AN INTERNET DELIVERED COGNITIVE BEHAVIOURAL THERAPY PAIN MANAGEMENT PROGRAMME FOR SPINAL CORD INJURY PAIN: A RANDOMISED CONTROLLED TRIAL.

--Manuscript Draft--

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Abstract:	Chronic pain is common after spinal cord injury (SCI) and dedicated SCI cognitive behavioural therapy pain management programmes (CBT-PMPs) have a growing evidence-base to support their uptake clinically. The development of internet-delivered treatment options may overcome barriers to the access and uptake of centre-based programmes. This study examines such an approach on quality of lie (QoL), pain, mood and sleep. Methods Adults with SCI pain (>3 months) were recruited and randomly assigned to the intervention or control group. The intervention comprised a six module CBT-PMP delivered once weekly. A blinded assessor determined changes in self-reported outcome measures post intervention and at three months. Linear Mixed Models and effect sizes based on changes between groups were reported. Significance was set $P<0.05$. Results The recruitment rate was 32% (intervention n=35, control n=34), and the drop-out rate at three months was 26%. On average participants accessed 3 (sd 2.1) of 6 modules. Whilst no difference in QoL was reported, a significant group*time interaction was found for NRS of current pain ($X2=8.22$, $p=0.016$) worst pain ($X2=11.20$, $p=0.004$) and Brief Pain Inventory (interference) ($X2= 6.924$, $p= 0.031$). Moderate to large effect sizes favouring the intervention were demonstrated at each timepoint for the pain metrics (Cohen's d: 0.38-0.84). At three month follow up 48% of the intervention group rated themselves improved or very much improved. Conclusions This study demonstrates the potential of an internet delivered SCI specific CBT-PMP in reporting significant statistical and clinical benefit in pain intensity and interference. Strategies to improve engagement are needed.

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Introduction

Chronic pain is a significant secondary health complication encountered by the majority of individuals post spinal cord injury (SCI) (Heutink *et al.*, 2011; Adriaansen *et al.*, 2013; van Gorp *et al.*, 2015). When present, it interferes with participation in daily life, is associated with greater anxiety and depression, and lower employment rates and quality of life (Qol) (Westgren & Levi, 1998; Avluk *et al.*, 2014; Andresen *et al.*, 2016; *Silvestri,* 2017). Mixed pain presentations are common, including nociceptive pain (musculoskeletal, visceral and other) and neuropathic pain (at-level, below-level and other) as classified by the International SCI Pain (ISCIP) Classification (Bryce *et al.*, 2012). The pooled prevalence rates from meta-analysis of chronic pain overall and neuropathic pain (NP) post injury are 61% (van Gorp *et al.*, 2015) and 53% (Burke *et al.*, 2017b) respectively, highlighting the extent of the problem.

Recently, evidence-based guidelines have been developed for models of care and management of NP post SCI (Guy *et al.*, 2016a; Guy *et al.*, 2016b). They highlight the need for multidisciplinary team management in SCI rehabilitation centres employing psychological principles such as cognitive behavioural therapy (CBT) and patient education. In addition they recommend anti-convulsants and anti-depressants as first line agents for NP (Guy et al., 2016b). It is noteworthy that individuals with SCI pain have also expressed a desire for the increased availability of effective, non-pharmacological interventions (Warms et al., 2002; Heutink et al., 2011; Lofgren & Norrbrink, 2012).

In the general population, international best practice for chronic pain management advocates cognitive behavioural pain management programmes (CBT-PMP) (International Association for the Study of Pain, 2009; Williams *et al.*, 2012). Due to the specific needs of the SCI cohort and the dual multi-disciplinary expertise in chronic pain and SCI required, CBT-PMPs specific to SCI pain, delivered by SCI clinicians are recommended (Perry *et al.*, 2011). To date, five centre-based studies (5-10 week duration) have tested programmes specific to SCI pain. One randomised controlled trial (RCT) and four cohort studies showed promising effectiveness for improving mood profiles, pain interference,

pain intensity and participation in daily life (Norrbrink Budh *et al.*, 2006; Perry *et al.*, 2010; Heutink *et al.*, 2012; *Burns et al.*, 2013; *Burke et al.*, 2017). Difficulties in programme recruitment due to the relative rarity of the condition by geographical location, transportation issues, the need for onsite accommodation in some cases and the specialised nature of the intervention were highlighted (Perry *et al.*, 2011; *Burns et al.*, 2013; *Burke et al.*, 2017).

The adaptation of CBT-PMPs for internet delivery in the general population has proved successful with results similar to centre-based programmes reported (Eccleston *et al.*, 2014). Moving CBT-PMPs online addresses transport and operational barriers to implementation, reduces costs of programme delivery and increases the participant's autonomy in completing the programme at their own pace and preferred times (Nguyen *et al.*, 2004; Griffiths *et al.*, 2006; Perry *et al.*, 2011). Whilst this mode of delivery has shown promising results for addressing depression, mood disorders and catheter management in SCI (Migliorini *et al.*, 2016; Verwer *et al.*, 2016; Wilde *et al.*, 2016), it has yet to be undertaken for SCI specific CBT-PMPs. Hence this RCT was undertaken to test the efficacy of **S**pinal Cord Injury **P**ain **Ire**land (SPIRE) pain management programme, an internet-delivered CBT-PMP for SCI pain. Our specific objectives were to:

1. Assess recruitment and engagement for the SPIRE programme
2. Evaluate between group comparisons for changes in quality of life, mood, pain acceptance and pain interference in daily life
3. Determine participants' global impression of change
4. Determine number of adverse events related to the SPIRE programme

Methods

Study Design

A CONSORT E-HEALTH compliant (Eysenbach, 2011) RCT was conducted following institutional ethical approval (LS-16-26-Burke-Fullen) and registration with ClinicalTrials.gov (NCT03150017). The

study contained two parallel groups; one that received access to an internet-delivered CBT-PMP SPIRE and the second that continued to manage their pain as per usual care. An internet delivered battery of outcome measures was sent to participants in both groups at three time points: baseline (T1), post-intervention 6 weeks (T2), and three months post programme completion (T3). On completion of the study those allocated to the control group were given access to the SPIRE programme. No methodological changes were made once the trial commenced.

Study Population

Adult participants with SCI pain (n=304) were recruited from a national survey database in which respondents had consented to their contact details being accessed for future research purposes (Burke *et al.*, 2017a). Information leaflets were mailed describing the study protocol. Inclusion criteria are summarised in Table 1. Once eligible and interested participants had questions relating to the study answered, written informed consent was obtained.

Sample Size Calculation

Sample size calculation, with 80% power and $p<0.05$ was based on the ability to detect a significant difference in the psychological domain of the World Health Organisation WHOQOL-Bref (WHOQOL Group, 1998), as guided by the findings and data from the centre-based study conducted by this research team (Burke *et al.*, 2017). No clinically meaningful change is published for this outcome measure and as such the change to be detected was the reliable change index, calculated as per the Jacobson and Truax method (1991) (Jacobson & Truax, 1991). The formula for detecting a change in means was $n >= 2K\sigma^2 / \Delta^2$ ($K = 7.8$) (Daly & Bourke 2000).

A minimum of 16 subjects per group was required to detect a significant change. Allowing for an expected maximum study drop-out of 20%, the study aimed to recruit a total sample size of 40 participants.

Randomisation

Participants were assigned an identification number and following completion of the pre-intervention assessments were randomly assigned in equal proportions to the intervention or control group using a sequence generator (Microsoft Excel, 2010) by a member of the research team (OL) who was blinded to the recruitment and assessment process.

Study Procedure

The intervention group were each assigned an individual account to access SPIRE and were emailed unique usernames and passwords for the study by the principle investigator (DB). A contact email address and support phone line was provided, and one telephone contact was made with each participant within one week of programme commencement to ensure successful access to the programme.

Once participants had started the programme, they were sent two weekly email prompts; one reminding participants to access the SPIRE content and a second notifying them when new content was uploaded.

The control group continued to manage their chronic pain as they normally did, and received no further intervention for the duration of the study. On completion of the study (12 weeks) this cohort was offered access to the SPIRE programme.

Intervention (SPIRE)

This internet-delivered CBT-PMP was developed from a hospital-based CBT-PMP (Burke *et al.*, 2017) and adapted within an established holistic framework (van Gemert-Pijnen *et al.*, 2011) involving key stakeholders including the end-users, SCI rehabilitation clinicians, pain specialists and an education technologist (e-health technology expertise). A SPIRE prototype which aligned to pre-defined end-

user preferences was developed by a multi-disciplinary project management group and evaluated by potential end-users and further key stakeholders using qualitative methodology. The usability issues highlighted in the prototype were addressed to ensure high programme usability and quality of content. No changes were made to the programme during the study period. The programme was created using Articulate® Storyline 2 and delivered via Moodle™. An outline of the programme content is summarised in Table 2.

The programme, based on principles of Fordyce (Fordyce, 1976) and Turk (Turk *et al.*, 1983), incorporated cognitive behavioural principles. It comprised six modules, delivered once weekly which included; cognitive behavioural therapy and educational sessions written in plain English (National Adult Literacy Agency, 2010), guided audio relaxation practice, and a progressive exercise programme which was adaptable to different levels of mobility and involved flexibility, strength, aerobic and pilates exercise in line with established exercise guidelines post SCI (Ginis *et al.*, 2011). Exercises were delivered using videos (1 minute 30 seconds - 4 minutes 15 seconds long) with accompanying images and text instructions. The education sessions were delivered by a team of SCI specialists; a rehabilitation consultant (medical aspects of SCI pain and the importance of CBT-PMPs), a clinical psychologist (CBT, communication, managing flare ups), physiotherapists (exercise after SCI, lifestyle and pain management), a pharmacist (medication use), occupational therapists (goal setting, pacing and sleep hygiene) and a SCI liaison nurse (support networks). These sessions incorporated interactive slides with images, summarised text, a voice-over explanation and a short introductory video (6-40 seconds long). Slides with text contained on average 50 words, presented in bullet-point format with up to three relevant images. Hyperlinks to external websites with useful resources were included where applicable. Video interviews with individuals with SCI (2 minutes 17 seconds-5 minutes 37 seconds long), successfully engaging in pain self-management strategies were also included.

Engagement with the physiotherapist and feedback on participant's progress was sought and encouraged in a number of ways. Prior to the programme starting, all participants were given the SPIRE support phone line and encouraged to use it for guidance or for any issues that occurred during the course of the programme. Weekly emails were sent reminding participants of the courses content for the week and the associated weekly tasks (goal setting, recording a sleep diary and a pacing plan etc). Reminders about the support line were also included. A live webinar using Google Hangouts was also scheduled in week four of SPIRE with the lead investigator and chartered physiotherapist (D.B). This was an opportunity for participants to discuss their progress on the programme, address issues regarding adherence to programme principles, or any other issues they were encountering. To promote peer support, SPIRE also included a peer forum where participants could post questions and discuss concepts of the programme with one another, again this was moderated by the principle investigator (D.B).

Weekly engagement in each module of the programme was encouraged. Modules from week two to six began with a short review of the key concepts covered in the previous week and weekly assignments to be completed were aimed at reinforcing CBT principles into daily life. The SPIRE programme was supported by a printed manual that was mailed to all intervention participants. It included an information leaflet for family members that summarised the programme goals and how best to support the participant in their pain management. Other documents included goal setting sheets, a pain management diary, a food diary and a worksheet for pacing activities.

Study Outcome Measures

1.Recruitment and Engagement

Recruitment rates to the study: the number of potential participants contacted, the number recruited and reasons for non-participation were recorded.

The online platform MoodleTM recorded the number of daily programme logins, in addition to weekly programme content accessed and when there was interaction with 80% of the module content or more. This metric was captured by the software system and we considered it the minimum intended usage to derive a benefit from the interaction (Kelders *et al.,* 2012). The number of posts on the peer forum was recorded as well the number of participants who engaged in the webinar.

2. SPIRE Outcome Measures

An internet delivered battery of outcome measures were collected at each time point. This included demographics, SCI characteristics and validated tools assessing quality of life (QoL), pain, mood, sleep quality, and for those in the intervention group their global impression of change. No changes were made to the trial outcome measures after the trial commenced.

Demographic characteristics recorded included age, gender, relationship, employment status and mobility status. Spinal cord injury characteristics recorded included the cause and year of injury, the neurological level of injury (NLI), the American Spinal Injury Association Impairment Scale (AIS)(American Spinal Injury Association., 2011) and a further question relating to completeness of injury.

The outcome measures are detailed below.

Primary Outcome Measure

Quality of Life: The World Health Organisation Quality of Life Bref (WHOQOL-BREF)

The WHOQOL-BREF is the primary outcome measure for the study (WHOQOL Group, 1998). This self-report questionnaire, previously validated in this patient population (Jang *et al.*, 2004; Lin *et al.*,

2007), is recommend as the optimal QoL measure post-SCI (Hill *et al.*, 2010). The 26 item scale is calculated into four weighted domains (0-100) of physical health, psychological health, social relationships, and environmental relationships. Higher scores indicate better psychological health and QoL (WHOQOL Group, 1998). The WHOQOL-BREF has high mean levels of internal consistency 0.74–0.87 (Cronbach's alpha)(Lin et al 2007), and demonstrate item-domain validity (r = 0.41–0.77) (Jang et al 2004).

Secondary Outcome Measures

Quality of Life: The International Spinal Cord Injury Quality of Life Basic Data Set

In line with recommended guidelines and to facilitate comparison with QoL post SCI internationally, a second validated QoL measure was included (Charlifue *et al.*, 2012; Post *et al.*, 2016). This questionnaire records three items; satisfaction with general quality of life, physical health, and psychological health, rated on a scale ranging from 0 (completely dissatisfied) to 10 (completely satisfied). There are strong inter-correlations (0.48–0.71) between the items, and Cronbach's α of the scale is good (0.81) (Post et al 2016).

Pain Profile: The International Spinal Cord Injury Pain Basic Data set (ISCIPBDS) (Version 1)

This SCI validated tool (Widerstrom-Noga *et al.*, 2008) investigates the respondent's three worst pain problems using a numeric rating scale (NRS) for pain intensity, questions on pain frequency and location, and includes six pain interference items. Participants also record their pain presentation in line with the International Spinal Cord Injury Pain (ISCIP) consensus on classification of pain after SCI (Bryce et al., 2012). The interference scale is calculated as an overall interference score and two sub-domains of limits in activity and changes in social and recreational activity and family related activity

(LSF) and interference with activities, mood and sleep (AMS) (Widerstrom-Noga *et al.*, 2008). Excellent internal consistency (Cronbach's α=0.94 has been established (Jensen et al 2010)

Pain Presentation: The Douleur Neuropathique en 4 Questions (DN4) interview

The DN4 interview (Bouhassira *et al.*, 2005) recorded the presence of NP. This DN4 tool has been validated with high diagnostic accuracy in the SCI population (Hallstrom & Norrbrink, 2011). The DN4 (interview) component is validated for self-report (Bouhassira *et al.*, 2008) and has been utilised in SCI (Andresen *et al.*, 2016; Burke *et al.*, 2017a). A score of three or more of seven descriptor items indicates a NP presentation (Bouhassira *et al.*, 2005; Bouhassira *et al.*, 2008). The DN4 has demonstrated a sensitivity of 93%, specificity of 75%, and reliability of k=0.79 (Hallstrom & Norrbrink, 2011).

Pain Acceptance: The Chronic Pain Acceptance Questionnaire-8 (CPAQ-8)

The eight item CPAQ-8 tool (Fish *et al.*, 2010) measures two domains; activity engagement (AE) which measures engagement in valued daily activities despite the presence of pain, and pain willingness (PW) which measures the level of disengagement in trying to control or avoid pain. Each item is scored on a Likert scale ranging from 0, 'never true', to six, 'always true' with higher scores indicating greater activity engagement and pain willingness. The CPAQ-8 has been validated for use in chronic pain (Fish *et al.*, 2013). Studies indicate reasonable reliability (α = .72–.91) and validity suggested by high correlations with measures of avoidance, distress, and daily functioning (Wicksell e al 2009).

Pain Interference: The Brief Pain Inventory (BPI) Interference Sub-scale

The BPI interference sub-scale is a recommended (Bryce *et al.*, 2007) and validated pain interference measure for use in SCI (Raichle *et al.*, 2006). The seven-item measure assesses the extent to which pain interferes with physical and emotional functioning and sleep. For use in SCI the item "Walking ability" is changed to "Mobility" (Raichle *et al.*, 2006). Scores range from 0 to 10, with higher scores indicating greater pain interference. Internal consistency is excellent with a Chronbach α >90% (Raichle et al 2006).

Mood: The Hospital Anxiety and Depression Scale (HADS)

The HADS questionnaire (Zigmond & Snaith, 1983) has shown good internal consistency and content validity in community dwelling individuals with SCI (Woolrich *et al.*, 2006). Higher scores indicate more emotional distress, scores of 0-7 (absence of trait), scores of between 8 and 10 (at risk of developing trait) and greater than 11 (presence of trait) (Zigmond & Snaith, 1983). The HADS has high mean levels of internal consistency HAD-A 0.83 and HAD-D 0.82 (Cronbach's α), and a sensitivity and specificity of 0.8 for both HAD (A) and HAD (D) (Bjelland et al 2002).

Sleep: The Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a validated sleep measure (Buysse *et al.*, 1989), which has previous application to SCI clinical research (Sankari *et al.*, 2014). It assesses sleep quality and disturbances in the previous month. Nineteen items are calculated into seven component scores which then total to one global score. A global score greater than 5 is indicative of poor sleep quality (Buysse *et al.*, 1989). The tool has a sensitivity of 98.7 and specificity of 84.4 (Backhaus et al 2002).

3. Participants' Global Impression of Change (PGIC)

This tool is recommended by the initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) as a core outcome measure of global improvement with treatment (Dworkin *et al.*, 2005). The 7 point scale ranges from "very much worse" to "very much improved". This measure was recorded in the intervention group after programme completion and at 3 month follow-up.

4. Adverse Events

Participants were instructed to report any adverse events to the principal investigator by email or using the mobile telephone number provided to them.

Data Analysis

Recruitment rates and reasons for non-engagement were reported using descriptive analysis. Completed outcome measures were coded, entered into Statistical Package for the Social Sciences (SPSS) Version 20 and subsequently cleaned by a member of the research team blinded to group allocation. Participant characteristics were reported using descriptive statistics [mean (SD), frequency (percentage)]. The primary analysis included all available data in an intention to treat approach, using Linear Mixed Models (LMM) with Maximum Likelihood Estimation, to assess change in each outcome over time (T1-T2-T3), between the intervention and control groups. The lme4 package in R (Bates et al 2015) was applied and separate models were constructed for each outcome (QoL, pain, mood etc.). These included the categorical variables group (intervention/control) and time (T1-T2-T3) as fixed effects and a random effect for the repeated measures within each individual. The hypothesis that the change in each outcome from T1 to T2 and T3 was different between the intervention and control groups i.e. the group*time interaction was specifically tested by comparing models with the interaction term to the 'no interaction' model, using Wald Tests

which are chi-squared distributed. Significance was set at $p<0.05$. Change scores recorded for each outcome from pre-intervention to post intervention (T1-T2) and pre-intervention to three month follow-up (T1-T3) were calculated. The mean change for the intervention group minus the mean change for the control group was divided by the pooled standard deviation of change, in order to estimate Cohen's d effect sizes for the between group treatment effects at T2 and T3 respectively. These were interpreted as; small =0.2, medium=0.5, large=0.8 (Cohen 1998).

Supplementary analysis repeated the linear mixed models, based on five multiply imputed datasets, where missing data post-intervention and at three month follow-up, were imputed with Markov Chain Monto Carlo simulations using a fully conditional specification. Results of this supplementary analsyis are presented in Appendix 1. From this set, the percentage of participants in each group who achieved a clinically significant change (CSC), identified as ≥30% of baseline score (Moore et al 2010) in pain, interference and mood were reported and compared with Chi square sets.

Additional analysis in the intervention group, using the complete dataset without imputation, explored the relationship between engagement with programme content (number of modules with 80% engagement or more) and the change recorded in outcome measures (including global impression of change measure) between T1 and T2 and T1 and T3 using Spearman's rank correlation coefficient rho (ρ). A correlation co-efficient of >5 was considered moderate and >7 considered a strong relationship (Cohen, 1988). Number and reasons for adverse events were descriptively reported.

Results

1. Recruitment

Participant flow and retention, in line with the CONSORT statement (Moher *et al.*, 2012) is outlined in Figure 1. The recruitment period ran from 9/1/2017 to 1/4/2017 with follow-up from 19/4/2017 to 23/8/2017 when the trial reached completion and was stopped. From 304 adults with SCI contacted initially by letter and followed by a telephone call, 85 did not meet the inclusion criteria,

54 declined to participate due to a lack of time or interest, and the remaining 95 were uncontactable by phone. Therefore, the recruitment rate was 32%; intervention group (n=35), control group (n= 34).

Post intervention 12 participants, six from each group were lost to follow-up (17% attrition rate). At the three month review 18 participants were lost to follow-up (26% attrition rate); the control group (n=10) and the intervention group (n=8). Known reasons for non-participation at each stage are outlined in Figure 1. Linear mixed models with Maximum Likelihood Estimation and imputation using Markov Chain Monto Carlo simulations accounts for this missing data in primary and additional longitudinal follow-up analysis respectively.

Demographics and SCI characteristics of the intervention and the control group are summarised in Table 3. Overall the mean (sd) age of participants was 51 (sd 13) years and three quarters 75% (n=52) were male. Road traffic accidents were the most common cause of SCI (n=17, 25%) and most injuries presented in the thoracic or lumbar region (n=44, 64%), with a mean (sd) time post injury of 16 (sd 12.2) years. The majority of participants scored three or more on the DN4 indicating a NP presentation (n=44, 64%), below-level NP (n=30, 44%) was the most common pain type selected for participants' worst pain, followed by nociceptive musculoskeletal pain (n=22, 32%). Most patients reported taking medication in the past six months with analgesics the most common medication category (61%) followed by non-steroidal anti-inflammatories (38%) (Table 3).

Programme Engagement

On average the intervention group recorded five (sd 5.3) logins to SPIRE, accessed 50% of the programme content [three (sd 2.1) out of six modules] and completed two (sd 1.9) modules with ≥80% engagement with content (Figure 2). Only one participant engaged with the peer forum and 29% (n=10) engaged with the webinar.

2. Comparative Analysis: Baseline and Follow-up Outcome Measures

Outcome measure scores for the intervention and control groups at T1, T2 and T3 are summarised in Table 4 with the results of the LMM reported. Effect sizes related to changes in these measures over time are reported in table 5. The LMM model demonstrates a difference in response between the intervention and control groups over time across several pain outcome measures (group*time interaction). The imputed data (Appendix 1) demonstrates the same interaction effect with the exception of one of these pain measures, as reported below.

Primary Outcome Measure

WHOQOL-BREF

No significant difference was noted between the intervention and control groups in QoL over time, in the four domains of the WHOQOL-BREF (group*time interaction p>0.05), although the interaction for the psychological domain demonstrated the greatest difference between groups over time (x2=5.783, p=0.055). Positive treatment effects in favour of the intervention group were seen in this domain with a small effect size following treatment (Cohen's d 0.319, T1-T2) and a large effect size (Cohen's d 0.723, T1-T3) at three month follow-up noted in this primary outcome.

Secondary Outcome Measures

Pain

A significant group*time interaction was found for overall pain (NRS) (X^2=8.22, p=0.016) showing that pain levels differed between the intervention and control groups over time. Moderate (Cohen's d 0.702, T1-T2) and small effect sizes (Cohen's d 0.380, T1-T3) in favour of the intervention group over the control group were found when changes from baseline were~~as~~ compared between the groups at the T2 and T3 time points respectively. Worst pain scores (NRS) also showed similar group*time results (X2=11.20, P=0.004) with large (Cohen's d 0.844, T1-T2) and moderate (Cohen's d

0.547, T1-T3) effect sizes in favour of the intervention reported at these time intervals. Finally, a significant group* time effect was found for the Brief Pain Inventory (Interference) scale (X^2=6.924, p=0.031). While a moderate (Cohen's d 0.532) effect size in favour of the intervention post programme (T1-T2) was found, a small effect size in favour of the control group at follow up was noted for this item (Cohen's d -0.284, T1-T3), limiting conclusions that can be drawn.

Similar group*time interactions were seen in the imputed dataset for overall pain (p=0.04) and worst pain (p=0.01), while no interaction was noted for the Brief Pain inventory.

Mood

No significant group*time interaction for the HADs questionnaire was observed. However, ~~,~~at the three month follow-up period (T1-T3) a moderate effect size in favour of the intervention in the HADs anxiety subscale (Cohen's d 0.509) and a small effect size in the depression sub-scales (Cohens d 0.467) were evident, but these did not reach statistical significance.

Sleep

No significant group*time interaction was found for sleep quality as measured by the PSQI. A small effect size (Cohens d 0.332) was evident post programme (T1-T2) in favour of the intervention, but this did not reach statistical significance.

Pain Acceptance

No significant group*time interaction was observed for pain acceptance (CPAQ). A small effect size (Cohens d=0.419) in the engagement sub-scale was found post programme (T1-T2) in favour of the intervention although this did not reach statistical significance.

Measures of Clinically Significant Change

The proportion of patients who established a CSC score (≥30% improvement) from T1-T3 are summarised in Table 6. None of the proportional differences between the intervention and control groups was significant (p>0.05). Greater proportions of patients in the intervention group achieved a CSC compared with the control group for metrics of pain, quality of life (except the social sub-scale) and mood. The proportion of patients who achieved a CSC in the BPI was higher for the control group.

Relationship between Programme Engagement and Outcome Measures in the Intervention Group (T1-T2 and T1-T3)

Post-intervention (T1-T2) a moderate linear relationship was observed between the number of modules where users engaged with 80% or more of the content and reductions in the following measures; overall pain intensity (NRS) (ρ=0.36, P=0.05), the ISCIPBDS pain interference score overall (ρ=0.33, P=0.08) and the LSF domain (ρ=0.39, P=0.04), the BPI interference scale (ρ=0.31, P=0.10) and the depression subscale of the HADS (ρ=0.32, P=0.10).

At the three month follow-up (T1-T3) a moderate linear relationship was observed between module engagement and improvements noted in; sleep quality (ρ=0.42, P=0.06), the AMS subcategory of the ISCIPBDS pain interference scale (ρ=0.33, P=0.09), and both the depression (ρ=0.42, P=0.03) and the anxiety (ρ=0.39, P=0.05) subscales of the HADS.

3. Participants' Global Impression of Change

Immediately post intervention, of the 29 (83%) participants who completed this questionnaire two (7%) reported being very much improved, 8 (28%) documented that they were much improved, 9 (31%) reported minimal improvement and 10 (34%) reported no change.

At the three month follow-up (T1-T3), of the three quarters of participants (77%, n=27) who completed this measure three (11%) reported they were very much improved, 10 (37%) documented that they were much improved, 7 (26%) reported minimal improvement and 7 (26%) reported no change.

4. Adverse Events

Two participants reported minor adverse events during the programme. One participant with a previous shoulder problem reported increase in symptoms and a second recorded an increase in leg spasms following lower limb stretches. Both were contacted and given advice on management of their symptoms by a chartered Physiotherapist and advised on how best to continue with the programme.

Discussion

Our RCT tested the efficacy of SPIRE, a six-week internet-delivered CBT-PMP for SCI pain. The trial demonstrated significant short term benefit for pain intensity and pain interference with improvements in pain maintained three months later. At this follow-up time point almost half of participants reported being very much or much improved (48%, n=13).

The investigation of the efficacy of CBT-PMPs specifically for SCI pain is limited. Only four studies have examined this approach in centre based formats; one RCT (Heutink *et al.*, 2012) and four cohort studies (Norrbrink Budh *et al.*, 2006; Perry *et al.*, 2010; Burns *et al.*, 2013; Burke *et al.*, 2017) Our RCT is the first to explore internet-delivered CBT-PMPs wth only a single group feasibility study

available for direct comparison (Dear et al 2018). Hence we believe the SPIRE trial adds to the emerging body of evidence in this field.

Internet delivery of CBT-PMPs is deemed a sustainable solution for the self-management of long-term health conditions away from expert healthcare centres, with their efficacy established in a recent Cochrane systematic review (Eccleston *et al.*, 2014). The results of the SPIRE programme are broadly consistent with results from this review, and the moderate effect sizes three months post intervention for pain, anxiety and depression reflect those reported by Dear and colleagues (2018).

The 32% recruitment rate was lower than anticipated given that pain and limited access to CBT-PMPs had been reported (Burke et al 2017a). Nonetheless it is comparable with an internet-delivered CBT programme for mood post SCI (27%). Poor computer skills, lack of internet access and a preference for interventions delivered in person were cited in that study as reasons for low recruitment rates (Migliorini *et al.*, 2016).

Participant~~'~~s' profiles were similar to those of different SCI specific internet delivered interventions (Migliorini *et al.*, 2016; Verwer *et al.*, 2016), and could be considered broadly representative of the Irish adult SCI population (Burke *et al.*, 2017a). Broadening recruitment methods e.g. direct referral from medical specialists or using social media should be considered in the future main RCT. However the rate achieved, and reasons for non-engagement are comparable.

Maximising participant engagement was a key consideration in the development of SPIRE. It was developed within a Holistic Framework (van Gemert-Pijnen *et al.*, 2011) that advocates end-user involvement as this increases programme engagement, leading to more positive outcomes (Fox, 2009~~;~~ Murray, 2012). Despite this, the engagement with the SPIRE modules at 50% is lower than the 93% reported in a feasibility study in SCI (Dear et al 2103), although similar to other feasibility and RCTs in online PMPs in general (Trompetter et al 2015, Fledderus et al 2015). The inclusion of weekly individual sessions with clinicians to guide interventions could improve outcomes. A peer forum, previously shown to demonstrate comparable effectiveness to the peer-encouragement of face-to-

face support groups was included (Winzelberg *et al.*, 2003; O'Riley *et al.*, 2014). However this was poorly utilised and we need to explore the reasons for this. Previous studies have cited a reluctance to post material that remains visible, a dislike of the group dynamic or feeling an online community is a poor fit for the user (Preece *et al.*, 2004). Clinician support (webinar) generally receive fair engagement, although may be less important where internet delivered programmes are sufficiently engaging, of a high quality and involve screening for suitability (Andersson, 2010; Dear *et al.*, 2015).

The positive association found between engagement with SPIRE content and improved treatment outcomes is promising and similar to findings in other eHealth interventions (Donkin *et al.*, 2011). Attrition rates post progamme for SPIRE at 17% are similar to other internet delivered programmes for those with a SCI; 19% (Migliorini et al 2017), and 15% (Dear et al 2018). The three month follow-up rate for SPIRE at 26% compared well with the 22% rate reported by Dear and colleagues in SCI (2018). These figures also compare favourably with the median withdrawal rate of 27% reported in a systematic review of internet delivered pain programmes (Bender *et al.*, 2011). Future iterations should consider using persuasive technology, a growing research field in eHealth (Kelders *et al.*, 2012).

We found no significant change in the primary outcome measure (WHOQOL-BREF) in the intervention group when compared to the control group over time, although a moderate effect size in favour of the intervention in the psychological sub-scale at the three month follow-up timepoint was noted, demonstrating promise. The baseline QOL scores were not very low which may explain its relative stability over time, as previously reported in hospital-based CBT-PMPs post SCI (Perry *et al.*, 2010; *Heutink et al.*, 2012). The mean time since injury in our study was 15 years, longer than others reported in the literature of 8 years (Dear et al 2018). An earlier intervention may improve QoL outcomes where pain beliefs and behaviours are less entrenched (Heutink *et al.*, 2012), leading to greater life participation and less pain, identified as key mediators of QoL post SCI (Muller *et al.*, 2017).

The secondary outcome measures, also important targets of CBT-PMPs (Nicholas *et al.*, 2012; Nicholas *et al.*, 2014), achieved some significant intervention effects. The reduction in pain-related scores, although similar to internet-delivered programmes for both SCI (Dear et al 2018) and non SCI pain (Bender *et al.*, 2011, Dear et al 2013), contrasts with findings from centre based SCI programmes (Norrbrink Budh *et al.*, 2006; Perry *et al.*, 2010; Burke *et al.*, 2017), and non SCI pain (Blake et al 2016, Fullen et al 2014, Nicholas et al 2012). To allow HCPs to identify patients who are not improving to direct future care, Moore et al., (2010) recommend establishing clinically significant change in outcome measures as helpful approach. Although this study was not powered to detect proportional changes between groups in CSCs, comparable percentage improvements in the intervention group to that in the literature were observed in outcomes of pain at 40%, compared with 31% and 17% (Dear et al 2013, Dear et al 2015), anxiety at 45% compared with 64% and 39% (Dear et al 2013, Dear et al 2015) and depression at 48%, compared with 61% and 40% (Dear et al 2013, Dear et al 2015).

Despite significant differences by group over time in the BPI (interference), this was not replicated in the ISCIPBDS interference items. Both the BPI and the ISCIPBDS interference scales are recommended by expert consensus as outcomes in SCI pain (Bryce *et al.*, 2007; Widerstrom-Noga *et al.*, 2008), *measuring* the same domain. Yet it would appear that these two measures do not present with good concurrent validity. Of note in this study was the BPI (interference) item recorded a short-term medium effect size favouring the intervention group and a longer-term small effect size favouring the control group, raising concern in relation to its reliability.

Including a global rating of improvement offers study participants the ability to integrate into one overall evaluation the different aspects of their response to treatment and can serve as an anchor in determining clinically important differences (Dworkin *et al.*, 2008). Almost half of the SPIRE participants (48%, 13/27) reported being very much or much improved at the three month follow-up, a rating that reflects what patients consider to be important changes (Dworkin *et al.*, 2008), and

could be categorised as clinically significant (Nicholas *et al.*, 2012). However, establishing why 19 participants reported minimal or no change is necessary and will allow for amendments to SPIRE to improve outcomes. Identifying baseline characteristics of these responder participants may assist with future patient stratification to enhance outcomes, as well as determining who does and does not benefit from internet-delivered programmes (Dear *et al.*, 2015). The increased recognition of the usefulness of qualitative research for detailed exploration of the patient perspective (Egan et al 2017), an area often inaccessible in other research methods (Rodham & Osborn 2010) may provide insight. The low number of adverse events recorded demonstrates the appropriateness of the exercise instructions and other programme components. Access to a health professional was a beneficial feature of SPIRE where minor events were noted, and expert advice offered.

To inform future iterations we now need to evaluate SPIRE qualitatively from the participants perspective to understand the participant, treatment and other factors affecting clinical efficacy, safety and acceptability of internet-delivered programmes (Dear *et al.,* 2015). Our six module programme is shorter than most reported in the latest Cochrane review of internet delivered interventions for pain management (Eccleston *et al.*, 2014) with, for the most part comparable results, demonstrating that a short programme can still yield benefits.

The findings of this study should be interpreted in light of the following limitations. Due to the nature of the intervention, it was not possible to blind the participants to the treatment allocation. The control group also did not receive the same level of email contact from the research group as the intervention group. Participants were not restricted from undergoing other concurrent treatments so cannot out rule their potential positive or negative effects. This confounding variable may have been partially controlled for by the inclusion of a control group. People self-selected for this study, so results may not be generalisable to the SCI population overall. Finally, the high attrition rate found during the follow-up period will need to be reviewed and addressed prior to any future studies.

In conclusion we believe that this study adds to the existing literature in demonstrating the potential of an internet-delivered SCI specific CBT-PMP by reporting significant improvements in pain and interference. However, results for the remaining measures (QoL, mood and pain acceptance) while demonstrating small to medium effect sizes in favour of the intervention, did not reach statistical significance. Exploring and implementing participants' feedback and giving further thought to methods for increasing engagement is now needed to improve longer term gain prior to the main RCT. Notwithstanding these issues, we have demonstrated the potential of an internet delivered SCI specific CBT-PMP as a way of increasing access to evidence based care and improving how those with a SCI manage their chronic pain.

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Authors Contributions

All authors contributed significantly to the study: study concept (OL, DB, BMF), design (OL, DB, BMF, CB, MN, ES, SB), programme delivery (MN, SB, ES, FM, JL, L'OC, LM, SC, S NiG), data analysis (CB, OL, DB, BMF), drafting of article (DB, OL, BMF, CB), critical review of manuscript (MN, SB, ES, FM, JL, L'OC, LM, SC, S NiG, OL, DB, CB, BMF). All authors have discussed the results, commented on and agreed the final manuscript.

Conflict of Interest

The authors listed were involved in the development of SPIRE. They have not received any payments for its use.

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able 1 Inclusion and exclusion criteria

Table 1. Study Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
American Spinal Injury Association Impairment Scale (AIS) score A-D (27)	Previous completed a CBT- PMP
Discharged from acute hospital and rehabilitation services	Mental health issues requiring active psychiatric management
Chronic pain (pain > 3months)	Confounding co-morbidities (cancer, unstable angina / uncontrolled cardiac arrhythmias/ severe aortic stenosis, acute systemic infection accompanied by fever, systemic/inflammatory diseases e.g. rheumatoid arthritis) and substance misuse
Over 18 years of age	
Fluency in English (verbal and written	
Regular internet access and basic computer / tablet skills	

Table 2. Outline of SPIRE

Module 1	Member of the MDT involved
Introduction and programme overview	Full MDT
The power of a pain management programme	Rehabilitation Consultant
Pain thoughts and feelings (CBT)	Psychology
Exercise, relaxation and neurophysiological pain processes	Physiotherapy
Living with SCI pain	Patient with SCI pain
Exercise: Warm up exercise routine in sitting	Physiotherapy
Guided relaxation (breathing technique)	Occupational Therapy
Module 2	
Review of last week's content	Physiotherapy
Medical aspects of pain after SCI	Rehabilitation Consultant
Introduction to goal setting	Occupational Therapy
Pacing activities of daily life	Occupational Therapy
Thinking errors (CBT)	Psychology
Exercise: Stretches for upper + lower limbs	Physiotherapy
Guided relaxation (breathing technique)	Occupational Therapy
Module 3	
Review of last week's content	Physiotherapy
Sleep hygiene	Occupational Therapy
Goal setting review	Occupational Therapy
The importance of exercise after SCI	Physiotherapy
Exercise: Strengthening exercises (upper + lower limbs)	Physiotherapy
Guided relaxation (visualisation)	Occupational Therapy
Module 4	
Review of last week's content	Physiotherapy
Medications for SCI pain	Pharmacy
Pain and nutrition	Dietetics
Assertive communication	Psychology
Exercise use for pain management	Patient with SCI pain
Exercise: Aerobic exercise (walking/pushing wheelchair)	Physiotherapy
Guided relaxation (progressive muscle relaxation)	Occupational Therapy
Webinar on programme	Physiotherapy
Module 5	
Review of last week's content	Physiotherapy
Managing pain flare ups	Psychology
Lifestyle and pain management	Physiotherapy
Support networks for managing your pain	Nursing
Coping with SCI pain, advice for family and friends	Patient with SCI pain
Exercise: Pilates exercises in lying + sitting	Physiotherapy
Guided relaxation (visualisation)	Occupational Therapy
Module 6	
Review of last week's content	Physiotherapy
Review of CBT	Psychology
Review of setting goals (short and long term)	Occupational Therapy
Summary of key messages from the programme	Physiotherapy
Using distraction to manage SCI pain	Patient with SCI pain
Exercise: Stretches, strengthening + aerobic exercise.	Physiotherapy
Relaxation (visualisation)	Occupational Therapy

CBT=Cognitive behavioural therapy, SCI=Spinal cord injury, MDT=Multidisciplinary team, += and

Table 3. Characteristics of Participants

Variable	Intervention n=35	Control n=34	Combined Sample n=69
Age (years)			
Mean (sd)	50 (12.3)	52 (13.8)	51 (13.0)
Time post SCI (years)			
Mean (sd)	16 (11.8)	16 (12.6)	16 (12.1)
		n (%)	
Gender			
Male	25 (71)	27 (79)	52 (75)
Female	10 (29)	7 (21)	17 (25)
Relationship Status			
Married/ In a relationship	25 (71)	24 (71)	49 (71)
Single / Separated	9 (26)	10 (29)	19 (28)
Not reported	1 (3)	0 (0)	1 (1)
Employment Status			
Not working / Retired	19 (54)	17 (50)	36 (52)
In Employment/ Training	15 (43)	16 (47)	31 (45)
Not reported	1 (3)	1 (3)	2 (3)
Cause of SCI			
Road traffic accident	10 (29)	7 (21)	17 (25)
Fall	6 (17)	7 (21)	13 (19)
Other traumatic SCI	5 (14)	10 (29)	15 (22)
Non traumatic SCI (medical)	12 (34)	10 (29)	22 (32)
Not reported	2 (6)	0 (0)	2 (3)
Level of SCI			
Cervical SCI	10 (29)	7 (21)	17 (25)
Thoracic SCI	13 (37)	17 (50)	30 (43)
Lumbar SCI	7 (20)	7 (21)	14 (20)
Tetraplegia	10 (29)	7 (21)	17 (25)
Paraplegia	20 (57)	24 (71)	44 (64)
Not reported	5 (14)	3 (9)	8 (12)
Completeness of Injury			
Complete	9 (26)	9 (27)	18 (26)
Incomplete	22 (63)	22 (65)	44 (64)
Not reported	4 (11)	3 (8)	7 (10)
AIS Score			
AIS A	1 (3)	3 (9)	4 (6)
AIS B	0 (0)	2 (6)	2 (3)
AIS C	2 (6)	1 (3)	3 (4)
AIS D	3 (9)	2 (6)	5 (7)
Not reported	29 (83)	26 (76)	55 (80)
Mobility Status			
Manual WC	15 (43)	16 (47)	31 (44)
Electric WC	5 (14)	1 (3)	6 (9)
Walking Independently	6 (17)	9 (26)	15 (22)

Walking with aid(s)	9 (26)	8 (24)	17 (25)
Pain Presentation (DN4)			
Neuropathic pain	17 (49)	27 (79)	44 (64)
Non-Neuropathic pain	18 (51)	7 (21)	25 (36)
Worst Pain (ISCIPC)			
Below-level NP	12 (34)	18 (53)	30 (44)
At-level NP	7 (20)	5 (15)	12 (17)
Musculoskeletal	14 (40)	8 (23)	22 (32)
Visceral	0 (0)	0 (0)	0 (0)
Other pain	0 (0)	1 (3)	1 (1)
Not reported	2 (6)	2 (6)	4 (6)
Second Worst Pain (ISCIPC)			
Below-level NP	8 (23)	9 (27)	17 (25)
At-level NP	3 (9)	6 (18)	9 (13)
Musculoskeletal	15 (43)	8 (24)	23 (33)
Visceral	2 (6)	1 (3)	3 (4)
Other pain	2 (6)	3 (9)	5 (7)
Not reported	5 (14)	7 (20)	12 (18)
Third Worst Pain (ISCIPC)			
Below-level NP	4 (11)	6 (18)	10 (15)
At-level NP	0 (0)	1 (3)	1 (1)
Musculoskeletal	6 (17)	4 (11)	10 (15)
Visceral	1 (3)	1 (3)	2 (3)
Other pain	0 (0)	1 (3)	1 (1)
Not reported	24 (69)	21 (62)	45 (65)
Pain medication use in past 6 months, n (%)			
Yes	32 (91)	30 (88)	63 (91)
Acetaminophen	23 (66)	19 (56)	42 (61)
NSAIDs	15 (43)	11 (32)	26 (38)
Anti-convulsants	18 (51)	18 (53)	36 (52)
Anti-depressants	3 (9)	10 (29)	13 (19)
Opioids	10 (29)	10 (29)	20 (29)
Topical agents	3 (9)	5 (15)	8 (12)
Other	2 (6)	2 (6)	4 (6)

AIS; American Spinal Injury Association Impairment Scale, NP; neuropathic pain, n; number, sd; standard deviation, SCI; spinal cord injury, ISCIPC; International Spinal Cord Injury Pain Classification,%;percent. AIS,

American Spinal Injury Association Impairment Scale;DN4, Douleur Neuropathique en 4 Questions; n, number; SCI, spinal cord injury;sd, standard deviation; WC, wheelchair.