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Functional Neurological Disorders: Evaluating the efficacy of facilitator-led psychoeducation for Psychogenic Non-Epileptic Seizures and the psychological profile of MRI Negative Cauda Equina Syndrome

Nicholas Keith-Barnett

Doctorate in Clinical Psychology

The University of Edinburgh

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Table of Contents

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Figures and Tables

Overview of Thesis

This thesis is written in portfolio format in part fulfilment of the Doctorate in Clinical Psychology. It is comprised of two chapters; the first a systematic review and the second an empirical research study. These chapters should be considered as two distinct articles, both aiming to provide further insight into Functional Neurological Disorders. Chapter One is a systematic review of the research literature of the efficacy of facilitator-led psychoeducation for the treatment of Psychogenic Non-Epileptic Seizures. It is written in accordance with author guidelines for the European Journal of Epilepsy (Appendix A). Chapter Two is an empirical pilot study investigating whether reported pain intensity or psychological constructs associated with Acceptance and Commitment Therapy can differentiate between patients with Cauda Equina Syndrome and those who were initially suspected of having the condition (due to common symptomology), but via the use of MRI are found not to and thus likely considered to have a Functional Neurological Disorder. Chapter Two is written in accordance with author guidelines for the British Journal of Neurosurgery (Appendix 10). Appendices containing additional information specific to the separate articles are presented at the end of each relevant chapter.

Lay Summary

This thesis is concerned with Functional Neurological Disorders (FNDs). FNDs are common health conditions that impair normal functioning or bodily processes, where symptoms in the body appear to be caused by problems in the nervous system but are not caused by any actual physical neurological disease or disorder. FNDs can be highly debilitating.

Chapter One of this thesis is concerned with a specific FND called Psychogenic Non-Epileptic Seizures (PNES). This is when people have seizures ('attacks'/'fits') similar to those experienced by those with epilepsy, but without the electrical activity in the brain associated with epileptic seizures. In this first chapter we investigated to see if psychoeducation led by a facilitator is an effective treatment for reducing PNES. Psychoeducation is when education/information is provided to a patient to help them better understand and manage their condition. After extensive searching, seven suitable studies were found that used facilitator led psychoeducation to treat PNES. Of these, only two studies were considered to have acceptable quality in the way they were designed and carried out. Neither of these two studies reported a reduction in PNES. It was therefore concluded that current evidence does not indicate facilitator led psychoeducation to reduce PNES. Further better quality research is needed before we can confidently conclude this to be the case.

Chapter Two of this thesis is concerned with the disabling chronic condition called Cauda Equina Syndrome (CES) caused by compression of nerves in the lower back. Of those who are considered likely to have the condition, because of their symptoms, only about a quarter are confirmed to via the use of an MRI scan. A high proportion of the remaining three quarters are considered likely to

have an FND which is also likely to be related to their psychological (mental and emotional) state. In this second chapter our aim was to better understand the psychological profile of those subsequently confirmed not to have CES (CES MRI-) by comparing them with those who were confirmed to have it (CES MRI+) on the psychological constructs of 'valued living', 'psychological inflexibility', 'intolerance of uncertainty' as well as on reported pain intensity. 75 patients who had MRIs for suspected CES within the last 8 years were recruited and completed questionnaires that measured these constructs. The findings of this study indicated no significant difference between the CES MRI- and CES MRI+ patient samples on any of the psychological constructs however the CES MRI- sample reported significantly greater pain than the MRI+ sample. More in-depth research into the relationship between pain and CES MRI- was recommended.

Thesis Abstract

Background: Functional Neurological Disorders (FNDs) are the second most common reason for outpatient neurology consultations, accounting for 30% of new referrals to general neurology outpatient clinics. These conditions are considered chronic and healthcare resource intensive, as well as having poor long-term health outcomes.

Aims: The first chapter is a systematic review of the efficacy of facilitator-led psychoeducation for the treatment of Psychogenic Non-Epileptic Seizures (PNES). The second chapter is an empirical pilot study investigating if the psychological constructs of 'valued living', 'psychological inflexibility' and 'intolerance of uncertainty' as well as reported pain intensity can differentiate between MRI+ and MRI- Cauda Equina Syndrome (CES) samples (the latter considered likely to be an FND).

Methods: A systematic literature search for studies of facilitator-led psychoeducation for the treatment of people with PNES was conducted. The methodological quality of included studies was assessed using the Cochrane Risk of Bias tool. In the empirical study, 75 eligible participants (who had MRI scans within the last 8 years to diagnose suspected CES) completed self-report measures of valued living, psychological inflexibility, intolerance of uncertainty and pain intensity.

Results: Seven studies met inclusion criteria for the systematic review. Of these, only two were considered to have acceptable methodological quality, with neither of these reporting a significant post intervention reduction in seizure frequency or duration. The findings of the empirical study indicated no significant difference between the CES MRI- and MRI+ patient samples on valued living, psychological inflexibility or intolerance of uncertainty. The CES MRI- sample reported significantly greater pain intensity than the MRI+ sample.

Conclusion: The systematic review concludes that current evidence does not indicate that facilitator-led psychoeducation reduces the frequency and/or intensity of PNES. Further methodologically rigorous, sufficiently powered studies are however needed before confident deductions can be inferred. The empirical pilot study concludes that reported pain appears to differentiate between MRI- and MRI+ CES samples, whereas the chosen psychological constructs do not. However, further research is required before more definitive conclusions can be drawn. Recommendations for future research were made, including more in-depth research into chronic pain as a component and potential precursor to CES MRI-.

Abstract word count: 350

Chapter One: SYSTEMATIC REVIEW

The efficacy of facilitator-led psychoeducation for Psychogenic Non-Epileptic Seizures: a systematic review

Nicholas Keith-Barnett
Department of Neuropsychology, NHS Grampian, The University of Edinburgh
Paul Graham Morris
Clinical and Health Psychology, The University of Edinburgh ( )
James Anderson
Department of Neuropsychology, NHS Grampian

Corresponding author: Nicholas Keith-Barnet, NHS Grampian Department of Neuropsychology, Room 2.19, Ashgrove House, Forresterhill, Aberdeen, AB25 2ZN
Email:

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Written in accordance with the author guidelines for the European Journal of Epilepsy (Appendix A)

Highlights

- 7 studies met the inclusion criteria for this systematic review
- The Cochrane risk of bias tool was used to assess their quality
- Only 2 studies were rated as 'fair' the other 5 were rated as 'poor' quality
- Neither of the fair studies reported significant post-intervention seizure reduction

Abstract

Background: Psychogenic Non-Epileptic Seizures (PNES) are events resembling an epileptic seizure, but without the characteristic electrical discharges in the brain associated with epilepsy. PNES, also known as Non-Epileptic Attack Disorder (NEAD), are relatively common and can occur in isolation or in combination with epileptic seizures. An effective strategy for the treatment of PNES has yet to be established. This current review aims to determine the efficacy of facilitator-led psychoeducation in reducing the frequency and/or intensity of PNES.

Methods: A literature search for studies of facilitator-led group and individual psychoeducation for the treatment of people with PNES was conducted. Electronic databases were searched, key journals were hand searched, corresponding authors were contacted and reference lists of included articles were scanned. Methodological quality of included studies was assessed using the Cochrane Risk of Bias tool, with a randomly selected 50% of the included studies co-rated.

Results: Seven studies met the inclusion criteria (three facilitator-led groups and four facilitator-led 'one-to-one' interventions). Only two studies were considered to have acceptable methodological quality, with neither reporting significant post intervention reduction in seizure frequency or duration.

Conclusions: Current evidence does not indicate that facilitator-led psychoeducation reduces the frequency and/or intensity of PNES, however further methodologically rigorous, sufficiently powered, randomised controlled trial studies are needed, representative of clinical populations and with longer follow-up periods, before more definitive conclusions can be drawn as to the efficacy of facilitator-led psychoeducation for Psychogenic Non-Epileptic Seizures.

Key words: Psychogenic Non-Epileptic Seizures (PNES), Non-Epileptic Attack Disorder (NEAD, facilitator-led, psycho-education

Introduction

What are PNES?

Psychogenic Non-Epileptic Seizures (PNES) are considered paroxysmal behavioural events, which, whilst resembling epileptic seizures (ES), are not associated with the abnormal electrical discharges in the brain that occur in ES. PNES are also commonly referred to as Non-Epileptic Attack Disorder (NEAD), pseudo seizures, dissociative seizures, functional epilepsy/seizures and conversion seizures. PNES are thought to be unconsciously produced and beyond the control of the individual experiencing them. There may be identified triggers for seizures, or they may be considered to 'just happen'.

The incidence rate of PNES in the UK is reported as 4.9 per 100,000 (Duncan 2011), but this is often considered an underestimate due to the high rate of mistaken diagnoses as epilepsy. The gold standard for diagnosis of PNES is via the use of video electroencephalography/video-telemetry (vEEG) where a specialist neurologist can review the EEG reading in concert with the concurrent seizure (Gedzelman & LaRoche, 2014).

To further complicate matters, co-morbidity of both ES and PNES is not uncommon, reportedly ranging from 5% (Duncan & Oto, 2008), 23% (Anderson et al., 2016) and 40% (Bodde, 2009) to as high as 60% (Magaudda et al., 2011). This wide degree of reported variability is likely, in most cases, due to a lack of video-telemetry for conclusive differential/comorbid diagnoses due to its high cost utility and resource limitations. There is also the issue that distinguishing between both types of seizure can be highly

challenging as there is a great 'inter and intra-individual variability' in PNES presentations (Gordon et al., 2014), with most PNES sharing some similarities with ES (Reuber et al., 2011). A recent systematic review and meta-analysis (Kutlubaev et al., 2018) however, reported the mean frequency of epilepsy in patients with PNES to be 22%.

The psychological causes of PNES

There is evidence of psychological antecedents to PNES. Arnold and Privitera (1996) found psychological trauma to be an important factor in the development of PNES. After critically reviewing the existing literature, Sharpe and Faye (2006) found preliminary support for a link between childhood sexual abuse and PNES in later life. Another review by Ludwig et al. (2018) found that both childhood and adult abuse as well as stressful life events are associated with an increased risk of FNDs including PNES. Fleisher et al. (2002) reported that a PNES diagnosis correlated with total number of lifetime traumas, adult traumas, abuse traumas and PTSD. It is worth noting that a recent systematic review by Brown and Reubers (2016) was not able to reach a conclusion regarding either the relative prevalence of trauma exposure in PNES or the significance psychological trauma plays in the development of PNES.

PNES is considered 'a conversion disorder that reflects underlying psychological distress' (Miyawaki et al., 2016). Individuals with PNES present with higher rates of psychopathology (anxiety and depression) as well as reporting lower quality of life (Myers et al., 2019). This effect of PNES on an individual's wellbeing may act to maintain/perpetuate and even exacerbate their condition, as having seizures is likely to

increase existing psychological distress (which would in turn lead to more seizures). With regard to prognosis, Bodde et al. (2009) report that between a third and a fourth of patients with PNES become chronic while Hocaoglu (2017) concludes that: 'Early diagnosis, young age and less psychiatric comorbidity have a positive effect on prognosis'.

Current Treatment for PNES

Standard treatments in the UK for PNES include cognitive behaviour therapy, counselling, psychotherapy and anti-depressants, however a 2014 Cochrane Review on psychological and behavioural treatments for adults with PNES concluded that there is little reliable evidence to support the use of any treatment (Martlew et al., 2014). It is notable that Martlew's 2014 review did not include psychoeducation as a treatment, despite published research indicating it to have a potential effect on PNES reduction.

What is Psychoeducation?

Psychoeducation is considered to be the provision of an educational intervention regarding an individual's condition, to improve their knowledge of the condition and the consequent management of it. This can be done by promoting awareness, teaching management strategies and by changing behaviours and attitudes related to the condition (Colom, 2011).

Psychoeducation can be facilitated 'face-to-face' or by the provision of literature. It can be facilitated in groups or individually and it can take the form of a brief single session or

be more long term, with multiple sessions over months or years. The proposed benefits of psychoeducation as a psychological intervention are that it is clinically focused, straightforward to deliver, and does not require long and complex training to facilitate (Colom, 2001). Interventions often have multiple components (or modules) which may consist of cognitive and/or behavioural training elements and peer support and/or discussion. These often have the primary aim of enhancing problem-solving and/or coping with caring-related or illness management issues (Xia, 2011).

Rationale for Current Review

An effective strategy for the treatment of PNES has yet to be established. Given that PNES is nearly as prevalent as multiple sclerosis or trigeminal neuralgia (Benbadis, and Hauser, 2000) and the adverse psychological and emotional effects associated with this condition (Myers et al., 2019), it is important to discover an effective treatment. The most recently conducted Systematic review on the 'psychological and behavioural treatments for adults with non-epileptic attack disorder' (Martlew et al. 2014) omitted any type of psychoeducation from its analysis, which this current author considers an oversight and worth further investigation as recent research, both before and after this afore mentioned review, has indicated psychoeducation to reduce PNES. Also as psychoeducation has the potential to be highly cost effective particularly when administered to groups in comparison to alternative approaches such as psychotherapy and individual therapist-led CBT. Some Scottish health boards already provide facilitator led group psychoeducation groups for patients with PNES, including a recently developed group provided by NHS Grampian for FNDs including PNES. It is important to see if there is a robust evidence

base for the provision of such groups and if not, the resources could be better reinvested into more appropriate and evidenced treatments.

This systematic review, therefore, aims to evaluate the efficacy of a promising treatment modality (facilitator-led psychoeducation) that has yet to be systematically reviewed for the debilitating condition of PNES. This review will further contribute to the knowledge and evidence base so that better informed choices may be made with regard to the most effective, efficient and evidenced treatment options for patients. This would hopefully result in increased patient health outcomes while simultaneously reducing cost utility.

Objective

This systematic review aims to establish the evidence base for facilitator-led psychoeducation in the treatment of Psychogenic Non-Epileptic Seizures. It will investigate the following questions:

I. Does facilitator-led psychoeducation result in a reduction in the frequency and/or intensity of PNES?

II. Is there a difference in efficacy between group and individual facilitator-led psychoeducation in the treatment of PNES?

Materials and Method

This review was informed by the PRISMA guidelines (Moher et al., 2015) for performing systematic reviews with further guidance drawn from the Centre for Reviews and

Dissemination (CRD, 2009). The inclusion and exclusion criteria were thus determined based on the 'PICOS' approach: Population, Interventions, Comparators, Outcomes and Study design (CRD, 2009).

Inclusion and Exclusion Criteria

Participants/Population

Participants were aged 16 years and older and had a diagnosis of PNES (other alternative definitional terms referring to the same condition were also accepted). Diagnosis had to have been made by either a neurologist, psychologist or psychiatrist and ideally confirmed by EEG while under observation or by vEEG. Where there was no use of v/EEG, the diagnosis had to be made by a specialist neurologist. Due to the high rate of comorbidity of those who experience both PNES and ES, it was decided not to exclude studies that included these patients as long as the comorbidity rate for each study did not exceed 10%.

Intervention

The intervention had to include at least one qualified facilitator. For the purpose of this review, a 'qualified facilitator' was defined as a healthcare professional with at least three years clinical training or clinical experience in a related/relevant field.

The intervention had to be in person ('face-to-face') with no maximum number of sessions, but with a minimum duration of 40 minutes. The content of the psychoeducation

intervention had to contain at least two of the following three core components to be considered acceptable for inclusion (Bäuml et al., 2006):

i) Education around symptoms/condition, prognosis and/or any other relevant information to the condition and its effects.

ii) Education around strategies for the management of condition.

iii) Some form of peer discussion/support/sharing within the session or outside the session with family members/significant others.

Interventions that were considered to contain a significant element from an alternative therapeutic approach (such as psychotherapy) above and beyond these three core components were excluded.

Comparators

No restrictions were placed in terms of the control groups used by suitable studies. Both controlled and observed/uncontrolled studies were included in the review. Any form of standard treatment/treatment as usual (active control) or waiting list control compared to the psychoeducation interventions was considered for inclusion.

Outcome Measures

Studies which assessed PNES reduction (either frequency, intensity or both) were eligible for inclusion. This would also include seizure cessation where relevant. Outcome measures were required to be completed for the intervention population (and control group where relevant) at baseline and at least once post-intervention.

Study Design

Published conference abstracts were considered for inclusion in this current review. Studies where the intervention was multi-modal, including other therapeutic aspects alongside psychoeducation were excluded, as were qualitative/case report studies and review articles. Studies not published in English were also excluded. No restrictions were made regarding the inclusion or length of follow-up, size of sample or publication status.

After consideration it was decided that a meta-analysis would not be appropriate for this review due a high level of heterogeneity in design of all the included studies with regard to factors including intervention content, duration, session numbers, group or individual design and outcome measures used.

Literature Search Strategy

The literature search was conducted on the 16th of August 2018. Initially, the Cochrane Database Abstracts of Reviews of Effects (DARE) was searched to explore relevant systematic reviews in the field and to ensure that no similar review was recently undertaken. A review protocol was published online on PROSPERO:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018112122

summarizing key details of the methodology to promote transparency and to reduce both bias and the chances of an identical review being performed subsequently. The Academic Support Librarian at The University of Edinburgh (R.S) was also consulted regarding the search terms used, the relevant databases to be searched and the search technique itself.

Subsequently, the following databases were searched: PsychInfo (to August ‘week 2’ 2018), Embase (1974 - to August 16 2018) and Ovid Medline® and E pub ahead of print (to August 16 2018). The terms used to search for keywords in all fields included: "non epileptic" or “nonepileptic” or "pseudo seizure*" or "psychogenic seizure*" or "pseudo epileptic" or “pseudoepileptic” or "non epileptic attack" or "functional seizure" or "dissociative seizure" or "hysterical seizure" or "functional epilepsy" or "psychogenic non epileptic seizure" and “psychoeducation” or “education” or “instruction” or “teaching”. The search also captured hyphenated versions of all terms/key words where relevant (e.g. “non-epileptic”) and was focussed only on work published in English due to limited resources for translation.

Further to the initial search method, manual searches were also undertaken to reduce potential limitations associated with the selection of these keywords. All papers referenced in the originally identified studies and the relevant Cochrane Reviews were examined. Moreover, subsequent publications which cited the included studies, as they appear in the Google Scholar search engine, were also screened.

To address publication bias, web searches and searches of citations in included papers for unpublished documents, conference presentations and dissertations were also conducted. An online international dissertation/thesis search was completed on the 26th October 2018 on Pro-quest using the previously mentioned key search terms. Grey Literature was also searched by exploring databases of theses and dissertations (EThOS,

British Library and Open Access Theses and Dissertations*)* as well as searching Google Scholar and conference abstracts.

The corresponding authors of all seven included papers identified in the search were contacted to request details of any unpublished studies that would meet the inclusion criteria. Where relevant, any specific information regarding their included study that was unclear or missing was also requested in the same email. Of the corresponding authors contacted, two could not be contacted and two did not respond. Five studies (published and unpublished) were suggested by the authors who responded, but these either did not meet inclusion criteria or were already included in the review.

Quality Assessment

Methodological Quality of the included studies was evaluated using the Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011), which assesses seven quality criteria ('random sequence generation', 'allocation concealment', 'blinding of participants and personnel', 'blinding of outcome assessment', 'incomplete outcome data', 'selective reporting' and 'other bias') as either 'Low Risk', 'High Risk' or 'Unclear Risk' using the quality rating criteria pro forma. The individual quality criteria ratings for each study were then converted into an Agency for Healthcare Research and Quality (AHRQ) standard score of either 'Poor', 'Fair' or 'Good' quality using the 'Conversion table for AHRQ standard score for overall quality'. The seven selected studies were rated for quality by NKB. Four papers were randomly selected (via www.random.org) and independently peer rated by fellow clinical doctorate trainee MB to assess inter-rater reliability. There was

found to be a 76% agreement in ratings. All criteria with differences between raters were reviewed and amended where appropriate.

Results

Characteristics of Included Studies

Of the 423 articles retrieved in the original search, 139 duplicates were removed and 269 studies were excluded following initial title and abstract screening as they clearly did not meet the review's criteria. Full-text articles were then assessed for the remaining 15 studies**,** which resulted in the exclusion of a further eight studies for reasons outlined in Appendix B. Figure 1 below presents the PRISMA Flow chart of the original literature search process.

The seven remaining studies comprised two randomised-controlled trials, one controlled trial, three uncontrolled/cohort trials and one respective/post hoc analysis study. Four of the reviewed studies involved individual psychoeducation and three involved group psychoeducation. Study characteristics and key findings are outlined in Table 1 below.

The rest of this review will adhere to the protocol published online on PROSPERO specific to seizure frequency/intensity reduction while also assessing the quality of the included studies using the Cochrane Risk of Bias tool for quality assessment**.** It is however worth also noting that when assessing these studies, if the focus is taken from the highly specific

critical assessment of seizure symptoms (intensity and frequency) and opened up more to the overall functional status, quality of life and well-being of patients, then the studies included in this systematic review of psychoeducation for PNES patients can be considered far more efficacious. A summary of all findings from and critical analysis of the included studies in this more holistic way is presented in table 2 below.

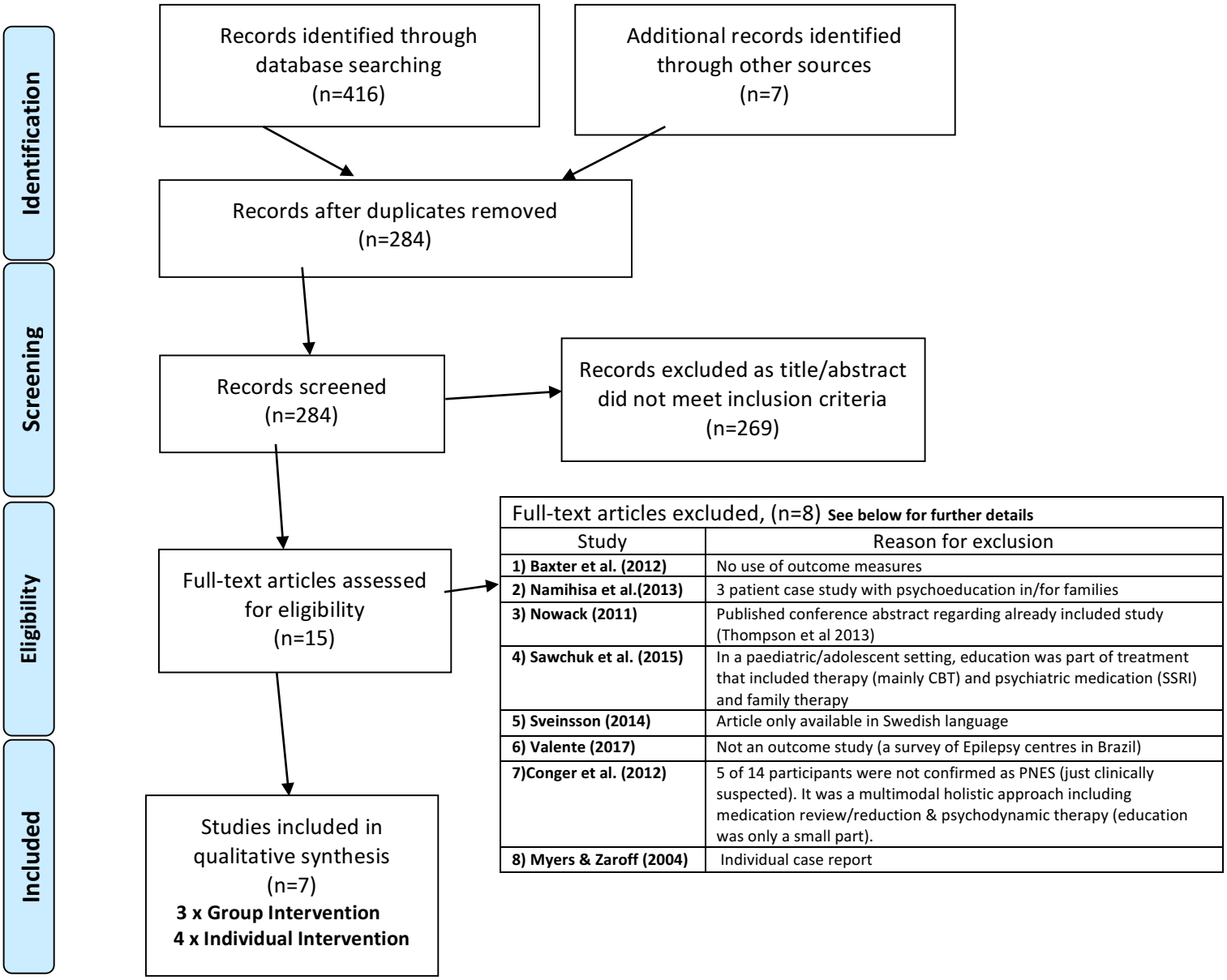
The majority of these studies did lack robust good quality designs, but as 'feasibility' or 'investigatory' studies most still made an important contribution in informing us of the multiple benefits that can be procured by the facilitation of psychoeducation for PNES. What is now extremely important is to follow these studies up with well-designed high powered (RCT) 'confirmatory' investigations.

Participant Sample Characteristics

Some of the included studies would have benefitted from larger sample sizes, which were often of a magnitude that led to the studies being underpowered, and limited (inferential) statistical analysis being administered. There was a combined total sample size of 239 across the included seven studies, with a mean study sample size of 34 (SD: 21.92).

The mean gender percentage of the included studies was 65% female, which is in keeping with the gender profile of the wider clinical population of those that have PNES (Szaflarski et al., 2000; Gates, 2002). The mean age of the participants was 38 years (SD: 6.14), which also reflects the normative clinical profile of the population, with Oto et al. (2005) reporting the mean age of PNES presentation to be 38 years also.

Figure 1. PRISMA Flow chart of original literature search process



Full-text articles excluded, (n=8) **See below for further details**	
Study	Reason for exclusion
1) Baxter et al. (2012)	No use of outcome measures
2) Namihisa et al.(2013)	3 patient case study with psychoeducation in/for families
3) Nowack (2011)	Published conference abstract regarding already included study (Thompson et al 2013)
4) Sawchuk et al. (2015)	In a paediatric/adolescent setting, education was part of treatment that included therapy (mainly CBT) and psychiatric medication (SSRI) and family therapy
5) Sveinsson (2014)	Article only available in Swedish language
6) Valente (2017)	Not an outcome study (a survey of Epilepsy centres in Brazil)
7)Conger et al. (2012)	5 of 14 participants were not confirmed as PNES (just clinically suspected). It was a multimodal holistic approach including medication review/reduction & psychodynamic therapy (education was only a small part).
8) Myers & Zaroff (2004)	Individual case report

Table 1: The key characteristic of included studies

	Study	design	n	% female n	Diagnosis type PNES	Comorbid ES Excluded ?	Mean age (SD)	Outcome measures	Intervention: number/ total duration	Pre/Post Follow Up of measures	Qualification of facilitator	Key findings: RE seizure Freq &/or intensity
Group Psychoeducation												
1	**Chen et al. (2014)**	RCT	**64** interv 34 contl 30	**24.9** interv 26.5 contl 23.3	vEEG	Yes	**50.73** interv 50.76 (12.27) contl 50.70 (11.55)	WSAS*, seizure intens/freq	3x 1.5h monthly total **4.5h**	Pre F/U 1: Approx 3 months post discharge F/U 2: 6 month post discharge	Led by either neurologist or neurology nurse practitioner	No sig group difference in Seizure intensity/frequency
2	**Prigatano, et al. (2002)**	No control	**15** (1st grp 8) (2nd grp 7)	**100**	vEEG	No: 1 comorbid participant (7%)	**36**	seizure frequency	24x 1.5h weekly total **36h**	Seizure reports compared between 1st half of sessions (1-12) Vs 2nd half of sessions (13-24)	Co-therapists were 1 female psychiatrist and 1 male neuropsychologist	Those who attended 50% or more of the sessions: 66% reported a decline in seizure frequency
3	**Zaroff et al. (2004)**	No control /cohort	**10** 7 completed	**60**	vEEG	*Info not available	**35.7**	QofL in Ep-31, seizure freq	10x1h weekly total **10h**	Pre & post	*Info not available	No sig group diff in seizure freq/cessation
Individual Psychoeducation												
4	**Mayor et al. (2013)**	Control Study	**56** interv 20 contl 36	**79.5** interv 76 contrl 83	A clinically secure diagnosis*	Yes (if ES seizure within 12 months)	**37.5** interv 37 control 38	seizure freq, Health related QoL,WSAS,	4x 1h weekly total **4h (manualised)**	Pre F/U: 3 months after completion of psych-ed	2x epilepsy nurses & 1 assist psychologist (with 1 day training)	The intervention was associated with higher rates of PNES cessation
5	**Thompson et al. (2005)**	No control/ Retrospecti ve/post hoc analysis	**50**	**76**	vEEG	yes	**34**	seizure frequency/ cessation	1x **45-60 min** after diagnosis	Pre F/U: (2 year after diagnosis)	Psychiatric consultation liaison nurse	-Reduction in seizure symptoms or freq in 86%. -24n (50%) reported seizures cessation 2 years post diagnosis. -19n (40%) reported less intense events &/or a decrease in freq
6	**Thompson et al. (2013)**	RCT pilot	**19**	**60**	vEEG	Yes	**33**	QofL in Ep-31, seizure intens/freq	Control (TAU) Vs Interv: 1x **40-60 min**	Pre F/U: (6 weeks post discharge)	Psychiatric Clinical nurse specialist	No sig reduction in the seizure frequency or intensity
7	**Wiseman et al. (2016)**	No control	**25** (1st grp 19) (2nd grp 4) (3rd grp 1) (4th grp 1)	**52**	Diagnosis by specialist neurologist	No: 1 comorbid participant (7%)	**41.8** (18.1)	seizure frequency, QoL,WSAS,	4x 1h weekly) total **4h (manualised)**	Pre & post	6x epil nurses, 3x Asst psychols, 1x Occ Therapist [across 4 sites]	48% of n were either seizure free or seizure reduction.

* Where NKB contacted corresponding author for further information but had received no response

*Clinically secure diagnosis: Neurologist was sufficiently certain of PNES diagnosis by either use of vEEG or because 'clinical information strongly suggested diagnosis'

Table 2: Summary of findings from and critical analysis of included studies

	Study	Study findings/results	Critical analysis of study
Group Psychoeducation			
1	**Chen et al. (2014)**	·Significant improvement on the Work and Social Adjustment scale for intervention group at both 3 month and 6 month post discharge follow-up. ·Observed trend towards lesser seizure related A&E visits and hospitalisations in intervention group ·No significant group difference in seizure intensity/frequency	·This study had a good robust randomized control design with follow ups and both 3 and 6 months post discharge. ·41% of intervention group dropped out possibly leading to bias. Participants were 75% male incongruent with clinical population. **Overall**: A decent quality study where patients benefitted from a brief psychoeducation intervention after just three sessions with less impairment in important areas of functioning.
2	**Prigatano, et al. (2002)**	·Of patients that attended 50% or more of sessions, 67% reported a decrease in seizure frequency. ·No other outcome measures were taken ·Self-reported seizure frequency highly correlated with paranoid ideation.	·Small participant population and no control group. Extensive intervention period (24x1.5 hours). Highly experienced facilitators. **Overall**: study had poor quality design for the purpose of this review. Findings lacking possible clinical relevance due to unlikelihood of provision of 24 intervention sessions over 6 months, but patients did have significantly fewer seizures after attending intervention.
3	**Zaroff et al. (2004)**	·Significant post-intervention decreases were reported in post-traumatic and dissociative symptoms as well as in emotionally based coping mechanisms. There was also a trend (non-significant) toward improved quality of life. ·No significant group improvement in seizure frequency or cessation.	·Some important information not provided by either publication or attempted correspondence with corresponding author with regard to exclusion criteria for comorbid ES and the training qualification of facilitators. ·Very small participant population and no control group. **Overall**: Although this study had poor quality design, findings indicate that psychoeducation may improve coping strategies and reduce PNES-associated psychopathology in some patients, enough to justify future better quality research (controlled designs and larger n) in this area.
Individual Psychoeducation			
4	**Mayor et al. (2013)**	·The intervention was associated with significantly higher rates of PNES cessation. ·Significant baseline to follow up improvements were also reported for the: *-Work and Social Adjustment Scale* *-Number of A&E visits (in the last 3 months)* *-Mental health related quality of life* *-Physical health related quality of life*	· Facilitators did receive specific training and adherence to the facilitation manual was rated highly (between 80-89.5%). There was only a 45% participant completion rate which could lead to bias. Small sample size. **Overall:** Although a poor quality design, as a 'feasibility' study, findings indicate that 1in 3 PNES patients could be seizure free after a brief simple manualised intervention as well as a range of other health related improvements in quality of life and overall functioning. Being manualised, lesser qualified/experienced clinical staff could still successfully administer it. This study justifies a future RCT with a bigger sample size.
5	**Thompson et al. (2005)**	·Of those contacted 2 years post intervention: -Seizure symptoms/ frequency reduction in 86% -50% reported seizure cessation -100% attended at least 1 recommended subsequent psychotherapy session. ·No other outcome measures were taken	·A retrospective design with no control group. An extremely brief manualised intervention (1x45-60 minutes). 2nd aim of intervention was to increase patient compliance with recommended future psychotherapy sessions. **Overall:** This study although lacking robustness in it's design achieved its two main aims of a significant reduction in seizure symptoms and compliance (100%) in subsequent referred psychotherapy after just a short single psychoeducation intervention. Thus making very interesting an important contributions to the research base for informing future research
6	**Thompson et al. (2013)**	·100% of patients in treatment group attended an appointment with a psychotherapist or psychiatrist within 6 weeks of hospital discharge (compared to 50% of control group). ·There was no significant difference between groups or pre to post intervention in reported 'quality of life with seizures'. ·Most PNES patients reported a history of physical and/or sexual trauma.	· A randomised control pilot study where control group received treatment as usual. · a single brief manualised psychoeducation intervention (40-90 minutes). · Follow up was 6 weeks after discharge which might not have been long enough for intervention benefits to fully develop. **Overall:** A decent design quality which would have benefitted from a larger sample size. Although there was no significant reduction in seizure symptoms or quality of life, the brief intervention led to 100% compliance in later therapy appointments which is likely to have a positive effect on the patients wellbeing and/or PNES from future therapeutic engagement.
7	**Wiseman et al. (2016)**	·48% of participants were either seizure free or had a seizure reduction post-intervention. ·There was a significant post intervention improvement in patients' psychological distress and their illness perception. ·There was no significant post-intervention improvement in quality of Life (both health related and epilepsy specific) and with regard to 'Impaired Functioning'.	·A multicenter brief manualised intervention, with no control. · Delivered over 4 (1 hour) sessions by facilitators with a varying range of clinical experience across 4 sites. · *Across the four centres where the study was performed, there was a reported lack of continuity with regard to referral process, assessment and resources.* The study would also have benefitted from a larger participant sample and a follow-up period. **Overall:** Another useful pilot study that was lacking a decent quality design but with findings of relevance & significance to propose follow-up RCT for confirmatory proof of efficacy that brief psychoeducation is an effective intervention for both seizure control and well-being of patients.

The gold standard tool for diagnosis of PNES is video-electroencephalography/video-telemetry (Gedzelman & LaRoche, 2014). vEEG was used as the primary diagnostic tool in five of the seven shortlisted studies. Of the two remaining studies, Mayor et al. (2013), stated a clinically secure diagnosis was made where the specialist neurologist was sufficiently certain of a PNES diagnosis by either use of vEEG or because clinical information strongly suggested diagnosis. After consulting the corresponding author of the Wiseman et al. (2016) study, it was ascertained that diagnosis of PNES was made by a specialist neurologist for the all recruited participants in their study.

With regard to comorbidity with epileptic seizures (ES), of the seven included studies, three had an absolute exclusion criteria regarding co-morbid ES and two studies allowed one participant to be included with PNES & ES comorbidity (4% & 7% of the study participant samples). For one study the relevant information could not be obtained (Zaroff et al., 2004) with no response from the corresponding author. A final study's inclusion criteria was: 'as long as participants had not experienced an ES within 12 months' (Mayor et al., 2013). Overall it can be assumed that the mean sample comorbidity with ES was likely to be significantly lower than the 22% estimated for the clinical population (Kutlubaev et al., 2018).

All included studies excluded individuals with learning difficulties/'sub-normal intelligence'. Prigatano et al. (2002) excluded patients who had experienced head trauma and/or psychiatric comorbidity. Wiseman et al. (2016) excluded participants with complex mental health problems as well as those considered not to 'be engaged and motivated to complete the program'. While these exclusion criteria are likely to limit how representative this overall sample is of the clinical population, it seems an

unavoidable limitation of responsible clinical practise with regard to addressing and managing the ethical issues around both mental capacity (associated with informed consent) and risk. Other included studies appeared to have recruited a more heterogeneous participant sample, such as Zaroff et al. (2004), who reported that half their recruited participants had a history of trauma.

Outcome Measures Used

Although a variety of different outcome measures were used, all seven studies measured 'seizure frequency', which this review considers to be the primary outcome measure of interest. Three studies also used the 'Work and Social Adjustment Scale' (WSAS) and four studies used a 'Quality of Life' measure.

Intervention Duration

The number of intervention sessions varied from a single session to 24, with a mean number of 6.7 sessions (SD: 8.20). The total (combined) time of interventions varied greatly from 40 minutes to 36 hours. The mean total intervention time across the studies was eight hours and 36 minutes (SD: 12 hours 46 minutes).

Outcome Measure Administration

With regard to the administration of outcome measures, two studies did this pre and post intervention, three studies did this pre intervention and follow up (ranging from six weeks to six months post intervention), one study compared outcome measures taken directly after the first half of the intervention (from session 1-12), with those taken after the second half of intervention (from session 13-24) and the retrospective study interviewed participants via telephone two years post intervention.

Qualification of Facilitators

Facilitators had a wide variety of professions, experience and expertise within the health care industry. This ranged from assistant psychologists to neuropsychologists, a psychiatrist and specialist neurologists. The most common post for a facilitator across the studies was specialist nurse: neurology nurse practitioner, epilepsy nurses, psychiatric consultation liaison nurse and psychiatric clinical nurse specialist. For only one study (Zaroff et al., 2004) no details regarding the facilitators were provided (and could not be obtained by contacting the corresponding author).

Quality of the Included Studies

The quality assessment (see table 2 below) indicates that Chen et al. (2014) and Thompson et al. (2013) conducted the methodologically strongest studies (both 'fair quality'). These were the only randomised controlled trials (RCTs) included in this review (and consequently were the only two studies to achieve a low risk rating for 'Random Sequence Generation'). Their overall superior quality should be considered a logical outcome as an RCT design is likely to significantly reduce the risk of bias when compared to observational trials (Stolberg et al., 2004), with a randomised design considered to be the most powerful among clinical trials (Stolberg et al., 2004).

Only one study (Chen et al., 2014) was able to achieve a low risk rating for 'Allocation Concealment'. In this study patients were independently designated a computer-generated random number, whereupon even number patients were assigned to receive the study intervention. Four of the included studies did not have a control group (this bias criteria therefore not being relevant to them).

Table 3: Cochrane Risk of Bias tool quality assessment of included studies

Risk Criteria	1. Random sequence generation	2. Allocation concealment	3. Blinding of participants and personnel	4. Blinding of outcome assessment	5.Incomplete outcome data	6. Selective reporting	7.Other bias	Overall Quality (AHRQ)
	Group Psychoeducation							
1) Chen et al. (2014)	Low	Low	Low	Unclear	Low	Unclear	High	**FAIR**
2) Prigatano et al. (2002)	High	High	Low	Unclear	Low	Unclear	Unclear	**POOR**
3) Zaroff et al. (2004)	High	High	Low	Unclear	Low	Unclear	High	**POOR**
	Individual Psychoeducation							
4) Mayor et al. (2013)	High	High	Low	Unclear	High	Unclear	High	**POOR**
5) Thompson et al. (2005)	High	High	Low	Low	High	Unclear	Unclear	**POOR**
6) Thompson et al. (2013)	Low	High	Low	Unclear	Low	Unclear	Low	**FAIR**
7) Wiseman et al. (2016)	High	High	Low	Low	Low	Unclear	High	**POOR**

-Each criterion was rated as either High, Low or Unclear for risk
-Subsequently, each study was rated using AHRQ Standards as either Good, Fair or Poor for overall quality

None of the included studies appeared to incorporate 'Blinding of Participants and Personnel'. However, it was not considered by the current review author that this would be likely to negatively influence the studies' outcomes in any significant way.

With regard to the quality criteria of 'Blinding of Outcome Assessments', this did not occur for any of the included studies, however for the majority of these (five studies), the current review author considered the risk 'unclear' as there was insufficient evidence to permit a judgment of either 'high risk' or 'low risk'. For the remaining two studies (Thompson et al., 2005 and Wiseman et al., 2016), study design resulted in this quality criteria either not being considered relevant or being 'low risk'.

For the quality criteria of 'Incomplete Outcome Data', the majority of the studies (five) were rated as 'low risk', as this was not considered to cause a significant bias. The exception was with regard to Mayor et al. (2013) which reported an extremely high rate of attrition of participants from the intervention group (38 to 13) likely to create a clinically relevant bias and threatening both internal and external validity (Flick, 1998).

Thompson et al. (2005) gained a ‘high risk’ rating for this criteria as there appeared to be a significant lack of outcome data presented in the paper, which was not made available when the corresponding author was contacted.

The nature of this systematic review meant that it was difficult to evidence the ‘Selective Reporting’ quality criterion. NKB was unable to locate a study protocol for any of the seven shortlisted studies and consequently was unable to ascertain each study’s pre-specified outcomes, therefore a rating of ‘unclear’ was given to each of the seven shortlisted studies.

With regard to the seventh and final quality criteria ‘Other Bias’**,** three of the shortlisted studies were given a rating of ‘high risk’. Chen et al. (2014) was due to the high attrition rate of the intervention group (41% attrition) and their 75.1% male participant sample (counter to the gender ratio norms of the clinical population) limiting the applicability of findings. This was combined with a low power due to small sample size. The Zaroff et al. (2004) paper gained a ‘high risk’ rating due to its very small sample size (n=7), with no information provided about the qualification/expertise of the facilitators or if patients with co-morbid ES were excluded or not.

The Wiseman et al. (2016) study also gained a ‘high risk’ score in this category because, across the four centres where the study was performed, there was a reported lack of continuity with regard to referral process, assessment and resources. All the other included studies were rated as ‘unclear risk’ except Thompson et al. (2013) which was considered low risk.

Discussion

There appeared to be an overall lack of quality and robustness of design in the included studies in this systematic review. None of the seven studies were rated as 'Good', with over 70% (five) of the included studies acquiring a quality rating of 'Poor'. All the included studies appeared underpowered and would have benefitted from larger sample sizes to improve ability to detect possible effects.

Of the seven shortlisted studies, three reported a significant post-intervention reduction in seizure frequency/intensity. However, all three of these studies were rated as 'poor quality' by first implementing the Cochrane Risk of Bias tool and then the associated conversion tool to gain an AHRQ quality standard. The two studies with the highest methodological strength (both rated as 'fair quality'), which were both RCTs, did not find any significant reduction in seizure frequency or intensity.

Clinical Implications

No previous systematic review has examined the efficacy of facilitator-led psychoeducation for Psychogenic Non-Epileptic Seizures. The current evidence base should be interpreted with caution due to methodological limitations including small sample sizes, lack of control groups, lack of follow-up and high attrition, all of which may reduce the generalisability of study findings across this current review.

Group Psychoeducation Vs Individual Psychoeducation

It was hoped to be able to compare facilitator-led group psychoeducation versus facilitator-led individual psychoeducation with regard to efficacy. If the two modes of

intervention were found to be comparably efficacious, group therapy would be significantly more cost effective/time efficient. However, due to a dearth of both types of study (three group vs four individual) eligible for inclusion in this current review and an overall lack of methodological/design quality of the studies included regardless of their group/individual design format, it would be of little value to attempt a current valid comparison between these two modes of psychoeducation administration at this time.

Future Research

It is necessary to enhance the evidence base so that that the proposed systematic review question can be answered confidently. This would be done by including more methodologically rigorous RCTs as standard, larger clinically representative sample sizes so that studies aren't underpowered and short and long term follow ups to reliably investigate the lasting effect of psychoeducation interventions. This rigorous methodology would generate more conclusive, valid and reliable findings.

Given the complex and multifaceted nature of PNES, where possible, future RCTs and controlled studies in this area should consider controlling for as many confounding variables as possible, such as comorbid psychological, functional and neurological conditions. It may also be helpful to further explore specific risk factors for PNES such as early life trauma and abuse (Fiszman et al., 2004) which should also be considered for inclusion when attempting to make samples representative of the clinical population.

Improving the reporting of methodology, particularly the psychoeducation protocol in studies would allow reviewers to come to more accurate and useful conclusions.

Furthermore, it is important to have sufficient details of the intervention content (session by session) to allow both replication and to ensure fidelity of administration. The majority of studies included in this current review did not report either a psychoeducation protocol or a detailed intervention content.

Future research could also consider and account for (as a possible confounding variable), the well-evidenced effect of diagnosis as a therapeutic intervention in itself for significantly improving the symptomology of PNES (Duncan, 2010). If future studies are fruitful in demonstrating the efficacy of psychoeducation for PNES, an important goal of consequent research might be to explore the mediators and active ingredients of effective interventions so that brief one-off interventions may be designed and used. This would not only be more cost effective but could also simultaneously combat the issue of the high attrition rate found with this population by reducing patient commitment pressures associated with more long-term treatment interventions. Investigations into the causes of high dropout rate could also be done so that they could be addressed and reduced through the modification of intervention design.

As patients with PNES have a very high healthcare cost burden (Ahmedani, 2013) within the NHS in addition to the wider economic impact associated with sick leave and not working or driving, finding an effective and acceptable intervention for this patient population is vital from a purely economic perspective.

Strengths and Limitations of this Review

This review sought to identify examples of both ‘best’ practice and ‘realistic’ practice in an NHS setting. In doing so, most reviewed papers may have been of too low quality

to reach meaningful conclusions on their own. However, the current synthesis aims to establish the best available evidence accessible at this time.

The Cochrane risk of bias (CRoB) tool was chosen for use in this systematic review. It is widely used and well established tool, considered to be the standard approach to assess risk of bias in randomized clinical trials. Possible limitations with regard to the tool's implementation in this current systematic review include the fact that only two of the included studies were RCTs when ideally all 7 would have been when using the tool. The bias domains of the CRoB tool are specific to RCTs (Higgins et al., 2011) and consequently its validity to address bias may have been compromised, however it could also be argued that although the tool is suited for review questions which would optimally be addressed by strong RCTs, it could still suitably appraise, a non-randomised trial by just giving a poor rating for randomisation. This would obviously not be applicable in circumstances where either randomisation or a control group (or any of the other quality criteria) were not methodological strengths in addressing the specific review question. It is important to note that depending on the review question of other studies, there may be other areas of methodology that the CRoB does not address.

Other criticisms of the tool that have been previously identified include that it does not address bias associated with funding/conflicts of interest as well as having only modest inter-agreement rates amongst reviewers (Hartiling et al., 2013). This suggests a need for more detailed guidance in using the tool to assess risk of bias is required. Although a complementary CRoB

tool was developed by Sterne, Higgins and Reaves in 2014 for non RCT studies, this was not considered appropriate for this current Systematic Review as it would put the RCTs at a disadvantage for having what would be universally considered superior designs regarding power among clinical trials (Stolberg et al., 2004).

The reviewed literature had several limitations. The studies were highly heterogeneous; with widely varying psychoeducation content, delivery, intervention formats, with largely varying number and length of interventions and inconsistent use of follow-up measures across the studies. This led to possible issues with regard to the ecological validity/generalisability of findings as well as a consequent inability to perform a meta-analysis, both of which may have inhibited the potential discovery of a common effect. All studies also relied on self-report measures which could lead to response bias, in particular with regard to social desirability.

Conclusions

Current evidence does not indicate that facilitator-led psychoeducation reduces the frequency and/or intensity of PNES, however further methodologically rigorous, sufficiently powered, studies are required, representative of clinical populations, before more definitive conclusions can be drawn as to the efficacy of facilitator-led psychoeducation for Psychogenic Non-Epileptic Seizures.

Declarations of interest: none

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Appendix A: Author guidelines for the European Journal of Epilepsy

GUIDE FOR AUTHORS

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Types of articles

Seizure - European Journal of Epilepsy publishes the following types of article:

1.1 Peer-reviewed articles
a. Full reviews.
Seizure welcomes comprehensive reviews on all subjects relating to epilepsy and other seizure disorders. Authors planning/proposing are invited to discuss their ideas with Editor-in-Chief prior to submission. Full reviews should be preceded by an abstract. Full reviews should not exceed 7,000 words, include no more than 6 figures or tables and 150 references.

b. Focused reviews.

Seizure is keen to publish focused reviews, especially on the latest developments in particular fields or on topics which are currently debated by clinicians and researchers. Authors are welcome to approach the Editor-in-Chief with their idea for a focused review prior to submission. Focused reviews should be preceded by an abstract. Focused reviews should be 1,500-2,500 words, and include no more than 3 figures or tables and 50 references.

c. Full-length original research articles.

The body of the text of these articles should be limited in length to 4,000 words, and there should be a maximum of 6 figures or tables. Additional figures, tables and other material (such as associated videos) can be submitted as online only Supporting Information (see section 'preparation of manuscripts' for further details). Full length research articles should be preceded by an abstract. The body of the text of the article should be clearly structured into 1) Introduction, 2) Methods 3) Results, 4) Discussion, 5) Conclusion and 6) References.

d. Short communications.

Comprise a number of different kinds of previously unpublished materials including short reports or small case series. Short communications should be preceded by an abstract. The body of the text is limited to 1,400 words. There are no more than 12 references, and 2 figures or tables (combined).

e. Case reports (Clinical Letters), see also ***Interactive Case Insights*** below
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Chapter Two: Empirical Research Journal Article

A pilot study investigating if valued living, psychological inflexibility, intolerance of uncertainty and reported pain intensity can differentiate between MRI+ and MRI- Cauda Equina Syndrome patients

Nicholas Keith-Barnett
Department of Neuropsychology, NHS Grampian, The University of Edinburgh
Paul Graham Morris
Clinical and Health Psychology, The University of Edinburgh
Fiona Summers
Department of Neuropsychology, NHS Grampian

Corresponding author: Nicholas Keith-Barnett, NHS Grampian Department of Neuropsychology, Room 2.19, Ashgrove House, Forresterhill, Aberdeen, AB25 2ZN
Email:

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Abstract

Background: Cauda Equina Syndrome (CES) is a debilitating condition caused by compression of the Cauda Equina nerve roots of the lower back. Of those suspected as having the condition, only 22-28% are confirmed via Magnetic Resonance Imaging (MRI+). A high proportion of the remaining 72-78%, due to having no observed structural causality of their symptoms (MRI-), are considered likely to have a Functional Neurological Disorder. This CES MRI- population is also likely to have a psychological component to their functional condition. This study seeks to better understand the psychological profile of CES MRI- patients, by investigating if there are significant differences when comparisons are made with CES MRI+ patients, on the psychological constructs of 'valued living', 'psychological inflexibility', 'intolerance of uncertainty' and pain intensity.

Methods: 433 NHS Grampian patients were identified via electronic records to have had an MRI between 1st Jan 2010 and 31st Jan 2019 for suspected CES. All were sent the outcome measures: Valued Living Questionnaire, The Acceptance and Action II Questionnaire, Intolerance of Uncertainty Scale (short form) and the Numeric Pain Rating Scale. 75 eligible participants returned completed questionnaires by the recruitment cut-off date.

Results: Findings indicated no significant difference between the CES MRI- and MRI+ samples for any of the psychological constructs. The CES MRI- sample reported significantly greater pain intensity than the MRI+ sample.

Conclusions: Reported pain intensity appears to differentiate between MRI- and MRI+ CES patient samples, whereas the chosen psychological constructs do not. However, further research is required before definitive conclusions can be drawn. More in-depth future research into chronic pain as a component and potential precursor to CES MRI- is recommended.

Abstract Word Count: 270

Key words: Cauda Equina Syndrome, Valued Living, Psychological Inflexibility, Intolerance of Uncertainty, Pain intensity

Introduction

Cauda Equina Syndrome

Cauda Equina Syndrome (CES) is a severe medical condition of the lower back caused by the compression of the cauda equina nerve roots which leads to the disruption of motor and sensory function to the lower extremities and bladder. The common symptoms of CES include severe lower back pain, weakness/numbness in legs, reduced sensation around the saddle and genital area, bladder and/or bowel function weakness or incontinence and sexual dysfunction. If an individual is diagnosed as having CES, they will normally have emergency surgery within 24 hours to relieve the nerve compression, to minimalize existing injury and to prevent further injury and potential disability occurring.

CES is considered to be a relatively rare condition with an incidence rate of between 1 in 33,000 to 1 in 100,000 people in the general adult population (Gardner et al., 2011; Anthony, 2000). However, the majority of patients who are initially suspected as having CES, due to common symptomology, are consequently identified via magnetic resonance imaging (MRI) not to have the organic/structural causality of their symptoms required for a diagnosis (MRI negative/MRI-). Bell, Collie and Statham (2007) found, after collecting data over a four-month period on all patients referred to the Department of Clinical Neurosciences, Western General Hospital, Edinburgh, who presented with a suspected diagnosis of CES, that only 22% were found to be 'scan positive', and actually have the condition. A more recent and comprehensive study by Hoeritzauer et al. (2017) in NHS Lothian retrospectively reviewed all 'e-records' of patients admitted with possible CES from August 2013 to November 2014. Of the 275 patients referred to neurosurgery with suspected CES over this time period, only 28% were found to be MRI+ (identifiable structural explanation), 2% were found to have an alternative cause for their symptoms and 70% were found to have no identifiable structural explanation for their

symptoms (MRI-). These findings are further supported by a recent audit by the current first author in NHS Grampian for the period covering the 1st of January 2010 to the 9th of October 2018 (Keith-Barnett, 2018, unpublished). Of the 383 identified individuals suspected of having CES, 284 (74%) were consequently found to be MRI- and 99 (26%) were confirmed to be MRI+.

Gibson et al. (2017) consider 'a proportion' of CES scan negative patients to be due to Functional Neurological Disorders. Hoeritzauer et al. (2018) conclude that at least some of this patient population are 'best understood to have a functional disorder explaining some, or all, of their presentation', while Rooney et al. (2009) suggest that it is likely that 'many' patients will have a functional causality for this condition. 'Functional' in this context refers to Functional Neurological Disorders (FNDs): neurological symptoms which impair normal functioning or bodily processes but in the absence of physical neurological disease or disorder (Stone and Carson, 2015). Psychological factors are considered highly likely to have a 'patho-physiological' role with regard to causality, perpetuation and/or expression of FND symptomology (Voon et al., 2016).

The Clinical Characteristics/Comorbidities of CES MRI-

CES MRI- patients also have higher rates of functional comorbidity, such as irritable bowel syndrome (32% vs 6% for MRI+), other FNDs, such as psychogenic non epileptic seizures (11% vs 1% for MRI+) and higher rates of psychiatric co-morbidity, such as anxiety or depression (46% vs 22% for MRI+) when compared to CES MRI+ patients (Hoeritzauer et al., 2017; Hoeritzauer et al., 2018). CES MRI- patients were also found to be more likely to report symptoms of dissociation (45% vs 14% for MRI+) and panic attacks (72% vs 29% for MRI+) when compared to CES MRI+ patients (Hoeritzauer et al., 2015).

The long-term health outcomes have also been found to be poorer for the CES MRI- patient population, with 58% identified to have chronic pain compared to 26% for MRI+ patients when followed up a year after diagnosis (Hoeritzauer et al., 2018). This indicates that there may be multiple psychological factors/vulnerabilities that are associated with people developing and maintaining the symptoms of CES without any structural/spinal causality of their symptoms.

Current Treatment/Therapy for CES MRI-

Currently, healthcare provision within the Scottish NHS can be considered both limited and poor for CES MRI- patients. There are currently no standard care pathways for this population across health boards in Scotland (or the UK), which may result in variation of treatment quality.

Data collection for this current research occurred within NHS Grampian. In this health board (as well as NHS Lothian where research advisor Dr Ingrid Hoeritzauer is currently based), when an MRI scan confirms no structural/spinal causality of symptomology, patients are commonly discharged with a prescription for analgesic pain medication and, depending on their affected mobility, a referral to physiotherapy may also be involved. An FND care pathway is, however, currently in development in NHS Grampian for which this study hopes to inform.

The current prognosis for this population upon discharge is also poor. 'Follow-up' investigation (after three years) of patient electronic records by Hoeritzauer, Pronin et al. (2017) indicated patients may re-present with 'scan negative' CES symptoms recurrently (12% of CES MRI- patients presented twice and 8% presented three or more times). Of these patients with recurrent 'scan negative' CES, 43% had a diagnosed (alternative) functional disorder, 57% had psychiatric comorbidity and 87% were found to have developed chronic back or leg pain. A

more suitable treatment focus for this clinical population may have a greater emphasis on the psychological and functional aspects (and comorbidities) of this condition.

This current study

This current study is an exploratory pilot study. There is a dearth of research investigating the psychological profile of patients with FNDs and/or patients with CES MRI-. There has, however, been far more research into the psychological profile of patients with chronic pain. As one of the primary symptoms of CES MRI- (as well as MRI+) is reported long term (chronic) intense pain, the relevant previous research regarding chronic pain will be used to inform the choice of psychological constructs chosen for use in this current exploratory study when investigation the psychological profile of the likely FND of CES MRI-. This study is also particularly interested in the impact of pain on the chosen psychological constructs, as well as their reciprocal impact on pain, as this may provide useful information with regard to the precipitation, exacerbation and perpetuation of a likely functional neurological disorder without organic causality.

The following information will provide the rationale for the choice of the psychological constructs to be measured in this study.

Acceptance and Commitment Therapy

Acceptance and Commitment Therapy or ACT (of which the constructs valued living and psychological flexibility used in this study are considered integral) has been shown to be an effective treatment for a range of disorders, including depression and anxiety (Foreman 2007), drug abuse and psychosis (Johns et al., 2016) and epilepsy (Lundgren, 2008). In chronic pain

patients, general functioning was enhanced and distress reduced with the implementation of ACT, when compared to inactive treatment comparisons (Hann & McCracken, 2014).

ACT and FNDs

Published research evidencing ACT as a successful therapeutic approach for FNDs is sparse. This may be considered at least in part due to ACT being a relatively new therapeutic approach yet to build a robust evidence base for treating this 'emerging' category of clinical conditions. Graham et al. (2018) found promising initial results using ACT, with interventions improving mood and reducing symptom interference (via increased 'psychological flexibility') in this clinical population. This indicates that further investigation of an ACT approach for treatment of FNDs is warranted.

Valued Living

The psychological construct of 'valued living' will be measured in this study. Valued living is a primary core process of the ACT model (Hayes et al., 2006; Strosahl, Hayes, & Wilson, 2004) and can be described as knowing what we want out of our life and then making committed actions 'in the service' of those values (Harris, 2011; Wilson, Sandoz, & Kitchens, 2010). Incorporations of the concept of valued living predate ACT significantly, be it in alternatively termed constructs such as 'organismic valuing process' (Rogers, 1964), 'intrinsic motivation' (deCharms, 1968) or 'self-actualisation' (Maslow, 1962). This indicates the conceptual importance of values in both psychological theory and therapy alike.

Chronic pain patients who were more successful at living and engaging in behaviour that was consistent with their values experienced better physical functioning and emotional well-being (McCracken & Yang, 2006). Low valued living scores on the Valued Living Questionnaire

were found to be a predictor of medically unexplained symptoms and chronic fatigue (Kang et al., 2019). A study that incorporated values into an ACT based acceptance intervention led to significantly greater pain tolerance than when acceptance was used alone (Branstetter-Rost et al., 2009). There is no research to this current researcher's knowledge regarding Valued Living specific to an FND population, however Wilson et al. (2010) found significant negative correlations between valued living and somatisation.

Acceptance/Experiential Avoidance

Within the context of ACT, acceptance can be defined as: 'the willingness to experience (i.e., not alter the form, frequency, or sensitivity of) unwanted private events, in the pursuit of one's values and goals' (Bond et al., 2011). Acceptance is therefore inextricably linked with valued living. If acceptance is considered to be on one end of a continuum, 'experiential avoidance' is on the other. Experiential avoidance is considered to be when one attempts to avoid these unwanted thoughts, feelings, memories, physical sensations, and other internal experiences. This unwillingness to stay in contact with unwanted internal experiences has been found to actually maintain psychological distress (Hayes et al., 1996). Acceptance and experiential avoidance can be considered inverse constructs.

McCracken and Zhao-O'Brien (2010) found that a measure of acceptance significantly correlated with measures of emotional, physical, and psychosocial functioning in people seeking treatment for chronic pain. Other research indicates that when people lack acceptance (high experiential avoidance) they are more vulnerable to emotional difficulties, such as depression and anxiety (Raes & Hermans, 2008; Feldner et al., 2003). Therapy that promoted both acceptance and valued living resulted in significant reductions in stress as well as

improvements in self-reported well-being for patients with treatment resistant panic disorder (Wersebe et al., 2017).

Psychological Inflexibility

The psychological construct of 'psychological inflexibility' will also be measured in this study. This is the inverse construct of 'psychological flexibility' defined by ACT as: 'contacting the present moment as a conscious human being and based on what that situation affords, acting in accordance with one's chosen values' (Hayes, et al., 2004). The goal of the ACT approach is to cultivate psychological flexibility within the individual. Value-based behaviour and acceptance of experiences are key 'mutually dependent processes' in achieving psychological flexibility (Fledderus et al., 2010). It should, however, be noted that the absence of psychological inflexibility does not necessarily mean the presence of psychological flexibility.

Research shows higher psychological flexibility to be associated with lower probability of having a psychiatric disorder (Donaldson-Feilder & Bond, 2004; Bond & Bunce, 2003) while longitudinal research findings indicate that levels of psychological flexibility impact on subsequent mental health, and not the reverse (Hayes et al., 2006). Psychological flexibility has also been found to have a positive impact on job satisfaction, quality of life and emotional well-being (Bond & Bunce 2003; Butler, & Ciarrochi, 2007).

Psychological inflexibility has been shown to predict poor wellbeing outcomes including psychological ill-health, depression and stress (Bond & Bunce, 2003; Bond & Flaxman, 2006; Donaldson-Fielder & Bond, 2004). Higher levels of psychological inflexibility (as measured by the Acceptance and Action Questionnaire II or AAQ-II) have been associated with higher levels of anxiety, depression and overall psychological distress and, longitudinally, higher

scores of psychological inflexibility on the AAQ-II, have been shown to predict worse self-reported mental health (Bond et al., 2009). As with valued living, there is no research to this current researcher's knowledge regarding psychological flexibility specific to an FND population but within a chronic pain context research by McCracken and Vellerman (2010) indicates that psychological flexibility can reduce the impact of chronic pain.

Intolerance of Uncertainty

The final psychological construct to be measured in this study is **'**intolerance of uncertainty'. It has been defined as: 'A dispositional characteristic that results from a set of negative beliefs about uncertainty and its implications and involves the tendency to react negatively on an emotional, cognitive, and behavioural level to uncertain situations and events' (Buhr & Dugas, 2009). Intolerance of uncertainty has been identified as a discriminating individual difference characteristic involved in state anxiety (Greco & Roger, 2001), excessive worry (Laugesen et al., 2003), and to have strong positive associations with anxiety conditions including generalized anxiety disorder (Dugas et al., 1998), obsessive compulsive disorder (Tolin et al., 2003) and panic disorder (Dugas et al., 2001). Furthermore, Dugas, Freeston & Ladoucer (1997) found that high intolerance of uncertainty may impair problem-solving skills, leading to inaction and avoidance of ambiguous situations. It is therefore likely to be associated with experiential avoidance. Buhr and Dugas (2012) found that experiential avoidance and intolerance of uncertainty both play a significant role (along with fear of anxiety) in the development and perpetuation of Generalised anxiety disorder.

As with the afore mentioned psychological constructs, Intolerance of Uncertainty has also not to the knowledge of this researcher been previously investigated within an FND context, however within a chronic pain context, higher intolerance of uncertainly scores were

associated with higher reported pain (Palma et al. 2018) and even more so when in an unpredictable situation (Bélanger et al. 2017).

Pain

Pain will also be measured in this study. Pain can be defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (International Association for the Study of Pain, 2017). Pain is considered a subjective as well as a multidimensional experience. It can be influenced by a range of factors beyond the sensory input, including cultural beliefs, previous experience and affect, (Katz & Melzack, 1999). As reported earlier in this study there is abundant research evidencing ACT (including acceptance and values based interventions) to be effective in the treatment of pain conditions including chronic pain.

Justification for this Current Research

The purpose of this study is to investigate if the psychological constructs of 'valued living', 'psychological inflexibility' and 'intolerance of uncertainty' as well as reported pain intensity differ between CES MRI+ and CES MRI- patient samples. By gaining a better knowledge and understanding of the psychological profile and pain experience of those with CES MRI- as well as identifying any differences when comparisons are made with those with CES MRI+, the clinical management of this patient population may be better informed through the development of a more standardised, appropriate and effective therapeutic treatment/care-pathway. This would hopefully result in more positive health outcomes whilst also reducing the associated high cost utility. It is also hoped that information gained from this research may be used to increase the awareness, understanding and psychological mindedness of health care professionals with regard to this specific condition.

This current research is also interested in investigating if the pain experienced by those with CES MRI- has an impact on their ability to live valued lives, be psychologically flexible and be tolerant of uncertainty (all constructs associated with psychological wellbeing) and also perhaps even more importantly if these psychological constructs have an impact on the pain they experience. It is hoped this research will help better explain the reasons why patients with CES MRI- are experiencing severe and chronic pain, but without any organic/structural causality for such pain.

Aims of the Current Study

This current research aims to investigate if participants with CES MRI- score lower on the psychological construct of valued living and higher on the psychological constructs psychological inflexibility and intolerance of uncertainty as well as higher for reported pain intensity when compared to the CES MRI+ patient sample. We will also investigate if higher reported pain intensity is associated with lower valued living, higher psychological inflexibility and higher intolerance of uncertainty scores and if these psychological constructs are independently able to predict reported pain for the combined CES (MRI- & MRI+) Samples.

Answers to these questions will allow us to better understand the very little that is known about the psychological profile of the CES MRI- patient population and any relevant associations with reported pain. It is hoped this research will inform treatment approaches and consequently improve health outcomes for this condition.

Primary Research Question

Does the CES MRI- patient sample score significantly higher on measures of psychological inflexibility and intolerance of uncertainty and significantly lower on valued living than the MRI+ patient sample?

Secondary Research Questions

A) Does the CES MRI- patient sample score significantly higher on the measure of reported pain intensity than the MRI+ patient sample?

B) Are lower valued living and higher psychological inflexibility and intolerance of uncertainty scores associated with higher reported pain intensity for the combined CES samples?

C) Do the measures of valued living, psychological inflexibility and intolerance of uncertainty independently predict reported pain intensity for the CES MRI- patient sample

Materials and Methods

Ethical Considerations

Ethical approval for this study was given by South Central-Berkshire Research Ethics Committee (IRAS project ID: 245155) and the NHS Grampian Research and Development Department (Project No 2018PC009). Approval was also obtained from the Caldicott Guardian for the use of patient identifiable data. See Appendices 1 to 3 for copies of all Ethics Approval Letters.

Participants

Participants were a volunteer sample of patients (aged 18 years and above) who had previously been referred to the department of Neurosurgery at Aberdeen Royal Infirmary (NHS Grampian)

with suspected CES and who consequently received a diagnostic MRI. A standard of English language was required for participants to be sufficiently able to understand and complete the consent form and questionnaires.

Exclusion criteria for the study included: intellectual/learning disability or a developmental disorder, current substance misuse (e.g. narcotics, alcohol or medication), a severe brain injury, a severe/advanced neurological condition (e.g. brain tumour, Parkinson's Disease, Motor Neuron Disease, Multiple Sclerosis) and/or having to stay overnight (or longer) in hospital for mental health reasons within the past year. Self-report 'check boxes' were used to determine whether participants met eligibility criteria for participation in the study. See Appendix 7 for a copy of the Inclusion/Exclusion Criteria Questionnaire sent out to all potential participants.

Recruitment

Prospective participants were identified via the NHS Grampian electronic patient database: Picture Archiving and Communication System (PACS). A search was performed of individuals who had received a diagnostic MRI scan at Aberdeen Royal Infirmary (NHS Grampian) for suspected CES between 1st January 2010 and 31st January 2019 along with their consequent MRI diagnosis (CES + or CES-) via use of the scan. Eligible patients' residential postal address details were then accessed via the NHS Grampian electronic database: Trakcare. These patients were posted the participant documentation, which included: study invitation letter, participant information sheet, consent form (including a copy for their own records), inclusion/exclusion criteria questionnaire, and the outcome measures along with a reply paid addressed envelope to return completed documents. See Appendices 4 to 8 for copies of all the participant documentation other than questionnaires. Participant recruitment lasted five months, starting on 1st September 2018 and ending 31st January 2019.

Procedure

Participants completed the participant documentation sent to them and posted them back, whereby completed consent forms and Inclusion/Exclusion Criteria Questionnaires were securely stored and the returned completed 'measure' questionnaires were scored by NKB who was 'blinded' to the MRI + or MRI– status of the respondents.

Measures

Measures of pain, valued living, psychological inflexibility and intolerance of uncertainty were completed by each recruited participant. The following measures were used:

Numeric Pain Rating Scale (NPRS)

The National Institute for Health and Care Excellence considers the NPRS (along with the Visual Analogue Scale for Pain or VAS-Pain to be the main 'Gold Standard' outcome measures for lower back pain, including that caused by Cauda Equina Syndrome (NICE, 2013).

On the NPRS, respondents are asked to report pain intensity 'over the last 24 hours'. The single item test takes one minute to complete and is easy to administer (either verbally or written) and score. It has a high test–retest reliability (Ferraz et al., 1990). For construct validity, the NPRS was shown to be highly correlated with the VAS-Pain in patients with rheumatic and other chronic pain (pain>6 months) conditions (Ferraz et al., 1990).

A criticism of the NPRS is that it evaluates only one component (intensity) of the highly complex and subjective pain experience (Melzack, 1999). Whereas Melzack & Casey (1968) consider pain to be a multidimensional experience incorporating three major components:

'sensory–discriminative', 'motivational–affective' and 'cognitive–evaluative'. These components would not be discriminated between by the NPRS, nor would the measure identify if the nature of the experienced pain was chronic, acute or intermittent.

It was, however, decided that a simple and brief (but less comprehensive) measure of pain would be the most suitable choice for this study, to keep participant demands low.

The Valued Living Questionnaire (VLQ)

Created by Wilson & Groom (2002), the VLQ attempts to measure the extent to which an individual contacts his or her chosen values in everyday life. The VLQ is a well-established and widely used measure. It is an easy to administer and relatively brief instrument that 'taps into' 10 valued domains of living: family, marriage/couples/intimate relations, parenting, friendship, work, education, recreation, spirituality, citizenship, and physical self-care. Respondents are asked to rate the 10 areas of life on a scale of 1–10, indicating firstly the level of importance and then secondly how consistently they have lived in accordance with those values in the past week (Wilson & Murrell, 2004).

There is a revised version (VLQ II; Wilson, 2009) however it has a more intricate/complicated format and takes longer to complete, and so the original version was considered more appropriate for the nature of this research study where the questionnaires would be posted and not administered by the researcher in person. The VLQ has a very good test-retest reliability (Wilson et al., 2010) however not enough robust research has been carried out to date to adequately demonstrate its validity clearly. Further criticisms of the VLQ include that some of the identified value domains may not be considered universal or relevant to some individuals.

A self-report measure of this kind is also susceptible to response (social desirability) bias. There are alternative techniques to score the VLQ, such as the composite scoring method proposed by Smout et al. (2014) which can lead to ambiguity of both interpretation and comparison between studies using the measure. Despite these reported issues, after critical appraisal of alternative 'values' measures the VLQ was still considered to be the best choice and most appropriate for this study.

The Acceptance and Action Questionnaire II (AAQ II)

The AAQ (Hayes et al., 2004) is the most widely used measure of psychological inflexibility and experiential avoidance. The revised version (AAQ II) adapted by Bond et al. (2011) consists of seven questions to be answered on a seven point Likert scale and has been found to measure the same concepts as the AAQ (r = .97) but with better psychometric consistency.

A meta-analysis of the AAQ II of 2,816 participants across six studies indicates the measure to have satisfactory structure, reliability and validity and able to predict a range of outcomes, from mental health to work absence rates, that are consistent with its underlying theory (Bond et al., 2011). Wolgast (2014), however, has questioned the construct validity of the questionnaire, reporting it to be more a measure of psychological distress rather than psychological flexibility and experiential avoidance. However, as with the VLQ, after investigating alternative measures the AAQ II was considered the most suitable measure, with regard to reliability, validity and brevity for use in this study.

The Intolerance of Uncertainty Scale Short Form (IUS-12)

The IUS scale was originally created by Freeston et al. (1994, in French) to gain a better understanding of why people worry. It is considered to be a measure of responses to uncertainty, ambiguous situations and the future.

The short form of the IUS, adapted by Carleton, Norton & Asmundson (2007), was chosen to be used in this study as it is significantly briefer than the original (12 instead of 27 items) while still being comparable to the original 'long form' with regard to reliability and validity (Khawaja & Yu, 2010). This is preferable for this current research so as to keep the completion demands on participants as low as possible.

The 12 items are rated on a 5-point Likert scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). With regard to the psychometric properties of the IUS-12, it has been found to have good convergent and discriminant validity, as well as internal consistency (McEvoy & Mahoney, 2011). No major criticisms could be found regarding this measure.

Power Analyses

Multiple methods were used to provide a comprehensive a priori estimate of the minimum sample size required to achieve sufficient power for this study. A power calculation for analysis by multiple regression (given this aspect of analyses will require the greatest power/number of participants), was calculated using G* Power 3 (Faul et al., 2007) to determine the minimum sample size required to detect a medium effect (0.15), with a power of 0.80 and with a 95% probability. As the regression is a three-predictor model (the predictors being valued living, psychological inflexibility and intolerance of uncertainty scores), a sample size of n=77 was

calculated to be needed to predict perceived pain intensity for the combined CES MRI- and MRI+ sample.

Green's (1991) formula ($N \geq 50 + 8m$) yielded a similar minimum sample size of n=74 (3 IVs) required for a multiple regression analysis. Using these two methods, the minimum sample size required to perform all possible desired statistical analysis is: n=74 to 77.

Design

This study is part retrospective in design as historical patient records from between 1st January 2010 and 31st January 2019 were accessed to recruit participants. All those within the CES MRI+ population sample would have had emergency decompressive surgery (most within 24 hours of their confirmatory MRI diagnosis). Although this surgery is likely to reduce further permanent motor weakness, urological dysfunction, chronic severe pain and sexual dysfunction, the surgery is certainly not likely to alleviate their experienced pain levels to anywhere close to premorbid levels, with multiple studies showing back pain, leg pain, sciatica and disability to be ongoing issues post-surgery for CES patients (Shapiro, 2000; Qureshi & Sell, 2007). Therefore, it is likely that the CES MRI+ sample will still have a comparable pain experience to the CES MRI- sample, with both clinical samples expected to have higher reported pain than a general population (non-clinical) sample. Any potential differences in experienced pain between the two CES populations could have an impact on the psychological constructs measured; valued living, intolerance of uncertainty and psychological flexibility, as well as vice-versa. This will be investigated in this study.

The current study is also interested in whether there is an observable difference in the pain and/or the psychological profile in a patient sample with organic causality of their pain and

symptoms (CES MRI+) when compared to a patient sample where there is no organic causality of their pain and symptoms (MRI CES-). Our findings may be able to help us make better sense of the psychological and pain related reasons for CES MRI-. Reported pain will be controlled for (when required) when comparisons are made between the CES MRI- and MRI+ samples on the psychological constructs.

Statistical Analyses

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp, 2016). The methods employed consisted of quantitative data analysis techniques including Pearson's r correlation matrices to provide an initial overview of the bivariate relationships between all the variables in the study.

Following this, a series of three T-tests were performed to address the primary research question: *Does the CES MRI- patient sample score significantly higher on measures of psychological inflexibility and intolerance of uncertainty and lower on valued living than the MRI+ patient sample?* A T-test was also used to address the first of the secondary research questions: *Does the CES MRI- patient sample score significantly higher on the measure of reported pain intensity than the MRI+ patient sample?*

The Pearson's r correlation matrices were referred to, to address the second of the secondary research questions: *Are lower valued living and higher psychological inflexibility and intolerance of uncertainty scores associated with higher reported pain intensity for the combined CES samples?*

Hierarchical multiple regression (for three predictors) was then computed to address the final

secondary research question: *Do the measures of valued living, psychological inflexibility and intolerance of uncertainty independently predict reported pain intensity for the CES MRI- patient sample?* Regression was used here to test the strength of association and to ascertain whether these specifically identified constructs individually (or when combined) explained variance in reported pain intensity while controlling for other variables.

Results

Of the 433 patients identified as potentially eligible participants and subsequently posted 'participant documentation', 84 returned completed questionnaires (19.4% response rate) during the recruitment period (1st Sep 2018 to 31st Jan 2019) and of those, 75 were recruited. Nine (10.7%) patients who returned completed participation documentation were excluded: three (3.6%) due to not meeting all the requirements of the inclusion/exclusion criteria and six (7.1%) due to incomplete questionnaire data beyond pre-set threshold parameters for analyses (see below for further details). See Figure 1 below for a flowchart of recruitment process and attrition rate.

Table 1 below presents the demographic characteristics of the participants. As expected, the recruited CES MRI- sample was proportionately much greater than the CES MRI+ sample as well as having a significantly higher proportion of female patients, both reflecting the demographics of the clinical population. Interestingly, the MRI+ sample had both slightly higher mean age as well as slightly higher mean Scottish Index of Multiple Deprivation vigintile score (indicating lower deprivation) than that of the recruited MRI- sample.

It appears that most missing data for the Valued Living Questionnaire (VLQ) was not missing at random but due to participants deliberately not answering questions on topics which they did not consider relevant such as 'Spirituality', 'Work' and 'Parenthood'. This was often indicated

Figure 1. Flow chart of participant recruitment process and attrition rate

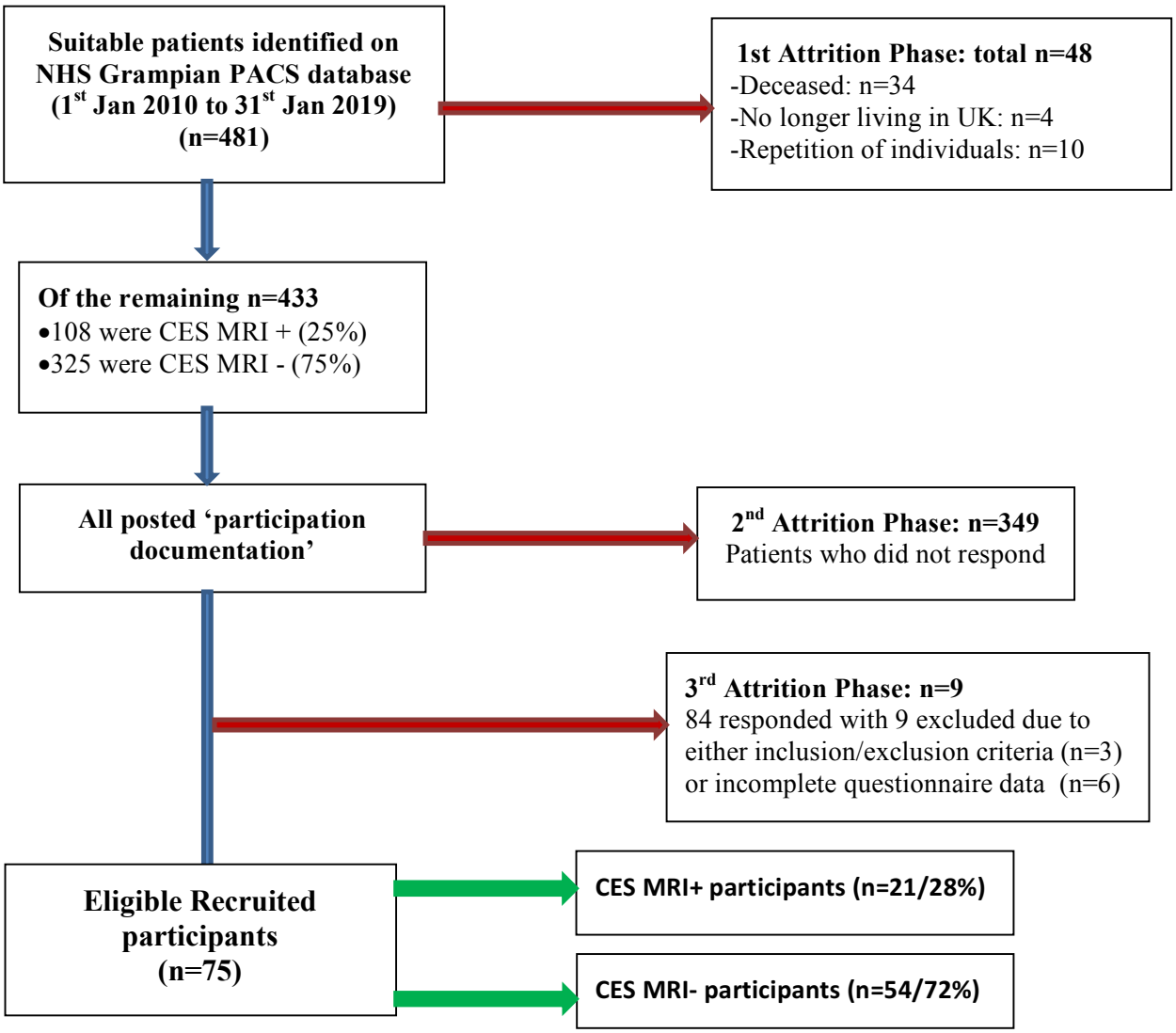

Table 1. Summary demographic characteristics of participants

	CES MRI +		CES MRI -		Overall	
n size	21	28%	54	72%	75	
Female	10	48%	37	69%	47	63%
Mean SIMD*	14.7	5.0 sd	14.1	4.5 sd	14.3	4.6 sd
Age/scan **	52.6	18.3sd	50.8	15.5 sd	51.3	16.2 sd

*Scottish Index of Multiple Deprivation (SIMD) Vigintile (out of 20) score: where 1= most deprived and 20= least deprived
** Mean age at time of MRI scan

by participants with a denotation such as 'N/A' or similar and consistent across both scales of the measure. As recommended by Smout et al. (2014) when calculating the mean VLQ composite scores for the sample, questionnaire packs with any missing data for this measure were excluded from analysis (six respondents). All other (non VLQ) missing questionnaire data were considered to be 'Missing Completely at Random' using Little's MCAR test for these measures.

A participant exclusion threshold for missing data of 10% (or more) was set on all other measures which was not met. Individual mean substitution was incorporated where less than 10% of data for each measure (excluding VLQ) was missing. While internal consistency could possibly be affected by using this method, it does allow for a greater utilisation of the collected data. A total of 12 cases had missing items replaced using individual mean substitution.

Exploratory Data Analyses

Preliminary analyses indicated there were no violations of the assumptions of linearity or homoscedasticity. The values of the residuals were observed to be normally distributed and independent with no significant outliers, no high leverage points and no highly influential cases biasing the model and all variables were normally distributed.

During the exploratory data analysis, the AAQ2 measure was found to have a very strong significant positive correlation with the IUS-12 measure *($r=.835$, $p<.001$).* This may indicate that these measures have a conceptual overlap (psychological inflexibility and intolerance of uncertainty) and/or be identifying the same construct, suggesting a lesser independence of the individual measures leading to a possible issue of multicollinearity (shared variance) which can lead to unreliable and unstable estimates of regression coefficients.

This potential issue was investigated in two steps. Firstly, by looking at the collinearity statistical scores of both 'tolerance' and (its reciprocal) 'variance inflation factor' (VIF). Hair et al. (2010) state that only when the VIF value exceeds 4.0, or when the tolerance score is less than 0.2 that there should be considered an issue with multicollinearity. Neither of these aforementioned thresholds were violated in this study's analysis. Secondly, it was decided to further investigate the possibility of shared variance by running two further regression analyses: the first with the IUS-12 measure removed and the second with the IUS-12 replaced and the AAQ-2 removed**.** No significant changes occurred in either analyses. Consequently, it can therefore be assumed that multicollinearity was not an issue in this case.

A possible confounding variable associated with this study's design was that the recruitment process involved patients whose MRI dates spanned a period of 8 years and 1 month. This 'time since scan' may have had a significant effect on outcome measure scores. It could be hypothesised that participants who completed the questionnaires within weeks or months of their MRI are likely to have more recently experienced the 'crisis point' that led to their MRI referral in the first place and to consequently be experiencing greater pain as well as having had less time to emotionally/psychologically adapt to and accept their condition and its associated issues at the time of questionnaire completion compared to those whose scans were longer (years) ago.

This possible issue was investigated by calculating the elapsed time between MRI and outcome measure completion for all participants and then entering this data into a Pearson's r correlation with the existing outcome measure data. No significant associations related to 'time since scan' were found for either the combined CES samples or the separated MRI- and MRI+ samples individually, indicating 'time since scan' not to be a significant confounding variable.

Inferential Statistical Analysis

To address the primary research question: *Does the CES MRI- patient sample score significantly higher on the measures of psychological inflexibility and intolerance of uncertainty and lower on valued living than the MRI+ patient sample?* and the first of the secondary research questions: *Does the CES MRI- patient sample score significantly higher on the measure of reported pain intensity than the MRI+ patient sample?*, a series of four independent samples t-tests were conducted to compare the CES MRI- with the CES MRI+ patient samples on their mean scores for valued living (VLQ), psychological inflexibility (AAQ2), intolerance of uncertainty (IUS-12) and reported pain intensity (NPRS). Equal variance was assumed for all four independent samples t-tests as Levene's test for equality of variances found there to be no significant variability between the CES MRI- and the CES MRI+ samples for the four measures. See Table 2 below for a summary of findings from the t-tests.

Table 2: T-test summary of findings
(with normative data for general and chronic pain populations)

Measure		**MRI-** (n=54)	**MRI+** (n=21)	***t*-value**	**p**	**Non clinical/ general population**	**Chronic pain population**
Valued Living (VLQ)	M (SD)	50.30 (20.88)	46.84 (18.75)	.660	.511	64.20 (15.41) *1	**Data not available**
Psychological Inflexibility (AAQ2)	M (SD)	19.50 (12.65)	20.19 (12.37)	-.214	.813	18.51 (7.05) *2	22.78 (12.44) *3
Intolerance of Uncertainty (IUS-12)	M (SD)	28.13 (11.49)	29.05 (12.48)	-.303	.763	29.93 (10.96) *4	Data not available
Reported Pain (NPRS)	M (SD)	5.63 (2.88)	3.67 (3.17)	2.58	.012	**Data not available**	6.52 (1.6) *5

*1 Wilson et al. (2010) NB. Sample drawn from USA undergraduate student population
*2 Bond and Hayes, et al. (2011)
*3 Yang et al (2016)
*4 Carleton et al (2012)
*5 Farrar et al. (2001)

There were found to be no significant differences between the CES MRI- and MRI+ patient samples with regard to valued living, psychological inflexibility and intolerance of uncertainty. The CES MRI- patient sample did however, as predicted, report greater pain, scoring significantly higher on the Numeric Pain Rating Scale, compared to the CES MRI+ patient sample: $t(73)=2.58$, $p = .012$.

With regard to comparing the means of the measures for the two current CES samples with those previously established for general population and/or for chronic pain population samples, the following observations were made: For Valued Living (VLQ) the only non-clinical data norms that could be found were for a USA undergraduate student population which as might be expected was significantly higher than the both the current CES populations. For psychological Inflexibility (AAQ2), the chronic pain population scored the highest, followed by the MRI+ sample, closely followed by the MRI- sample and then the general population sample had the lowest score. With regard to Intolerance of uncertainty (IUS-12), no data was available for the chronic pain population, but the highest score, interestingly was for the general population sample closely followed by the MRI+ sample and then the MRI- sample. This was unexpected. Finally, with regard to reported pain (NPRS) where no normative data was available for general population sample, the highest rating score was for the chronic pain sample, followed by the MRI- sample with the MRI+ sample scoring significantly less than both.

Pearson's r correlational analysis was used to address the second of the secondary research questions: *Are lower valued living and higher psychological inflexibility and intolerance of uncertainty scores associated with higher reported pain intensity for the combined CES samples?* See Table 3 below for a summary of findings.

As predicted, higher psychological inflexibility (AAQ2) was significantly associated with higher reported pain intensity (NPRS scores): *r=.260, p=.024*. Also as predicted, but not to a significant level, reported pain was inversely associated with valued living and positively associated with intolerance of uncertainty.

Table 3: Pearson's r correlation matrices summary of findings

	1	2	3	4	5
1. Multiple Deprivation (SIMD vigintile Score)	-------				
2. Reported Pain Intensity (NPRS score)	-.090	-----			
3.Age at Scan (MRI)	.161	-.196	------		
4. Psychological Inflexibility (AAQ2 sum score)	-.320**	.260*	-.055	------	
5. Intolerance of Uncertainty (IUS-12 sum score)	-.260*	.220	-.064	.835**	-------
6. Valued Living (VLQ composite score)	.128	-.176	.330**	-.428**	-.377**

*Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

Regression Analyses

Multiple regression analyses were conducted to address the final secondary research question: *Do the measures of valued living, psychological inflexibility and intolerance of uncertainty independently predict perceived pain intensity for the CES MRI- patient sample.* See Table 4 below for the model of the multiple regression.

Table 4. Multiple regression model (for the CES MRI- sample)

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	3.257	1.724		1.889	.065	-.206	6.721
	VLQ	.008	.021	.060	.399	.692	-.033	.050
	IUS-12	.060	.064	.241	.947	.348	-.068	.189
	AAQ2	-.013	.060	.058	.219	.827	-.107	.133

a. Dependent Variable: Numeric pain rating scale

Valued living, psychological inflexibility and intolerance of uncertainty were entered as predictor variables in a model with reported pain intensity as the criterion variable. The multiple regression model with all three predictors was found not to statistically significantly predict reported pain intensity either collectively or individually. F (3, 50) =1.352, p.268, R2=.075. The adjusted R2 was .020.

It was possibly expected for psychological inflexibility (AAQ-2) to have been significantly predictive of pain (NPRS) after the two measures were found to have a significant positive association in the earlier Pearson's r correlation matrices for the combined CES sample. To further investigate this a Pearson's r correlation analysis was also re-run for both separate MRI- and MRI+ participant samples. When this was done there were no significant correlations for the MRI- participant sample between reported pain and valued living, psychological inflexibility or intolerance of uncertainty. However, the MRI+ participant sample's reported pain was found to be highly significantly negatively correlated with valued living (r=-.631, p.002).

This finding indicates that some effect is masked by combining the CES MRI- and MRI+ participant samples for analyses. It is also important to note that it is likely that when splitting the participant samples in this way, the CES MRI+ group would be too small (n=21) in this study and thus underpowered to allow definitive conclusions to be drawn from the correlation analysis. Bujang and Baharum (2016) propose a minimum sample size of 29 to determine a reasonably high correlation between two variables.

Discussion

The results of this study do not support the primary research question: no significant difference was found between the CES MRI- and MRI+ samples on their scores for the measures of the psychological constructs of valued living, psychological inflexibility or intolerance of uncertainty. These findings are at odds with the expectations of this research, however, as an exploratory pilot study, there was no previous research to either attempt to replicate or on which to inform the predictions of this study.

The first of this study's secondary research questions was supported: the CES MRI- sample reported significantly higher pain intensity than the CES MRI+ sample. This was as expected, based on research indicating that functional neurological disorders are commonly triggered by pain (Stone et al., 2009; Pareés et al., 2014) and CES MRI- is considered likely to be a functional condition. More specifically, Hoeritzauer et al. (2018) found CES MRI- patients to be more likely to have chronic pain recorded in their electronic patient records when 'followed up' a year later compared to CES MRI+ patients (58.5% vs 26%).

The second of this study's secondary research questions was partially supported: higher psychological inflexibility was significantly associated with higher reported pain intensity for the combined CES samples. This was expected as previous research has found psychological flexibility to be a key component in patients' ability to cope with (Vowles et al., 2014) and function with (McCracken & Vowles, 2007) chronic pain**.** Furthermore, McCracken and Velleman (2009) consider enhanced psychological flexibility to reduce the impact of chronic pain and Lin et al. (2018) found increased psychological flexibility to optimise the treatment effects of online ACT for a chronic pain population.

This study found non-significant associations between lower valued living and higher reported pain intensity and also between higher intolerance of uncertainty and higher reported pain intensity in the directions anticipated by the second of this study's secondary research questions. Future replicating research (perhaps with larger sample sizes) would be advised to further clarify these associations. These associations were anticipated to be significant due to the findings of previous research: McCracken & Yang (2006) found that chronic pain patients that were more engaged with valued living experienced better physical functioning and emotional well-being, while research that incorporated values into an ACT based acceptance intervention led to significantly greater pain tolerance than acceptance alone (Branstetter-Rost et al., 2009). Previous research also indicates that intolerance of uncertainty plays a crucial role in the relationship between pain, pain anxiety, and physical functioning (Fischerauer et al., 2018). Naylor et al. (2017) found that patients who experience higher harm avoidance and lower self-directedness are more likely to experience chronic pain.

The final of the secondary research questions was not supported by the use of multiple regression analysis and neither valued living, psychological inflexibility, or intolerance of uncertainty were found to independently predict perceived pain intensity for the CES MRI- sample.

Methodological Strengths

As all participants were identified and recruited from an NHS patient (PACS) database, confidence can be taken that they are likely to be clinically representative samples of both the CES MRI- and CES MRI+ patient populations, at least within the NHS Grampian health board's geographic region. A rigorous inclusion/exclusion criteria was incorporated to aid both

the reliability and the external validity (Patino & Ferreira, 2018) of this current study's results. A counterargument to having such criteria is the possible 'selection bias' associated with excluding certain demographics of the clinical population. This may make for an unrepresentatively homogenised participant sample. This study considers the methodological strengths associated with incorporating rigorous inclusion/exclusion criteria to sufficiently outweigh the possible associated weaknesses.

Methodological limitations

This study and its findings should be viewed within the context of several limitations. Firstly, the cross-sectional design of this research does not allow for causal inferences to be ascertained, making it impossible determine the precise direction of associations between variables. Causality could be investigated in future research with longitudinal or experimental designs.

A binary approach to identify between CES MRI- and CES MRI+ patients was used in this current study, whereas recent research by Hoeritzauer et al. (2018) published after the implementation of this current study, found clinical benefit in further distinguishing between CES MRI- patients with nerve compromise or 'impending CES' and those CES MRI- patients without any nerve compromise at all. This further categorisation is likely to allow for better clinical differentiation and management of this MRI- population, particularly with regard to 'functional' or 'organic' causality. Considerations to further categorise this current research's participant sample in a similar fashion were considered to be beyond the scope of this study due to time restrictions associated with necessary amendments to ethical approval, combined with the intensiveness of the further re-categorisation process.

This current study's design also did not account for the possibility of a CES case to have a non-structural cause such as vasculitis, lymphoma, epidural abscess or meningeal malignancy (Rooney et al., 2009). A non-structural cause would not necessarily appear on imaging and would therefore give a false MRI- diagnosis. The occurrence rate of these specific conditions is considered rare enough to be highly unlikely to have a significant impact upon the findings of this study. Hoeritzauer et al. (2018) found that of 276 CES patients, only 3% had an alternative organic cause mimicking or causing nerve dysfunction unrelated to compression of the Cauda Equina nerves.

The issues of potential response bias should also be considered. Due to the volunteer sampling method used, those who took part may be have been more available, able and willing (volunteer bias) than the clinical population as a whole, that they are drawn from (Dollinger & Leong, 1993). Also, the use of self-report measures may have introduced an element of subjective bias to study findings, particularly when examining pain which is considered a highly subjective concept based on individual perspective (Katz & Melzack, 1999). Individuals who complete questionnaires about themselves may also be inclined to represent themselves in a disproportionately positive way, leading to social desirability bias (Fisher, 1993).

An interesting observation possibly related to sampling bias towards less deprived participants, is that compared to most chronic illness populations, this current CES patient sample appears to be from disproportionately affluent areas, scoring 14.3 out of a maximum of 20 for affluence on the Scottish Index of Multiple Deprivation/SIMD (SD: 4.63). This is at odds with previously observed trends which show that for all age categories in Scotland, people who live in deprived circumstances have higher rates of chronic disease (Kendrick 2004). This also indicates that patients from more deprived areas in NHS Grampian are underrepresented in this current

research. This may be for a number of reasons: more deprived people may be less likely to volunteer to participate in research, less likely to present to their GP with their symptoms or possibly less likely to be referred for either a diagnostic MRI or to clinical specialist services.

This observation regarding possible 'deprivation bias' is further supported when comparisons were made with this current author's earlier audit (Keith-Barnett, 2018), which identified 383 CES (MRI-/+) patients from NHS Grampian who had a lower mean SIMD vigintile score (12.8) compared to this study's sample (14.3). There were no major comparable differences between the MRI- and the MRI+ samples for SIMD for either the audit sample (12.9 vs 12.6) or this study's participant sample (14.1 vs 14.7) indicating that deprivation isn't a differentiating factor between CES MRI- and CES MRI+ status.

Implications for Clinical Practice

When considerations are being made for the design and implementation of a care pathway for CES MRI- patients, the observation that their experiential pain is significantly greater than CES MRI+ patients indicate more of a focus on pain management could be made for this population. Regarding this association, Hoeritzauer et al. (2018) concluded that 'scan-negative cauda equina arises as an end pathway of acute pain….'. If this is the case, earlier pain management interventions could perhaps prevent the consequent development of this debilitating condition in vulnerable clinical populations.

At a service level, it may also be useful to raise clinicians' awareness of this relationship between pain and the development of CES MRI-. Care pathways would also likely benefit from the inclusion of interventions with a greater focus on the functional/psychological aspects associated with this condition.

Implications for Future Research

This study is novel in its attempt to differentiate between MRI+ and MRI- Cauda Equina Syndrome patient samples on the grounds of valued living, psychological inflexibility, intolerance of uncertainty and reported pain intensity. It would be considered worthwhile for future research to replicate this study. Future research is also likely to benefit from a greater MRI+ sample size (possibly adding to this existing study sample) to allow more appropriately powered analysis to be possible for comparing the MRI+ and MRI- patient samples.

The significant incidental findings from the correlational analysis could be further investigated, including the findings that older CES (combined samples) patients seemed to live a more valued existence and more affluent CES (combined samples) patients had lower psychological inflexibility and lower intolerance of uncertainty than more deprived patients.

Future research could also investigate in greater depth which aspects in particular of experienced pain (such as sensory or affective) are more pertinent in differentiating between the CES MRI- and CES MRI+ patients. More comprehensive pain measures such as the McGill Pain Questionnaire or the West Haven-Yale Multidimensional Pain Inventory could be used.

Another consideration for future research could be to further develop this current study by further categorising the MRI- patients into the more clinically distinct groups of: 'some nerve compromise/impending CES' and 'no nerve compromise at all', thus allowing for more precise clinical differentiation and analysis particularly with regard to 'functional' or 'organic' causality.

Now that a large CES (MRI+/-) patient database has been identified (n=481) by this current researcher, fruitful follow-up longitudinal research could be performed using this resource. This could include comparing the MRI- and the MRI+ patient samples on post-diagnosis NHS service engagement (how often? which services?) as well as investigating health service cost utility. This could further inform the clinical pathway and model for the Cauda Equina Syndrome MRI- population, including as its long-term financial and resource impact.

Conclusions

This pilot study set out to investigate if the psychological constructs of valued living, psychological inflexibility, intolerance of uncertainty and reported pain intensity can differentiate between MRI+ and MRI- Cauda Equina Syndrome patient samples. To the best of our knowledge, this study is the first empirical investigation to examine this. Findings indicate that there are no distinguishable differences between the two CES MRI samples with regard to these psychological constructs. The CES MRI- patient sample did however report significantly higher pain intensity than the CES MRI+ patient sample.

Disclosure of interest:
No potential conflict of interest was reported by the authors

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APPENDICES INDEX

Appendix 1: Ethics approval Letter: South Central - Berkshire Research Ethics Committee

NHS
Health Research Authority

South Central - Berkshire Research Ethics Committee
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: (020) 71048043

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

21 August 2018

Dr Paul Graham Morris
Clinical Psychology Dept
School of Health in Social Science
Medical Quad, Teviot Place
Edinburgh EH8 9AG

Dear Dr Morris

Study title:	**A pilot study to investigate if the psychological constructs of 'Valued Living', 'Acceptance', 'Intolerance of Uncertainty' as well as pain intensity can differentiate between patients who through Magnetic Resonance Imaging (MRI) are found to either have Cauda Equina Syndrome (CES MRI+) or not (CES MRI-) as the cause of a common physiological symptomatology**
REC reference:	**18/SC/0468**
Protocol number:	**CAHSS1806/01**
IRAS project ID:	**245155**

The Proportionate Review Sub-committee of the South Central - Berkshire Research Ethics Committee reviewed the above application in correspondence.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

A Research Ethics Committee established by the Health Research Authority

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Insert the correct REC name to the PIS.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Confirmation of any other Regulatory Approvals (e.g. CAG) and all correspondence [Caldicott approval for use of patient identifiable data]		19 April 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [4 x insurance documents]		
IRAS Application Form [IRAS_Form_02082018]		02 August 2018
IRAS Checklist XML [Checklist_07082018]		07 August 2018
Letters of invitation to participant [Cover Letter to participants]	1.0	26 July 2018
Participant consent form [Consent Form]	1.0	26 July 2018
Participant information sheet (PIS) [Participant Information Sheet]	1.0	26 July 2018
Research protocol or project proposal [Cauda Equina Syndrome: MRI – and MRI + population differences on psychological constructs]	1.0	26 July 2018
Summary CV for Chief Investigator (CI) [Paul Graham Morris Summary CV]	1.0	26 July 2018
Summary CV for student [Nicholas Keith-Barnett Summary CV]	1.0	26 July 2018
Summary CV for supervisor (student research) [Paul Graham Morris Summary CV]	1.0	26 July 2018
Validated questionnaire [Validated Questionaires]	1.0	26 July 2018

Membership of the Proportionate Review Sub-Committee

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

There were no declarations of interest

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.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

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 use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

With the Committee's best wishes for the success of this project.

18/SC/0468	**Please quote this number on all correspondence**

Yours sincerely

PP - Mr David Carpenter
Chair

Email: nrescommittee.southcentral-berkshire@nhs.net

A Research Ethics Committee established by the Health Research Authority

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

Copy to: *Dr Charlotte Smith*
Dr Susan Ridge, NHS Grampian R&D Permissions - Non Commercial Team

South Central - Berkshire Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting in correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr David Carpenter	Social Scientist	Yes	
Mr Richard Merewood	Director	Yes	
Ms Susan Tonks	Senior Research Support Associate	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Charlotte Ferris	REC Manager

Appendix 2: Ethics approval Letter: NHS Grampian Research and Development Department

Research and Development
Foresterhill House Annexe
Foresterhill
ABERDEEN
AB25 2ZB

NHS Grampian

Mr Nicholas Keith-Barnett
NHS Grampian
Department of Neuropsychology
Ashgrove House
Foresterhill
AB25 2ZN

Date 24/08/2018
Project No 2018PC009

Enquiries to Louise
Extension 53846
Direct Line 01224 553846
Email grampian.randdpermissions@nhs.net

Dear Mr Keith-Barnett

Management Permission for Non-Commercial Research

STUDY TITLE: A pilot study to investigate if the psychological constructs of 'Valued Living', 'Acceptance', 'Intolerance of Uncertainty' as well as pain intensity can differentiate between patients who through Magnetic Resonance Imaging (MRI) are found to either have Cauda Equina Syndrome (CES MRI+) or not (CES MRI-) as the cause of a common physiological symptomatology

PROTOCOL NO: v1, 26/07/18
REC REF: 18/SC/0468
NRS REF: n/a

Thank you very much for sending all relevant documentation. I am pleased to confirm that the project is now registered with the NHS Grampian Research & Development Office. The project now has R & D Management Permission to proceed locally. This is based on the documents received from yourself and the relevant Approvals being in place.

All research with an NHS element is subject to the Research Governance Framework for Health and Community Care (2006, 2nd edition), and as Chief or Principal Investigator you should be fully committed to your responsibilities associated with this.

R&D Permission is granted on condition that:

1) **The R&D Office will be notified and any relevant documents forwarded to us if any of the following occur:**
   - **Any Serious Breaches in Grampian (Please forward to pharmaco@abdn.ac.uk).**
   - **A change of Principal Investigator in Grampian or Chief Investigator.**
   - **Any change to funding or any additional funding**

2) **The R&D Office will be notified when the study ends.**

3) **The Sponsor will notify all amendments to the relevant National Co-ordinating centre. For single centre studies, amendments should be notified to the R&D office directly.**

We hope the project goes well, and if you need any help or advice relating to your R&D Management Permission, please do not hesitate to contact the office.

Yours sincerely

Susan Ridge
Non-Commercial Manager

cc: CI/Sponsor
Research Monitor

Sponsor: University of Edinburgh

Appendix 3: Ethics approval letter: Caldicott Guardian for the use of patient identifiable data

CG/2018/24

NHS Grampian

APPLICATION FORM FOR CALDICOTT APPROVAL FOR USE OF PATIENT IDENTIFIABLE DATA

After completion please return this form to

Caldicott, Information Governance, NHS Grampian, Rosehill House, Foresterhill Site, Cornhill Road, Aberdeen AB25 2ZG

Email: nhsg.caldicott@nhs.net

Project Title: A pilot study to investigate if the psychological constructs of 'Valued Living', 'Acceptance' and 'Intolerance of Uncertainty' can differentiate between MRI+ and MRI- Cauda Equina Syndrome populations

Description: This current research aims to further investigate the differing psychological profiles of CES MRI+ and MRI-populations. It will specifically look at psychological constructs taken from Acceptance and Commitment Therapy (ACT). These will include 'Valued Living', 'Acceptance' and 'Intolerance of Uncertainty' as well as reported pain intensity. Findings will hope to better inform care pathways, service development and treatment for the CES MRI- population, which currently has both a high cost utility and poor health outcomes.

Participant Population

Patients who were referred to The department of Neurosurgery at Aberdeen Royal Infirmary (NHS Grampian) between 2010 and August 2018 with suspected CES and who received a diagnostic MRI scan.

Methodology

-Individuals who have received a diagnostic MRI scan at Aberdeen Royal Infirmary (NHS Grampian) for suspected CES between 2010 & August 2018 will be identified by the researcher from an electronic patient database (PACS) along with their MRI diagnosis (CES+ or CES-). The patients' names and residential postal address details will also be accessed and used.

-These individuals will be posted a cover letter/participant information sheet, an inclusion/exclusion criteria questionnaire, and the outcome measures (Valued Living Questionnaire, The Acceptance and Action II Questionnaire, Intolerance of Uncertainty Scale (short form) & Numeric Pain Rating Scale along with a reply paid envelope to return completed documents.

-Returned questionnaires will be scored by an honorary assistant psychologist 'blinded to the MRI + or MRI– status of the respondents. Statistical analysis will be administered to answer the proposed research questions.

After the study is completed, participants will be able to access a web-link/wiki

Application Number .....(for office use only) 1

NHS Grampian

page (the details of which will have been previously provided in the Participant Information Sheet) with a research finding summary sheet presented on it and a contact email if they have any questions regarding the findings and research implications.

Name of Applicant: Nicholas Keith-Barnett

Address: NHS Grampian Department of Neuropsychology,

Ashgrove House, Foresterhill, Aberdeen, AB25 2ZN

Tel No 01224 554350 (sec)

Email address:

Name of organisation receiving data: NHS Grampian

and their Data Protection Registration Number:

What patient identifiable information are you looking to use?

CHI Number	**n/a**
Forename	**yes**
Surname	**Yes**
Initials	**n/a**
Date of Birth	**n/a**
Address	**yes**
Postcode	**yes**
Other, please specify: Date of and diagnosis from MRI scan for suspected CES (taken from PACS electronic database)	**yes**
Age	n/a
Gender	**n/a**

NHS Grampian

How will the data be transferred?
Paper records □**No**
Computer records □**Yes**

(Note – patient/user identifiable data must not be transferred via e-mail unless anonymised, encrypted or using secure NHS network i.e. nhs.net)

Who else will have access to the data?
(If data recipients are not employed by the NHS please state whether NHS honorary contracts are in place. If not – detail confidentiality agreements)

The applicant's clinical thesis project supervisor (Dr Fiona Summers) and research advisor (Dr James Anderson), both employed by the NHS and working in NHS Grampian department of Neuropsychology

How will the service users be contacted?
Potential participants will be posted a cover letter/participant information sheet, an inclusion/exclusion criteria questionnaire, and the outcome measures (Valued Living Questionnaire, The Acceptance and Action II Questionnaire, Intolerance of Uncertainty Scale (short form) & Numeric Pain Rating Scale along with a reply paid envelope to return completed documents.

How will service users consent be obtained?
Written consent will be returned to the lead researcher by post. This includes consent to:

- Participate in the named study voluntarily
- Access to medical notes regarding details of diagnostic MRI scan for suspected CES (via the PACS electronic database)
- Publish or present the unidentifiable results
- Use unidentifiable data in future ethically approved studies
- Store/archive unidentifiable data with the University of Edinburgh for Research Governance purposes.

If no consent being obtained, please detail the reason why not?
n/a

Where will the data be stored?
An unidentifiable electronic database will be stored on the applicant's NHS secure network drive, which will also be password protected. Password protection limits access control (to those mentioned in the in the current application). Unidentifiable research data will be securely stored on servers within the University of Edinburgh and will accessible to members of the research team (i.e. lead researcher, supervisors and research collaborator) and potentially by thesis examiners.

NHS
Grampian

How will the data be protected? (Please detail security measures to be taken)
All electronic data will be unidentifiable and saved on the applicants NHS secure network drive and will password protected. Unidentifiable research data will also be securely stored on servers within the University of Edinburgh and will only be accessible to members of the research team (i.e. lead researcher, supervisors and research collaborator) and potentially by thesis examiners. Only unidentifiable data may be electronically shared between the applicant and the project team using NHS and University of Edinburgh secure email server.

All data will be treated on a confidential and need-to-know basis for the duration of the project (including access to passwords for electronically shared unidentifiable data).

Identifiable Data will be kept for the limited length of time needed for the project (estimated September 2019) and will undergo appropriate disposal and deletion upon completion, as dictated by local policy and national guidelines.

Unidentifiable research data will be archived within the University of Edinburgh for 10 years upon completion of the project, with a review to occur then and every subsequent 5 years to determine whether data should continue to be retained or if it should be securely deleted. This is required for research governance purposes (e.g. for checks or clarifications by government or other appropriate organisations) and the consent form specifically requests consent to store this unidentifiable data for these purposes.

If the data is on a computer is there access via a network?
The unidentifiable database will be stored securely on the applicant's individual NHS secure network drive (password protected) and securely stored on servers within the University of Edinburgh for the duration of the project. Access to the individual NHS secure network drive is limited to the applicant's user login-in and password. Access to University of Edinburgh secure server will be limited to the project team (i.e. Lead investigator and supervisors) and potentially by thesis examiners and will require a unique password to gain access.

How long will the data be stored?
Unidentifiable research data will be archived within the University of Edinburgh for 10 years upon completion of the project, with a review to occur then and every subsequent 5 years to determine whether data should continue to be retained or if it should be securely deleted. This is required for research governance purposes (e.g. for checks or clarifications by government or other appropriate organisations) Specific informed consent forms will be collected for this purpose.

At the end of this period, how will the data be disposed of?
All data will be disposed of in line with local policy and national guidelines. Paper recorded data will be treated as confidential waste and destroyed in line with trust policy and procedures. Unidentifiable electronic data stored on the applicant's individual NHS secure network drive will be permanently deleted from the applicant's NHS account using the appropriate software (assisted by the department of eHealth support team-extension 54444) upon completion of the project.

NHS Grampian

Who will be responsible for ensuring that the data is disposed of in a confidential manner?
Applicant: Nicholas Keith-Barnett, Trainee Clinical Psychologist
Supervisor: Dr Fiona Summers, Clinical Psychologist

Please refer to the last page for the six Caldicott Principles before answering the questions below.

Q.1 What is the purpose for which data are to be used? (Principle 1)

Currently care pathways within the Scottish NHS are considered both limited and poor for Cauda Equina Syndrome patients who are found to be MRI negative (likely to Functional Neurological Disorder). After a diagnostic MRI scan, this patient population is normally discharged from Neurosurgery with a pain medication prescription and perhaps with a physiotherapy referral, while ignoring any psychological aspects of their condition. This condition could be better addressed by incorporating a referral to psychological therapies which may improve overall health outcomes. The current prognosis for this population upon discharge is also poor.

This current research aims to investigate if participants with CES- score lower on the psychological constructs of valued living, 'acceptance' and higher on 'Intolerance of Uncertainty' and 'pain intensity' compared to CES+ participants and if Valued Living scores are associated with pain intensity scores for the MRI- population. We will also investigate what impact multiple deprivation plays with regard to these relationships/dynamics. Answers to these questions will allow us to better understand the very little that is known about the CES population profile and the differences between MRI- and MRI+ within it. This increased knowledge could help to better inform future adaptations and improvements to the clinical management (and thus the care pathway) so as to better serve these patients more efficiently within NHS Grampian and within the NHS as a whole, hopefully resulting in more positive health outcomes. This could include increasing the awareness, understanding and psychological mindedness of health care professionals about this condition who come into contact with this patient population as well as possible improvements to the referral process (care pathway) to psychological therapeutic services with an evidence base for the successful treatment of similar conditions (functional neurological disorders) such as CBT (Kroenke et al, 2000) or ACT therapy (McCraken et al 2005) as well as increasing the awareness, understanding and psychological mindedness of health care professionals about this condition who come into contact with this patient population.

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Q.2 Why is it necessary to use identifiable data? (Principle 2)

It is necessary for the lead investigator (the applicant) to access identifiable patient data from the PACS electronic database to first screen for suitable participants (those who have received a diagnostic MRI scan for suspected CES and the consequent diagnosis for the time period of between 2010-2018) and then to post out the participation documentation to the patients' full name and home address for them to then choose whether to participate or not.

Q.3 Justify the use of each patient-identifiable data field (Principle 3)

See above answer to question 2

Q.4 Who will have access to patient-identifiable information and what control will there be? (Principle 4)

All data will be treated as confidential and on a need-to-know basis with limited access controls in place. Access to person identifiable information will be limited to the applicant (Nicholas Keith-Barnett) and clinical supervisor (Dr Fiona Summers), which will be locked away and stored securely and separately from the unidentifiable data within the secure premises of NHS Grampian Department of Neuropsychology, Ashgrove House, Foresterhill, Aberdeen, Ab25 2ZN. All other parties mentioned in this application will only have access to unidentifiable data. The unidentifiable electronic database will be stored securely on the applicant's individual NHS and University of Edinburgh secure network drive for the duration of the project.

All protocols associated with the principles of 'Good Clinical Practice' and 'NHS Information Governance' (for which the applicant has done the relevant e-training modules) will be adhered to with regard to the storage and access procedure of the data.

Q.5 Outline actions taken to ensure individuals with access to patient-identifiable information are aware of their responsibilities and obligations to respect patient confidentiality (Principle 5)

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The applicant and lead researcher (Nicholas Keith-Barnett) and his Clinical Supervisor (Dr Fiona Summers) have read the NHS Grampian policy on data protection and confidentiality and have completed all relevant 'Good Clinical Practice' and 'NHS Information Governance' training and both have a high awareness and vigilance with regard to their responsibilities and obligations to respect patient confidentiality.

As lead researcher I (Nicholas Keith-Barnett) will also be accountable to both my academic supervisor (Dr Paul Morris) and my Clinical research supervisor (Dr Fiona Summers) who will also ensure the maintenance of high standards of patient confidentiality.

Q.6 Outline the organisational arrangements for complying with legal requirements (Principle 6)

All aspects of data handling, storage and deletion will stringently follow legal requirements and the requirements of NHS Grampian and will be informed by the principles of 'Good Clinical Practice' and 'NHS Information Governance' protocols. If legal advice is needed it will be sought from the NHS legal department.

I confirm that the data will be held and used according to the condition and information given as described with this approval form.

Applicant: Nicholas Keith-Barnett

Job Title: Trainee Clinical Psychologist

Signature: Nicholas Keith-Barnett **Date: 05-April-2016**

NHS Grampian

FOR OFFICE USE ONLY

Data Protection Act compliant **Yes** ☐ **No** ☐

Comments:

Information Governance Manager: Mr Chris Morrice

Signature ..... Date .....

Authorisation Granted **Yes** ☑ **No** ☐

Comments:

Caldicott Guardian (NHS Grampian): Dr Nick Fluck, Medical Director, NHS Grampian

Signature ..... Date 19/4/18

Applicant Notified YES ☑ NO ☐ DATE 19/04/18

Application Number .....(for office use only) 8

NHS
Grampian

1. The data received from NHS Grampian will be treated as confidential
2. The data received from NHS Grampian will be used only for the purpose(s) described
3. In the case of anonymised or confidential aggregated data, no attempt will be made to identify or contact individuals or organisations identified through this data.
4. The data received from NHS Grampian may be disclosed to staff of the above organisation but only for the described purpose(s)
5. The data received from NHS Grampian may not be disclosed to any third party
6. The data received from NHS Grampian will be stored in secure conditions at all times whether held in electronic medium or as printed hard copies
7. The organisation to which the data is released will maintain and comply with a Data Protection Registration which encompasses the data an data storage usage
8. The data will be destroyed when the work is completed: any printed copies will be destroyed, and files deleted from computer systems (including any copies held on backup or archive media)

All staff given access to data will be made aware of these conditions (Principle 5).

Caldicott Guardian Principles

1. **Justify the purpose(s)**

   Every proposed use or transfer of patient-identifiable information within or from an organisation should be clearly defined and scrutinised, with continuing uses regularly reviewed by an appropriate guardian.

2. **Don't use patient-identifiable information unless it is absolutely necessary.**

   Patient-identifiable information items should not be used unless there is no alternative.

3. **Use the minimum necessary patient-identifiable information.**

   Where use of patient-identifiable information is considered to be essential, each individual item of information should be justified with the aim of reducing identifiability.

4. **Access to patient-identifiable information should be on a strict need to know basis.**

   Only those individuals who need access to patient-identifiable information should have access to it, and they should only have access to the information items that they need to see.

5. **Everyone should be aware of their responsibilities.**

   Action should be taken to ensure that those handling patient-identifiable information – both clinical and non-clinical staff – are aware of their responsibilities and obligations to respect patient confidentiality.

6. **Understand and comply with the law**

   Every use of patient-identifiable information must be lawful. Someone in each Organisation should be responsible for ensuring that the organisation complies with legal requirements.

Appendix 4: study invitation letter

THE UNIVERSITY of EDINBURGH

NHS Grampian

Dear Madam/Sir

Please find enclosed information about an ongoing research project, which we hope you will be interested to participate in. You are being invited to participate as our records show that you have received an MRI scan within the last 8 years to investigate the cause of your back pain and/or other physical symptoms. If you would like to take part please read and complete the enclosed documents and return them using the stamped addressed envelope provided.

If you have any questions, please contact me using any of my contact details provided below.

Thank you for your time

Kind Regards

Nicholas Keith-Barnett
Lead Researcher
NHS Grampian Department of Neuropsychology
2nd Floor
Room 2.19
Ashgrove House
Foresterhill
Aberdeen
Telephone 01224 559352 Fax 01224 661570
Email

Appendix 5: Participant Information Sheet

NHS Grampian

THE UNIVERSITY of EDINBURGH

PARTICIPANT INFORMATION SHEET

A pilot study to investigate if psychological factors and reported pain intensity can differentiate between patients who through an MRI scan are found to either have Cauda Equina Syndrome or not as the primary cause of their common physical symptoms.

Chief Investigator: Nicholas Keith-Barnett

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, such as your GP and relatives, if you wish. Ask us if there is anything that is not clear of if you would like more information. Take time to decide whether you wish to take part. Thank you for reading this.

1. What is the purpose of the study?

This research study has been designed to explore the possible association between psychological factors and pain in the diagnosis, or not, of a specific back pain called Cauda Equina Syndrome (CES). CES can be identified by an MRI scan.

2. Why have I been invited?

You have been approached because you have received an MRI scan within the last 8 years performed by the neurology department at NHS Grampian to investigate if the cause of your back pain and/or physical symptoms was due to Cauda Equina Syndrome.

3. Do I have to take part?

No. It is up to you to decide whether to take part. If you do decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

4. What will happen to me if I take part?

If you decide to participate in the study, we ask you to please complete fully the enclosed participant documentation containing a consent form, inclusion and exclusion form and questionnaires and return them in the prepaid addressed envelope provided. Consent is considered given when you initial each separate consent point (indicating your acceptance or agreement) and then sign the bottom of the form. A second blank copy of the consent form will also be enclosed for you to keep for your own records. Completion of the questionnaires will take about 30 minutes and will involve circling answers to questions that best represent your situation or opinion on a range of topics including pain, values, acceptance and uncertainty. It is your choice when to complete and to return the participant documentation. After this there will be no further involvement required of you and no further contact will be made by the chief investigator or the research team.

5. What are the possible disadvantages of taking part?

We are not aware of any significant disadvantages or risks of taking part. However, some people may find completing multiple questionnaires time-consuming or tedious. Completion of all the forms and questionnaires is likely to take about 30 minutes and can be completed over several occasions if preferred.

6. What are the possible benefits of taking part?

There is no direct benefit to be gained from taking part in this research. In the longer term, the information gained from this research project may be used to better understand the psychological effects of back pain and help us develop better services and treatments for patients.

7. Will my taking part in this study be kept confidential?

All identifiable information which is collected about you during the course of the research will be kept strictly confidential. Your personal details and completed consent form will be kept in a locked filing cabinet in the NHS Grampian Department of Neuropsychology. All the documentation you complete and return back to us is made anonymous by the use of an allocated participant identification number in the place of your name. So you will not be identifiable from any of this documentation that you post back. Your identifiable data will only be viewed by the Chief Investigator and research team.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

8. What will happen to the results of this research study?

The findings will be written up by the Lead Researcher, Nicholas Keith-Barnett, as a thesis submitted as part of the Doctorate of Clinical Psychology at the University of Edinburgh. The findings may also be presented at a professional conference or submitted for publication in a scientific journal. Unidentifiable research data from the project will be archived at the University of Edinburgh and may be used to support future projects that are clearly in the public benefit.

Following the completion of the research project, participants will be able to access a summary of the research findings and implications on the following University of Edinburgh Wiki page link www.wiki.ed.ac.uk/x/6a6sFQ. It is estimated that the research finding and implications will be made available on the 30th of August 2019.

9. Who is organising the research?

The study is being organised by Nicholas Keith-Barnett, Trainee Clinical Psychologist, working in conjunction with the University of Edinburgh and NHS Grampian's Department of Neuropsychology. This study is being undertaken as part of an educational qualification.

10. Who has reviewed the study?

All research in the NHS is reviewed by an independent group of people, called a Research Ethics Committee (REC). A favourable ethical opinion has been obtained from the South Central-Berkshire REC. NHS management approval has also been obtained.

11. Contact for Further Information

If you have any questions or wish to find out more information then please contact the lead researcher, Nicholas Keith-Barnett (Trainee Clinical Psychologist) or clinical thesis supervisor, Dr Fiona Summer (Consultant Clinical Neuropsychologist):

NHS Grampian Department of Neuropsychology
2nd Floor
Room 2.19
Ashgrove House
Foresterhill
Aberdeen
Telephone 01224 559352 Fax 01224 661570
Email nicholas.keith-barnett@nhs.net

This research is being conducted as part of a doctoral programme at the University of Edinburgh and is supervised by Dr Paul Graham Morris (Lecturer in Clinical and Health Psychology). He can be contacted by telephone on 01316513956 or email on

If you would like to contact someone independent of the study team please contact: Dr Maggie Whyte, Consultant Clinical Psychologist in the NHS Grampian Department of Neuropsychology, on 01224 559352.

If you wish to make a complaint about the study, please contact NHS Grampian:
NHS Grampian Feedback Service
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE
Telephone 0345 337 6338 E-mail nhsgrampian.feedback@nhs.net

For general information about how we use your data go to:
https://www.ed.ac.uk/records-management/privacy-notice-research

Thank you for taking the time to read this information sheet and for considering taking part in this research study.

If at any time you become emotionally distressed during participation in this research the following organisations may be able to help:

Samaritans
is available 24 hours a day for anyone struggling to cope and provide a safe place to talk where calls are completely confidential. Phone: 116 123 Email: jo@samaritans.org
Web: www.samaritans.org

Breathing Space
offers a confidential phone and web based service for people in Scotland experiencing low mood, depression or anxiety. Phone: 0800 83 85 87 (Mon-Thu 6pm-2am, weekends 24 hours)
Web: www.breathingspace.scot

Appendix 6: Consent form

CES MRI - and + population differences on psychological constructs Version: 1 Date: 26-07-2018
Corresponding to PIS version 1 (26-07-2018)

Date:_____ Participant No:_____

NHS Grampian

THE UNIVERSITY of EDINBURGH

Consent Form

Please initial each of the 6 points below and then sign your name at the bottom of the form

Lead Researcher: Nicholas Keith-Barnett
NHS Grampian
Department of Neuropsychology
2nd Floor
Room 2.19
Ashgrove House
Foresterhill
Aberdeen
Telephone: 01224 559352
Fax 01224 661570
Email:

		Initial each box
1)	I confirm that I have read and understand the enclosed information sheet (Version 1, (26-07-2018) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2)	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. Identifiable data collected up until the point of withdrawal may still be used in analysis (unless otherwise requested by myself).	☐
3)	I agree to unidentifiable data derived from my participation in this study to be accessible to be used by future studies that are clearly in the public interest.	☐
4)	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the regulatory authorities and from the Sponsor (the University of Edinburgh) or from the/other NHS Board(s) where it is relevant to my taking part in this research. I give permission for those individuals to have access to my records.	☐
5)	**I agree to take part in the above study.**	☐

SIGNED:_____ **DATE:**_____
[Signed consent form to be returned to researcher and retained in secure site file. Blank copy of consent form to be retained by participant for their records]

If you have any questions regarding any this consent form, please contact the Lead Researcher (Nicholas Keith-Barnett) using the contact details at the top of this sheet. Once completed please return this form along with the questionnaires using the provided stamped addressed envelope.

NB. Unless all boxes are initialed and your signature is provided; consent is not considered to be given to participate in this study

Appendix 7: Inclusion/Exclusion Criteria Questionnaire

Date:_____ Participant No:_____

NHS Grampian

THE UNIVERSITY of EDINBURGH

Inclusion/Exclusion Criteria Questionnaire

Please do not put your name or any other identifiable details on this or any other form that you will be asked to return (other than the consent form)

Please read each statement and then respond with a tick in either the YES or NO column.

Inclusion Criteria	YES	NO
I am 18 years of age or older		
I was referred to the Department of Neurosurgery (NHS Grampian) within the last 8 years for an MRI scan		
I have read and understand the Participant Information Sheet and have completed the consent form		
My English is sufficient to understand and complete the enclosed questionnaires		

Exclusion Criteria	YES	NO
Within the past year I have had to stay overnight (or longer) in hospital for mental health reasons		
I have an intellectual/learning disability or a developmental disorder		
I am currently misusing substances, for example, narcotics, alcohol or medication		
I have a severe brain injury		
I have a severe/advanced neurological condition (e.g. brain tumour, Parkinson's Disease, motor neuron disease, multiple sclerosis).		

If you have any questions regarding the completion of the above questionnaire please contact me via the following details:

Lead Researcher: Nicholas Keith-Barnett
NHS Grampian
Department of Neuropsychology
2nd Floor
Room 2.19
Ashgrove House
Foresterhill
Aberdeen
Telephone: 01224 559352
Fax 01224 661570
Email:

Please return this completed form and questionnaires using the provided stamped addressed envelope.

Appendix 8: Participant copy of consent form

CES MRI - and + population differences on psychological constructs Version: 1 Date: 26-07-2018

Corresponding to PIS version 1 (26-07-2018)

Date:_____ Participant No:_____

NHS Grampian

THE UNIVERSITY of EDINBURGH

Consent Form

Please initial each of the 6 points below and then sign your name at the bottom of the form

Lead Researcher: Nicholas Keith-Barnett
NHS Grampian
Department of Neuropsychology
2nd Floor
Room 2.19
Ashgrove House
Foresterhill
Aberdeen
Telephone: 01224 559352
Fax 01224 661570
Email:

	Initial each box
1) I confirm that I have read and understand the enclosed information sheet (Version 1, (26-07-2018) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. Identifiable data collected up until the point of withdrawal may still be used in analysis (unless otherwise requested by myself).	
3) I agree to unidentifiable data derived from my participation in this study to be accessible to be used by future studies that are clearly in the public interest.	
4) I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the regulatory authorities and from the Sponsor (the University of Edinburgh) or from the/other NHS Board(s) where it is relevant to my taking part in this research. I give permission for those individuals to have access to my records.	
5) I agree to take part in the above study.	

SIGNED:_____ **DATE:**_____

[Signed consent form to be returned to researcher and retained in secure site file. Blank copy of consent form to be retained by participant for their records]

If you have any questions regarding any this consent form, please contact the Lead Researcher (Nicholas Keith-Barnett) using the contact details at the top of this sheet. Once completed please return this form along with the questionnaires using the provided stamped addressed envelope.

NB. Unless all boxes are initialed and your signature is provided; consent is not considered to be given to participate in this study

Appendix 9: Research Protocol

Cauda Equina Syndrome: MRI – and MRI + patient population differences on psychological constructs

Protocol Version 1.0 – July 26th, 2018

Protocol authors	**Nicholas Keith-Barnett** **Dr Paul Graham Morris** **Dr Fiona Summers**
Chief Investigator	**Nicholas Keith-Barnett,** **Trainee Clinical Psychologist**
Sponsor number	**CAHSS1806/01**
REC Number	**18/SC/0468**
Version Number and Date	**Version 1 – July 26th, 2018**

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1
INTRODUCTION

1.1
BACKGROUND

Common symptoms of Cauda Equina Syndrome (CES) include severe lower back pain, weakness in legs, reduced sensation around the saddle and genital area, bladder or bowel function weakness or incontinence and sudden onset sexual dysfunction.

However, at least half of all patients who are initially identified as having CES are consequently identified to have no organic/structural causality of their symptoms (MRI negative/MRI-). with a recent study by Hoeritzauer et al. (2017) finding the number of suspected CES to be MRI- to be at 70%. Rooney et al. (2009) proposed that the symptoms in those patients found to have no radiological evidence of structural pathology are likely to be of a 'functional' origin.

Functional Neurological Disorders (FND's) have been found to be the second most common reason for an outpatient neurology consultation (Carson et al., 2011), with 30% of new referrals to general neurology outpatient clinics having symptoms which were rated by the assessing neurologist as 'not at all' or 'somewhat' explained by organic disease.

This also appears to be a chronic problem with an associated 'heavy resource utility' with the patient population diagnosed with FNDs. Over half the patients who presented to neurologists with symptoms that were rated as largely or completely medically unexplained had not improved eight months later (Carson et al., 2003). In an Edinburgh based study into functional weakness 83% of patients were still symptomatic after a 12 year follow up (Stone et al., 2010).

The estimated cost to the NHS of FNDs

Scotland is a world leader in functional neurology and, in 2003, conducted comprehensive research to estimate the size, cost and extent of the problem. The Scottish Neurological Symptoms Study found:

- 31% of people attending neurology outpatient clinics had functional symptoms. As a whole, this is the largest single group accessing neurological services.
- 27% of people attending with functional symptoms were not working for health reasons. This impacts on the wider economy, including an increase in benefits claims.
- At least 5,000 people per year are estimated to be diagnosed with a functional neurological disorder.

The cost to the health economy in Scotland for people with functional symptoms is estimated at

- £1.3 million per year for outpatients
- £6.01 million for inpatients
- £4.01 million for primary care

Scottish studies suggest a 50% decrease in health service utilisation may be possible if patients receive appropriate treatment.

The Chronicity of CES/MRI-

Hoeritzauer et al. (2017) found that patients who were CES MRI- had higher rates of functional and psychiatric co-morbidity than patients who were CES MRI+.

Psychological factors associated with FNDs

In many patients with FNDs a history of trauma or stressful events can be identified (Roelofs et al., 2002/Bowman & Markand 1999). There is a general agreement that functional disorders are an important marker of psychiatric morbidity (Katon et, 2001). Carson et al. (2000) found of 300 consecutive new patients seen in a neurological outpatient clinic, 67% of patients with unexplained symptoms but only 38% of patients with explained symptoms had depressive or anxiety disorders. Binzer et al. (1997) found 33% of patients with functional motor symptoms but only 10% of patients in the control group to have a major psychiatric disorder.

Psychological factors associated with CES/MRI-

Research suggests there are pronounced psychological differences between CES patients who have no clear organic/structural causality of their symptoms (MRI-) compared to those patients that do (MRI+). Hoeritzauer et al. (2015) found that CES patients subsequently found to be MRI- were more likely to report symptoms of dissociation (45% vs 14%) and panic attack (72% vs 29%) when compared to MRI+ patients. This suggests that there are psychological factors/vulnerabilities that may be associated with people developing the symptoms of CES without any structural/spinal causality of their symptoms. Hoeritzauer et al. (2017) in later research also found CES MRI- patients to have higher rates of functional and psychiatric comorbidity when compared to CES MRI+ patients.

Treatment/therapy for FNDs

There appears to be a shortage of robust research (such as randomised controlled trials) in the area of successful treatments for functional neurological symptoms. Evidence from the treatment of other medically unexplained symptoms and similar disorders, however, supports the hypothesis that psychotherapeutic methods may be helpful in some patients (Goldstein et al., 2004/ Hiller et al., 2003/ Allen et al., 2002), with the strongest evidence being for variants of cognitive behavioural therapy (Speckens, et al., 1995/ Barsky AJ & Ahern, 2004/ Bleichhardt et al., 2004).

Treatment/therapy for CES/MRI-

There is no standard care pathways for this population across health boards in Scotland and the UK which may result in significant variation. For the sake of this research NHS Grampian will be of the main focus of attention. Within this health board (as well as NHS Lothian where a research advisor is currently based) when an MRI scan confirms no structural/spinal causality of symptomology, CES patients are commonly discharged with a prescription for pain medication and depending on the circumstances around the patients' presentation a referral to physiotherapy may also be involved.

The psychological constructs chosen for this research and why

This research project has chosen to use outcome measures that record the psychological constructs of 'Valued Living' and ''avoidance''. Both constructs are integral to Acceptance and Commitment Therapy (ACT) and the 'Psychological Flexibility' that it aims to promote for increased wellbeing. 'Valued Living' is considered to be: 'having a notion about what we want out of life and then making a commitment to ourselves to take action in service of those values' (Harris, 2011). 'Acceptance' (also referred to as experiential avoidance as its inverse measure) can be defined as: 'the willingness to experience (i.e., not alter the form, frequency, or sensitivity of) unwanted private events, in the pursuit of one's values and goals' (Bond et al., 2011).

Wersebe et al. (2017) found that therapy that promoted both acceptance and valued living was found to have a significant reduction in stress and improvement in patients' self-reported well-being. McCracken (1998) found that for patients with chronic pain, psychosocial disability was better predicted by the 'experiential avoidance' of pain than by the actual reported degree of pain itself.

Low Valued living scores on the Valued Living Questionnaire were found to be a predictor of Medically Unexplained Symptoms and fatigue (Kang et al., 2019). Incorporations of the concept predate ACT significantly, be it in alternatively termed constructs such as 'Intrinsic Motivation' (deCharms, 1968) or self-actualisation (Maslow, 1962).

The construct of **'Intolerance of uncertainty'** will also be measured in this study. It has been defined as "a dispositional characteristic that results from a set of negative beliefs about uncertainty and its implications and involves the tendency to react negatively on an emotional, cognitive, and behavioural level to **uncertain** situations and events" (Buhr & Dugas, 2009).

Intolerance of uncertainty has been identified as a discriminating individual difference characteristic involved in excessive worry (Laugesen et al., 2003), state anxiety (Greco & Roger, 2001), and to have strong positive associations with anxiety pathologies such as Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), and Panic Disorder (Dugas, Gagnon, Ladouceur, & Freeston, 1998; Dugas et al., 2001; Tolin, Abramowitz, Brigidi, & Foa, 2003).

Furthermore and with specific interest to this study, high intolerance of uncertainty may impair problem-solving skills, leading to inaction and avoidance of ambiguous situations (Dugas, Freeston, & Ladoucer, 1997). ACT has been shown to have a positive effect on the treatment of a range of disorders; depression, anxiety, (Forman 2007), drug abuse, psychosis (Johns et al., 2016) and epilepsy (Lundgren, 2008).

Published research evidencing ACT as a successful therapeutic approach for FNDs is sparse which may be considered at least in part, to it being a relatively new therapeutic approach yet to build up a robust evidence base. In chronic pain patients, ACT has been found effective at enhancing general functioning and reducing distress, compared to inactive treatment comparisons (Hann & McCracken, 2014) and ACT was found to be successful in the reduction of Medically Unexplained Symptoms in a single patient case study (Graham et al., 2014).

1.2 RATIONALE FOR STUDY

Extremely little is understood regarding the psychological profile of patients with CES MRI-, particularly when compared to patients who are CES MRI+. A more informed knowledge and understanding of the demographic differences (and similarities) between these two patient populations, would better inform care pathways to more efficiently treat them.

Currently care pathways within the Scottish NHS are considered both limited and poor for CES patients who are found to be MRI negative (likely FND). After a diagnostic MRI scan, this patient population is normally discharged from Neurosurgery with a pain medication prescription and perhaps with a physiotherapy referral, while ignoring any psychological aspects of their condition. This condition could be better addressed by incorporating a referral to psychological therapies which may improve overall health outcomes. The current prognosis for this population upon discharge is also poor as discussed previously.

This current research aims to investigate if participants with CES MRI- score significantly lower on the psychological construct of valued living, and higher on psychological Inflexibility, intolerance of uncertainty and reported pain intensity when compared to CES+ participants. We will also investigate if scores on these psychological constructs are predictive of pain intensity scores for the MRI populations. Answers to these questions will allow us to better understand the very little that is known about the CES population profile and the differences between MRI- and MRI+ populations within it. This increased knowledge could help to better inform future adaptations and improvements to the clinical management (and thus the care pathway) so as to better serve these patients more efficiently within NHS Grampian and within the NHS as a whole, hopefully resulting in more positive health outcomes. This could include increasing the awareness, understanding and psychological mindedness of health care professionals about this condition who come into contact with this patient population as well as possible improvements to the referral process (care pathway) to psychological therapeutic services with an evidence base for the successful treatment of similar conditions (functional neurological disorders) such as CBT (Kroenke et al., 2000) or ACT therapy (McCraken et al., 2005) as well as increasing the awareness, understanding and psychological mindedness of health professionals about this condition who come into contact with this patient population.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To determine whether a Cauda Equina Syndrome MRI- patient sample score significantly lower on the measure of ‘Valued Living’ and higher on the measures of ‘Psychological Inflexibility’, ‘Intolerance of Uncertainty’ and 'Pain Intensity' than a Cauda Equina Syndrome MRI+ patient sample.

2.1.2 Secondary Objectives

- To determine if pain intensity in both the CES MRI-/MRI+ population samples is associated with a lower valued living, and higher psychological inflexibility and intolerance of uncertainty scores

- To determine if the measures of valued living, psychological inflexibility and intolerance of uncertainty independently predict perceived pain intensity for the combined CES MRI- and MRI+ samples?

3 STUDY DESIGN

-**Recruitment:** Eligible participants' residential postal address details will be accessed from NHS Grampian electronic records. These individuals will be posted a cover letter/participant information sheet, a consent form, an inclusion/exclusion criteria questionnaire, and the outcome measures; Valued Living Questionnaire, The Acceptance and Action II Questionnaire, Intolerance of Uncertainty Scale (short form) & Numeric Pain Rating Scale along with a reply paid envelope to return completed documents. Those who complete all the required documentation and return it by the cut-off date will be considered for participation.

-Dissemination of research findings: After the study is completed, participants will be able to access a web-link/wiki page: https://www.wiki.ed.ac.uk/x/6a6sFQ (the details of which will have been previously provided in the Participant Information Sheet) with a research finding summary sheet presented on it and a contact email/telephone number if they have any questions regarding the findings and research implications.

This study design was chosen in order to maximise the potential scientific and clinical impact of the study, while working within the time, financial, and academic constraints of the Clinical Psychology Doctorate program.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

- **Sample size:** Estimates of the required sample size were calculated using G*Power (Faul et al., 2007). This indicated that a minimum sample size of between 74 and 77 participants will be required to detect any clinically meaningful differences between the two population groups. This is based on a G power calculation with an allocation ratio of 0.3, effect size of 0.5 and power size of 0.8. On average about 6 patients a month are admitted to Aberdeen Royal Infirmary neurosurgery department with suspected CES for sacral/lumbar or full spine MRI scan. If data is collected for the time period beginning 2010 to the August 2018 for MRI scans, this will give us access to an eligible/suitable population of approximately 624 participants. A realistic postal response rate would be between 20% and 30% (Edwards et al., 2002), this would mean the generation of approximately between 125 and 187 participants. There will be a further attrition/reduction of participant numbers due to participants; not meeting the inclusion criteria, having out of date address details, those who have died and

those who have missing essential information on the PACS database. Based on these calculations we would be fairly confident achieving the required sample size. If due to ill fortune we were unable to fulfil the required sample size, we would retrospectively identify suitable participants from before 2010 from the NHS Grampian surgical database of neurosurgical operations completed and continue to do so (in a reverse time order) until the participant quota for MRI+ participants was indeed fulfilled and if there is still a dearth of participants, I would access a pre-existing CES population database from NHS Lothian as compiled by Dr Ingrid Hoeritzauer (research advisor to this study).

4.2 INCLUSION CRITERIA

- Participant aged 18 and above
- Participant was referred to the department of Neurosurgery (NHS Grampian) within the last 10 years for a diagnostic MRI scan for suspected Cauda Equina Syndrome.
- An MRI diagnosis to have been made by a qualified specialist and accessible to the researcher via PACS database regarding the patient (MRI- or MRI+ for CES).
- Participant to have English language ability sufficient to understand and complete the enclosed questionnaires.
- Postal return of completed consent form, outcome measures and inclusion/exclusion criteria questionnaire.

4.3 EXCLUSION CRITERIA

The following will be determined via responses to the Inclusion/exclusion criteria questionnaire

- Within the past year have had to stay overnight (or longer) in hospital for mental health reasons
- Has an intellectual/learning disability or a developmental disorder
- Currently misusing substances, for example, narcotics, alcohol or medication
- Has a severe brain injury.
- Has a severe/advanced neurological condition (e.g. brain tumour, Parkinson's Disease, motor neuron disease, multiple sclerosis.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

With approval from the Caldicott Guardian, the lead researcher will identify patients through the PACS (picture archiving and communication system) database who were referred to the department of Neurosurgery at Aberdeen Royal Infirmary (NHS Grampian) between January 2010 and August 2018 with suspected CES and who received a diagnostic MRI scan (CES MRI-/MRI+).

5.2 CONSENTING PARTICIPANTS

Patients who are confirmed eligible to participate (from completing the inclusion/exclusion criteria questionnaire) and who also complete both the consent form and the outcome measures and post them back to the researcher by the cut-off

date will be considered participants. Completion of the outcome measures is estimated to take 30 minutes. All returned questionnaires will be scored by an honorary assistant psychologist 'blinded' to the MRI +/MRI– status of the respondents.

5.2.1 Withdrawal of Study Participants

It is made clear to potential participants in both the consent form and the participant information sheet that they are free to withdraw from the study at any point without having to give any reason and without their medical care or legal rights being affected.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

The following self-report questionnaires will be posted out to the potential participants along with the cover letter/participant information sheet, a consent form and the inclusion/exclusion criteria questionnaire. Participants are requested to complete the questionnaires and return them in the provided stamped/addressed return envelopes. Completion of the participation documentation will take approximately 30 minutes to complete.

- **Participant Information Sheet/Inclusion Exclusion Criteria questionnaire/consent form** (10 minutes to complete)

(Posted to and to be read & completed by participant at home in their own time)

- **Numeric Pain rating scale** (1 minute to complete)

The National Institute for Health and Care Excellence considers the NRS (along with the Visual Analogue Scale or VAS) to be the main 'Gold Standard' outcome measures for lower back pain including that caused by Cauda Equina Syndrome (NICE 2013). On the NRS, respondents are most commonly asked to report pain intensity "in the last 24 hours" or current pain intensity. The test takes one minute to complete and is easy to administer (verbally/written) and score. It has a high test–retest reliability has been observed in both literate and illiterate patients with rheumatoid arthritis (r = 0.96 and 0.95, respectively) before and after medical consultation (Ferraz et al., 1990). For construct validity, the NRS was shown to be highly correlated with the VAS in patients with rheumatic and other chronic pain conditions (pain>6 months): correlations range from 0.86 to 0.95 (Ferraz et al., 1990).

- **The Acceptance and Action II Questionnaire** (5 minutes to complete)

The Acceptance and Action Questionnaire (AAQ; Hayes et al., 2004) is the most widely used measure of Psychological Inflexibility. The revised version (AAQ II) consists of 7 questions to be answered on a 7 point Likert scale and has been found to measure the same concept as the AAQ (*r* = .97) but with better psychometric consistency.

A meta-analysis of the AAQ II of 2,816 participants across six studies indicate the measure to have satisfactory structure, reliability, and validity and that it is able to

predict a range of outcomes, from mental health to work absence rates, that are consistent with its underlying theory (Bond et al., 2011). Research has found that when people lack psychological flexibility they are more vulnerable to emotional difficulties, such as depression and anxiety (Raes et al., 2008; Feldner et al., 2003).

McCracken and Zhao-O'Brien (2010) found that a measure of general psychological acceptance (strongly associated with psychological flexibility) significantly correlates with measures of emotional, physical, and psychosocial functioning in people seeking treatment for chronic pain.

- **Intolerance of Uncertainty Scale (short form)** (5 minutes to complete)

The measure of the Intolerance of Uncertainty Scale was originally created in by Freeston et al. (1994) (in French) to gain a better understanding of why people worry. It is considered to be a measure of responses to uncertainty, ambiguous situations, and the future.

The short form of the IoU (created by Carleton, Norton, & Asmundson in 1997) was chosen to be used in this research project as it is significantly briefer than the original (12 instead of 27 items) which should have a positive impact on participant measure completion and return rate, while still being comparable to the original 'long form' with regard to reliability and validity (Carleton, Norton, et al., 2007). The 12 items are rated on a 5-point Likert scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). It has been found to have two factors; 'prospective IU' (7 items; e.g., "I can't stand being taken by surprise") and 'inhibitory IU' (5 items; e.g., "When it's time to act, uncertainty paralyses me"), both with identically high internal consistencies, $\alpha = .85$ (Carleton, Norton, et al., 2007).

With regard to the psychometric properties of the Intolerance of Uncertainty Scale (short form), it has been found to have good convergent and discriminant validity, as well as internal consistency, as demonstrated by the total score and both subscale scores (Carleton, Norton, et al., 2007; McEvoy & Mahoney, 2011).

Intolerance of uncertainty has been identified as a discriminating individual difference characteristic involved in excessive worry (Laugesen et al., 2003), state anxiety (Greco & Roger, 2001), and to have strong positive associations with anxiety pathologies such as Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), and Panic Disorder (Dugas, Gagnon, Ladouceur, & Freeston, 1998; Dugas et al., 2001; Tolin, Abramowitz, Brigidi, & Foa, 2003). Furthermore, high intolerance of uncertainty may impair problem-solving skills, leading to inaction and avoidance of ambiguous situations (Dugas, Freeston, & Ladoucer, 1997).

- **Valued Living Questionnaire** (9 minutes to complete)

According to ACT theorists, values serve to motivate behaviour and facilitate acceptance despite the experience of painful emotions and stimuli (Hayes et al., 1999). The VLQ is a well-established and widely used measure. It is a relatively brief and easily administered instrument derived directly from the primary text on ACT. The measure 'taps into' 10 valued domains of living (Family, Marriage/couples/intimate relations, Parenting, Friendship, Work, Education, Recreation, Spirituality, Citizenship, and Physical self- care). Respondents are asked to rate the 10 areas of life on a scale

of 1–10, indicating the level of importance and how consistently they have lived in accord with those values in the past week (Wilson and Murrell, 2004). There is a revised version (VLQ II) however it has a more intricate/complicated format and takes longer to complete, and so the original version was considered more appropriate for the nature of this research study where the questionnaires would be posted and not administered by the researchers in person.

This instrument has shown to have very good test-retest reliability (Wilson et al., 2010) but not enough robust research has been carried out to date to demonstrate its validity clearly.

- McCrakcken & Yang (2006) found that chronic pain patients who were more successful at living and engaging in behaviour that was consistent with their values, experienced better physical functioning and emotional well-being.
- Nilsson et al. (2011) found nurses in Sweden to experience pain significantly less if they scored higher on physical self-care on the VLQ
- An intervention that incorporated values into an ACT based acceptance intervention led to significantly greater pain tolerance than acceptance alone (Branstetter-Rost et al., 2009)
- Low Valued living scores on the Valued Living Questionnaire were found to be a predictor of Medically Unexplained Symptoms (and fatigue) (Kang et al,. 2019)

Nb. All to be posted to and to be completed by participant at home in their own time

7 DATA COLLECTION

Data will be extracted from the questionnaires that have been returned by post, and entered into the study database. The researchers will not have consent to contact those who have not returned their questionnaires and consent form.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

Multiple methods were used to provide a comprehensive a priori estimate of the minimum sample size required to achieve sufficient power for this study. A power calculation for analysis by multiple regression (given that this aspect of the analysis will require the greatest power/number of participants), was calculated using G* Power 3 (Faul et al., 2007) to determine the minimum sample size required to detect a medium effect (0.15), with a power of 0.80 and with a 95% probability. As the regression is a three-predictor model (the predictors being valued living, psychological inflexibility and intolerance of uncertainty scores), a sample size of n=77 was calculated to be needed to predict perceived pain intensity for the combined CES MRI- and MRI+ sample.

Green's (1991) formula ($N \geq 50 + 8m$) yielded a similar minimum sample size of 74 (3 IVs). required for a multiple regression analysis. Using these two methods, the

minimum sample size required to perform all possible desired statistical analysis is: n=74 to 77.

These numbers assume a medium effect (D=0.50). There is general consensus that a medium effect is the smallest clinically-relevant effect for psychological constructs.

9 OVERSIGHT ARRANGEMENTS

9.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

9.2 RISK ASSESSMENT

Risks to participants: There is a possibility that some potential participants with CES (MRI-/MRI+) may become agitated when contacted by 'Psychology' if they consider their health condition to be of a purely physiological nature. However, it is likely that these participants would not 'opt in' to the research by completing and returning the research documentation and would therefore have no further involvement in the research beyond the initial contact.

All the outcome measures selected for this research have all been used extensively across a wide range of clinical populations, with no reportage of any significant adverse emotional or psychological consequences associated with the completion of the measures.

Measures in place to help mitigate possible risk will include participants being provided with information and contact details of the lead researcher so as to be given the opportunity to make contact to discuss any queries or report any distress they may encounter as a result of participation. In case participants do become distressed during their participation in this study, information regarding and the contact details of both the Samaritans and Breathing Space are provided on of the Participant Information Sheet.

Completion of questionnaires may be perceived as time-consuming and tedious with some of the questions from different measures appearing repetitious. Completion of all the required research documentation (outcome measures and Inclusion/exclusion criteria questionnaire) is likely to take under 30 minutes. The Participation Information Sheet will make clear what participation involves, and participants will be under no pressure to participate. There is no time limit imposed, so participants can complete the research documentation at their own pace and across multiple sessions if preferred and within the comfort of their own home. The outcome measures included have been selected with careful consideration of their ease of understanding and completion and

only the minimum number of measures considered necessary for the research were included, to reduce potential burden to participants. A pre-paid addressed return envelope will be provided for all participants to return the required research documentation, increasing convenience and eliminating financial cost to participants.

As the project involves the use of patient information, there is a risk of breach of confidence, or failure to maintain data security. Measures in place to help keep this possible risk to a minimum include Caldicott principles being used to inform both the design and the facilitation of the research. The lead researcher has also received recent and up to date NHS training in both Clinical Governance and Good Clinical Practise which will also inform both the design and the facilitation of the research and help to maintain participant confidentiality. Each participant will be assigned a number that will be used to anonymise completed questionnaires. Questionnaires will be scored by assistant psychologists 'blinded' to the identity and MRI status (+/-) of the participants. Completed questionnaires will be stored in a locked cabinet within a locked Neuropsychology office on NHS Grampian premises. Data will be saved on a restricted access drive on the NHS Grampian server. Any documents containing patient identifiable information will be kept separate from unidentifiable information.

If a participant does accidentally disclose any personal identifiable information on any of the returned participation documentation (consent form, Inclusion/exclusion criteria questionnaire, questionnaires). The documentation will be checked within a period of 2 weeks, any identifiable data/information will be blacked out, the documents will then be photocopied with the originals destroyed and the censored (now unidentifiable) copies will be used from then on.

Risks to researchers

There are no known risks to the researchers as they will not have any direct personal contact with participants (other than potentially by telephone). All main correspondence will be by post or online. The researchers will protect their own personal identities (ie. post or online information) in line with the guidance of their professional body.

9.3 STUDY MONITORING AND AUDIT

(See section 9.1 above also) This project is supervised by Dr Paul Morris (academic supervisor) and Dr Fiona Summers (clinical supervisor). The project will be reviewed and monitored on a monthly basis by both supervisors.

10 GOOD CLINICAL PRACTICE

10.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

10.2 INVESTIGATOR RESPONSIBILITIES

The chief Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

10.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate written information – appropriate Participant Information and Informed Consent Forms will be provided.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be asked to voluntarily consent to the possibility of their identifiable data being inspected by regulatory authorities and representatives of the sponsor(s).

A copy of the participants' completed consent form will be filed in the Investigator Site File (ISF).

10.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

10.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

10.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

10.2.5 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 and the GDPR Act 2016 (EU) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

11 STUDY CONDUCT RESPONSIBILITIES

11.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

11.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

11.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the participants of the trial; or (b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact

of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

11.4 STUDY RECORD RETENTION

All unidentifiable participant data (completed questionnaires, Scottish index of multiple deprivation, MRI- or + diagnosis) will be kept for a minimum of 10 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

All identifiable participant information (participant; names, addresses, date of births/ages) as well as anonymized consent forms will be stored (in accordance with the data protection act) on a password protected computer database located on secure NHS Grampian premises for a period of up to 6 months after the end of this study and will then will be destroyed.

11.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the sponsor have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and sponsor within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co- sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

11.6 INSURANCE AND INDEMNITY

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

12 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the Chief Investigator. Findings will be disseminated via a doctoral thesis with the chief investigator as first author and supervisors and research collaborator following- with them being offered choice of subsequent author position in the order of their relative intellectual contribution to the project overall (project idea, research questions, methodology, analysis, interpretation etc).

It is also the plan of the chief investigator to publish the findings and implications of this current research project in a peer reviewed journal. If this is not done within an agreed period of having completed the research and doctoral thesis (approximately 1 year), it is understood that the supervisors (clinical & academic) and/or the research collaborator may wish to publish the findings instead, while still acknowledging the Chief Investigator as a secondary author.

Appendix 10: British Journal of Neurosurgery- Instructions for authors

Instructions for authors

Thank you for choosing to submit your paper to us. These instructions will ensure we have everything required so your paper can move through peer review, production and publication smoothly. Please take the time to read and follow them as closely as possible, as doing so will ensure your paper matches the journal's requirements. For general guidance on the publication process at Taylor & Francis please visit our Author Services website.

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This journal uses ScholarOne Manuscripts (previously Manuscript Central) to peer review manuscript submissions. Please read the guide for ScholarOne authors before making a submission. Complete guidelines for preparing and submitting your manuscript to this journal are provided below.

About the Journal

British Journal of Neurosurgery is an international, peer-reviewed journal publishing high-quality, original research. Please see the journal's Aims & Scope for information about its focus and peer-review policy.

Please note that this journal only publishes manuscripts in English.

British Journal of Neurosurgery accepts the following types of article: Original Articles, Short Reports and Case Reports, Review Articles and Letters to the Editor..

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Preparing Your Paper

All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits

Please include a word count for your paper. There are no word limits for papers in this journal.

Style Guidelines
Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy.
Please use British (-ise) spelling style consistently throughout your manuscript.
Please use single quotation marks, except where 'a quotation is "within" a quotation'. Please note that long quotations should be indented without quotation marks.

Formatting and Templates
Papers may be submitted in Word format. Figures should be saved separately from the text.
To assist you in preparing your paper, we provide formatting template(s).
Word templates are available for this journal. Please save the template to your hard drive, ready for use.
If you are not able to use the template via the links (or if you have any other template queries) please contact us here.

References
Please use this reference guide when preparing your paper.

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Checklist: What to Include

1. **Author details.** Please ensure everyone meeting the International Committee of Medical Journal Editors (ICMJE) requirements for authorship is included as an author of your paper. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.
2. Should contain a structured abstract of 300 words. A structured abstract should cover (in the following order): the purpose of the article, its materials and methods (the experimental system and procedures used), the results and conclusions.
3. **Graphical abstract** (optional). This is an image to give readers a clear idea of the content of your article. It should be a maximum width of 525 pixels. If your image is narrower than 525 pixels, please place it on a white background 525 pixels wide to ensure the dimensions are maintained. Save the graphical abstract as a .jpg, .png, or .gif. Please do not embed it in the manuscript file but save it as a separate file, labelled GraphicalAbstract1.
4. You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.
5. Read making your article more discoverable, including information on choosing a title and search engine optimization.
6. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:
7. For single agency grants
8. This work was supported by the [Funding Agency] under Grant [number xxxx].

9. For multiple agency grants
10. This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].
11. **Disclosure statement.** This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research. Further guidance on what is a conflict of interest and how to disclose it.
12. **Biographical note.** Please supply a short biographical note for each author. This could be adapted from your departmental website or academic networking profile and should be relatively brief (e.g. no more than 200 words).
13. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.
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