The REVIVE study
A multi-centre RCT of the effect of a programme of exercise on physical function in survivors of critical illness after hospital discharge

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Disclosures

- None
REVIVE study team

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- G Lavery

NI Clinical Trials Unit
- Evie Gardiner, Statistican
<table>
<thead>
<tr>
<th>Physical Problems</th>
<th>Non-Physical Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Anxiety &amp; depression</td>
</tr>
<tr>
<td>Fatigue</td>
<td>ICU-associated delirium</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>Relocation stress</td>
</tr>
<tr>
<td>Diminished cardiac &amp; respiratory reserve</td>
<td>Mood changes</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Sleeping difficulties</td>
</tr>
<tr>
<td>Disuse atrophy</td>
<td>Irritability</td>
</tr>
<tr>
<td>Reduced physical function</td>
<td>Poor concentration</td>
</tr>
<tr>
<td>Restricted activities of daily living</td>
<td>Lower health related quality of life</td>
</tr>
<tr>
<td>Reduced exercise capacity</td>
<td>Post Traumatic Stress Disorder</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>Reduced social functioning</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td>Voice &amp; taste changes</td>
<td>Increased healthcare medical costs</td>
</tr>
<tr>
<td>Problems with swallow</td>
<td>Burden on families &amp; carers</td>
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</tbody>
</table>

Hypothesis

- Does a 6-week programme of exercise in patients discharged from hospital following critical illness compared to standard care improve outcome
Objectives

• To investigate the effectiveness of the programme of exercise on
  – physical function and exercise capacity
  – health-related quality of life
  – psychological morbidity
  – self-efficacy to exercise

• To determine the feasibility (safety, practicality and acceptability) of the exercise programme

• To explore patient’s perceptions of the exercise programme

• To examine the medium-term (6 months) effects
REVIVE trial design

- Phase 2 trial
- Multi-centre
  - 6 hospitals in Northern Ireland, UK
- Randomised, allocation concealed
- Outcome assessment blinded
REVIVE trial design

Baseline (Weeks 0-2 post hospital discharge)

Standard Care

6 week exercise programme

Primary outcome assessment

Assessment (6 months)

Semi-structured interview
## Population

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 18 years</td>
<td>Declined consent or unable to give consent</td>
</tr>
<tr>
<td>ICU admission requiring mechanical ventilation &gt; 96 hrs</td>
<td>Neurological dysfunction affecting ability to exercise</td>
</tr>
<tr>
<td>Planned discharge to home (self-care/carer)</td>
<td>Significant cognitive impairment</td>
</tr>
<tr>
<td>Willing and able to participate in exercise intervention</td>
<td>Participation in another rehabilitation programme due to ongoing chronic disease</td>
</tr>
<tr>
<td>Medically fit to take part in the intervention</td>
<td></td>
</tr>
</tbody>
</table>
Intervention

• 3 exercise sessions per week for 6 weeks (2 supervised, 1 unsupervised)

• Delivered by physiotherapist

• Supervised sessions were hospital-based (or participant’s home if not possible)

• Standardised exercises, tailored to the each individual participant

• Strategies to optimise fidelity of the delivery of the intervention
Intervention

Warm Up

Circuit
a) Whole body
b) Hand

Aerobic Exercise

Cool Down

3. Slowly circle your shoulders up, back, down and forwards in a circle.

4. Bend your elbows, wrists and fingers. Then straighten out fully.

5. Sit on the floor, wrap your arms around your knees and hold them, then stand up straight.

5. Sit on the floor, wrap your arms around your knees and hold them, then stand up straight.

6. Stand facing a wall, with your hands against the wall at shoulder height. Move your elbows to bend then push out straight.

7. Sit comfortably in your chair, keep your feet flat on the floor and sit up straight. Lean forwards over your knees and push up to stand up straight. Use your hands if you need to. Then sit down again.

Allow your body to REST for 10 minutes before continuing your usual daily activities.

6. Relaxation
   - Choose a comfortable chair to sit in.
   - Close your eyes and take a few deep breaths.
   - Gradually relax all your muscles, starting at your feet and working up the body. Relax major muscles first.
   - Notice these muscles, noticing their new tension as you can.
   - Think of a pleasant, calm and peaceful thought or image.

You should aim to do at least 10 minutes of continuous aerobic exercise and gradually progress this as you are able. Your physiotherapist will help you to decide which aerobic exercises are best for you and how long you should aim to do each week.

Remember, some breathlessness when exercising is normal. Use the 'Borg Breathlessness Scale' on page 7. Usually exercises should be progressed to maintain moderate breathlessness. Moderate breathlessness is 3-4 on the Borg Scale: 'moderate to somewhat severe'.

Aerobic exercises can include:
- walking indoors / outdoors / on the flat / up a hill
- marching on the spot
- step ups
- using the treadmill or exercise bike
- cycling
- swimming
- dancing
Intervention

Your exercise and activity diary

After your exercise programme is finished it is important to continue to stay active.

You can use the diary on the next few pages to record the exercise or activity that you plan to do each week.

Each week record an exercise or activity that you are confident you will be able to do.

At the end of each week record if you have met your goal. If not - don’t be discouraged, everyone can have setbacks.

Think about what you can do to help you meet your weekly goals. You may wish to try a different exercise or activity, or try it at a more gentle level.

Here is an example.

| What exercise or activity will I do this week? | Go for a walk outside |
| How much? | Around the block for 10 minutes. |
| How often? | 3 days |
| When will I do it? | Before lunch Monday, Wednesday & Friday. |
| Did I meet my goal? | Yes. Walking with a friend made this fun. It helped me reach my goal |

Exercise and activity diary - Month 1

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>What exercise or activity will I do this week?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When will I do it?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did I meet my goal?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Please comment.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monthly reflection: At the end of every month, look back at your progress. Think about what you can do to help you meet your weekly goals.
## Outcome Measures

<table>
<thead>
<tr>
<th>Primary Outcome Measure:</th>
<th>SF-36 Physical Functioning subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcome Measures:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>Rivermead Mobility Index (RMI)</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>Incremental Shuttle Walk Test (ISWT)</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>Functional Limitations Profile (FLP)</td>
</tr>
<tr>
<td></td>
<td>SF-36 (subscales &amp; component scores)</td>
</tr>
<tr>
<td>Self-efficacy to exercise</td>
<td>Chronic Disease Self-efficacy Scale</td>
</tr>
<tr>
<td>Readiness to exercise</td>
<td>Readiness to Change</td>
</tr>
<tr>
<td>Anxiety, Depression</td>
<td>Hospital Anxiety &amp; Depression Scale (HADS)</td>
</tr>
</tbody>
</table>
Statistical Analysis

Sample size
• n=52 with primary OM at 6 weeks

Analysis
• Intention to treat analysis
1118 Assessed for eligibility

- 293 Died
- 60 Randomised

765 Excluded
- 566 Did not meet criteria
  - Participation in other structured rehab (236)
  - Not medically fit for the intervention (143)
  - Neurological/spinal/skeletal dysfunction (85)
  - Cognitive impairment (71)
  - Not discharged to home (31)
- 125 Declined
- 23 Unable to contact
- 51 Other

26 included in analysis for primary outcome (6 weeks)
  - 3 Unable to contact
  - 1 Withdrew consent

29 included in analysis for primary outcome (6 weeks)
  - 1 Hospital inpatient
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years</td>
<td>51 (13)</td>
<td>51 (14)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (43)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>ICU diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>17 (56.7)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4 (13.3)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3 (10)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Neurological</td>
<td>2 (6.7)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Trauma</td>
<td>2 (6.7)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Genito-urinary</td>
<td>1 (3.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.3)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>APACHE 2</td>
<td>17.3 (7.7)</td>
<td>15.2 (5.6)</td>
</tr>
<tr>
<td>Duration mechanical</td>
<td>293.6 (269.8)</td>
<td>311.9 (235.8)</td>
</tr>
<tr>
<td>ventilation – hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay ICU – days</td>
<td>17.6 (15.3)</td>
<td>18.2 (11.7)</td>
</tr>
<tr>
<td>Length of stay Hospital</td>
<td>35.7 (26.0)</td>
<td>39.5 (22.6)</td>
</tr>
</tbody>
</table>
SF-36 Physical Functioning at 6 weeks

p=0.26
Incremental Shuttle Walk Test at 6 weeks

![Graph showing the comparison of Incremental Shuttle Walk Test between intervention and control groups at baseline and 6 weeks. The p-value is 0.03.](image)
SF-36 Role Physical at 6 weeks

p=0.02
Functional Limitations Profile at 6 weeks

p=0.02
Chronic Disease Self Efficacy Scale at 6 weeks

p=0.01
### Other outcomes at 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivermead Mobility Index</td>
<td>1.3 (2.1)</td>
<td>1.1 (1.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>7.0 (7.8)</td>
<td>3.2 (6.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>5.8 (13.6)</td>
<td>1.1 (13.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Readiness to Exercise</td>
<td>1.1 (0.97)</td>
<td>-0.21 (0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>-0.59 (3.6)</td>
<td>0.18 (3.3)</td>
<td>0.43</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>-1.2 (4.4)</td>
<td>0.36 (3.1)</td>
<td>0.15</td>
</tr>
</tbody>
</table>
## Delivery and feasibility

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Adherence</strong></td>
<td>77%</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>7.6 (1.7) weeks</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>81% attended hospital gym for all supervised sessions</td>
</tr>
<tr>
<td></td>
<td>Home visits necessary for 5 participants on at least one occasion</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td>Primarily one to one</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>One unexpected related SAE</td>
</tr>
</tbody>
</table>
SF-36 Physical Functioning at 6 months

p=NS
Incremental Shuttle Walk Test at 6 months

*p=NS*
SF-36 Role Physical at 6 months

p=NS
Functional Limitations Profile at 6 months

\[ p = \text{NS} \]
Chronic Disease Self Efficacy Scale at 6 months

p=NS
Patient’s perceptions of the exercise programme

- Semi-structured interviews
- Interview schedule including supplementary prompts
- Carried out by researcher not involved in the delivery of the intervention or blinded outcome assessment
- All interviews were audio recorded and transcribed verbatim

Analysis
- Thematic content analysis of interview transcripts
Semi structured interview - Results

<table>
<thead>
<tr>
<th>Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>The detrimental impact of critical illness and reflections on the critical care journey</td>
</tr>
<tr>
<td>Satisfaction and endorsement of the programme of exercise</td>
</tr>
<tr>
<td>Beneficial impact of the programme of exercise</td>
</tr>
<tr>
<td>Facilitators of beneficial impact</td>
</tr>
<tr>
<td>Barriers to beneficial impact</td>
</tr>
<tr>
<td>Continuing exercise after the programme and factors that impacted on this</td>
</tr>
<tr>
<td>The quantitative outcome measures</td>
</tr>
</tbody>
</table>
The detrimental impact of critical illness and reflections on the critical care journey

“You know, the nightmares, the dreams I’ve had, and, really, really frightening like, … I still waken, crying, dreaming, you know and different things happening…”

“But um when I approached my GP after, he was very dismissive and I think it was just genuinely through not enough knowledge. He had no idea he just basically said to suck it up and get on with it, you know which is not what you want to hear.”
Semi structured interview - Results

The quantitative outcome measures

Many of these themes were not captured in the quantitative OMs
Conclusion

• Exercise rehabilitation initiated after discharge from hospital following critical illness
  – No significant difference in the primary outcome measure (SF-36 PF)
  – Significant improvements demonstrated in patient-reported and performance based outcomes at 6 weeks
  – Feasible, safe and acceptable
  – Not sustained at 6 months
  – Need to determine dose regimen for future studies
  – Need to define outcomes
Acknowledgements

• This project was supported by
  • REVIVE
  • HSC R&D Division, Public Health Agency in NI
Critical Care Reviews Meeting 2016
Titanic Centre, Belfast
Friday January 29th 2016
Discussing the Biggest Critical Care Studies of 2015
with their Chief Investigators

The Great Debate
Vincent vs Gattinoni: RCTs are Killing Critical Care

2016’s Big Trials
Holcomb: PROPRR
Young: HEAT
Walsh: ABLE (UK)
RECOVER
Gordon: VANISH
Mac Sweeney: The Best of the Rest

How I Manage…..
Holcomb: Traumatic Haemorrhage
Young: Pyrexia in ICU
Walsh: Anaemia in ICU
Vincent: Septic Shock
Gattinoni: Hypoxaemic Respiratory Failure

John Hinds’ Trauma Lecture
Burns: Trauma Care - Back to the Future

An Informal Chat with……….
Holcomb | Vincent | Walsh | McAuley
Burns | Gordon | Young | Mac Sweeney | You

Speakers
Young
Gattinoni
Walsh
Burns
Vincent
McAuley
Gordon
Holcomb
Mac Sweeney

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Belgium
N Ireland
England
USA
N Ireland

Further Details & Registration at: www.criticalcarereviews.com