
11. I cannot ignore my worrying thoughts	1	2	3	4
12. I monitor my thoughts	1	2	3	4

	Do not agree	Agree slightly	Agree moderately	Agree very much
13. I should be in control of my thoughts all of the time	1	2	3	4
14. My memory can mislead me at times	1	2	3	4
15. My worrying could make me go mad	1	2	3	4
16. I am constantly aware of my thinking	1	2	3	4
17. I have a poor memory	1	2	3	4
18. I pay close attention to the way my mind works	1	2	3	4
19. Worrying helps me cope	1	2	3	4
20. Not being able to control my thoughts is a sign of weakness	1	2	3	4
21. When I start worrying, I cannot stop	1	2	3	4

	Do not agree	Agree slightly	Agree moderately	Agree very much
22. I will be punished for not controlling certain thoughts	1	2	3	4
23. Worrying helps me to solve problems	1	2	3	4
24. I have little confidence in my memory for places	1	2	3	4
25. It is bad to think certain thoughts	1	2	3	4
26. I do not trust my memory	1	2	3	4
27. If I could not control my thoughts, I would not be able to function	1	2	3	4
28. I need to worry, in order to work well	1	2	3	4
29. I have little confidence in my memory for actions	1	2	3	4
30. I constantly monitor my thoughts	1	2	3	4

**Please ensure that you have responded to all items. Thank you**

From Wells (1997), with permission.



**RTQ-10 (Trait) (From McEvoy, Thibodeau & Asmundson, 2015 with permission)**

In this questionnaire we are interested in understanding how you respond to distressing situations. Please recall how you tend to respond when you feel distressed or upset.

How true (1-5) are each of these statements with respect to your experience **when you are distressed or upset?**

	Not True at all	1	2	Some what True	3	4	Very True	5
1. I have thoughts or images about all my shortcomings, failings, faults, mistakes.	1	2	3	4	5			
2. I have thoughts or images about events that come into my head even when I do not wish to think about them again	1	2	3	4	5			
3. I have thoughts or images that "I won't be able to do my job/work because I feel so badly."	1	2	3	4	5			
4. I have thoughts or images that are difficult to forget.	1	2	3	4	5			

	Not True at all		Some what True		Very True
5. Once I start thinking about the situation, I can't stop.	1	2	3	4	5
6. I notice that I think about the situation.	1	2	3	4	5
7. I have thoughts or images of the situation that I try to resist thinking about.	1	2	3	4	5
8. I think about the situation all the time.	1	2	3	4	5
9. I know I shouldn't think about the situation, but can't help it.	1	2	3	4	5
10. I have thoughts or images about the situation and wish it would go better.	1	2	3	4	5

**Please ensure that you have responded to all items. Thank you**



## **Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983)**

Clinicians are aware that emotion play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know about how you feel. Read each item below and select the reply which comes closest to how you have been feeling in the past week. Don't take too long over your responses, your immediate reaction to each item will probably be more accurate than a thought-out response:

### **1. I feel tense or wound up:**

- Most of the time
- A lot of the time
- Time to time, occasionally
- Not at all

### **2. I still enjoy the things I used to enjoy:**

- Definitely as much
- Not quite so much
- Only a little
- Not at all

### **3. 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

### **4. 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



**5. Worrying thoughts go through my mind:**

- A great deal of the time
- A lot of the time
- From time to time, but not too often
- Only occasionally

**6. I feel cheerful**

- Not at all
- Not often
- Sometimes
- Most of the time

**7. I can sit at ease and feel relaxed:**

- Definitely
- Usually
- Not often
- Not at all

**8. I feel as if I am slowed down:**

- Nearly all of the time
- Very often
- Sometimes
- Not at all

**9. I get a sort of frightened feeling like 'butterflies in the stomach':**

- Not at all
- Occasionally
- Quite often
- Very often

**10. 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 care as ever

IN MND

**11. I feel restless as if I have to be on the move:**

- Very much indeed
- Quite a lot
- Not very much
- Not at all

**12. 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

**13. I get sudden feelings of panic**

- Very often indeed
- Quite often
- Not very often
- Not at all

**14. I can enjoy a good book or radio or TV programme:**

- Often
- Sometimes
- Not often
- Very seldom

**Please ensure that you have responded to all items. Thank you**

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*Record form items originally published in Acta Psychiatrica Scandinavica 67, 361–70, copyright © Munksgaard International*

*Publishers Ltd, Copenhagen, 1983.*

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## **Appendix S – Exploration of Normality and Parametric Assumptions**

### **Normal Distribution**

Several variables showed evidence of skewness and kurtosis and visual inspection suggested non-normal distributions (see figures S1, S3, S5, and S7). Kolmogorov-Smirnov test of normality was conducted on the distribution of adapted hospital and anxiety depression scale total (HADS-T), Repetitive negative thinking (RTQ-10), positive beliefs about worry (MCQ-POS) and negative beliefs about the danger and uncontrollability of worry (MCQ-NEG) (see table S1).

HADS-T [Statistic (77) = 0.141,  $p = 0.001$ ], RTQ-10 [Statistic (77) = 0.101,  $p = 0.05$ ], MCQ-POS [Statistic (77) = 0.240,  $p < 0.001$ ], MCQ-NEG [Statistic (77) = .0.150,  $p < 0.001$ ], were found to significantly deviate from the normal distribution. Therefore, the assumption of normally distributed data was not met.

### **Outliers**

An examination of box plots revealed the presence of outliers on HADS-T Positive beliefs about worry (MCQ-POS) (see figures S2, S4, S6, S8). These were not extreme points and on closer inspection appeared to be valid responses so outliers were retained for use in the analyses.

Table S1

*Tests of normality*

	Tests of Normality					
	Kolmogorov-Smirnov <sup>a</sup>			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
HADS total score adapted for MND (items removed) A11 & D8 & D10	.141	77	.001	.932	77	.000
MCQ positive beliefs subscale, items 1, 7, 10, 19, 23, 28	.240	77	.000	.766	77	.000
MCQ negative beliefs about worry: 2,4,9,11,15,21	.150	77	.000	.886	77	.000
MCQ cognitive confidence: 8,14,17,24,26,29	.184	77	.000	.840	77	.000
MCQ need for control: 6,13,20,22,25,27	.173	77	.000	.894	77	.000
MCQ Cognitive self confidence 3,5,12,16,18,30	.101	77	.049	.969	77	.055
RTQ-10 Total	.101	77	.050	.954	77	.007

a. Lilliefors Significance Correction

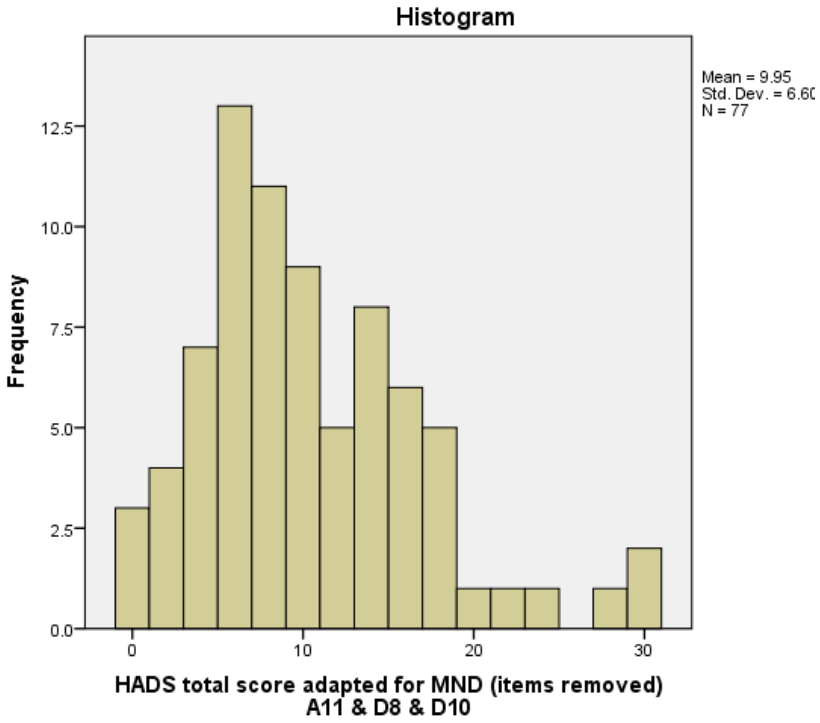


Figure S1. Histogram of HADS-T distribution

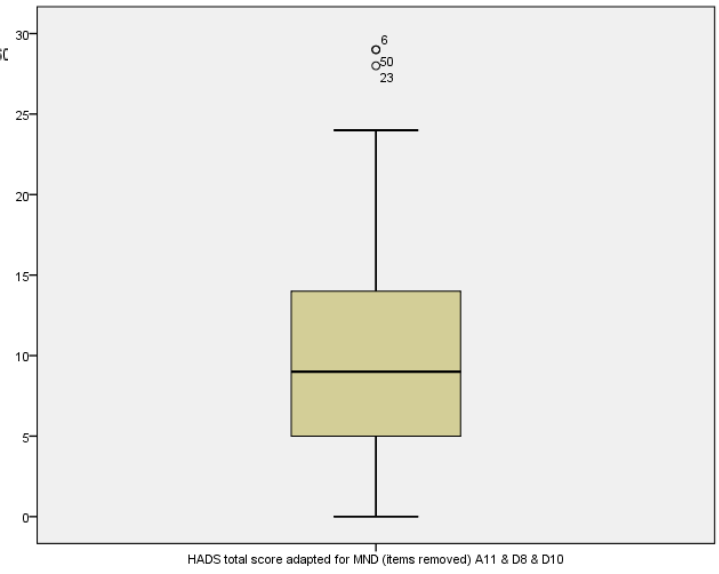


Figure S2. HADS-T boxplot

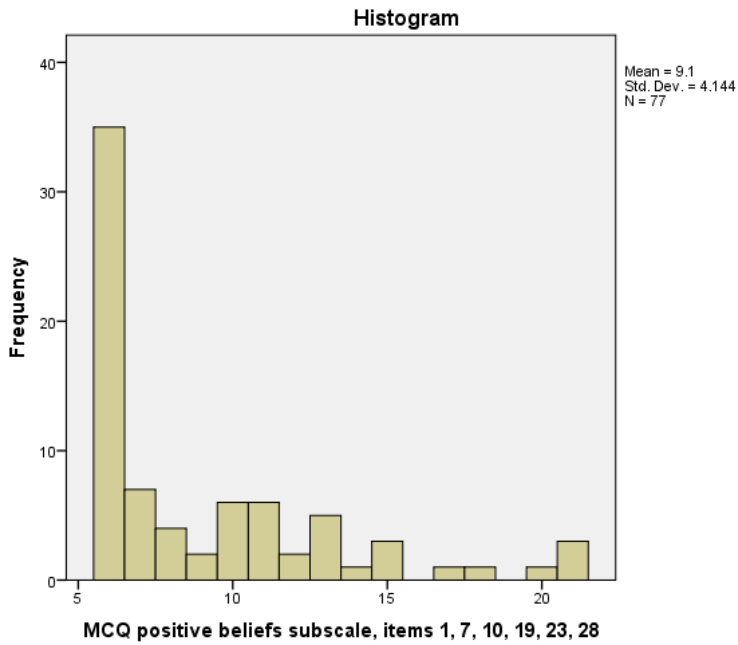


Figure S3. Histogram to display PMCB

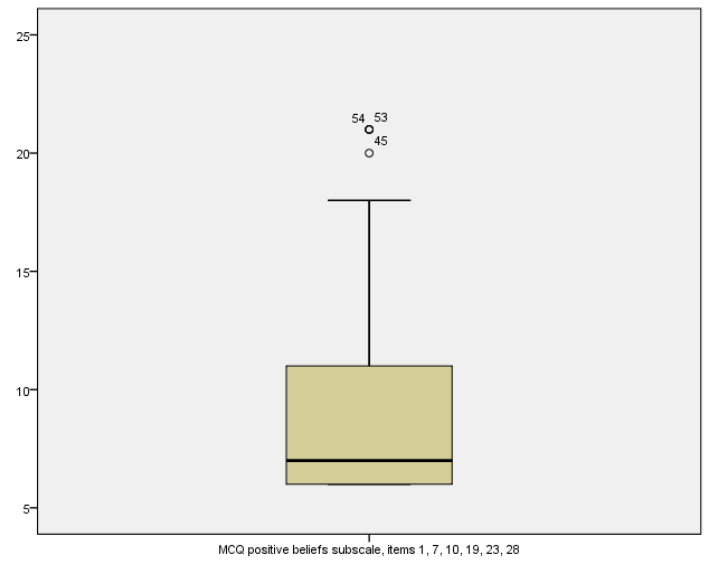


Figure S4. PMCB boxplot

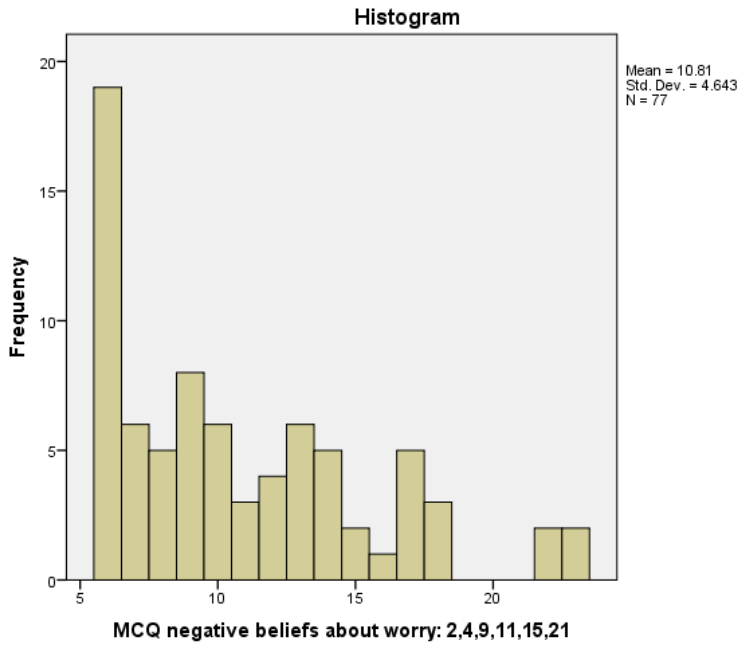


Figure S5. Histogram to display NMCB

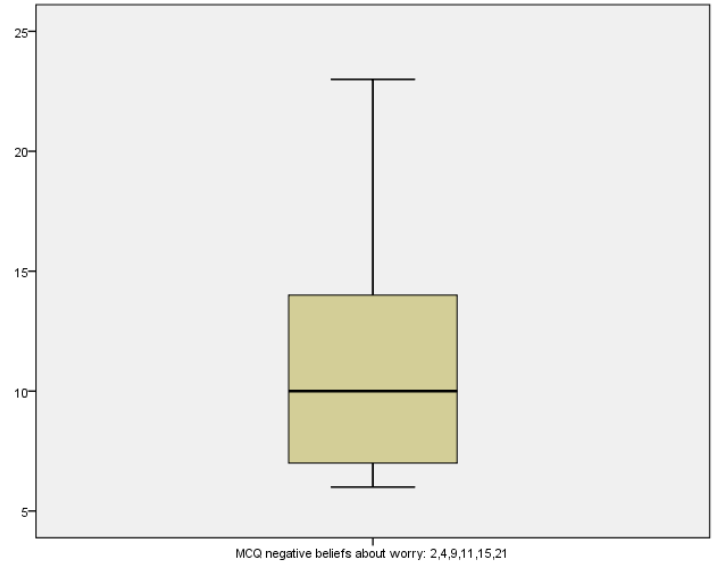


Figure S6. NMCB boxplot

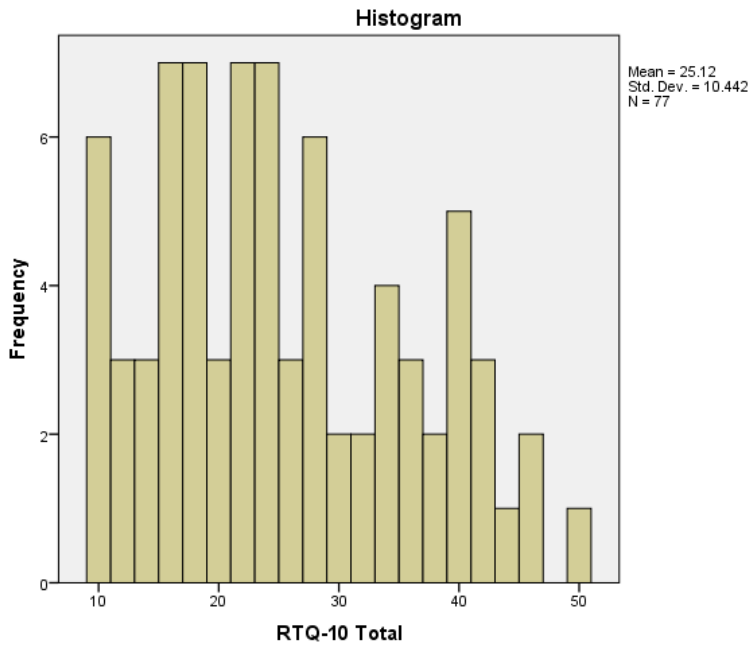


Figure S7. Histogram to display RTQ-10



Figure S8. RTQ-10 boxplot

## **Exploration of regression assumptions**

### **Multicollinearity**

To check variables for the presence of multicollinearity the correlation matrix was inspected to ensure no predictors correlated too highly with each other ( $r > 0.9$ ). Tolerance values were all above 0.2 and variance inflation factors (VIFs) all below 10. The average VIF value was 1.15, close to 1. Eigenvalues has no large variance proportions on the same small eigenvalues.

### **Assumption of independent errors**

Durbin-Watson value was 2.18, within expected range of 1 to 3.

### **Extreme cases**

Casewise diagnostics did not identify any cases with standardised residuals outside of the range or -3 to 3. Cooks distance values were all below 1, therefore no cases have an undue influence on the model. All leverage values were within the expected boundary of three times the average leverage value. Malanchobis distance was scanned for values above 23.21 based upon the chi square distribution. One value exceeded this score (case 27 = 30.88) however was included given that there are no major problems with undue influence on the model. DFBeta, values all within the expected range ( $<1$ ).

### **Linearity and homoscedasticity**

Zresid vs Zpred plot indicated homoscedasticity and linearity. Partial plots indicated some slight funnelling of positive metacognitive beliefs and time since diagnosis.

**Normal distribution**

On visual inspection data was normally distributed (see figures S9, S10, S11).

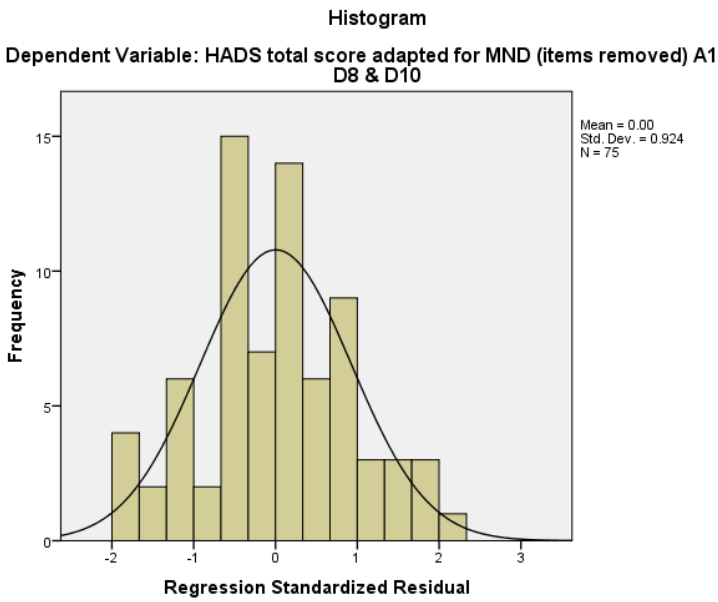


Figure S9. Histogram to display HADS-T

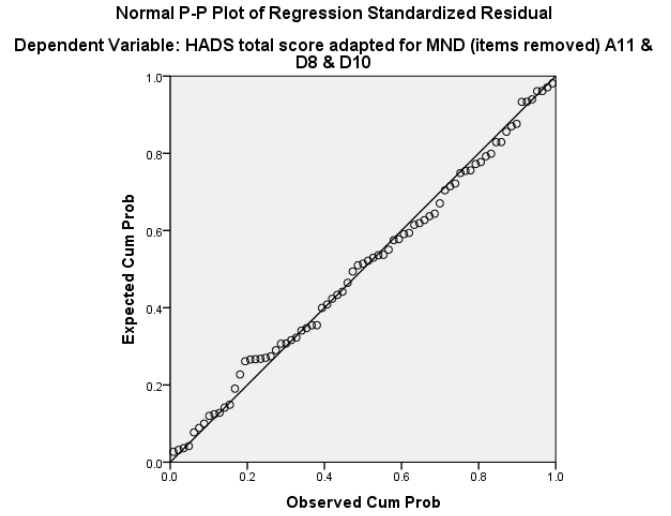


Figure S10. P-Plot of HADS-T

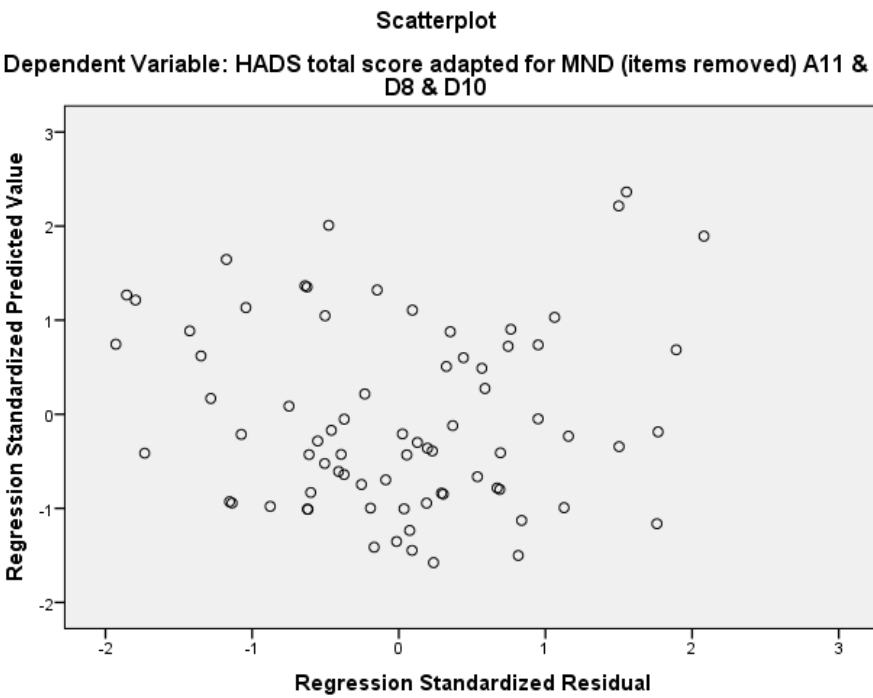


Figure S11. HADS-T scatterplot