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**TITLE PAGE**

A randomised, waiting list controlled trial of cognitive-behavioural therapy for persistent postconcussional symptoms after predominantly mild-moderate traumatic brain injury

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**ABSTRACT**

## Background

Persistent post-concussional symptoms (PCS) can be a source of distress and disability following traumatic brain (TBI). Such symptoms have been viewed as difficult to treat but may be amenable to psychological approaches such as cognitive behaviour therapy (CBT).

## Objectives

To evaluate the effectiveness of a 12-session individualised, formulation-based CBT program.

## Method

Two-centre randomised waiting list controlled trial with 46 adults with persistent PCS after predominantly mild-to-moderate TBI (52% with PTA  $\leq$  24 hours), but including some with severe TBIs (20% with PTA  $>$  7 days).

## Results

Improvements associated with CBT were found on the primary outcome measures relating to quality of life (using the Quality of Life Assessment Schedule and the Brain Injury Community Rehabilitation Outcome scale). Treatment effects after covarying for treatment duration were also found for postconcussional symptoms and several secondary outcomes including measures of anxiety and fatigue (but not depression or PTSD). Improvements were more apparent for those completing CBT sessions over a shorter period of time, but were unrelated to medicolegal status, injury severity or length of time since injury.

## Conclusions

This study suggests that CBT can improve quality of life for adults with persistent PCS, and potentially reduce symptoms for some, in the context of outpatient brain injury rehabilitation services.

## Trial registration

ISRCTN49540320

## INTRODUCTION

Traumatic brain injury (TBI) is associated with a range of cognitive, emotional and physical symptoms. In the context of mild TBI (MTBI), the label postconcussional symptoms (PCS) is commonly applied to reported problems including difficulty with concentration and memory, irritability, depression and anxiety, and physical symptoms such as fatigue, headaches, dizziness.[1] Such symptoms are common in the first few days or weeks after injury, but typically improve and remit. However, in a minority these symptoms persist.[2] When lasting beyond three months post-MTBI, they are viewed as problematic and likely to be chronic[3] or even worsen[4] and have previously been viewed as resistant to treatment.[5] Although the term PCS is typically associated with MTBI, the same constellation of symptoms can be reported after more severe injuries, although their aetiology and course may differ.[6] With this caveat, “PCS” will be used here, operationally, to describe the set of self-reported persistent postconcussional or PCS-like symptoms across a spectrum of TBI severity.

There is growing evidence indicating that psychosocial factors influence the persistence of PCS after MTBI [7-11] and overlapping symptoms or outcomes such as anxiety, depression and employment status in studies including individuals with severe TBIs.[12,13] Lishman[14] suggested that while direct effects of brain injury may contribute towards early PCS, persistence may increasingly involve broader psychosocial factors and mechanisms. Similar diathesis-stressor models have been described [15,16] where symptoms are maintained via “vicious cycles” involving factors indirectly related or independent of any direct effects of brain injury. If this is the case then psychological approaches to management may be applicable and effective in helping address or manage symptoms across a continuous spectrum of TBI severity, including more-than-mild TBIs, acknowledging that the likelihood and degree of persisting difficulties related to brain injury increases as injury severity increases.

Although supported by expert opinion, [17] evidence for the effectiveness of cognitive-behavioural therapy (CBT) to tackle persistent PCS is limited.[18] Trials incorporating CBT for individuals with TBI have tended to focus on specific symptoms such as depression,[19] insomnia,[20] or

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3 headache.[21] Typically using single-case or case series designs, results do point to possible  
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5 improvements in these domains using CBT. There is some support for prophylactic interventions in  
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7 patients at risk for persistent PCS in some[22] but not all studies.[23] Only one RCT has specifically  
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9 focussed on persistent PCS [24] randomising 20 individuals with mild-moderate TBI (seen on average  
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11 between 5 and 6 years post-injury) to a waiting list group or an intensive neuropsychological  
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13 rehabilitation treatment program (5 hours per week for 11 weeks) combining CBT and cognitive  
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15 remediation. Improvements were demonstrated on a global symptom measure, in symptoms  
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17 associated with anxiety and depression, and some measures of cognitive functioning (although not  
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19 subjective functioning). The relative contribution of the CBT and cognitive remediation components  
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21 could not be assessed and it is unclear whether improvement could be achieved using CBT alone.  
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24  
25 The current study tested the impact of individual, formulation-driven CBT, without explicit cognitive  
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27 remediation or cognitive rehabilitation. The study was conducted as a preliminary RCT (with waiting  
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29 list control) delivered in the context of two outpatient brain injury services. Eligibility criteria were  
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31 designed to help ensure that the results would be generalizable to routine clinical practice. It was  
32  
33 predicted that individuals would report reduced PCS and greater quality of life and health status after  
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35 receiving CBT when compared with those in the control group. Supplementary analyses examined the  
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37 impact on specific domains of PCS and quality of life, such as symptoms associated with depression,  
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39 PTSD, pain and fatigue.  
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## 43 **METHODS**

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45 Participants were randomised to the immediate Intervention group or waiting list Control group: the  
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47 latter were offered treatment at the end of the waiting list period. There was no financial incentive or  
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49 other compensation offered to participate in the study. Ethical approval was received by the  
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51 committees overseeing the two trial sites. The trial was registered with the International Standard  
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53 Randomised Controlled Trial Number Register (ISRCTN49540320).  
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## 56 **Recruitment**

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3 Participants were recruited through consecutive out-patients referrals to two National Health Service  
4 secondary/tertiary care brain injury clinics at the Lishman Brain Injury Unit at South London and  
5 Maudsley NHS Foundation Trust, London, UK, and the Brain Injury Rehabilitation Unit, at Edgware  
6 Community Hospital, London, UK, between March 2003 and June 2009.  
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13 Inclusion criteria were age between 18 and 65 at the time of initial assessment; evidence for (at  
14 minimum) a mild traumatic brain injury (MTBI)[25] at least six months before; and symptoms  
15 consistent with the ICD-10 criteria for Postconcussional Disorder (F07.2), as laid out in the  
16 Diagnostic Criteria for Research (DCR-10).[1]  
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23 Exclusion criteria were: non-fluent English; Mini Mental State Exam[26] scores of less than 20 and/or  
24 Frontal Assessment Battery[27] scores of less than 10; moderate-severe physical disability  
25 (Barthel[28] score less than 15); previous receipt of 4 or more sessions of CBT after their TBI; other  
26 neurological disorder independent of the TBI (e.g. non-post-traumatic epilepsy); drug/alcohol misuse  
27 meeting ICD-10[29] criteria for a dependence syndrome (F1x.2); and clinically-assessed risk of self-  
28 harm or severe psychiatric illness necessitating involvement of a Community Mental Health Team.  
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38 Potential participants were screened for eligibility at an initial neuropsychiatric or multidisciplinary  
39 assessment, and offered a neuropsychological assessment and feedback session if this had not been  
40 completed previously. In the absence of consistent contemporaneous injury severity information from  
41 GCS or post-traumatic amnesia (PTA), the latter was retrospectively estimated at initial assessment(s)  
42 using the Rivermead protocol[30] which provides reasonable accuracy in terms of overall categorical  
43 classification of TBI severity.[31] Median PTA duration was 24 hours (Intervention: 30 hours, range  
44 0-1440 hours; Control: 16 hours, range 0-1800 hours).  
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54 All eligible participants were invited to participate. After providing informed consent, but before  
55 randomization, participants completed the first (T1) set of outcome measures with the study therapist.  
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Their general practitioner was requested that, as far as possible, any psychoactive medications were kept constant, and to inform the project team of any changes.

### Randomisation

Independent randomization was carried out independently by a Clinical Trials Unit using four pre-planned categorical variables for minimisation with an 80/20 minimised/random weighting applied case-by-case: site (Maudsley: Edgware); injury severity (PTA  $\leq$  24 hours [mild]:  $>$  24hrs PTA  $\leq$  7 days [moderate]: PTA  $>$  7 days [severe]); length of time since injury (6 to  $<$  12 months: 12-24 months  $>$ 24 months), and medicolegal status (previous or current involvement, vs. no previous/current involvement). A minimum of 40 participants was recommended for randomization with 4 minimization factors: sample size was determined on that basis, with a minimum of 20 participants per group.

Flow through the study is shown in Figure 1, with 26 randomised to the Intervention arm and 20 to the Control arm. Median interval between injury and randomization was 25 months (Intervention: 28 months, range 6-171); Control: 23 months, range 8-175). Demographic details of the participants are shown in Table 1. There were no significant differences between the two groups at T1 on any minimisation variables (all  $p$ 's  $>$  0.4) or gender ( $\chi^2$  (1)=0.450;  $p=0.502$ ), age ( $t$  (1)=-0.86;  $p=0.393$ ), education ( $t$  (1)=-0.109;  $p=0.914$ ) or current occupational level ( $\chi^2$  (2)=0.073;  $p=0.964$ ) (Table 1). PTA duration did differ between the groups (Mann-Whitney  $U=225.5$ ;  $p=0.44$ ).

Table 1: Individual demographic and injury characteristics at T1 (before randomisation)

	Intervention Group	Waiting List Group	Total sample
	(n = 26)	(n = 20)	(N = 46)
Age	40.1 $\pm$ 10.3	43.1 $\pm$ 13.1	41.4 $\pm$ 11.6
Gender (male)	58% (15)	50% (10)	54% (25)
Education (years)	15.0 $\pm$ 2.8	15.1 $\pm$ 3.4	15.0 $\pm$ 3.0



Qualifications (or equivalent) obtained			
No qualifications	4% (1)	10% (2)	7% (3)
GCSE	31% (8)	20% (4)	26% (12)
A-Level	12% (3)	25% (5)	17% (8)
Undergraduate degree	35% (9)	20% (4)	28% (13)
Postgraduate degree	19% (5)	25% (5)	22% (10)
Employment status			
Full-time	27% (7)	30% (6)	28% (13)
Part-time	19% (5)	20% (4)	20% (9)
Unemployed	54% (14)	50% (10)	52% (24)
Injury Type			
Road traffic accident	62% (16)	55% (11)	59% (27)
Assault	12% (3)	10% (2)	11% (5)
Other	27% (7)	35% (7)	30% (14)
PTA duration (hours)			
≤ 24 hours [mild]	170 ± 354	138 ± 399	156 ± 370
> 24 hours, ≤ 7 days [moderate]	46% (12)	60% (12)	52% (24)
> 7 days [severe]	31% (8)	25% (5)	28% (13)
> 7 days [severe]	23% (6)	15% (3)	20% (9)
Time since injury (months)			
6 – 12 months	42 ± 39	34 ± 38	39 ± 39
> 12 months, ≤ 24 months	23% (6)	35% (7)	28% (13)
> 24 months	23% (6)	15% (3)	20% (9)
> 24 months	54% (14)	50% (10)	52% (24)
Previous or current involvement in litigation (yes)			
Current litigation (yes)	73% (19)	70% (14)	72% (33)
Site of treatment (% Maudsley)	85% (22)	90% (18)	87% (40)

Values are shown as either mean ± *SD* or percentage (n)

### Outcome Measures

Outcome measures are shown in Table 2. Three co-primary outcome measures examined broad aspects of PCS and their impact. Six secondary outcome measures were used to examine more specific domains (such as those relating to depression or fatigue), as well as a supplementary quality of life scale.

**Table 2: Primary and secondary outcome measures**

Primary outcome measures	Description	Index (cut-off if applicable)
Rivermead Post Concussion Symptoms Questionnaire (RPQ)[32]	16-item measure of the severity and impact of PCS	Total score (>12)[33]
Brain Injury Community Rehabilitation Outcome scale (BICRO-39)[34]	39-item measure of functioning and disability	Total and subscale scores
Quality of Life Assessment Schedule (QOLAS)[35]	10-item personalized measure of quality of life and health status.	Total score
Secondary outcome measures		
Hospital Anxiety and Depression Scale (HADS)[36]	14-item measure of anxiety and depression	Anxiety (HADS-A) and Depression (HADS-D) subscale totals (>10).
Impact of Event Scale - Revised (IES-R)[37]	22-item measure of PTSD	Total score (>32)[38]
Checklist of Individual Strength (CIS20R)[39]	20-item measure of fatigue	Total score (cut-off of $\geq 40$ for the "subjective fatigue" subscale)[40]
McGill Pain Questionnaire (MPQ)[41]	Multi-dimensional assessment of pain	Present Pain Intensity
State-Trait Anger Expression Inventory-2 (STAXI-2)[42]	57-item measure of state/trait anger and anger expression	Anger Expression Index, raw score
EuroQoL from EQ-5D[43]	Visual analogue scale of global	

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subjective health rating (0-100).

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For the QOLAS, individuals are asked to identify their two greatest problems/issues in each of five different domains: physical health, cognitive problems, psychological issues, social issues, and daily activities. Each problem is rated on a 0-5 scale (from to “no problem” to “it could not be worse”) and the items summed. Validity, reliability and sensitivity to change for the QOLAS has been shown in other clinical populations.[35,44] It was judged particularly suitable for assessing PCS due to the potential heterogeneity of symptoms, and to help identify those symptoms most troubling to an individual and prioritise them during treatment.. Blind expert rating of individual responses in the physical, psychological and cognitive domains indicated that 84.2 % were directly/closely related to DCR-10 description of Postconcussional Disorder;[1] 10.2% as indirectly/partially related; and only 5.5% not apparently/obviously related.

With the exception of the EuroQol, higher scores on all of the outcome measures indicate a greater degree of symptoms, distress or impact. All measures were self-report and therefore non-blind. Assessments were completed prior to randomization (T1) and at the end of treatment (Intervention arm) or after 4-months (Control arm) (T2).

#### **Treatment methods: CBT format and content**

The planned intervention comprised 12 weekly one-hour sessions of individual CBT, but the protocol allowed for longer inter-session intervals. Treatment was provided by the same therapist (SP), a clinical neuropsychologist with previous experience of CBT in the context of TBI, depression and chronic fatigue syndrome.

Given the heterogeneity of PCS, an individualised, formulation-driven approach within a semi-structured protocol was used. Agenda-based sessions, collaborative target-setting and homework tasks were central features of treatment. Details of the intervention are described in more detail elsewhere

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3 [16] and in the supplementary online information. A session structure similar to that described by  
4 Miller and Mittenberg[45] was used. The first three sessions were broadly focussed on problem  
5 identification, psychoeducation based on a range of sources, socialising the patient to the CBT model,  
6 and formulation. Sessions 4-12 focussed on the individual target problems identified collaboratively  
7 with the therapist. In the final 3 sessions, time was increasingly focussed on relapse prevention and  
8 how to maintain therapeutic gains. Copies of the protocol and booklets are available from the authors  
9 on request.  
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19 Central to individual CBT case formulations were (a) that persistent PCS could be maintained or  
20 exacerbated by vicious cycles[15] (b) that these cycles could be understood by reciprocal relationships  
21 between thoughts, emotions and actions, and (c) that alleviation in symptoms, associated distress and  
22 functional limitations was possible by changing thinking and behaviour. Whilst it was recognised in  
23 the treatment protocol that persistent cognitive difficulties attributable to the injury might exist for  
24 some individuals (especially for more-than-mild injuries),[46] no attempt was made to provide  
25 explicit cognitive remediation or rehabilitation. With increasing injury severity and more-than-mild  
26 TBIs, psychological mechanisms were framed as likely to still play an important role in maintaining  
27 ongoing symptoms via “vicious cycles”, presenting a therapeutic target for CBT to help reduce  
28 symptoms and their impact. Overt resistance to psychologically-orientated treatment did not appear to  
29 be a common issue for individuals completing the initial screening assessments but who did not wish  
30 to take part in the trial. Although the reasons for declining participation were not systemically  
31 collected, of the 21 individuals who declined, 9 were prepared to be referred for CBT outside the trial,  
32 and another 5 cited distance as an obstacle to attending regular treatment sessions.  
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#### 49 **Control waiting list group**

50 Individuals randomised to the Control arm received a letter following randomisation with the date of  
51 an out-patient appointment to complete the T2 measures. Patients in this arm did not receive any form  
52 of additional information or psychological intervention from the service for the period that they were  
53 on the waiting list.  
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5 Participants in both groups were offered clinical follow-up after their CBT sessions finished.  
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### 8 9 **Statistical Analyses**

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11 Analysis was planned on an intention-to-treat basis. In practice almost all individuals in the  
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13 Intervention arm completed their course of CBT and T2 outcome measures: three individuals stopped  
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15 after 8, 9 and 10 sessions respectively due to significant symptom improvement and a lack of  
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17 outstanding treatment targets. Only one patient discontinued treatment after 6 sessions and was lost to  
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19 follow up due to difficulties attending the sessions. No attempt was made to impute missing data for  
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21 this one case.  
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25 Data were double-entered from the completed paper forms on to computer, and analysed using SPSS  
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27 15.0. For the main treatment effects, analysis of covariance (ANCOVA) was used,[47] comparing  
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29 outcome between groups at T2 with T1 as a covariate: effect sizes are shown using partial eta squared  
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31 and an estimate of Cohen's  $d$  ( $\bar{d}$ ), calculated as the mean difference between the contrasts divided by  
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33 square root of the mean squared error.  
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37 It was predicted that the Intervention arm would report fewer symptoms and better quality of life after  
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39 CBT compared with those in the Control arm after their time on the waiting list. Given the  
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41 exploratory nature of the study and the paucity of evidence from relevant previous controlled trials,  
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43 primary outcome measures were analysed independently without correction for multiple comparisons.  
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45 For secondary outcomes, corrections for multiple comparisons were applied using the Benjamini and  
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47 Hochberg method.[48]  
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51 Mean duration of the T1-T2 interval for the Intervention arm was 29 weeks (SD=10.3, median=26,  
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53 range 14-53) and 17 weeks for Control arm (SD=2.9, median=17, range 11-24) (Mann-Whitney -  
54  
55  $U=46.0$ ;  $p<0.001$ ), producing a potential confound to the analyses. The analyses therefore also  
56  
57 included T1-T2 interval as a covariate.  
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## RESULTS

Data for the primary and secondary outcome measures at T1 (baseline) and T2 are shown in Table 3.

The two groups were broadly similar at baseline in terms of symptoms and quality of life reported: there were no significant differences between the Intervention and Control arms at T1 on any of the primary or secondary outcome measures ( $p>0.05$ ) after correcting for multiple comparisons on the latter.

Table 3: Summary data for primary and secondary outcome measures

Outcome measure	Intervention Group (n = 25)		Control group (n = 20)	
	T1	T2	T1	T2
RPQ	34.1 ± 11.4 (100%)	26.3 ± 16.4 (76%)	33.4 ± 9.2 (100%)	27.8 ± 9.0 (95%)
QOLAS	35.6 ± 6.9	27.0 ± 10.5	36.4 ± 6.7	33.5 ± 8.2
BICRO-39	85.7 ± 23.1	80.6 ± 24.6	76.5 ± 16.5	80.5 ± 17.3
- Personal care	2.3 ± 6.3	1.7 ± 3.9	0.2 ± 0.7	0.3 ± 1.1
- Mobility	7.2 ± 7.4	6.5 ± 6.7	4.4 ± 3.7	5.4 ± 5.2
- Self-organisation	9.2 ± 8.7	9.0 ± 8.5	7.3 ± 8.0	7.7 ± 7.2
- Contact (partner/children)	5.7 ± 3.9	5.4 ± 4.4	3.1 ± 3.6	3.8 ± 3.3
- Contact (parents/siblings)	10.1 ± 3.1	10.5 ± 2.5	9.5 ± 4.7	10.0 ± 3.7
- Socialising	18.6 ± 5.7	18.8 ± 4.3	19.1 ± 5.0	7.0 ± 5.2
- Productive employment	16.5 ± 2.8	15.6 ± 3.6	15.7 ± 3.5	15.9 ± 3.7
- Psychological well-being	16.1 ± 6.4	13.2 ± 6.9	17.3 ± 5.8	17.4 ± 7.0
HADS-A	9.9 ± 4.8 (44%)	8.9 ± 4.9 (40%)	11.8 ± 3.9 (70%)	11.0 ± 4.1 (55%)
HADS-D	8.9 ± 4.0 (44%)	7.7 ± 5.0 (28%)	8.9 ± 3.3 (40%)	8.6 ± 4.5 (20%)
IES-R	27.0 ± 20.1 (32%)	20.8 ± 18.7 (28%)	29.5 ± 20 (40%)	25.3 ± 19.9 (40%)
CIS20R	98.2 ± 19.5 (76%)	86.8 ± 25 (40%)	104.2 ± 18 (75%)	100.8 ± 26.3 (75%)
STAXI-2	41.8 ± 14.1	36.7 ± 16	42.1 ± 17.6	40.4 ± 18.0
MPQ	1.6 ± 1.3	1.7 ± 1.3	1.2 ± 1.0	1.4 ± 0.9

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3 EuroQol 57.2 ± 15.9 65.3 ± 16.3\* 46.7 ± 15.5 52.7 ± 18.4  
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5 Values are mean ± SD (% above cut-off, where applicable); table shows data for individuals with data at both T1 and  
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7 T2 (n=45); \*n=24 due to missing data  
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### 10 **Effects of treatment on primary and secondary outcome measures**

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12 A significant treatment effect was noted for quality of life as assessed by the QOLAS (Table 4 &  
13  
14 Figure 2). For postconcussional symptoms (RPQ) the findings were only significant when using T1-  
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16 T2 interval as a covariate (Table 4).  
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20 No treatment effect was noted in terms of global functioning (BICRO-30). Previous research into  
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22 broader community rehabilitation using the BICRO-39 has indicated individual scales may be more  
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24 sensitive to change than the total score:[49] these scale scores are also given in Table 4. Psychological  
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26 Well-Being and Socialising showed evidence of a treatment effect (the latter only when using T1-T2  
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28 interval as a covariate), with little overall change in the other subscales in either group.  
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Table 4: Analyses of primary and secondary outcome measures, with T1-T2 interval as covariate

		Without T1-T2 interval as covariate									With T1-T2 interval as covariate							
		T1 (adjusted)	T2 (adjusted)		Difference	95% CI	p	Effect Size		T2 (adjusted)	Difference	95% CI	p	Effect Size				
			Intervention	Control				†	‡					Intervention	Control	†	‡	
Primary	RPQ	33.78	26.00	28.10	2.09	(-3.85 to 8.03)	$F(1, 42) = 0.51$	0.481	0.012	0.21	23.62	31.07	7.46	(0.42 - 14.50)	$F(1, 41) = 4.578$	0.038*	0.100	0.81
	QOLAS	35.93	27.32	33.11	5.79	(0.97 to 10.61)	$F(1, 42) = 5.886$	0.020*	0.123	0.73	25.64	35.21	9.57	(3.78 - 15.37)	$F(1, 41) = 11.120$	0.002*	0.213	1.26
	BICRO-39	81.57	77.87	83.97	6.10	(-4.35 to 16.55)	$F(1, 42) = 1.387$	0.245	0.032	0.36	77.56	84.35	6.80	(-6.19 - 19.79)	$F(1, 41) = 1.117$	0.297	0.027	0.40
BICRO subscales	Personal care	1.36	1.56	0.45	-1.12	(-2.96 to 0.73)	$F(1, 42) = 1.491$	0.229	0.034	-0.38	1.50	0.53	-0.97	(-3.28 to 1.35)	$F(1, 41) = 0.710$	0.414	0.017	-0.32
	Mobility	5.94	5.74	6.33	0.59	(-2.46 to 3.65)	$F(1, 42) = 0.154$	0.697	0.002	0.12	6.26	5.68	-0.57	(-4.32 to 3.1)	$F(1, 41) = 0.096$	0.759	0.002	-0.12
	Self-organisation	8.36	8.45	8.44	0.00	(-3.26 to 3.26)	$F(1, 42) = 0.000$	0.998	0.000	0.00	9.10	7.63	-1.47	(-5.52 to 2.58)	$F(1, 41) = 0.537$	0.468	0.013	-0.28
	Contact (partner/children)	4.53	4.52	4.95	0.43	(-1.21 to 2.06)	$F(1, 42) = 0.276$	0.602	0.007	0.17	4.15	5.41	1.26	(-0.76 to 3.27)	$F(1, 41) = 1.593$	0.214	0.037	0.50
	Contact (parents/siblings)	9.82	10.29	10.19	-0.10	(-1.25 to 1.04)	$F(1, 42) = 0.033$	0.857	0.001	-0.05	10.40	10.05	-0.34	(-1.80 to 1.11)	$F(1, 41) = 0.229$	0.635	0.006	-0.18
	Socialising	18.82	18.86	20.02	1.16	(-1.07 to 3.40)	$F(1, 42) = 1.108$	0.299	0.026	0.32	17.83	21.32	3.49	(0.89 to 6.09)	$F(1, 41) = 7.325$	0.010*	0.152	1.03
	Productive employment	16.13	15.26	16.23	0.97	(-0.49 to 2.44)	$F(1, 42) = 1.802$	0.187	0.041	0.41	15.34	16.12	0.78	(-1.08 to 2.63)	$F(1, 41) = 0.715$	0.403	0.017	0.32
	Psychological well-being	16.60	13.66	16.77	3.11	(0.42 to 5.81)	$F(1, 42) = 5.429$	0.025*	0.114	0.70	12.54	18.18	5.64	(2.49 to 8.80)	$F(1, 41) = 13.069$	0.001*	0.242	1.37
Secondary	HADS-A	10.74	9.43	10.37	0.94	(-1.41 to 3.30)	$F(1, 42) = 0.654$	0.423	0.015	0.25	8.25	11.84	3.59	(1.03 to 6.15)	$F(1, 41) = 8.003$	0.007*	0.163	1.06
	HADS-D	8.90	7.70	8.62	0.92	(-1.06 to 2.91)	$F(1, 42) = 0.882$	0.353	0.021	0.28	7.25	9.19	1.94	(-0.531 to 4.44)	$F(1, 41) = 2.513$	0.121	0.058	0.60
	IES-R	28.11	21.48	24.40	2.92	(-5.49 to 11.32)	$F(1, 42) = 0.044$	0.853	0.012	0.26	19.19	27.26	8.06	(-2.28 to 18.41)	$F(1, 41) = 2.479$	0.123	0.057	0.59
	CIS20R	100.82	89.04	97.98	8.94	(-3.48 to 21.36)	$F(1, 42) = 2.112$	0.153	0.048	0.44	85.26	102.70	17.44	(2.34 to 32.53)	$F(1, 41) = 5.441$	0.025*	0.117	0.89
	STAXI-2	41.93	36.80	40.30	3.50	(-2.65 to 9.65)	$F(1, 42) = 1.317$	0.258	0.030	0.34	34.31	43.41	9.10	(1.826 to 16.370)	$F(1, 41) = 6.384$	0.015*	0.135	0.95
	MPQ	1.40	1.61	1.51	-0.10	(-0.71 to 0.51)	$F(1, 42) = 0.112$	0.739	0.003	-0.10	1.57	1.56	-0.12	(-0.78 to 7.52)	$F(1, 41) = 0.001$	0.974	0.000	-0.12
	EuroQoI	52.57	69.93	55.59	-7.34	(-17.46 to 2.77)	$F(1, 41) = 1.433$	0.238	0.050	-0.47	67.74	49.82	-17.92	(-28.57 to -7.26)	$F(1, 40) = 11.555$	0.002*	0.224	-1.31

\*p&lt;0.05; †partial eta squared; ‡Cohen's d



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3 FIGURE 2 AROUND HERE  
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7 For secondary outcome measures, treatment effects were only noted after covarying for T1-T2  
8 interval, for anxiety (HADS-A), fatigue (CIS20R), anger (STAXI-2) and a quality of life (EuroQol).  
9 These results remained significant after correcting for multiple comparisons. No treatment effects  
10 were found for depression (HADS-D), symptoms associated with PTSD (IES-R) or pain (MPQ).  
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17 Examination of the data indicated that, where T1-T2 interval was a significant covariate, *shorter*  
18 intervals were associated with *better* outcomes. This is illustrated by the data for PCS symptom  
19 severity (RPQ) (Figure 3) after dividing the Intervention arm into those completing treatment more  
20 quickly (n=13) and slowly (n=12) based on a median T1-T2 interval split of 188/189 days. Those  
21 taking longer to complete CBT show little change while those who completed CBT more quickly  
22 demonstrate larger improvements. This was in contrast to the possibility that a longer interval might  
23 allow additional time for individuals to show recovery, and be associated with better outcomes.  
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33 FIGURE 3 AROUND HERE  
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35 Uncorrected *post hoc* t-tests on unadjusted means were completed to explore within-group changes  
36 from T1 to T2 on those measures showing a significant difference between the Intervention and  
37 Control conditions on ANCOVA at T2 after covarying for treatment duration. For primary outcome  
38 measures, both the Intervention ( $t(24)=3.32, p=0.003$ ) and Control ( $t(19)=4.00, p=0.001$ ) groups  
39 showed statistically significant improvements on the RPQ over this period, with a similar results for  
40 the QOLAS (Intervention:  $t(24)=4.55, p<0.001$ ; Control:  $t(19)=2.29, p=0.034$ ). The Intervention  
41 group showed a significant improvement on the Psychological Well-Being subscale from the BICRO  
42 ( $t(24)=2.99, p=0.006$ ), whereas the Control group did not ( $t(19)=0.12, p=0.197$ ). Neither group  
43 showed evidence of significant improvement on Socialising on the BICRO (Intervention:  $t(24)=0.12,$   
44  $p=0.903$ ; Control:  $t(19)=1.35, p=0.197$ ). For secondary outcome measures, the Intervention group  
45 showed significant improvements on the CIS-20R ( $t(24)=2.91, p=0.008$ ), STAXI-2 ( $t(24)=2.20,$   
46  $p=0.038$ ) and EuroQol ( $t(23)=2.18, p=0.040$ ), whilst the Controls did not show any improvements  
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on these variables ( $t(19)=0.71, p=0.785$ ;  $t(19)=0.90, p=0.382$ ;  $t(19)=1.58, p=0.132$ ). Neither group showed evidence of significant improvement on HADS-A (Intervention:  $t(24)=1.01, p=0.323$ ; Control:  $t(19)=1.18, p=0.253$ ).

### Factors moderating treatment effects

To explore the possible influence of other factors on improvements in the Intervention group, data from the QOLAS was examined, as it showed the largest effects of treatment. Those factors used as minimisation variables at randomisation were considered separately as additional categorical factors: data stratified by these variables is shown in Table 5. Neither injury severity ( $F(2)=0.33, p=0.72$ ), length of time since injury ( $F(2)=1.09, p=0.36$ ), medicolegal status ( $F(1)=1.20, p=0.29$ ), nor treatment site ( $F(1)=0.02, p=0.90$ ) were related to outcome. Current (as opposed to either previous or current) medicolegal involvement was also unrelated to outcome ( $F(1)=0.19, p=0.67$ ).

Table 5: Summary data for QOLAS, stratified by TBI severity, length of time since injury and medicolegal status

	Intervention Group			Control group		
	n	T1	T2	n	T1	T2
TBI severity						
Mild	12	34.0 ± 8.3	24.5 ± 12.0	12	35.8 ± 6.8	32.7 ± 9.9
Moderate	7	37.1 ± 6.0	28.2 ± 8.2	5	37.4 ± 6.9	34.1 ± 3.9
Severe	6	36.9 ± 4.7	30.6 ± 10.1	3	37.2 ± 8.4	35.7 ± 8.0
Time since injury						
6 – 12 months	6	34.9 ± 7.9	21.7 ± 10.0	7	36.6 ± 4.7	33.9 ± 4.8
≤ 24 months	5	30.0 ± 7.0	24.1 ± 7.9	3	34.8 ± 4.4	27.5 ± 11.8
> 24 months	14	37.8 ± 5.5	30.4 ± 10.8	10	36.8 ± 8.6	35.0 ± 9.1
Medicolegal status						
Previous/current	19	36.7 ± 7.0	28.9 ± 9.4	14	36.0 ± 7.4	33.4 ± 8.9

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None	6	32.0 ± 5.4	20.9 ± 12.4	6	37.3 ± 5.0	33.8 ± 7.2
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Values are shown as mean ± SD; table shows data for individuals with data at both T1 and T2 (n=45)

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## DISCUSSION

This study, consistent with positive findings from a previous RCT,[24] found that individual CBT improved the quality of life for patients with persistent postconcussional symptoms. CBT also appeared to be effective in alleviating postconcussional symptoms in those patients who completed treatment more quickly. Possible benefits on a range of secondary outcomes including anxiety, fatigue and anger were also noted, albeit only after treatment duration was considered as a covariate. Some outcome measures showed medium to large effect sizes from before to after treatment, although the mean scores of the CBT group indicated that a majority of patients were not symptom- or problem-free at the end of treatment (as with the previous trial[24]), although 24% of treatment completers fell below a proposed clinical cut-off of 12 or less on the RPQ.[33] The current study also demonstrates that clinical improvement in PCS is possible using CBT without an explicit cognitive remediation component, and with a programme of only 12 hours of patient-therapist contact. Contrary to expectations, neither medicolegal status, injury severity nor length of time since injury had significant effects on improvements in the CBT group.

Of the outcome measures used, the QOLAS gave the most robust evidence for an effect of CBT, perhaps because it captured specific symptoms identified by the patient as directly relevant to their quality of life. Its identification of “key” problem areas also helped identify personal treatment targets for therapy, increasing its sensitivity to change and its clinical utility. The potential advantages for individualised patient reported outcome measures and their responsiveness to change has led to their appearance into brain injury rehabilitation via methods such as Goal Attainment Scaling.[49]

Contrary to expectations that persistent symptoms are static or may even worsen with time, individuals in the control group did show evidence of improvements over their waiting list period in terms of postconcussional symptoms (RPQ) and their impact on quality of life (QOLAS). The neuropsychiatric and neuropsychological assessment, feedback and prospect of either immediate or

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3 delayed treatment may have contributed to this change, by providing a coherent possible explanation  
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5 for symptoms and offering hope that change and improvement was possible.[50]  
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9 There was no evidence for significant effects of treatment on depression or PTSD, both of which have  
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11 been linked with PCS.[9] This may have been due to floor effects as less than 50% of individuals  
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13 scored above clinical cut-offs on the HADS-Depression and RIES at the initial assessment. However,  
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15 the results imply that general improvement in PCS and quality of life were not simply mediated by  
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17 improved mood.  
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21 The impact of the time taken to complete CBT was noteworthy. Not using treatment duration as a  
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23 covariate removed positive group differences for postconcussional symptoms (as measured by the  
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25 RPQ), although those for quality of life (QOLAS and BICRO-Psychological Well-Being) remained.  
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27 Session frequency may be a factor, with evidence that increased intensity may be associated with  
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29 better outcomes in psychological therapies in other areas,[51] although this may not always be the  
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31 case.[52] Faster completion may also have indicated greater engagement to therapy. Although the  
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33 large majority completed therapy, a longer time to complete the CBT sessions was often due to  
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35 patients repeatedly cancelling and re-arranging appointments, perhaps reflecting lower commitment.  
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37 Whatever the source of this effect, it does indicate that there may be significant variability between  
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39 individuals with persistent PCS in their treatment response to CBT.  
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44 Caution should be exercised in the interpretation of the null results from the moderator analyses  
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46 examining the impact of variables possibly affecting treatment response, such as injury severity and  
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48 medicolegal status. The relationship between injury severity and treatment response may be complex:  
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50 a residential programme focussing on treating PTSD in military veterans found that individuals with  
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52 moderate-severe TBIs showed greater improvements in their PTSD symptoms compared with those  
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54 with mild TBIs.[53] Although compensation seeking has been associated with increased symptom  
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56 report even after early intervention,[54] medicolegal status itself may serve as a poor proxy for  
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58 phenomena such as poor effort or malingering in neuropsychological assessments.[55] The latter is  
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3 more likely to affect treatment outcome, but formal cognitive measures of effort were not available  
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5 for all participants. More generally, the smaller subgroups used and the corresponding decrease in  
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7 power may well have obscured modest influences on treatment outcome, and precluded examining  
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9 possible interactions such as medicolegal status playing a more significant role in influencing  
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11 outcome in mild but not severe TBI.[8] Nonetheless, the null results for variables that might be  
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13 expected to affect treatment outcomes suggests that they may not be *major* determinants of  
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15 improvement in CBT, at least for the individuals seen in the current trial.  
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### 18 19 **Study limitations**

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21 The variation in time taken to complete the sessions of CBT (with the CBT group taking longer to  
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23 complete their treatment than the interval spent on waiting list in the control group) was undesirable,  
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25 although the alternative of having a fixed assessment interval regardless of the completeness of  
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27 treatment imposes its own difficulties. Use of a cross-over waiting list design complicates the  
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29 controlled assessment of the maintenance of therapy benefits and longer-term outcome. Data on other  
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31 variables that might have influenced outcomes (such as homework completion, or perceptions of the  
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33 usefulness of treatment) were not collected.  
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37 Another limitation stems from the use of a single therapist combined with individualised treatment.  
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39 Although fitting the needs of patients, rather using a highly manualised protocol, generalisability of  
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41 the findings may be limited by the therapist's expertise. Whilst typical of clinical practice, completion  
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43 of study questionnaires given by the treating therapist may also contribute a potential response bias.  
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45 Future larger/multicentre studies may usefully include a measure of therapist competence and  
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47 protocol adherence, and outcome measures given by a non-treating researcher.  
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### 50 51 **Conclusions**

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53 The current trial adds to the sparse evidence that the impact of persistent PCS, especially on  
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55 individuals' quality of life, can be ameliorated even for individuals sustaining more-than-mild TBIs.  
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57 Individual differences in treatment response were noted, as indicated by the impact of treatment  
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3 duration, and some treatment effects were only statistically significant after controlling for this  
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5 variable. An explicit, concomitant cognitive rehabilitation component did not appear necessary for  
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7 these improvements: further work is needed to examine the value of this approach with or without  
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9 CBT, whether certain symptoms respond differently to different treatment types, and how best to  
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11 integrate different treatments both practically and theoretically. As research into psychological factors  
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13 affecting the development and maintenance of persistent PCS continues, understanding the role of  
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15 variables such as coping,[11] symptom and injury perceptions,[10,11] and broader personality  
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17 traits[2] may also help in refining CBT interventions and identifying mediators and moderators of  
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19 change.[16]  
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5

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52 List of figures  
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55 Figure 1: CONSORT flow diagram of patient progress through trial  
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3 Figure 2: QOLAS total score at baseline (T1) and follow-up (T2)  
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6 Figure 3: RPQ total score at baseline (T1) and follow-up (T2), with Intervention group median-split  
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8 according to T1-T2 interval  
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## **SUPPLEMENTARY ONLINE MATERIAL: ADDITIONAL INFORMATION ABOUT CBT PROTOCOL**

Two psychoeducation information booklets were used. The first was a general introduction to PCS based on the material of Mittenberg, Zielinski and Fichera,[1] which reviewed common postconcussional symptoms, expected course of recovery, and the possible role of vicious cycles in maintaining persistent symptoms. The second booklet focussed on cognitive difficulties and reasons why they might persist after a brain injury (including the role of stress, effort and over-exertion);[2] the role of confidence in memory and other cognitive domains, and the impact of mood, rumination and worry;[3] and the possible effects of elements of perfectionism[4,5] and reinvestment.[6]

Where formulations identified overlap with relevant conditions such as anxiety and depression, cognitive-behavioural techniques used were based on the work of Beck,[7] and Hawton and colleagues,[8] and utilised modifications for chronic fatigue syndrome,[9] PTSD[10] and perfectionism[5] when appropriate.

Behavioural components included work on sleep hygiene[8] and behavioural activation,[11] with a particular focus on making sustainable increases in activity over time avoiding “boom-and-bust”,[9] as well as addressing possible avoidance and procrastination[12].

Cognitive approaches included negative automatic and dysfunctional thoughts records in responses to symptoms, explored through Socratic questioning, and challenged/tested particular through verbal reattribution techniques or behavioural experiments. A focus on

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3 beliefs about symptom causes was typically avoided in favour of broader attributions and  
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5 implications such as catastrophic misinterpretations to cognitive errors.  
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9 Metacognitive beliefs were often an explicit target in the sessions. Amongst other homework  
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11 tasks, patients were often encouraged to keep positive data logs[13] to keep track of cognitive  
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13 or other successes, to modify attentional bias towards mistakes or failures and build  
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15 confidence.  
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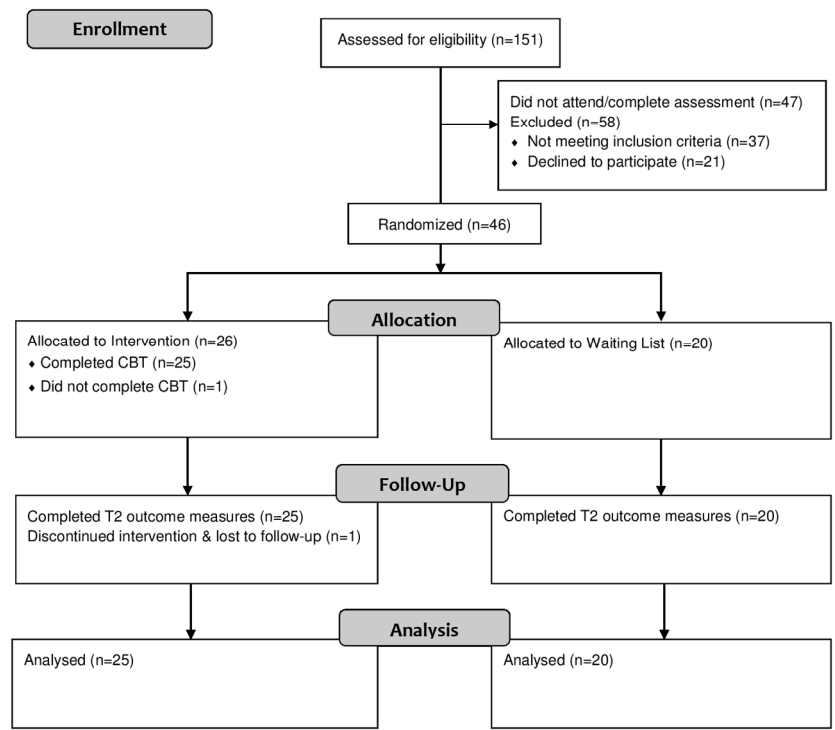


Figure 1: CONSORT flow diagram of patient progress through trial  
215x279mm (200 x 200 DPI)

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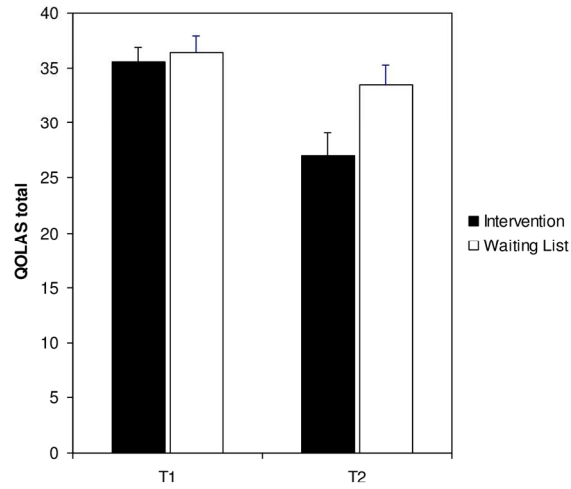


Figure 2: QOLAS total score at baseline (T1) and follow-up (T2)  
210x297mm (200 x 200 DPI)

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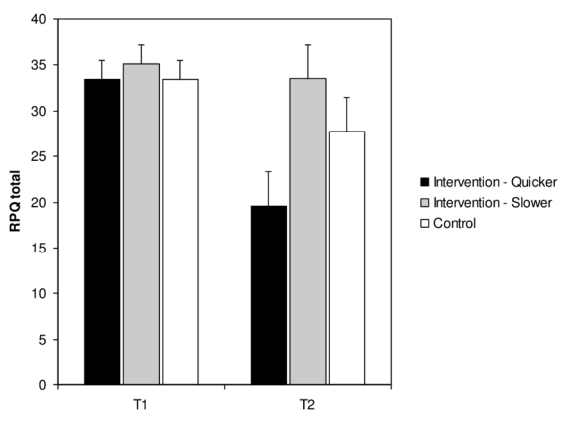


Figure 3: RPQ total score at baseline (T1) and follow-up (T2), with Intervention group median-split according to T1-T2 interval  
210x297mm (200 x 200 DPI)

