Online Supplement

Effectiveness of an exercise programme on physical function in patients discharged from hospital following critical illness: a randomised controlled trial (The REVIVE trial).

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Contents

Methods: Additional information on statistical analysis

Exploratory subgroup analyses for the primary outcome measure (Short-Form-36 health survey (SF-36) physical functioning subscale (PF))[1] were performed for the following subgroups at Visit 1 (Baseline) defined a priori (≤mean, above mean):

(i) All secondary outcomes

(ii) APACHE II score

(iii) Duration of mechanical ventilation

The primary analysis was repeated excluding the non-adherers in the intervention group. Adherence was defined *a priori* as completion of 75% of supervised exercise sessions or greater.[2] In addition, in the intervention group the primary analysis was compared between the adherers and non-adherers.

Methods: Physiotherapist intervention training pack index

The REVIVE Study

Exercise Intervention Pack

Index

1.	**Trial Documentation**
	REVIVE study protocol
	REVIVE study protocol flowchart
	REVIVE Patient Intervention pathway
2.	**Exercise Programme Instructions**
	Instruction Booklet and appendices
	Key points for planning initial treatment
3.	**REVIVE exercise Programme**
	Copy of REVIVE exercise manual
	Spare sheet unsupervised exercise session plan (if patient forgets manual)
	Copy of appointment card
	Examples of progression and adaptation
4.	**Patient Intervention chart documents**
5.	**Safety and Orientation Information**
	Lone worker protocol
	Site specific orientation and safety information
	Condition specific information leaflets

6.	Adverse Events
	Contact details
	Adverse Events Protocol
7.	A.O.B

Results: Further information on the delivery and fidelity of the intervention

The first 5 participants had two staff present for the majority of sessions. This was a seen as an induction period for staff in the early stages of the trial. Following this period the majority of sessions (an average of 83% of all sessions) were delivered by one physiotherapist. On occasions where two staff were present at the sessions, reasons included participant safety, for example, due to balance problems, cardiac risk factors, or for progression of exercises. It also included for staff safety especially for home visits and periodical quality monitoring visits.

The fidelity of the intervention was optimised by ensuring that key elements that contribute to high fidelity were included. The table below provides examples of how fidelity was optimised in the REVIVE exercise intervention according to the five domains of treatment fidelity (treatment design, training providers, delivery of treatment, receipt of treatment, and enactment of treatment skills). [3]

Table: Examples of how fidelity was optimised in the intervention

Treatment fidelity domain	**Examples of how fidelity was optimised in the REVIVE intervention**
Treatment design: *"treatment fidelity practices relating to design ensure that a study adequately tests its hypothesis in relation to its underlying theoretical and clinical processes"*	• The treatment length and dose: *a prioiri* the intervention was planned to take 6 weeks to complete, however, could be delivered over approximately 10 weeks to allow for participant non-attendance. • Underlying theoretical model that the intervention was based on: the development of the components of the exercise programme took place through synthesis of evidence from a range of sources including: a review of studies of critical care rehabilitation that were available during its' development; synthesis of key elements of exercise prescription, provision and content from a review of the current guidelines for other and chronic disease populations (including information on training frequency, intensity, dose, supervision and monitoring); and sources of self-efficacy. Development was also guided by the experience of the research team and patient and carer input. • Provider credentials: the intervention was delivered by a trained physiotherapist who worked closely with the critical care team. Physiotherapists' skills in exercise prescription, clinical reasoning and knowledge of the patient population facilitated the personalised and supervised nature of the programme.

	• Plan to address possible setbacks in implementation (i.e. back-up systems or providers): Outpatient supervised sessions took place in the hospital gymnasium, or if this was not possible, in the participant's home and unsupervised sessions took place at home. • Potential confounders: during the planning phase the study sites were contacted to establish that standard care did not include a structured exercise programme. This was in order to avoid contamination with the control group who were to receive standard care only.
Training providers: *"treatment fidelity of provider training involves standardising training between providers, ensuring that providers are trained to criterion, and monitoring and maintaining provider skills over time."*	• Comprehensive training for treatment providers: physiotherapists delivering the programme completed standardised training procedures and received a comprehensive intervention training pack including examples of how exercises could be personalised and progressed. Quarterly training updates. • Monitoring of treatment providers: weekly phone calls with the research team to discuss individual patient treatment plans and on site visits to observe the intervention delivery. • To help optimise the fit between the provider and the intervention the programme was delivered by a trained physiotherapist who worked closely with the critical care team. Physiotherapists' skills in exercise prescription, clinical reasoning and knowledge of the patient population facilitated the personalised nature of the programme.
Delivery of treatment: *"the assessment and monitoring of treatment fidelity during treatment delivery involves treatment differentiation (did the providers only deliver the target treatment and not other treatments), treatment competency (did providers maintain the skill set learned in training), and treatment adherence (delivery of the treatment components as intended)."*	• Methods to ensure that the content of the intervention was delivered as specified: all participants who completed the programme of exercise received an exercise manual, which was used during all sessions to facilitate exercise completion. The manual contained standardised description and pictures of the exercises alongside space for the physiotherapist to document details of personalisation of the programme. • The components of the programme and exercises that were delivered were recorded on an exercise case report form by the physiotherapist. • The majority (>80%) of the planned components of the intervention were adhered to when cross checked against the exercise case report form completed by the physiotherapist at each session. • There was face to face observation (by a member of the research team) of the physiotherapist delivering the treatment to patients for a number of sessions to observe and monitor that the delivery of the intervention was as intended.
Receipt of treatment: *"whether the treatment that was delivered to the participant was*	• Strategies to support patient receipt and understanding of the intervention were included, for example, the literacy level and readability of the patient manual was assessed before the study and reviewed by patient representatives. • Supervision by the physiotherapist ensured that patients'

actually "received" by the participant."	ability to perform the exercises was assessed and performance corrected if needed; physiotherapists could use planned and agreed modifications from their training pack to optimise delivery and safety. • A functional goal was set by the patient and achievement of this recorded. • BORG scale was used and breathlessness with exercises recorded at each session. • The majority (>80%) of the planned components of the intervention were adhered to when cross checked against the exercise case report form completed by the physiotherapist at each session. • Semi-structured interviews with patients who received the intervention established their degree of understanding and receipt of the intervention.
Enactment of treatment skills ***"****assessment, monitoring, and improving the ability of participants to perform treatment related behavioral skills and cognitive strategies in relevant real life settings"*	• Patient performance of the intervention exercises was assessed at the outpatient site/or home visit, for example. patient performance of the exercises was observed and assessed during supervised sessions. • At each appointment patients were asked how they were doing and to report any changes since the last time treatment. • Unsupervised sessions were planned and patients asked if they had completed these and a record was kept if the patient completed these. • A functional goal was set by the patient and achievement of this recorded. • Semi-structured interviews with patients who received the intervention established their degree of enactment of the exercises.

Results: Participant baseline Functional limitations profile (FLP) category scores [4] of intervention group and control group (Visit 1)

Variable	**Intervention (N = 30)** Mean (SD)	**Control (N = 30)** Mean (SD)
Functional Limitation Profile (FLP) category scores*		
Ambulation	28.3 (16.5)	23.4 (18.4)
Body care and movement	21.1 (16.6)	13.6 (14.1)
Mobility	26.90 (21.2)	20.4 (18.9)
Household management	48.1 (26.6)	39.7 (27.4)
Recreation and pastime	37.9 (23.4)	36.4 (22.0)
Social interaction	21.9 (22.5)	15.8 (17.7)
Emotion	31.1 (25.2)	13.3 (20.5)
Alertness	35.5 (34.6)	19.2 (22.1)
Sleep and rest	32.0 (19.1)	24.1 (18.6)
Eating	6.6 (6.4)	3.1 (5.1)
Work	48.6 (32.4)	47.8 (31.8)
Communication	8.7 (11.8)	6.9 (9.8)

*Range is 1-100 with a higher score indicating better health-related quality of life (self-reported)

Results: Functional limitations profile (FLP) category scores [4] for intervention group and control group: mean (SD) change and mean difference (95% confidence interval) from Visit 1 (Baseline) (Visit 2 minus Visit 1)

Outcome Measure	**Intervention (N = 26)** Mean (SD) change	**Control (N = 29)** Mean (SD) change	**Difference in mean change scores** (95% CI)	**p-value**
Functional limitations profile (FLP) category scores*	n=22	n=28		
Ambulation	-11.2 (13.7)	-5.6 (11.8)	-5.6 (-12.9,1.6)	0.13
Body care and movement	-8.5 (8.9)	-2.7 (8.4)	-5.8 (-10.7,-0.9)	0.02
Mobility	-9.3 (14.4)	-7.6 (13.9)	-1.7 (-9.8,6.4)	0.67
Household management	-13.2 (17.8)	-10.1 (19.2)	-3.1 (-13.8,7.5,)	0.56
Recreation and pastime	-9.5 (21.2)	-6.6 (19.1)	-2.9 (-14.4.8.6)	0.62
Social interaction	-6.2 (12.9)	-2.2 (11.2)	-4.1 (-10.9,2.8)	0.24
Emotion	-12.9 (16.0)	0.66 (9.5)	-13.6 (-21.4,-5.8)	<0.001
Alertness	0.82 (28.3)	-1.0 (19.3)	1.9 (-11.7,15.4)	0.78
Sleep and rest	-12.2 (17.4)	-5.7 (16.4)	-6.5 (-16.2,3.1)	0.18
Eating	-2.0 (6.7)	-0.97 (3.7)	-1.1 (-4.1,1.9)	0.48
Work	-11.1 (24.9)	8.1 (27.4)	-19.2 (-34.3,-4.2)	0.01
Communication	0.90 (9.6)	-2.0 (7.8)	2.9 (-2.1,7.9)	0.25

*Range is 1-100 with a higher score indicating better health-related quality of life (self-reported)

Results: Results of additional statistical analysis for the primary outcome (change from Visit 1 (Baseline) to Visit 2 (6 weeks) for SF36-PF)

a) Imputation

After exploring missing data, imputation with group average scores for the primary and secondary outcomes was chosen as the most appropriate due to the small proportion of missing data.
The primary outcome was missing for 8% of the participants. In order to adhere to the intention to treat principle, imputation (group average) was performed on the primary analysis but the result remained non-significant (p=0.30).

For the secondary outcomes, there were more missing data in the intervention group than control group, and although we would have expected similar numbers missing in the two groups if missing at random there was no explanation for the differences in % missing. Imputation using the group average was also completed on secondary outcomes. Significant results remained significant, with ISWT and FLP (overall score), moving from being significant, to highly significant. The SF-36 social functioning subscale (SF), SF-36 Physical component summary) (PCS), and FLP physical dimension moved from non significant (p=0.06) to significant (SF p=0.04, PCS p=0.04, FLP physical dimension p=0.02).

b) Subgroup analysis

The interaction terms between randomisation group and subgroup were all non- significant apart from anxiety (p=0.01). In the control group the mean change in physical function (PF) score increases in participants who had a higher HADS anxiety score at baseline , whereas in the intervention group change in physical function decreases (Table). The subgroup analysis for HADS was repeated using recommended cut-off points.[5] For anxiety only, the interaction was significant for the normal to mild (0-10) versus moderate to severe (11-21) cut-off points and confirmed the trend above.

Subgroup Analysis for change in SF-36 PF[*] from Visit 1 (Baseline) to Visit 2 (6 weeks)

Subgroup	**Intervention (N = 26)** Mean (SD)	**Control (N = 29)** Mean (SD)	**Difference in mean change scores** (99% CI)
HADS anxiety score at Visit 1			
<=mean	11.0 (8.2)	2.2 (6.9)	8.8 (1.4,16.2)
above mean	3.3 (11.9)	7.5 (10.2)	-4.2 (-17.9,9.5)

[*]SF-36 scores are calculated from norm-based scores for a UK population with a mean of 50 and SD10. A higher score represents better health-related quality of life (self-reported)

b) Outlier

During the analysis, one outlier was identified. This outlier had a very large decline in SF-36 PF (-28.5). This was inconsistent with the both the direction and size of change of all other measures which improved. Therefore the primary analysis was repeated with this outlier removed. This gave a p value of p=0.058 with a mean difference (95% CI) between groups of 4.4 (-0.16, 8.9) for change in SF-36 PF.

c) Exclusion of non-adherers

The primary analysis was repeated excluding the non-adherers in the intervention group per the *a priori* definition of adherence (75% of exercise sessions or greater [2]). The analysis

remained not significant (p=0.18), however, when the outlier was removed this gave a p value of p=0.02 with a mean difference (95% CI) between groups of 5.8 (0.9, 10.7) for change in SF-36 PF. In the intervention group, adherers were compared to the non-adherers and showed no significant difference (p=0.46) in change in physical function however there was an improvement of 3.9 in SF-36 PF in the adherer compared to non-adherer group.

Results: Safety Outcomes

Safety outcomes during the intervention/control period (Visit 1 (Baseline) to Visit 2 (6 weeks))

	Intervention	Control
Total Adverse Events (AEs)	**12**	**3**
AEs which were serious (SAEs)	**2**	**2**
AEs		
Musculoskeletal pain/injury which is more than expected muscle soreness	**2**	**1**
Any pain which is more than expected	**1**	**0**
Cardiac symptoms or chest pain	**1**	**0**
Any other event that the researcher is concerned about	**6**	**0**
Related/possibly related to study participation[a]	*6*	*1*
SAEs		
Hospitalization or prolonged hospitalisation	**2**	**2**
Related to study participation and unexpected[b]	*1*	*0*

[a]Seven non-serious AEs were related/possibly related to the study procedures. These included: musculoskeletal pain that was more than expected in 3 participants (2 intervention group, 1 control group); one participant vomited on the way home from their exercise session (intervention group); and 2 participants with known Type I diabetes were hypoglycaemic during or after the exercise session (3 occasions) (intervention group).

[b]One unexpected and related SAE was hospital admission following an acute exacerbation of asthma associated with anxiety, occurring within 24 hours of the intervention (intervention group).

Safety outcomes during the follow-up period (Visit 2 (6 weeks) to Visit 3 (6 months))

Events	Intervention	Control
Total Adverse Events (AEs)	**6**	**2**
AEs which were serious (SAEs)	**4**	**2**
AEs		
Musculoskeletal pain/injury which is more than expected muscle soreness	**1**	**0**
Any other event that the researcher is concerned about	**1**	**0**
Related/possibly related to study participation	*0*	*0*

SAEs		
Hospitalization or prolonged hospitalisation	**4**	**2**
Related to study participation and unexpected[d]	0	0

[c]For one participant hospitalisation resulted in death. This was hospital readmission following previous SAE of pneumonia and transfer to specialist care relating to lung transplant during 6 week intervention/control period (control group).

[d]All SAEs were unrelated to study participation and unexpected.

References

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