

Improving outcomes in abdominal aortic aneurysm patients

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Majd Rawashdeh MBBS MRCS

Academic Section of Vascular Surgery
Division of Surgery
Department of Surgery and Cancer
Faculty of Medicine

Supervisors

Professor Alun H Davies

Academic Section of Vascular Surgery
Division of Surgery
Department of Surgery & Cancer
Faculty of Medicine

Mr Tristan R A Lane

Academic Section of Vascular Surgery
Division of Surgery
Department of Surgery & Cancer
Faculty of Medicine
Cambridge Vascular Unit,
Addenbrooke's Hospital,
Cambridge University Hospitals NHS Trust

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Abstract

Background

Patients undergoing abdominal aortic aneurysm repair suffer from multiple comorbidities and frailty. Perioperative and postoperative complications are common following AAA repair, and research should be undertaken to improve overall outcomes. Preoperative exercise therapy (Prehabilitation) is a well-described method for improving surgical outcomes; however, it is uncertain if patients scheduled for AAA repair would benefit from prehabilitation. The goal of this thesis is to provide new evidence for prehabilitation in AAA patients awaiting surgery and explore the feasibility of using a novel adjunct to facilitate rehabilitation following surgery.

Methods

This thesis is mainly made up of three main studies. Analysis of National Vascular Registry data to highlight the impact of frailty on patients undergoing AAA repair. A proof-of-concept feasibility study assessing a novel 6-week remote prehabilitation programme for patients scheduled for AAA repair. A pilot randomised controlled study aimed at improving rehabilitation of general and vascular surgery patients using a neuromuscular electrical stimulation device.

Results

The first study highlighted the negative impact of frailty status on short-term outcomes following AAA repair, with a significantly increased risk of combined cardiovascular and mortality events in patients undergoing open AAA repair. A 6-week remote prehabilitation programme for AAA patients scheduled repair is feasible and improves functional capacity. Introducing a neuromuscular electrical stimulation device as an adjunct to rehabilitation for general and vascular patients is acceptable and safe.

Conclusion

Frailty is associated with worse outcomes for patients undergoing repair. Remote prehabilitation of AAA patients is feasible and can potentially improve outcomes following repair. The use of NMES as an adjunct to rehabilitation has the potential to enhance recovery following surgery and should be further explored. This thesis provided new evidence to support a national multicentre study to investigate novel interventions aimed at improving outcomes of AAA patients.

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Statement of originality

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List of abbreviations

6MWT	6-minute walk test
AAA	Abdominal Aortic Aneurysm
AAAQIP	Abdominal Aortic Aneurysm Quality Improvement Project
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ADL	Activity of Daily Living
ASA	American Society of Anaesthesiologists
AT	Anaerobic Threshold
AUC	Area Under Curve
BMC	BioMed Central
BMI	Body Mass Inde
BSET	British Society of Endovascular Therapy
BSIR	British Society of Interventional Radiology
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CFS	Clinical Frailty Scale
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Testing
CSHA	Canadian Study of Health and Aging
CVD	Cerebrovascular Disease
EFS	Edmonton Frailty Scale
HDL	High-Density Lipoproteins
HDU	High Dependency Unit
HIT	High Intensity Training
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NMES	Neuromuscular Electrical Stimulation
NVR	National Vascular Registry
PAD	Peripheral Artery Disease
PSSRU	Personal Social Services Research Unit
PT	Physiotherapy
QOL	Quality of Life
RCT	Randomised Controlled Trial
TUG	Time Up and Go
VCO2	Volume of Cardon Dioxide produced
WHO	World Health Organisation

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4. **Appendix 5.2** Example of exercise prescription provided to PREHAB-AAA participants

Chapter 1 : Introduction

Abdominal Aortic Aneurysm

Definition and Anatomy

The Aorta is the largest blood vessel in the body and is responsible for carrying oxygenated blood from the left ventricle to the brain, abdominal organs and peripheral tissues. The aorta is anatomically classified as either thoracic (extending from the left ventricle cranially until the top of the diaphragm caudally) or abdominal (extending from below the diaphragm cranially till it bifurcates caudally to iliac arteries). An aneurysm is the term given for a persistent and localised weakening and enlargement of a blood vessel, most commonly an artery [1], and as a result abdominal aortic aneurysm (AAA) is an irreversible enlargement of the abdominal aorta. Typically, AAAs are 'true aneurysms' characterised by the involvement and dilation of all three layers of the vascular wall. In contrast, a pseudoaneurysm or 'false aneurysm' is characterised by blood infiltration between the layers of the wall [2]. Approximately 80% of AAAs are located infra-renally (below the renal arteries), while the remaining AAAs are juxtrarenal, pararenal, and suprarenal, which involve or occur above the renal arteries. Wall dilation in AAAs typically entails the entire circumference of the aorta ('fusiform'). Less common are other morphological varieties, such as saccular AAAs, which involve only a portion of the circumference. For men, the average diameter of a healthy infrarenal aorta is 19.3mm and relatively smaller (16.7mm) for women[3]. Radiologically, an infrarenal abdominal aortic aneurysm is defined when its maximum diameter reaches 30 mm or more, as measured by ultrasound (inner to inner diameter) or computed tomography angiography (CTA) in corrected axial views[4]. However, this threshold may not be suitable for patients whose infrarenal aortic diameters differ from these dimensions, because of their height[4]. An alternative definition compares the maximal infrarenal aortic diameter to its expected normal value or the diameter of a healthy adjacent segment of the aorta. When this ratio exceeds 1.5, a dilation should be considered aneurysmal[5]. This definition may be more useful for women, as well as for distinct ethnic populations with varying diameter values.

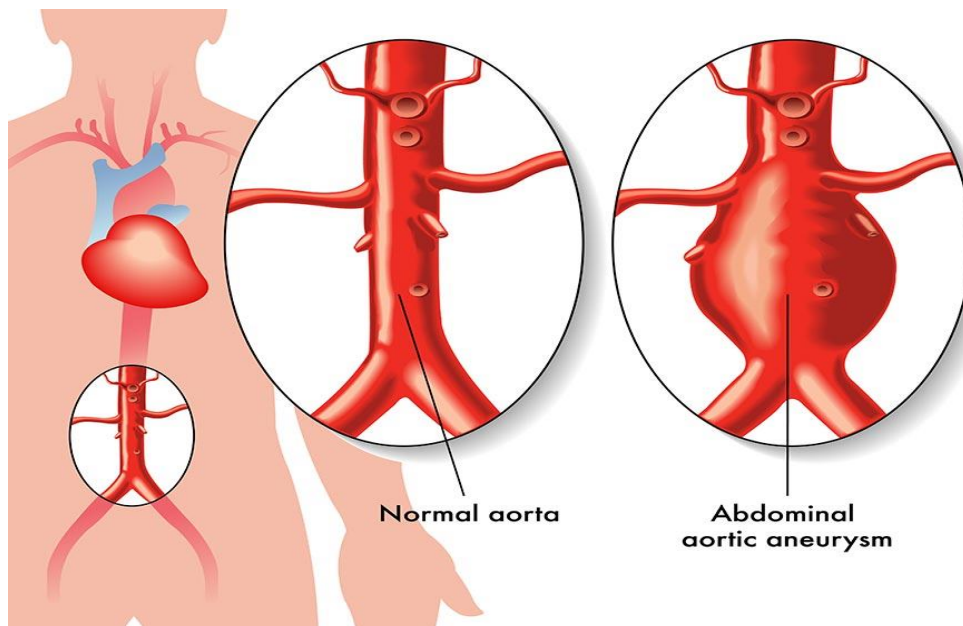


Figure 1.1: Demonstration of Abdominal Aortic Aneurysm. Courtesy of A.D.A.M Medical Encyclopaedia

Epidemiology

Abdominal aortic aneurysm (AAA) is a fairly common condition in the older population. A 24-year prospective study (ARIC)[6] demonstrated that 1 in 9 middle-aged smokers were diagnosed with AAA at some point in their lifetime. Studies from screening programmes and autopsies ranging from 1995-2004 showed that 1.4% - 8.9% of men had AAA. The annual incidence of AAA has been estimated to range from 0.4% to 0.67% in Western populations[7–10], but it may be lower in Asian populations[11]. Recent evidence suggests that the incidence of AAA is decreasing, most likely due to a decline in tobacco use and an improvement in the management of cardiovascular disease risk factors[12]. Current prevalence rates are approximately 1.5% for males over 65 and 0.7% for women over 60 [13–17]. This is also coupled with a decrease in AAA mortality in most developed countries [18][12].

Risk Factors of AAA

The exact reason to why aneurysms form is still unknown, however studies identified risk factors that are strongly associated with aneurysm formation. Men, smoking, age, presence of cardiovascular disease and positive family history are the strongest risk factors associated with AAA[19][20].

The age of an individual is considered a significant risk factor in the onset of an abdominal aortic aneurysm (AAA). According to a study[21], the risk of a 75-79-year-old man experiencing the condition is almost 200 times higher than that of a 40-44-year-old man, with rates of 164 and 0.83 per 100,000, respectively. A meta-analysis of epidemiological data and population screenings suggests that the risk of AAA in women comparably increases with age, albeit at a lower magnitude[22]. Estimates show that if a threshold value of more than 26 mm is used for women, based on a 50% increase in size from the average baseline, the prevalence of AAA in 70-year-old women would more than double compared to previous studies[23][24].

Regarding male individuals, advanced age and present smoking habits represent the most potent risk determinants for female counterparts[25]. Studies have shown that the growth rate of AAAs in women is comparatively higher than that in men, and the risk of rupture is approximately four times greater in women than in men[26][27] and typically rupture at a smaller AAA diameter compared to men[28].

The modifiable risk factor that is widely acknowledged to be associated with AAA is smoking, as it plays a significant role in the development, growth, and rupture of AAAs. According to previous research[29], it has been approximated that smoking may be responsible for 75% of all abdominal aortic aneurysms with a diameter greater than 4.0 cm. In a screening study conducted in the United States with a sample size of 3.1 million participants, it was observed that 80.2% of all abdominal aortic aneurysms (AAAs) were detected in individuals who smoked, despite comprising only 42.8% of the cohort. The habit of smoking has been found to elevate the growth rate of AAA by 15-24% and closely linked with a higher likelihood of rupture, irrespective of the diameter of the AAA (HR : 2.02)[30–32] . The annual incidence of abdominal aortic aneurysm (AAA) is positively correlated with the duration of smoking, with each year of smoking increasing the relative risk (RR) by 4% [33]. The cessation of smoking has been observed to decrease the likelihood of the formation of AAA, slow down the growth of aneurysms, and reduce the incidence of AAA rupture[34]. According to various studies, the reduction of excessive risk among individuals who have quit smoking may take up to a decade to reach 50%, and it may take at least 25 years after cessation for the risk to

approach that of individuals who have never smoked[35–37]. Studies have also indicated a correlation between smoking and AAA development in females, with a reported 10-fold higher risk for active female smokers compared to ex-smoker[23,35].

Between 6 to 20% of patients diagnosed with AAA exhibit a positive family history. However, with the exception of infrequent hereditary connective tissue diseases like Marfan syndrome or Ehlers-Danlos syndrome, no specific patterns of inheritance have been established to account for the occurrence of familial AAA[38–40]. Currently, the factors that have been identified only account for a portion of the heritability of aneurysmal disease. However, these factors have the potential to clarify pathophysiological mechanisms and may be useful as biomarkers or targets for therapy in the future [41].

Patients diagnosed with AAA frequently exhibit cardiovascular comorbidities. The co-occurrence of abdominal aortic aneurysm (AAA) in patients with coronary artery disease (CAD) is 8.4% (95%CI 6.9 to 10.3)[42], peripheral artery disease (PAD) with odds ratio of 2.5 [43], and cerebrovascular disease [6] is well established. Studies have demonstrated that the likelihood of developing a AAA is significantly higher in individuals with a history of atherosclerotic disease with further compounded in those with severe or multiple CVDs[42]. According to research findings, amongst men who had verified angiographic CAD or underwent CABG, the pooled prevalence was 9.5%(95% CI 7.6 to 11.7)[44] . Additionally, the prevalence of AAA appears to be greater in patients with three-vessel disease as compared to those with a lower-degree CAD[45].

AAA patients are more likely to suffer from atherothrombotic events and accelerated progression of its severity with increased rates of hospitalisation[46]. According to recent studies, individuals diagnosed with a small abdominal aortic aneurysm (AAA) exhibit a 1.5-fold increase in the likelihood of experiencing a cardiovascular event compared to those without an aortic aneurysm with annual risk of cardiovascular mortality of approximately 3%[47,48]. Notwithstanding the elevated fatality rates associated with ruptured abdominal aortic aneurysms (AAA), cardiovascular incidents

persist as a prevalent factor contributing to mortality in patients diagnosed with AAA[49]. There has been a recent emergence of evidence regarding sex-based differences in atheromatous disease burden among patients with AAA, with women exhibiting a greater burden compared to men. Research findings from a single centre study[50] indicate a higher AAA thrombus burden (56% vs 30%, $p = 0.003$) and increased incidence of IMA occlusion (40% vs 22%, $p = 0.025$).

The presence of hypertension has also been strongly identified with increased risk of AAA[51][52] but not associated with AAA sac growth[53]. Additionally, it has been suggested that diastolic blood pressure may have a more significant impact than systolic blood pressure[54]. Moreover, there is positive correlation between the mean blood pressure and the risk of rupture, for every 10-mmHg increase[55].

In relation to the development of (AAA), it is widely acknowledged that elevated levels of high-density lipoprotein (HDL) in the serum provide a clear protective effect[56][57]. However, the available data on the impact of low-density lipoprotein (LDL), and triglyceride levels on AAA development are not as consistent. A retrospective examination of laboratory records of patients dating back 12 years prior to their initial diagnosis of abdominal aortic aneurysm (AAA) revealed a significant correlation between previously elevated levels of total cholesterol (TC)(OR 1.9), low-density lipoprotein (LDL)(OR 2.3), and triglycerides(OR 1.9) with current AAA [58]. Conflicting results were observed in two meta-analyses investigating the association between LDL levels and AAA presence. One of the meta-analyses confirmed the association[56], while the other did not find any such association for LDL[57]. However, the latter meta-analysis did find a significant effect on AAA development for elevated total cholesterol levels. A meta-analysis[59] of 22 studies comprising of 80,428 patients diagnosed with AAA has demonstrated that the utilisation of antilipidemic agents (e.g., statins) is linked with a reduction in the mean AAA growth rate by 0.82 mm/y, decreased risk of rupture, and reduced 30-day mortality following elective AAA repair ($p = .005$). The observed incidence of rupture in the study population was 34% among patients receiving statin therapy and 47% among those in the control group.

Clinical presentation of AAA

The natural history of AAA consists of expansion followed by acute rupture. The classic presentation of an acute rupture is the triumvirate of abrupt, severe abdominal or back pain, a pulsating abdominal mass, and hemodynamic collapse[60]. As aneurysms expand, the aortic wall weakens and cannot withstand the luminal blood pressure which eventually will progress into further expansion and rupture[61]. AAA are typically asymptomatic and are typically detected incidentally during imaging or clinical examinations for other conditions[62].

The estimated average annual progression in diameter of small aneurysms (less than 5.5 cm) is between 2.0 and 3.0 mm/year, whereas progression is greater for aneurysms with a larger initial diameter[63,64]. According to a multicentre study, there was a recorded progression of the aorta from a sub-aneurysmal aortic dilation (with a diameter of 2.5-2.9 cm) to the threshold for elective surgical intervention of 5.5 cm in 0.9% of patients within a span of five years [65].

The primary complication of abdominal aortic aneurysms (AAAs) is rupture, which has been linked to an overall mortality rate ranging from 65% to 80% [66]. AAA rupture is responsible for causing an estimated 150,000 fatalities annually on a global scale[67], with more AAA burden observed in developing regions (e.g. Southeast Asia, Latin America)[68]. Approximately, 35% of patients arriving to hospital with ruptured AAA will not survive hospital admission[69] leading to 3000-4000 deaths per year in England and Wales[12].

The classic presentation of an acute rupture is the triad of abrupt, severe abdominal or back pain, a pulsating abdominal mass, and hemodynamic collapse. However, this triad is only present in 50% of cases and can be misdiagnosed with ureteric colic, myocardial infarction or perforated peptic ulcer[70]. The correlation between the diameter and rupture has been firmly established and serves as the foundation for determining the surveillance intervals for patients diagnosed with AAA[71]. According to a meta-analysis, based on individual surveillance data, doubling of rupture rates were observed

for each 0.5 cm increase in diameter[32] . The risk of rupture increases with the aneurysm's diameter, especially above approximately 5.5 cm[72][73].

Management of AAA

AAA Screening programmes

Guidelines for AAA screening have been developed by national healthcare bodies after several population-based studies [74–77]. In the United Kingdom, national screening was introduced in 2009 and implemented nationally in 2013 with all men with the age of 65 years are offered free single ultrasound scan to screen for AAA which subsequently showed effectiveness in detecting and treating men with AAA[78]. Current findings from these population-based studies validate the advantages of conducting screenings in reducing AAA- mortality in men not all-cause mortality[79]. Although population screenings for women are not recommended by most current guidelines, primarily due to low prevalence and cost-effectiveness concerns[80][81], Canada has put forth a proposal for one-time screening through ultrasonography for women of advanced age who have a history of smoking or cardiovascular disease[82]. A recent study[83] published in 2022 reviewing prospectively collected Vascular Quality Initiative data between 2003 and 2019, demonstrated over 60 % of patients who received surgical repair for ruptured AAA were not eligible for screening with largest contributors were males less than 65 years of age with smoking or family history (25%), males over the age of 75 with smoking history (25%) and women older than 65 years with positive smoking history (19%). This may suggest AAA screening programmes eligibility criteria may require amendment to target high risk population to maintain cost effectiveness of screening programmes and reduced AAA related mortality. In the other hand, a study[84] demonstrated that AAA men undergoing surveillance are more likely to die from cardiovascular event when compared to patients with no AAA (24.3% vs 13.4%, HR: 2.07 (95% CI 1.85 – 2.32)).

Management of Small AAAs

Guidelines from the European Society of Vascular Surgery (ESVS)[85], the American College of Cardiology (ACC)[86] and American Heart Association (AHA)[87] recommend that: when an AAA reaches a diameter of ≥ 5.5 cm (men) or ≥ 5.0 cm (women), demonstrates rapid expansion, or becomes symptomatic (regardless of size), the risk of rupture exceeds the risk of surgical repair and the individual should be referred to a vascular surgeon for consideration of surgical intervention. Patients with small AAAs do not benefit from early elective repair. Instead, it is recommended that they undergo surveillance while receiving optimal medical care and making necessary lifestyle changes[88]. Periodic surveillance of aneurysm expansion for small AAA is recommended[85][89]. For aneurysms measuring 3.0-3.9 cm in diameter, monitoring should occur every three years. For aneurysms measuring 4.0-4.9 cm in diameter, annual monitoring is recommended. For AAAs with a diameter of 5.0 cm or greater, monitoring should occur every 3-6 months.

AAA Cardiovascular risk management

The management of cardiovascular risk factors in AAA patients can be achieved through the implementation of lifestyle modifications and the use of adjunctive pharmacotherapy to address exacerbating conditions, such as hypertension or hyperlipidaemia.

Smoking cessation is a crucial element in the prevention of cardiovascular disease. Furthermore, if smoking cessation is accomplished more than eight weeks before elective AAA repair, it significantly reduces post-surgical pulmonary complications[90][91]. Engaging in physical activity has the potential to mitigate the health hazards associated with cardiovascular disease resulting from excessive weight and improve outcomes postoperatively[92,93]. According to a retrospective cohort study, implementation of a cardiac rehabilitation programme has been found to decrease the growth rate of small AAAs[94]. Consistent with this notion, patients with abdominal aortic aneurysm (AAA) measuring less than 55 mm who engage in routine

physical activity have exhibited an enhancement in their cardiopulmonary capacity. Hence, it is recommended to promote consistent aerobic exercise among these individuals due to its advantageous impact on overall cardiovascular risk and improving cardiopulmonary function[95].

It is recommended that pharmacotherapy of cardiovascular risk factors be implemented for all patients with abdominal aortic aneurysm, unless there are contraindications present [85]. The use of statins has shown effectiveness in slowing the growth of AAA (SMD, -0.42 95%CI -0.57 to -0.18) with improved survival[96][59]. It is recommended to maintain systolic blood pressure levels below 140 mmHg. The selection of a particular antihypertensive medication is contingent upon individual comorbidities and tolerability. A study published in 2016 reviewing 12 485 patients with AAA demonstrated appropriate risk factor modification (statins, antiplatelet agents and antihypertensives) may improve survival and could save 62 lives per 1000 per year. [49]. The study also highlighted the proportion of AAA patients receiving such medication is poor. Collaborative endeavours among primary care, secondary care, and screening programmes have the potential to mitigate the deficiency in cardiovascular risk management of AAA patients.

Surgical management of intact AAA

Currently, there are two curative surgical modalities present to treat AAA; Open Surgical Repair (OSR) and endovascular aortic repair (EVAR). In the last decade, there has been noticeable increased adoption of EVAR as intervention for elective AAA repair[97–99] despite recent data suggesting it being inferior in long term survival outcomes when compared to open repair[100]. As highlighted previously, surgical repair is only reserved for patients when the risk of rupture exceeds surgical risk.

OSR is an invasive procedure which is commonly performed through a midline laparotomy incision. The aneurysmal aorta is exposed just below the renal arteries proximally. Further exposure of the common iliac arteries will follow to ensure proximal and distal control. After cross-clamping with systematic heparinisation, the aortic

aneurysmal sac will be opened, and lumbar arteries will be transfixed. The prosthetic graft will be anastomosed proximally just below the renal arteries in end-to-end fashion. Distal segment of the prosthetic graft will be anastomosed to either a healthy distal segment of the aorta (just above iliac bifurcation) or to both iliac arteries depending on the extent and morphology of the aneurysm. After ensuring adequate haemostasis and patency of prosthetic graft, the aneurysm sac is closed over the graft. Perioperative and postoperative complications are common due to the extent of the surgical insult coupled by the existent cardiovascular risk of AAA patients. Common complications include cardiac (myocardial infarction), respiratory, thromboembolic (lower limb ischaemia) and renal insufficiency[101]. Long term possible complications include incisional hernia[102], secondary aorto-enteric fistulas[103], graft occlusion or infection.

The EVAR technique is a minimally invasive procedure that entails making a small incision in the patient's femoral arteries to insert a covered stent graft into the aorta. This is done with the aim of excluding the aneurysmal portion from systemic circulation. Utilising radiological guidance, the stent graft is introduced via a stiff guidewire and subsequently deployed and conformed to the aortic wall. The consideration of specific morphological features is imperative in the planning of endovascular aneurysm repair (EVAR) to ensure effective sealing and exclusion of the aneurysm. The success and durability of endovascular aneurysm repair (EVAR) are significantly influenced by various factors such as the length and diameter of proximal and distal sealing sites, as well as the degree of neck angulation[104][85][105]. Complications such as endoleaks resulting from insufficient sealing or stent graft kinking leading to limb occlusion can arise due to disease progression, poor sizing or incorrect positioning of the stent graft. An endoleak is characterised by the continuous flow of blood within the aneurysm sac, leading to an increase in pressure which would eventually resume aneurysm sac growth, and which may eventually rupture[106]. Endoleaks of different types represent the prevailing complication of endovascular aneurysm repair (EVAR) and frequently necessitate further surgical intervention[107]. Additional complexities associated with endovascular aneurysm repair (EVAR) involve issues related to the access site, whether it was done percutaneously or via a femoral cut down[108].

Outcomes of surgical repair of intact AAA

The selection of the surgical approach is contingent upon the morphology of the aneurysm and the patient's characteristics, including functional capacity and comorbidities[19]. An additional factor to take into account is the patient's capacity and inclination to comply with essential follow-up monitoring, as EVAR necessitates ongoing monitoring with periodic imaging due to the potential of delayed endoleak, stent graft displacement, or infection[109]. The National Vascular Registry (NVR) 2024 annual report of UK vascular procedures shows early mortality rates of 2.7% for OSR and 0.3% for EVAR procedures[110]. The annual report also showed understandably lower critical care resource usage and overall hospital stay for patients receiving EVAR (2 days vs 7 days).

The outcome of both surgical modalities has been heavily investigated in multiple large scale randomised clinical trials. ACE[110], DREAM[111], EVAR 1[112], OVER[113] trials investigated the outcome difference between OSR and EVAR. Similar outcomes were observed in all trials confirming the early survival benefit of EVAR due to significant low 30- day mortality[114]. The incidence of cardiopulmonary complications in endovascular aneurysm repair (EVAR) is notably lower in comparison to open surgical repair (OSR) owing to the minimally invasive nature of the former. The initial advantages of EVAR are counterbalanced by reduced longevity. According to a Canadian study examining 17 683 patients who underwent surgical repair for AAA, EVAR patients exhibit considerably higher rates of reintervention (45.9% vs 42.2%) and AAA-related mortality in comparison to OSR[115]. Elective repair of abdominal aortic aneurysm (AAA) using open surgical repair (OSR) or endovascular aneurysm repair (EVAR) results in comparable long-term functional level and health-related quality of life outcomes[116]. Moreover, early EVAR survival benefit disappears on long term follow up secondary to aneurysm sac rupture[100,117,118].

Tailoring peri-operative care to individual patients and centralising vascular care to high-volume specialised centres are crucial factors in enhancing short-term survival[119,120]. The AAA Quality Improvement Programme (AAAQIP) protocols have

been effectively implemented in the United Kingdom, resulting in a reduction of reported mortality rates associated with elective AAA surgery to approximately 2-3% in 2013. In addition to advanced age and the co-occurrence of cardiac, pulmonary and renal comorbidities, frailty [121] and preoperative functional [122] status have been identified as prognostic indicators of postoperative morbidity and mortality.

Frailty

Definition

The WHO has conceptually defined frailty as “clinically recognisable state in older people who have increased vulnerability, resulting from age -associated declines in physiological reserve and function across multiple organ systems, such that the ability to cope with every day or acute stressors is compromised” [123].

Rockwood et al. (1994) proposed a dynamic model that resulted in the reconceptualization of frailty as encompassing not just physical deterioration but also increased reliance on others, so incorporating the social dimension of patients[124]. Considering this, Rockwood’s team in 1999 developed a concise clinical tool for the purpose of classifying frailty in older individuals[125]. This was achieved by conducting a study involving around 9000 community members, who were subsequently categorised into four grades. Grade 0 consists of individuals who are able to walk without assistance, perform basic activities of daily living such as eating, dressing, bathing, and bed transfers, are continent of bowel and bladder, and do not have cognitive impairments. Grade 1 includes individuals who experience bladder incontinence but do not require assistance with mobility or activities of daily living, and do not have cognitive impairments. Grade 2 comprises individuals who require assistance with mobility or activities of daily living, have cognitive impairment not severe enough to be classified as dementia, or experience bowel or bladder incontinence. Finally, Grade 3 consists of individuals who are dependent on others for transfers or one or more activities of daily life, experience bowel and bladder incontinence, and have been diagnosed with dementia. Upon adjusting for sex and age, the findings from the assessment of frailty using the frailty scale revealed a distinct and consistent pattern of association between varying degrees of frailty and subsequent outcomes of institutionalisation and mortality. The relative risk estimates for institutionalisation were found to be 1.7 (95% CI 1.3-2.1) for grade 1, 3.6 (95% CI 3.1-4.3) for grade 2, and 9.4 (95% CI 7.7-11.5) for grade 3. Similarly, the relative risk estimates for mortality were found to be 1.2 (95% CI 1.0-1.4) for grade 1, 2.0 (95% CI 1.8-2.2) for grade 2, and 3.1 (95% CI 2.7-3.6) for grade 3. Figure(1.2) demonstrated Kaplan- Meier curves for frailty grades for institutionalisation and death.

Utilising the data from Cardiovascular Health Study (CHS), efforts were undertaken to explore the potential convergence of three fundamental concepts (frailty, comorbidity and disability) within a cohort of 5888 patients. In that particular study[126], Fried et al. team defined comorbidity as the presence of two or more concurrent medical conditions within an individual. They identified comorbidities include arthritis, claudication, chronic obstructive airways disease, angina, congestive heart failure, myocardial infarction, cancer, diabetes, and hypertension. Disability was characterised as the presence of impairment in one or more activities of daily living (ADLs). Frailty, on the other hand, is conceptually defined utilising a phenotypic mode. In the presence of three or more components, patients were considered frail. Components include unintentional weight loss or loss of muscle mass (Sarcopenia), weakness tested via grip strength, poor endurance, slowness and poor physical activity. Among the individuals who satisfied the established criteria for frailty, it was observed that 27% exhibited frailty as the sole condition, while 46% presented with comorbidities in addition to frailty. Moreover, 6% of the participants displayed disability alongside frailty, and 22% manifested both comorbidity and disability in conjunction with frailty. The findings presented in this study offer compelling evidence to suggest that frailty should not be considered synonymous with either comorbidity or disability. However, it is important to note that comorbidity can be identified as an etiologic risk factor for frailty, while disability can be regarded as an outcome of frailty.

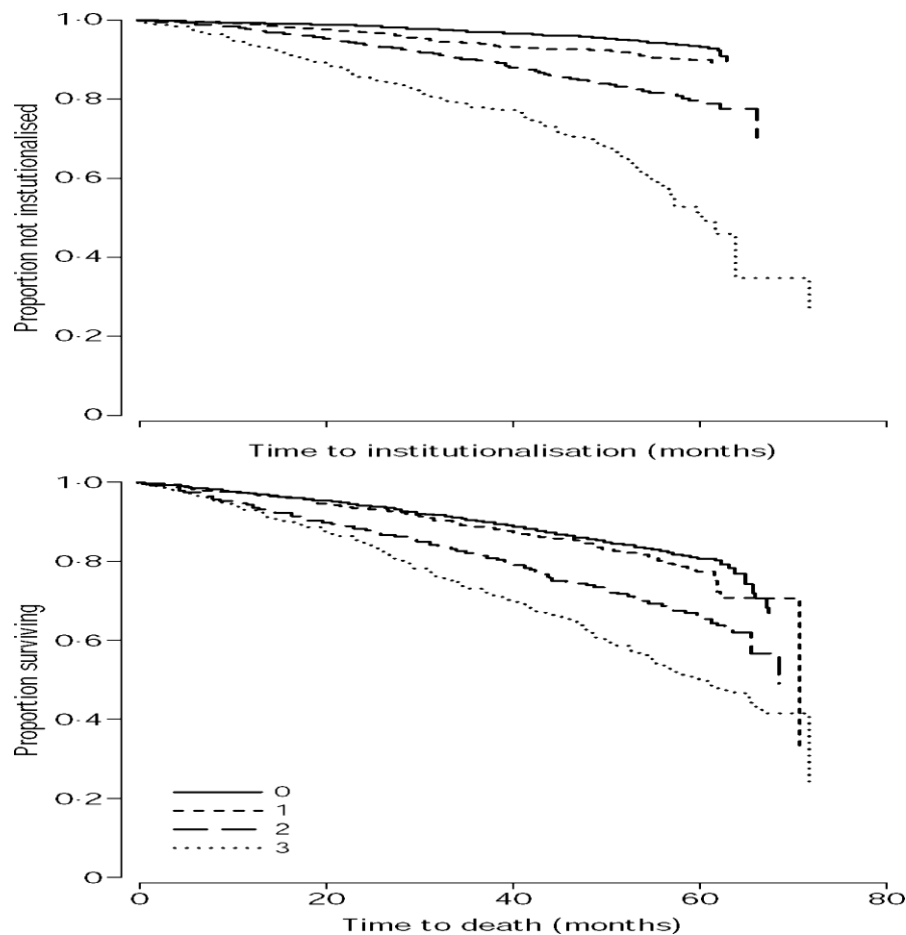


Figure 1.2: Time to institutionalisation (Top) and death (Bottom) on frailty scale, adjusted for age and sex[125]

Epidemiology

Worldwide population is increasing in age. It is estimated by 2030 one in six people will be above the age of 60. The population aged 60 years and above will increase from 1 billion to 1.4 billion in the coming 10 years with proportion nearly doubling from 12% to 22% of the world's population according to WHO[127]. With an increasing proportion of older individuals, common complex geriatric syndromes will rise. Frailty is an age-associated state of vulnerability after stressor event with cumulative decline in physiological systems reserve[126]. In a systematic review and meta-analysis of 120,000 older adults from 28 countries, the incidence of frailty is about 40.0 cases per 1000 person-years when using the physical frailty phenotype method [128].

ADVANTAGE which is The Joint Action (JA) initiative on Frailty founded by the European Third Health Programme produced a population level systematic review and meta-analysis showed overall frailty prevalence of 18% and about 45% (95% CI 27% , 63%) of individuals in non-community-based studies were frail[129].

Collard et al.[130] conducted a review on the epidemiology of frailty, which encompassed 21 community-based studies involving a total of 61 500 individuals aged 65 years and above. The study found that the prevalence of frailty exhibited a range of 4.0 to 59.1%, with a weighted prevalence of 10.7%. Out of the total of 21 studies that were incorporated, 14 of them employed the frailty phenotype model [126] as a measuring instrument.

A prospective study, known as the Women's Health Initiative Study[131], involved a cohort of just over 47 000 women over the age of 65, it was determined that the occurrence of frailty within a span of three years was estimated to be around 15%. Significant correlations were observed between frailty and advancing age, socioeconomic disadvantage, reduced educational attainment, African American or Hispanic ethnicity, extreme body mass index values, as well as the presence of chronic physical and mental illnesses ($p < 0.01$). Independently, frailty baseline predicted risk of mortality, disability and hospitalisation. The findings of this study suggest a notable disparity in the prevalence rates of frailty between women and men. This was similarly corroborated in the comprehensive analysis conducted by Collard et al., wherein the calculated weighted average prevalence of frailty exhibited a statistically significant disparity between genders. Specifically, the prevalence was found to be notably higher in the female population compared to their male counterparts, with respective rates of 9.6% and 5.2% ($p < 0.01$).

Frailty assessment tools

A plethora of assessment modalities have been developed to evaluate an individual's frailty status [132]. However, the absence of a universally recognised gold standard score remains a notable gap in the field. The study conducted by Aguayo's et al.[133] aimed to examine the degree of agreement observed among different frailty scores

within the framework of the English Longitudinal Study of Ageing (ELSA). Through a comprehensive analysis of literature, Aguayo team successfully identified a corpus of 35 distinct frailty scores that exhibit the capacity to be computed within the framework of the English Longitudinal Study of Ageing (ELSA). The presence of substantial discordance among various frailty scoring systems has been duly observed. In alignment with the established thresholds for individual frailty scores, a notable degree of variation was identified in the prevalence of frailty. Figure 1-3 demonstrates the significant disagreement between these scores.

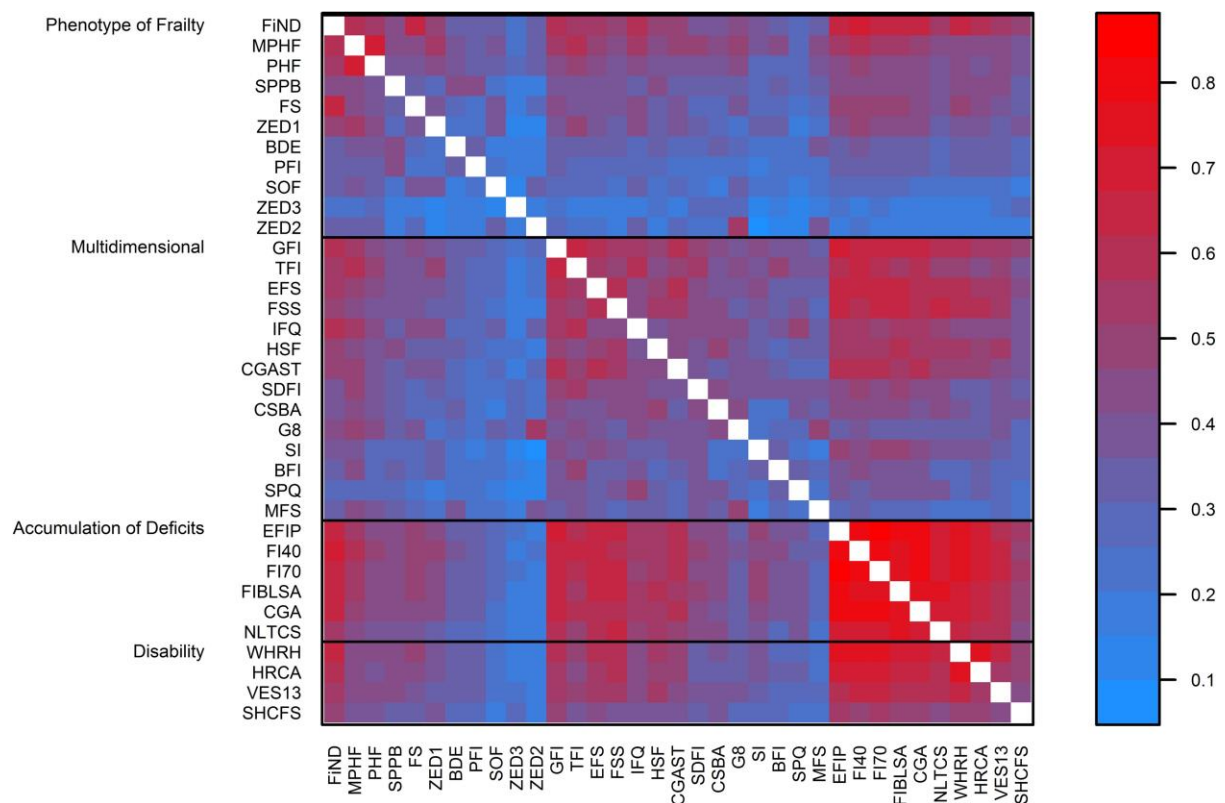


Figure 1.3 Agreement between Frailty scores[133]

Agreement (calculated with Cohen's κ) between pairs of frailty scores (595 combined pairs of scores) among participants in wave 2 of the English Longitudinal Study of Ageing, 2004–2005. The plot is sorted by frailty model and then from highest (red) to lowest (blue) median value of Cohen's κ coefficient. BDE, Beaver Dam Eye Study Index; BFI, Brief Frailty Index; BMI, body mass index; MFS, Modified Frailty Score; CGA, Comprehensive Geriatric Assessment; CGAST, Comprehensive Geriatric Assessment Screening Tests; CSBA, Conselice Study of Brain Aging Score; EFIP, Evaluative Frailty Index for Physical Activity; EFS, Edmonton Frail Scale; FI40, 40-item Frailty Index; FI70, 70-item Frailty Index; FIBLSA, Frailty Index Beijing Longitudinal Study of Ageing; PFI, Physical Frailty Index; FiND, Frail Non-Disabled (FiND) Questionnaire; FS, Frail Scale; FSS, Frailty Staging System; G8, G-8 geriatric screening tool; GFI, Groningen Frailty Indicator; HRCA, Hebrew Rehabilitation Center for Aged Vulnerability Index; HSF, Health Status Form; NLTCS, National Long Term Care Survey Frailty Index; PHF, Phenotype of Frailty; MPHF, Modified Phenotype of Frailty; SDFI, Static/Dynamic Frailty Index; SHCFS, Canadian Study of Health and Aging Clinical Frailty Scale; SI, Screening Instrument; SOF, Study of Osteoporotic Fractures; SPPB, Short Physical Performance Battery; SPQ, Sherbrooke Postal Questionnaire; IFQ, Inter-Frail Questionnaire; TFI, Tilburg Frailty Indicator; VES13, Vulnerable Elders Survey; WHOAF, World Health Organization Assessment of Functional Capacity; WHRH, WHOAF and self-reported health; ZED1, Zutphen Elderly Study (Physical Activity and Low Energy); ZED2, Zutphen Elderly Study (Physical Activity and Weight Loss); ZED3, Zutphen Elderly Study (Physical Activity and Low BMI).

The National Health Service (NHS) in England has emerged as one of the first health care systems in the world to identify individuals aged 65 and over who are living with moderate and severe frailty. The implementation of alterations to the general practitioner (GP) contract during the period of 2017/2018 brought about the incorporation of systematic identification of frailty as a means to focus on critical interventions such as falls assessment and medication review. The objective of the contract modification is to ascertain individuals exhibiting moderate to severe frailty, thereby enabling the implementation of tailored interventions and assistance.

Consequently, the electronic Frailty index (eFI) has been implemented across all general practitioner (GP) practices to facilitate the identification of individuals exhibiting signs of frailty. The eFI, or electronic Frailty Index, is a clinically validated instrument that leverages electronic primary care data to identify individuals with frailty at a population level. The validation process encompassed a substantial cohort of more than 900,000 individuals, all of whom were aged 65 years and older[134]. It constitutes of 36 potential deficits (Figure 1.4). Subsequently, the quantification of an individual's deficits is achieved by dividing the number of deficits they exhibit by the total number of deficits (36), thereby generating a score. The present stratification risk tool serves the purpose of assessing an individual's level of frailty, thereby enabling the classification of individuals into distinct categories based on their scores. Specifically, individuals with scores below 0.12 are deemed fit, those with scores ranging from 0.12 to 0.24 are classified as mildly frail, individuals with scores ranging from 0.24 to 0.36 fall into the category of moderately frail, and those with scores equal to or exceeding 0.36 are considered severely frail. While the Frailty Index (FI) has demonstrated its efficacy as a dependable tool for screening frailty, it is worth noting that its implementation in a clinical setting can be rather time-consuming for healthcare practitioners.

Electronic frailty index

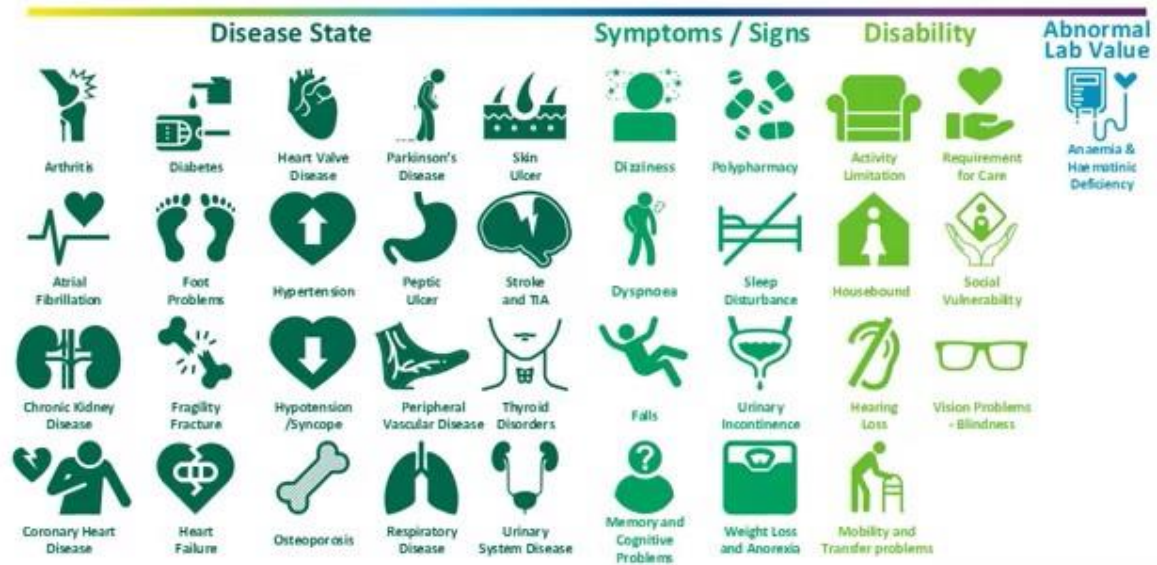


Figure 1.4: Electronic frailty Index[134]

As a result, a number of different tools emerged for the use in clinical setting. Studies involving surgical patients, the common tools encountered are the Clinical Frailty Scale (CFS), Edmonton Frail Scale (EFS) and other brief electronic frailty indexes (mFI) .

The Clinical Frailty Scale (CFS), initially introduced by Rockwood et in 2005 [135] underwent subsequent revisions in 2020[136] during the second clinical assessment of the Canadian Study of Health and Ageing (CSHA). This scale serves as a valuable tool in capturing the comprehensive assessment of an older adult's physical fitness or frailty, following an evaluation conducted by a clinician. Based on clinical judgement, patient is scored on a scale from 1 (very fit) to 9 (terminally ill). Each numerical scale is accompanied by a comprehensive written depiction of frailty. Individuals with a score equal or exceeding 5 is indicative of frailty. CFS (Figure 1.5) has garnered significant adoption within NHS due to its brevity. A nationwide survey in UK aimed to examine the prevalence of frailty assessment tool utilisation within hospital settings involving 3218 patients has found 77.5% underwent assessment using CFS[137]. CFS has been validated as a robust tool[135,136], supported by a body of research that showcases its ability to predict adverse clinical outcomes in elderly individuals admitted to hospitals[138,139].

The Edmonton Frail Scale (EFS) is a validated instrument employed in the assessment of physiological and functional changes associated with frailty. It examines nine distinct subscales which include cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance which is further delineated into 11 specific items. The most attainable score is 17. The quantification of frailty is accomplished through a scoring system, wherein a range of 0 to 4 points signifies the absence of frailty, scores between 5 and 6 denote vulnerability, a range of 7 to 8 corresponds to low-level frailty, a score of 9 to 10 represents moderate frailty, and scores surpassing 11 indicate severe frailty[140]. Thus far, the existing body of literature has not yielded any studies that have successfully achieved a reduction in the quantity of EFS subscales or established significant correlations between these subscales and alternative measures of frailty.

One of the purported advantages of this intervention lies in its capacity to elucidate facets of frailty that may be susceptible to preoperative optimisation. It also exhibits several key attributes that align with the criteria of a viable frailty measurement tool suitable for incorporation into surgical practise. Notably, the British Geriatric Society (BGS) has endorsed EFS as a recommended assessment instrument for evaluating frailty within the perioperative context. It is relatively a short (5 - 10 minutes) questionnaire and covers core physical and cognitive aspects which CFS lacks. Figure (1.6) shows the scale. The applicability of EFS in surgical research has been extensive and conclusively agree that EFS has prognostic prediction of post operative outcomes[141–143].

In the realm of research pertaining to the utilisation of frailty assessment tools within the domain of vascular surgery, a multitude of studies have been dedicated to evaluating the prognostic efficacy of various tools in relation to the occurrence of postoperative morbidity and mortality. In a recent systematic review[144], a comprehensive analysis was performed on a total of 111 studies. These studies employed a diverse range of 42 different frailty assessment tools, of which a subset of 19 tools were found to have undergone validation. The comprehensive analysis has determined that there exists a significant degree of variability in the choice of tools and the methods employed for data analysis. Additionally, it was determined that the CFS score has been extensively investigated and exhibits favourable psychometric characteristics specifically within a surgical cohort, a quality that is absent in other assessment tools.

CLINICAL FRAILTY SCALE

	1	VERY FIT	People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
	2	FIT	People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally , e.g., seasonally.
	3	MANAGING WELL	People whose medical problems are well controlled , even if occasionally symptomatic, but often are not regularly active beyond routine walking.
	4	LIVING WITH VERY MILD FRAILTY	Previously "vulnerable," this category marks early transition from complete independence. While not dependent on others for daily help, often symptoms limit activities . A common complaint is being "slowed up" and/or being tired during the day.
	5	LIVING WITH MILD FRAILTY	People who often have more evident slowing , and need help with high order instrumental activities of daily living (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.

	6	LIVING WITH MODERATE FRAILTY	People who need help with all outside activities and with keeping house . Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
	7	LIVING WITH SEVERE FRAILTY	Completely dependent for personal care , from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
	8	LIVING WITH VERY SEVERE FRAILTY	Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
	9	TERMINALLY ILL	Approaching the end of life. This category applies to people with a life expectancy <6 months , who are not otherwise living with severe frailty . (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. In **severe dementia**, they cannot do personal care without help. In **very severe dementia** they are often bedfast. Many are virtually mute.



DALHOUSIE UNIVERSITY

Clinical Frailty Scale ©2005–2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: www.geriatricmedicine.ca
Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

Figure 1.5: The Clinical Frailty Scale (CFS)[136]

The Edmonton Frail Scale

Acute Care (EFS-AC)

Examiner: _____

Date: _____

Additional Source: _____

Scoring the EFS

	FIT			VULNERABLE		MILD		MODERATE		SEVERE	
	1	2	3	4	5	6	7	8	9	10+	
	FRAILTY										

PATIENT IDENTIFICATION

Figure 1.6: The Edmonton Frail Scale[140]

Impact of Frailty on Vascular Surgery patients

The prevalence of frailty is frequently observed in individuals who are subjected to arterial vascular surgery [145]. The findings of a scoping review comprising 23 studies indicate that the prevalence of frailty among patients undergoing vascular surgery procedures varied between 20% and 60% [146]. Research has demonstrated a correlation between frailty and unfavourable health consequences, including but not limited to falls, hospitalisation, institutionalisation, and mortality [147].

The hospitalisation of frail adults has been found to be linked with in-patient mortality, delirium, non-home discharge, and an extended length of stay [139][138]. The findings of research conducted on patients who underwent elective abdominal aortic aneurysm repair and were registered in the National Surgical Quality Improvement Programme (NSQIP) database from 2005 to 2012 revealed that the adjusted odds ratio for mortality was 1.9 (95% CI, 1.2-3.0) for the group with the highest frailty score following EVAR and 2.3 (95% CI, 1.4-3.7) following OAR [148].

A recent research endeavour examining the immediate and intermediate consequences of vascular surgery on frail patients revealed that models based on frailty were highly effective in predicting mortality at the 12-month mark (AUC = 0.81), extended hospital stays (AUC = 0.79), and discharge to a care facility (AUC = 0.78) [149]. Furthermore, it has been observed that individuals undergoing peripheral arterial bypass surgery exhibit a rise in 30-day mortality rates, with the percentage increasing from 0.6% in the non-frail group (mFI < 0.09) to 7.4% in those with a mFI score greater than 0.54 [150]. The study found a significant correlation between intermediate and high CFS scores and a 1.6- and 2-fold increase in the risk of 2-year mortality among patients diagnosed with critical limb ischaemia. Hence, it is imperative to implement efficacious and pragmatic interventions to counteract frailty upon its detection.

The Centre for Perioperative Care (CPOC) and the British Geriatrics Society (BGS) collaborated to create a comprehensive pathway guideline for perioperative care of individuals with frailty who are undergoing elective or emergency surgery. The provision of comprehensive perioperative care of high quality necessitates a multifaceted approach that involves the integration of various components across community, primary, secondary, and social care. The successful implementation of each element of the pathway requires a collaborative and interdisciplinary approach, involving professionals from various sectors working together as a cohesive team. Components of the pathway (Figure 1.7) include the following:

- The active participation of patients and their carers, as well as their education and empowerment, are crucial components in healthcare.
- The preoperative evaluation of risk and optimisation of physiological status, comorbidities, and geriatric syndromes, including frailty.
- Lifestyle modifications are recommended to enhance both perioperative and long-term health outcomes.
- The concept of Shared Decision Making (SDM) is a process whereby healthcare providers and patients collaborate to make informed decisions about healthcare options that align with the patient's values.
- The aim is to achieve the most effective surgical and anaesthetic management during the intraoperative period, followed by high-quality postoperative care in a suitable environment that includes rehabilitation.
- Proactive discharge planning is essential, along with the provision of links and referrals to relevant community, primary care, and follow-up services.

Guideline for Perioperative Care for People Living with Frailty Undergoing Elective and Emergency Surgery

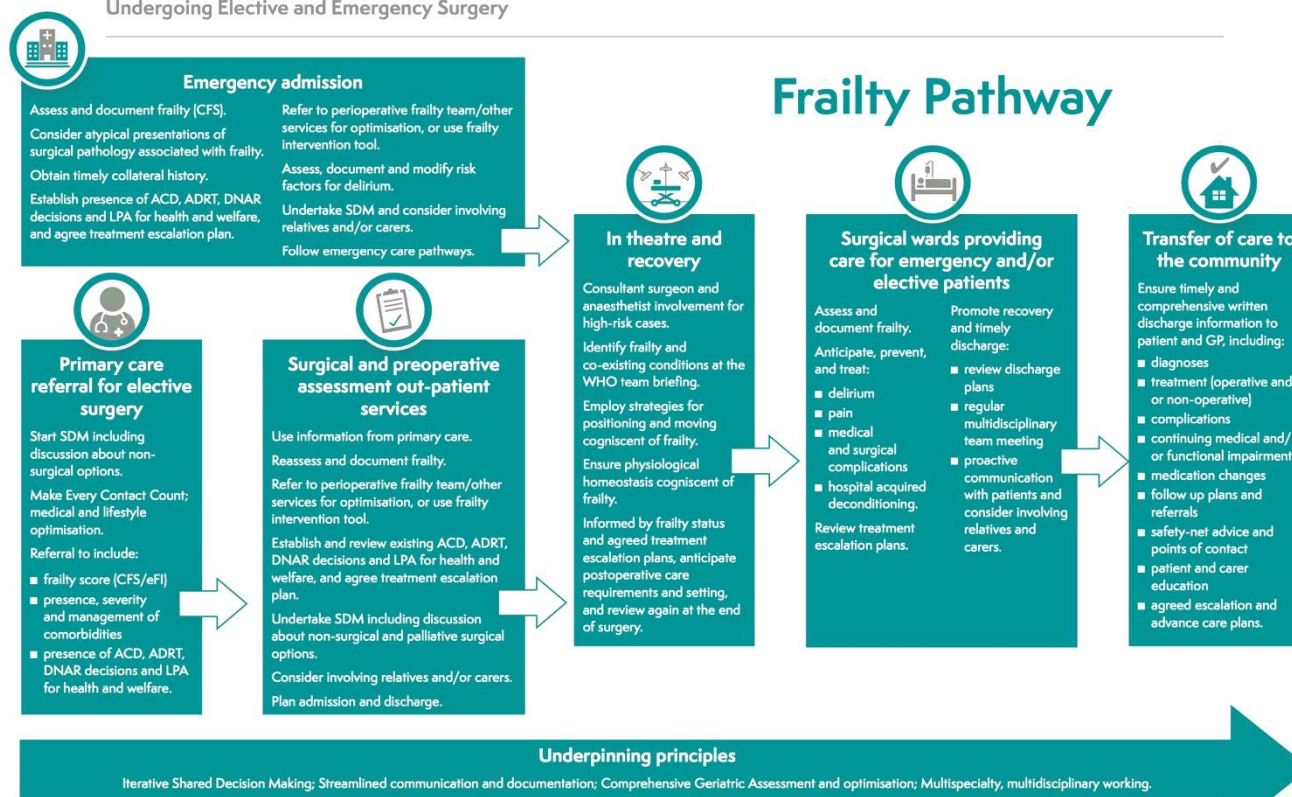


Figure 1.7: Guideline for Perioperative Care for Frail patients undergoing surgery[151]

Prehabilitation

Concept and definition

Prehabilitation is the practice of boosting patient's functional capacity prior to surgery, with the goal of improving surgical outcomes and recovery[152–154]. The concept of prehabilitation was first described in 1946 by the British Army[155], entitled "Prehabilitation, rehabilitation, and 'revocation' in the army,". It describes the circumstances during the Second World War when young recruits seeking to enlist were turned down due to their inadequate physical and mental state caused by poverty, poor nutrition, and limited education. The British army adopted a two-month program comprising educational, physical, and nutritional interventions successfully transformed these substandard recruits to capable soldiers. Out of the 12,000 men who underwent prehabilitation, over 85% demonstrated notable improvements in both their physical and mental well-being.

The field of sports medicine reignited interest in prehabilitation during the 1980s[156], however the focus of that interest was mainly of injury prevention in athletes. Although the idea of preparing patients for surgery was already familiar in the physical therapy community, it had not been thoroughly studied in a systematic manner. Later in the 2000's a theoretical model of prehabilitation was introduced (Figure 1.8) which emphasized presurgical exercise to enhance functional capacity prior to a surgical procedure[153,154]. This approach was found to result in quicker postoperative recovery when compared to patients who remained physically inactive during the preoperative period. Throughout the years, this model evolved into a multi-modal approach incorporating improving modifiable risk factors associated with poor surgical outcomes such as smoking, anaemia and anxiety. In a 2019 study[157] examining 299 patients awaiting surgery, researchers investigated the prevalence of modifiable behavioural risk factors. The study revealed that 42% of the patients exhibited two or more risk factors, such as physical inactivity, smoking, or hazardous alcohol

consumption. The same study investigated the attitudes of these patients towards preoperative behavioural change showing that majority of participants show motivation towards addressing their risk factors. This approach may prove to be essential when addressing a frail, vulnerable population known to have poor surgical outcome.

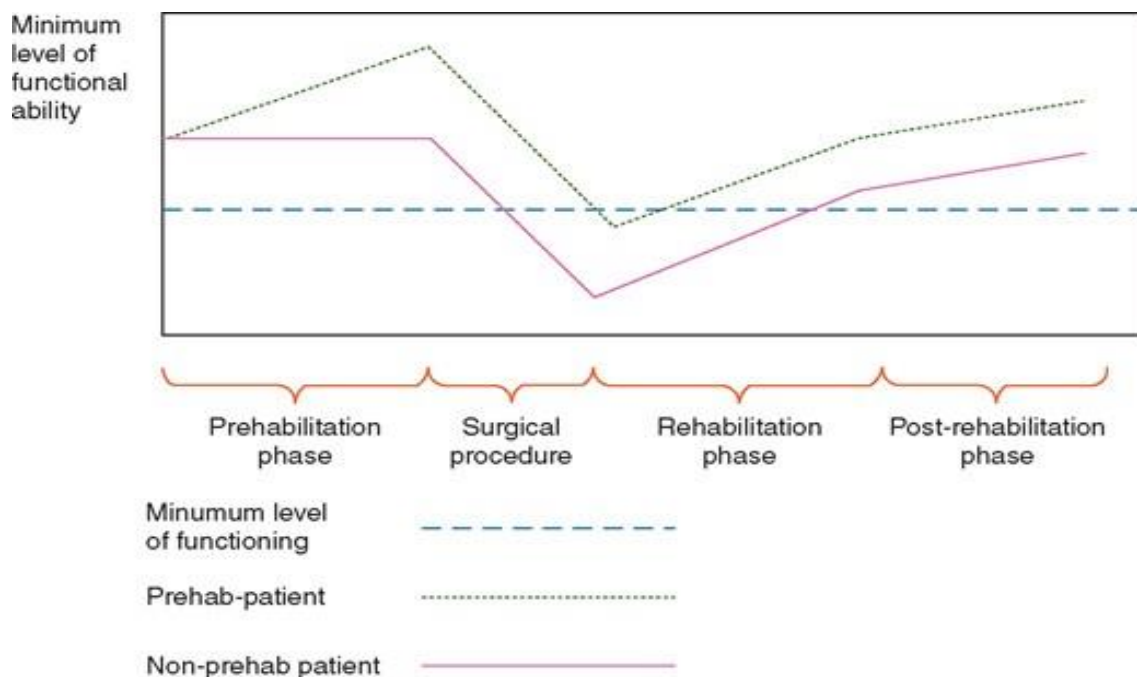


Figure 1.8: Theoretical model of prehabilitation.[153]

Components of a prehabilitation programme

The benefit of multimodal approach for prehabilitation programmes is increasingly realised[158]. While the conceptual focus of prehabilitation was on improving physical activity, studies showed that a pre-operative exercise interventions only are not sufficient to improve post operative outcomes in surgical patients[159]. It is well recognised that the reduction of functional capacity in cardiovascular patients is multifactorial[160]. The cardiovascular disease itself and its associated symptoms such as respiratory comorbidities, anaemia, malnutrition, sarcopenia, depression or anxiety can be found among the factors causing a state of deconditioning for patients undergoing surgery[161–163].

Four pillars of prehabilitation been identified in literature[164], which include i) medical optimisation, ii) physical exercise, iii) nutritional support, iv) psychological support. As a result, multidisciplinary approach to prehabilitation is crucial to address the multiple behavioural modifiable risk factors. (Figure 1.9)

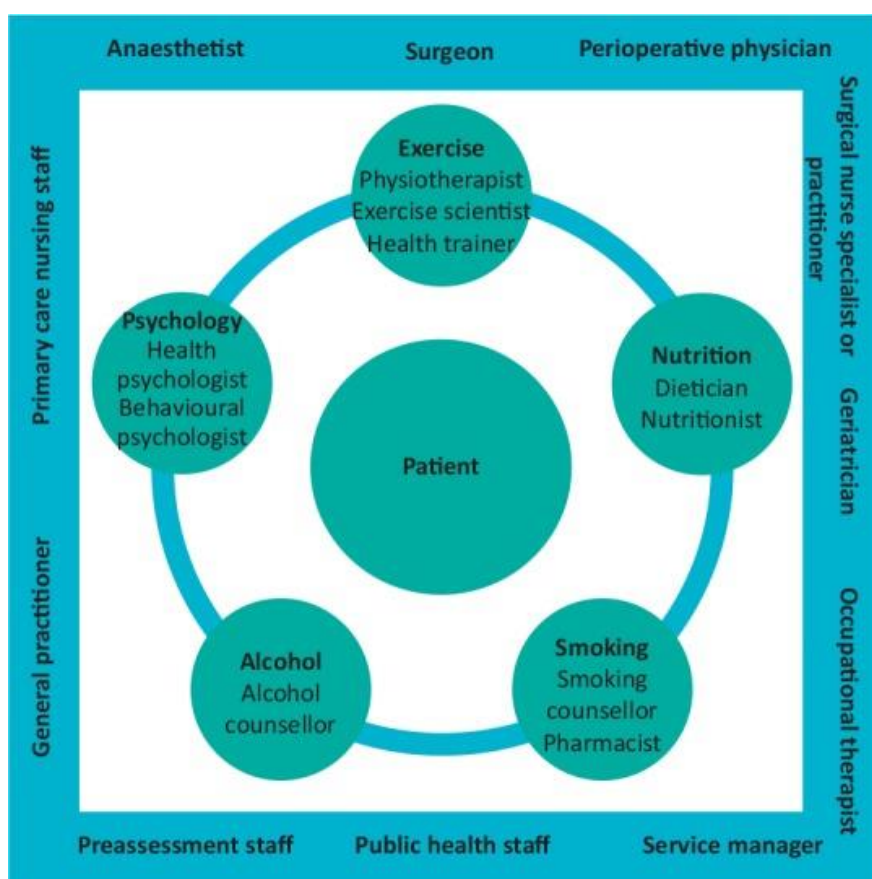


Figure 1.9: Multidisciplinary prehabilitation programme[164]

Physical exercise

Physical activity must be distinguished from exercise, which is a distinct subset of physical activity that is planned, structured, and repetitive with the improvement or maintenance of physical fitness as a final intermediate goal[165,166]. Physical activity can be understood as any bodily movement produced by skeletal muscles that results in energy expenditure. As part of a short-term, tailored prehabilitation treatment designed to address a specific weakness or disability a patient may be given instructions

for localised or specialised therapeutic strengthening exercises[167]. It is crucial to underline that each of these elements is a crucial part of prehabilitation and that, when combined, they offer a complex intervention to alter lifestyle habits and boost physical function.

Unless there is a special contraindication, patients can safely engage in the 150 minutes of moderate or 75 minutes of strenuous physical activity per week that is now advised for the general population. The 'FITT' concept should be followed when prescribing an exercise programme: frequency (how often?), intensity (how hard?) , time (how long?), and type (what form of exercise has been prescribed?)[168]. For the purpose of prescribing an exercise programme, the recommendations are typically based on the recommendation of 150 minutes per week, divided into bouts of aerobic exercise that should happen at least every other day, last for about 30-45 minutes, and be moderately intense (e.g., 50-75% of age-predicted maximum heart rate)[169]. Depending on the patient's preferences or the equipment that is available, the exercise itself may be of a variety of forms. Along with the aerobic activity, strength training including all major muscle groups should be done at least twice per week. Exercises that improve balance and flexibility are also suggested as part of a thorough training regimen[164,170,171]. Regular assessments must be performed on the patient during the prehabilitation phase to ensure that the stimulus is appropriate and prevent either too much or too little activity. The FITT concept of prescription must be seen as a framework only, and each patient's demands and physiological condition must be taken into account. It is crucial to keep in mind that prescribing exercise is not a "one size fits all" option in order to target the positive emotional response to exercise. Exercise preferences differ throughout populations and between people within populations.

There is growing evidence suggesting paying attention to the add a "F" (Fun) to the FITT concept as it may increase the adherence to physical exercise. There are simple techniques available to help health care practitioners measure emotional response before, during, and after exercise. The Physical exercise pleasure (PACES)[172] short form, might be used to measure trait pleasure of exercise in order to decide whether other factors of motivation will need to be incorporated. This measure, or similar ones,

might be used as a standard practise in formulating prescriptions and encouraging the evaluation of exercise satisfaction across groups.

Given this, it is critical that the exercise be planned and managed by knowledgeable professionals who can successfully individualise and provide safe and focused courses. The advantages of the activity must be maximised in order to avoid tiredness and physical maladaptation, as well as to provide enough recuperation between workout sessions.

Medical optimisation

Poor nutritional status is clearly associated with poor postoperative outcomes[173,174]; length of stay, infectious complications, readmission rates, and mortality are all negatively impacted. Nutritional risk is influenced by nutritional status prior to surgery, the severity of the surgical insult, and the character of the surgery (e.g., significant gastrointestinal resection). During the perioperative period, episodes of malnutrition only serve to exacerbate the problem. Prior to any significant surgery, formal nutrition risk assessment should be performed, and malnourished patients should ideally receive 7–10 days of enteral nutritional support[175].

Malnourished patients, regardless of the grade of surgery, and well-nourished patients undergoing high-risk major surgery are most likely to benefit from preoperative nutrition therapy. Carbohydrate supplementation prior to surgery reduces insulin resistance and promotes an anabolic state, thereby minimising loss of protein, lean body mass, and muscle function. A few hours prior to exercise, carbohydrate consumption increases liver and muscle glycogen and facilitates the completion of the workout[158].

Dietary prehabilitation is typically paired with exercise prehabilitation, but it has been shown to enhance outcomes even when administered alone[176]. For patients at risk of malnutrition, early dietetic status assessment with a nutritional scoring instrument, such as the well-validated 5-step Malnutrition Universal Screening instrument

(MUST)[177,178], is followed by dietician-led input. A "food first" strategy is advised, with a focus on adequate protein consumption (1.5-2 g/kg/day). Oral nutritional supplementation with high-protein beverages is a common dietetic intervention for those at moderate or high risk of malnutrition and has been found to independently reduce postoperative complications and length of stay[179].

There is some evidence that immune-nutrition, the consumption of amino acids (such as glutamine and arginine), omega-3 fatty acids, and nucleotides, counteracts the hyperinflammation and immune impairment caused by the surgical stress response, thereby promoting wound healing, reducing infection rates, and shortening hospital stays[175]. In emaciated patients, this regimen should ideally begin 5–7 days prior to surgery and continue for a similar length of time following surgery.

Psychological support

Fear in the patient awaiting surgery has multiple causes. Concerns include the underlying diagnosis, surgery, anaesthesia, discomfort, survival, and recovery. These psychosocial stressors induce immunological dysregulation by means of the immune–brain loop, activating through the same pathways as the surgical stress response[180]. Psychological support has a dual purpose. Reduce psychological distress and anxiety associated with diagnosis and surgery, both of which contribute to increased postoperative pain, delayed recovery, postoperative complications, and impaired wound healing. Second, to maximise patients' motivation and equip them to adhere to the program's exercise and nutritional components.

Effective psychological interventions include providing sensory information (e.g., what the perioperative experience will feel like), cognitive interventions, e.g., development of positive attitudes, behavioural instruction on what can be done to improve outcome, and relaxation techniques such as hypnosis and progressive muscle relaxation (sequentially tensing and relaxing each muscle group). Providing procedural information (i.e., details regarding all aspects of the patient's journey) and emotion-focused interventions involving the discussion of emotions are also beneficial[181]. The

latter may be facilitated by the support and camaraderie gained from meeting other prehabilitation programme participants.

Benefit of Prehabilitation in AAA patients

AAA repair, whether open or endovascular, entails a high risk for patients with poor exercise capacity due to frailty, deconditioning, and comorbidities[182]. The surgical stress response consists of neuroendocrine, metabolic, and inflammatory alterations that result in increase in global tissue oxygen uptake[183]. Many risk factors for abdominal aortic aneurysm (AAA), including smoking, hypertension, obesity, and advanced age, are also associated with coronary artery disease[10]. Low aerobic fitness, as indicated by an anaerobic threshold (AT) 10.2 mL/kg/min, peak oxygen consumption (VO₂peak) 15 mL/kg/min, and reduced ventilatory efficiency, as indicated by a VE/VCO₂ > 42, are independent predictors of decreased survival after open and endovascular aortic surgery[184]. Patients with aneurysms who have a high risk of rupture and substantial comorbidities may still need to be considered for treatment. Optimising aerobic capacity prior to AAA repair is gaining attention, and such strategies make intuitive sense; fitter patients are anticipated to have improved outcomes[185][186]. In 2005, one of the key findings of the Endovascular Aneurysm Repair (EVAR) 2 trial was that vascular teams should prioritise techniques to increase patient fitness prior to surgery[187]. In fact, the waiting period for significant elective vascular interventions, such as aneurysm repair, provides an optimal opportunity to optimise patient fitness and potentially enhance perioperative outcomes.

Recent research has focused on the effects of prehabilitation on cancer patients awaiting major surgery. Patients with colon and rectal cancer have been shown to benefit from preoperative exercise in terms of cardiorespiratory fitness, respiratory muscle endurance, fatigue, and perception of physical health[188,189]. Recent evidence suggests that exercise training may have direct antitumor effects, resulting in enhanced tumour regression after neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer.[190]

The perioperative "standard care" pathways, prehabilitation regimens, and outcome measures are highly variable, and their methodological designs are typically of low or moderate quality[191,192]. In general, studies are small and underpowered to detect differences in postoperative clinical outcomes, and they frequently focus on the intervention's feasibility.

The preoperative functional status of a patient is crucial to their ability to tolerate the surgical stress response associated with AAA repair[193,194]. Consequently, physical fitness is a significant predictor of perioperative outcome: patients who are less physically fit have higher rates of morbidity and mortality after major surgery.

Historically, the safety implications of engaging in exercise training among patients diagnosed with abdominal aortic aneurysm (AAA) remained uncertain. There was ongoing fear that exercising AAA patients may be associated with increased risk of blood pressure -induced expansion leading to AAA rupture. Nevertheless, recent research[195] has unequivocally demonstrated the safety of exercise training for a duration of up to three years in individuals diagnosed with abdominal aortic aneurysm (AAA). The findings of this clinical trial indicate that the implemented exercise regimens do not demonstrate any observable influence on the growth rate of abdominal aortic aneurysms (AAA) or result in any adverse clinical events commonly associated with exercise. This observation was reiterated in a recent meta-analysis[196] examining clinical trials involving the implementation of exercise interventions in patients diagnosed with abdominal aortic aneurysm (AAA). The analysis encompassed a cohort of 489 individuals, wherein the study revealed a prevalence of 0.8% for cardiovascular incidents, encompassing myocardial infarction, unstable angina, serious adverse arrhythmia, aortic rupture, and AAA-related events, as observed within the compiled studies. Additionally, the study findings indicated a lack of disparity in abdominal aortic aneurysm (AAA) diameter among individuals presenting with subthreshold AAA, defined as having a diameter less than 55mm.

A recent Cochrane review[197] published in 2021, evaluating the impact of preoperative exercise on patients with abdominal aortic aneurysms identified only four

RCTs that met eligibility requirements. Studies employed a variety of exercise regimens, with training intensity and frequency varying considerably between studies. Authors judges the overall risk of bias to be “high risk”. The studies included in the review were small, enrolling 20 to 136 patients each. One group investigated inspiratory muscle training for at least 2 weeks prior to surgery [198] while others evaluated the impact of 6 weeks of preoperative supervised exercise[199], the feasibility of high-intensity training (HIT) 3 times per week for 4 weeks[200]. The overall conclusion is that it is uncertain whether prehabilitation exercise, when compared to standard care (no exercise), reduces the incidence of 30-day mortality following AAA repair (RR 1.33, 95% CI 0.57 to 5.77). However, preoperative exercise may reduce the risk of cardiac complications (RR 0.36, 95% CI 0.14 to 0.92) and renal complications (RR 0.31, 95% CI 0.11 to 0.88). It was not clear if prehabilitation exercise, compared to usual care (no exercise), reduces the incidence of pulmonary complications (RR 0.49, 95% CI 0.26 to 0.92), the need for reintervention (RR 1.29, 95% CI 0.33 to 4.96) or postoperative bleeding (RR 0.57, 95% CI 0.18 to 1). There was little to no difference in ICU length of stay, hospital length of stay, or quality of life between the exercise and usual care groups.

However, Fenton et al’s Cochrane review did not include a recent a RCT [201] published in 2022 which hypothesised a 24-week, community-based exercise training could achieve improvement in CPET parameters. 28 patients randomised to community exercise achieved significant peak VO₂ improvement from baseline at 24 weeks (RR 2.3, 95% CI 1.2 to 3.3) compared to control patients (p = 0.31).

The 2020 National Institute for Clinical Excellence guidance on AAA management identifies prehabilitation to improve postoperative outcomes after aneurysm repair as a future research objective, highlighting the lack of definitive evidence regarding the utility and cost-effectiveness of preoperative exercise in AAA surgery. Additional research is necessary to ascertain the clinical and cost-effectiveness of preoperative exercise programmes, as well as their optimal design[202]. Similarly, the Royal College of Anaesthetists' 2021 guidelines for the provision of anaesthesia services identify the implementation of prehabilitation programmes as an area for future research, based on

a systematic review of the evidence in a guideline for the provision of anaesthesia for vascular procedures[203].

The concept of home based prehabilitation for patients undergoing surgery is gaining interest. Through the utilisation of digital health technologies, there exists the potential to facilitate the augmentation of health communication and information dissemination between healthcare practitioners and individuals seeking medical care, thereby circumventing the limitations imposed by geographical constraints in healthcare accessibility. Furthermore, this innovative solution effectively addresses the challenges associated with patient transportation to healthcare facilities and the temporal constraints imposed by the need for patients to allocate time for transportation at a predetermined moment. Significantly, it has been demonstrated that the presence of transportation and logistical obstacles can lead to a reduction in adherence to prehabilitation protocols[204]. This observation serves as a justification for the exploration and establishment of home-based prehabilitation interventions.

Chapter 2 : Aims

Overall aim

- Improving the outcomes in patients undergoing AAA repair

Specific aims

- Investigate the prevalence and impact of frailty among individuals who underwent elective repair of abdominal aortic aneurysm within a national registry to provide a real-world contemporary data (Chapter 3).
- Examine the compliance and acceptability of prior preoperative exercise programmes for patients with abdominal aortic aneurysm. (Chapter 4).
- Investigate a novel remote prehabilitation programme for patients awaiting abdominal aortic aneurysm repair (Chapter 5,6,7).
- Investigate the safety and acceptability of using Neuromuscular electrical stimulation device as additional method for recovery following surgery (Chapter 8).

Chapter 3 : The impact of frailty on treatment outcomes for non-ruptured abdominal aortic aneurysms. A National Vascular Registry cohort study

Introduction:

Analysis of hospital records of NHS England reveals that the number of individuals aged 75 or older who underwent surgery increased nearly 50% from 1999 to 2015[205]. Frailty which is linked with ageing; is a syndrome characterised by a progressive decline in a person's physiological reserve and functional capacity. This decline makes them vulnerable to a variety of stressors, including surgical procedures and falls. There is a correlation between the frailty and unfavourable outcomes, such as an increased likelihood of morbidity or mortality and an increase in dependency levels. Frailty has been recognised as an independent predictor of mortality [206][207] and the correlation between frailty and increased morbidity and mortality after surgery been demonstrated in many studies[208–210].

In the United Kingdom, approximately 3000 patients undergo elective abdominal aortic aneurysm (AAA) repair, either through open surgical repair or endovascular aneurysm repair (EVAR). It is estimated that 80% of the patient cohort were aged 65 years or older. Patients diagnosed with AAA often do not exhibit any symptoms, and the primary objective of surgical intervention is to extend their lifespan and mitigate the risk of rupture.

Nevertheless, the act of performing surgery is linked to postoperative morbidity, a decrease in quality of life, and mortality. Therefore, it is crucial to take into account the operative risk and life expectancy of patients when proposing surgical interventions.

The UK National Vascular Registry (UK-NVR) has recently acknowledged the significance of assessing frailty status and has implemented a mandatory requirement to record this metric for all patients undergoing index vascular procedures, including AAA repair, lower limb revascularization, and carotid endarterectomy.

The hypothesis posits that there exists a correlation between elective AAA repair in frail patients and an increased likelihood of experiencing postoperative mortality and morbidity. In this study, our objective was to examine this hypothesis by analysing data obtained from the National Vascular Registry for elective Abdominal Aortic Aneurysm (AAA) procedures. We sought to stratify patients based on the NVR frailty index in order to conduct our analysis.

The aim of this study was to :

- Investigate the prevalence of frailty in patients undergoing elective AAA repair
- Investigate the association between frailty and reported NVR outcomes.

Methods

Database

A Data Access Request Form (DARF) was put forward to the Healthcare Quality Improvement Partnership (HQIP) to gain access to depersonalised patient-level healthcare data from the National Vascular Registry(NVR) electronic database.

Ethical Approval

After appropriate consultation with the Research and Governance Integrity Team (RGIT), the decision made that there is no requirement for ethical approval as the data request involved depersonalised data. (Appendix 3.1)

Data handling

Data handling was conducted according to the General Data Protection Regulation (GDPR) articles 6 (1) (e) and 9 (2) (i). Appropriate security arrangements for data storage and analysis were demonstrated by the presence of compliant Data Security and Protection Toolkit (ODS code : RYJ – 18/8/2020). Data transfer flowchart (Figure3.1) created to ensure the appropriate secure transfer of depersonalised data from NVR to our data storage with secure limited access to the only personnel directly involved in the study.

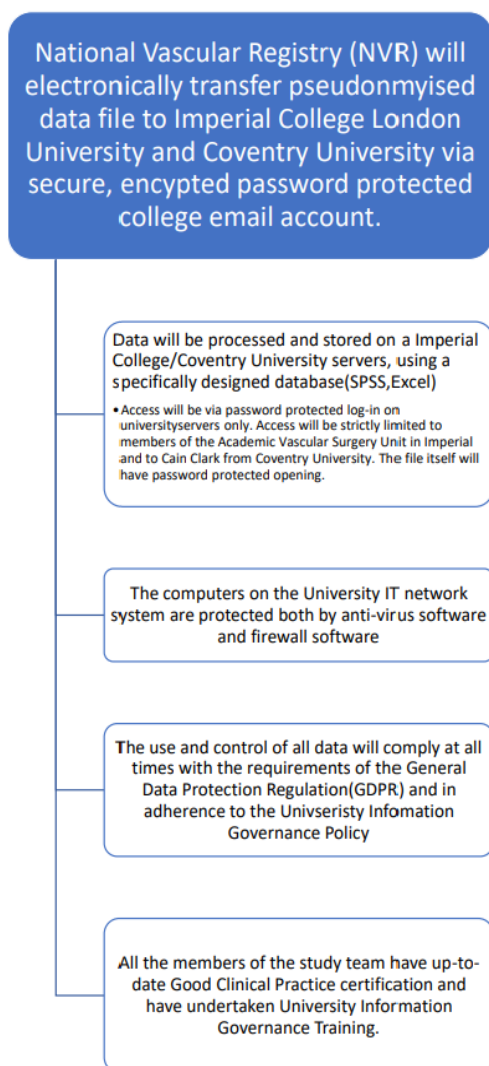


Figure 3.1: Data Transfer Flow Chart from NVR data holders to research team

Study population:

The study included all patients who had undergone infrarenal open and endovascular elective repair and registered in the NVR between January 2019 until March 2020. Patients who had urgent, complex and redo repair including symptomatic AAA were excluded. Patients who also had absent frailty score recorded were excluded from analysis.

Frailty assessment

The National Vascular Registry has developed a 4 category frailty groups; (Not frail, Mildly frail, Moderately Frail and Severely Frail) to accommodate and consolidate all validated frailty tools used by NHS hospitals (for e.g Clinical Frailty Scale (CFS), Edmonton Frail Scale). As a result, in this study, frailty prevalence was demonstrated using the NVR frailty categorisation as reported. An example of how Clinical Frailty Scale is translated to NVR frailty categorisation is demonstrated in Figure 3.2.

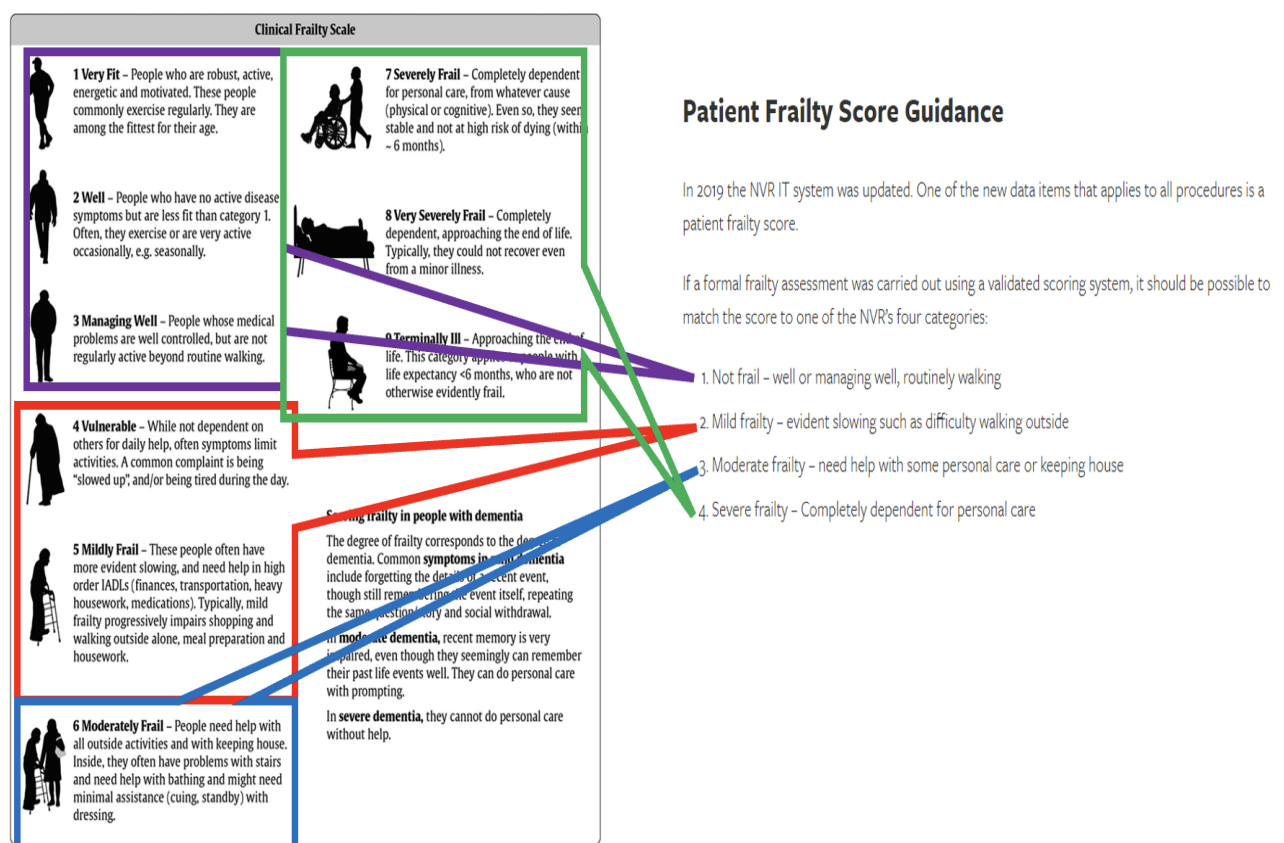


Figure 3.2: Demonstration of how NVR team categorised frailty according to Clinical Frailty Scale

Outcomes measured:

The main clinical outcomes were analysed for the whole cohort and subgroup analysis was performed according to the type of surgery (OSR or EVAR). Then further analysis was performed to analyse the effect of frailty in each subgroup. All variables analysed are defined according to the NVR data dictionary (<https://www.vsqip.org.uk/resource/nvr-data-dictionary/>).

Primary Outcomes:

1. In hospital/ 30-day mortality
2. Major Adverse Cardiac Events (MACE): Composite of the incidence of cardiovascular events (cardiac, cerebrovascular, bowel ischaemia, paraplegia, limb ischaemia) and/or in hospital/30-day mortality.

Secondary Outcomes:

1. Standards of Care:

The Abdominal Aortic Aneurysm Quality Improvement Project (AAAQIP), European Society for Vascular Surgery and the Society of Vascular Surgery outlined essential standards of care practises for all patients who will undergo AAA repair in the effort to improve outcomes[211–214]. In this study, we identified if SOC were met accordingly, and we explored if there is any difference in achieving the standards of care in frail patients.

- Elective AAA patients should be receiving surgical intervention within 8 weeks from the time of MDT discussion.
- Elective AAA patients should've met the standards of care in terms of Cardiovascular Risk Prevention.
 - a. All AAA patients should have been prescribed a statin.

- b. All AAA patients who have cardiac history (IHD, CHF) should have been prescribed statins, antiplatelet or anticoagulant and angiotensin - converting enzyme inhibitor (ACE).
 - c. All AAA patients who have peripheral vascular disease, should have been prescribed an antiplatelet or any form of anticoagulation.
 - Elective AAA patients should receive an MDT discussion and preoperative fitness of measure assessment.
 - All AAA patients should receive antibiotic and deep venous thrombosis prophylaxis.
2. Hospital Stay: total number of days as provided by the NVR team including critical care usage. (To minimise the level of personalisation, NVR team elected not to provide the date of procedure or the date of discharge)
 3. Complications: Cardiac, respiratory, TIA, Cerebral (stroke), Renal failure, haemorrhage, limb ischaemia, paraplegia, bowel ischaemia, post-operative confusion, major gastrointestinal complication, surgical site infection, flow limiting dissection.

Statistical Analysis

Univariant analysis used to detect any difference in baseline characteristics between frail and not frail patients. Continuous variables were demonstrated as means $\pm$ standard deviation (SD) or as medians with interquartile ranges if they were not normally distributed. Means were compared using unpaired t-tests. Dichotomous variables are expressed as counts and percentages, and Fischer exact tests were used to compare proportions.

Multivariate logistic regression analysis was performed to obtain unadjusted and adjusted (OR) values predictive of in hospital/30- day mortality and for MACE using backward stepwise selection. The model was then assessed using Harrell's concordance index (C-index).

The final multivariate models were built for all AAA repairs and then separately for patients undergoing EVAR and OSR. The baseline comparative group for the multivariate regression analysis was the cohort of “not frail” patients. The statistical analysis was performed using SPSS software. P values <0.05 were considered statistically significant.

Results

We received NVR details of 5791 patients where we excluded 518 patients either symptomatic AAAs or received Complex AAA repairs or Redo repairs. Then we excluded 1353 patients (25.2%) who did not have frailty score recorded. We did however clarify with the data providers that the patients who did not have frailty score are consecutive patients rolled over from previous audit year. As a result, we had 4020 (69.4%) patients for final analysis. Figure 3.3 shows the flowchart of data cleaning and eventually including 4020 patients for final analysis.

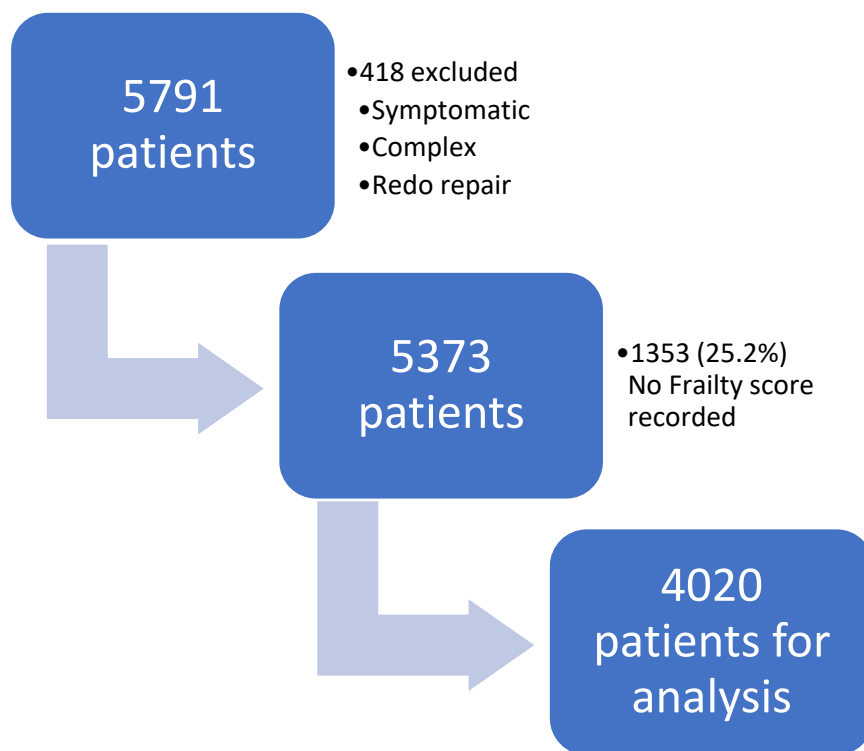


Figure 3.3: Flowchart of data cleaning to include 4020 patients for analysis

Baseline Characteristics and prevalence of frailty

- **Overall baseline characteristics stratified according to type of procedure.**

The overall cohort had mean age of 74.4 years. Patients who received EVAR were significantly older compared to open repair (76.6 vs 71.3, $p < 0.05$). There was no difference in gender, BMI or AAA diameter between EVAR and OSR. Regarding comorbidities, we noted that EVAR cohort are more likely to have ischaemic heart disease (39.1% vs 27%, $p < 0.05$), chronic obstructive pulmonary disease (30.5% vs 20.9%, $p < 0.05$), Chronic renal disease (14.3 % vs 10.5%, $p < 0.05$) when compared to OSR repair group. However, the incidence of peripheral vascular disease between the two groups were similar (EVAR: 6.1% vs OSR: 7.4%, $p = 0.06$). Interestingly, we found that OSR patients are more likely to be active smokers at the time of surgery (24.7% vs 16.5%, $p < 0.05$). The majority of patients who received a repair were ASA ≤ 3 with higher percentage seen in the OSR group (97.2% vs 94.7%, $p < 0.05$).

Table 3-1 reports baseline characteristics of patients undergoing elective AAA repair stratified by type of procedure.

Table 3-a: Baseline Characteristics of patients undergoing elective AAA repair stratified by type of procedure

	Overall (n = 4020)	EVAR (n = 2354)	OSR (n = 1666)	p-value
Age mean (SD)	74.4 ± 7.8	76.6 ± 7.5	71.3 ± 7.1	<0.01
Female	381 (9.5%)	148 (8.9%)	233 (9.9%)	0.15
BMI	29.4 ± 19.4	29.4 ± 23.1	29.3 ± 16.4	0.93
AAA size	60.3 ± 9.5	60.2 ± 9.5	60.4 ± 9.4	0.32
HTN	2782 (69.2%)	1672 (71%)	1110 (66.6%)	<0.01
Diabetes	601 (15%)	413 (17.5%)	188 (11.3%)	<0.01
COPD	1066 (26.5%)	717 (30.5%)	349 (20.9%)	<0.01
IHD	1370 (34.1%)	920 (39.1%)	450 (27.0%)	<0.01
CHF	181 (4.5%)	150 (6.4%)	31 (1.9%)	<0.01
CRD	511 (12.7%)	336 (14.3%)	175 (10.5%)	<0.01
Stroke	266 (6.6%)	179 (7.6%)	97 (5.2%)	<0.01
Cancer	355 (8.8%)	251 (10.7%)	104 (6.2%)	<0.01
PVD	267 (6.6%)	144 (6.1%)	123 (7.4%)	0.06
Smoker	800 (19.9%)	388 (16.5%)	412 (24.7%)	<0.01
Ex- Smokers	2593 (64.5 %)	1575 (66.9%)	1018 (61.1%)	<0.01
Never Smoked	626 (15.6%)	391 (16.6%)	235 (14.1%)	<0.01
Creatinine	93.0 ± 34.1	96 ± 38.9	88.8 ± 25.4	<0.01
Anaemia	830 (20.6%)	561 (23.8%)	269 (16.1%)	<0.01

ASA 1	30 (0.7%)	13 (0.6%)	17 (1.0%)	0.07
ASA 2	967 (24.1%)	469 (19.9%)	498 (29.9%)	<0.01
ASA 3	2851 (70.9%)	1747 (74.2%)	1104 (66.3%)	<0.01
ASA 4	170 (4.2%)	124 (5.3%)	46 (2.8%)	<0.01
ASA 5	2 (0.0%)	1 (0.0%)	1 (0.1%)	0.66
ASA ≤ 3	3848 (75.7%)	2229 (94.7 %)	1619 (97.2%)	<0.01

BMI = Body Mass Index, AAA = Abdominal Aortic Aneurysm, HTN = Hypertension, COPD = Chronic Obstructive Pulmonary disease, IHD = Ischaemic Heart Disease, CHF = Congestive Heart Failure, CRD = Chronic Renal Disease, PVD = Peripheral Vascular Disease, ASA = American Society of Anaesthesiologists Physical Status Classification

- **Prevalence of frailty according to repair type**

Just over 1660 patients (41.1%) received open surgical repair (OSR). As mentioned above patients were stratified into 4 frailty groups, 1= not frail, 2= mildly frail, 3 = moderately frail and 4= severely frail. Majority of patients who received a repair (71.6%) were not frail. With increase in frailty index, patients were more likely to receive EVAR. 1402 (84.2%) of the open repair patients were not frail compared to 1476 (62.7%) of the EVAR patients ($p<0.05$). demonstrates the prevalence of frailty index according to type of procedure.

Table 3-b: Prevalence of frailty NVR index according to type of procedure.

	All (n=4020)	EVAR (n=2354)	OSR (n=1666)	P value
Not frail	2878 (71.6%)	1476 (62.7%)	1402 (84.2%)	<0.001
Mild Frail	947 (23.6%)	713 (30.3%)	234 (14.0%)	<0.001
Moderate	189 (4.7%)	162 (6.9%)	27 (1.6%)	<0.001
Severe	6 (0.1%)	3 (0.1%)	3 (0.2%)	0.49

EVAR = Endovascular Aneurysm Repair, OSR = Open Surgery Repair

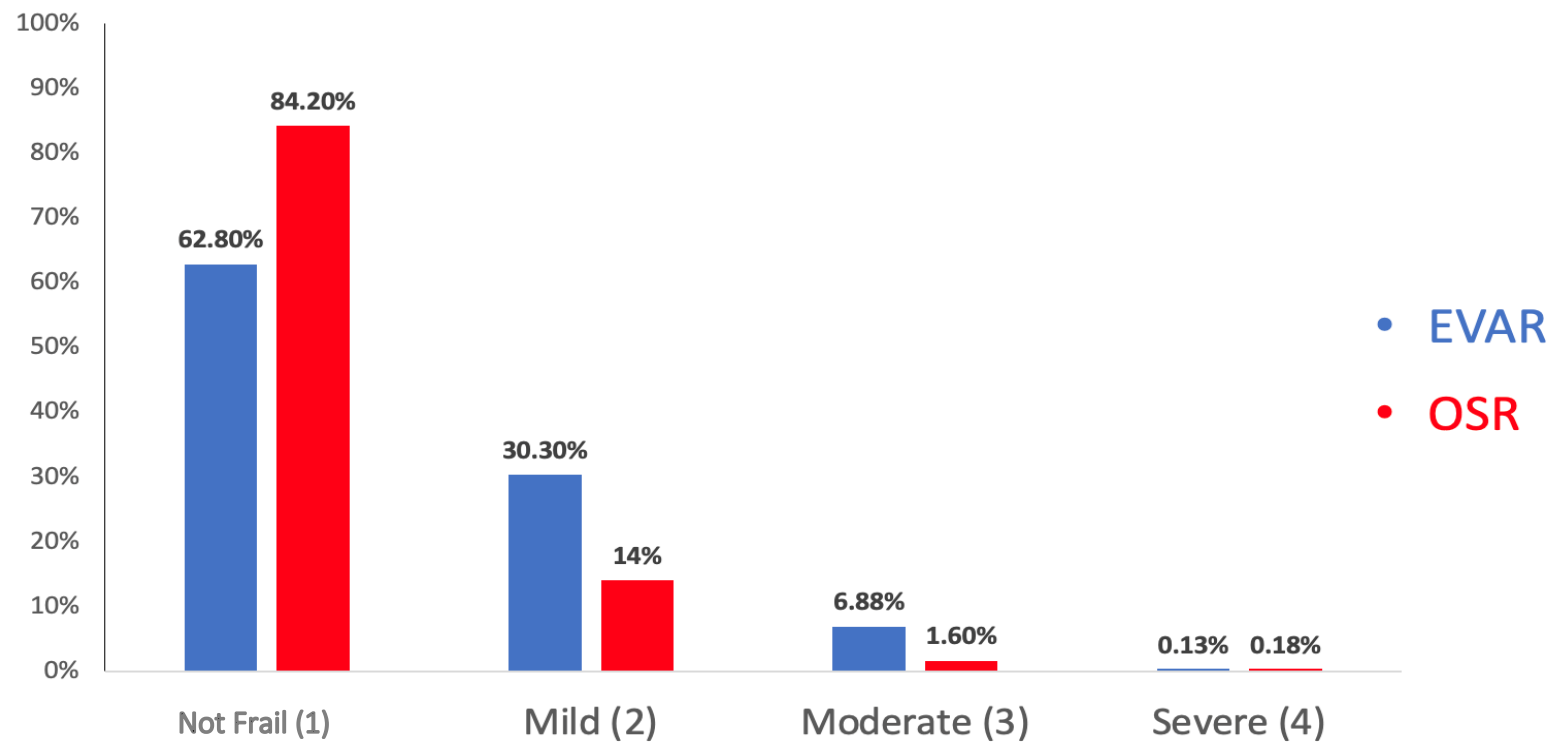


Figure 3.4: Prevalence of frailty in patients who received elective AAA repair stratified by type of procedure. OSR: Open Surgery Repair, EVAR: Endovascular Aneurysm Repair

As there were relatively small numbers in the “moderate and severe” groups we elected to combine them with the “mild frail” group and called them “frail”. Comparative analysis was performed against “not frail” group stratified according to repair type.

- **Baseline Characteristics of frail patient who received Open repair.**

Overall, the frail patients who received open repair are older (73.1 vs 71 years, $p < 0.001$). In regards to their comorbidity status, they are more likely to suffer from IHD (35% vs 26%, $p < 0.001$), CHF (5.3% vs 1.2%, $P, < 0.001$), CKD (19.7 % vs 8.8%, $p < 0.001$) and PAD (15.5% vs 5.8%, $p < 0.001$). We also noted that they are more likely to be anaemic (26.9% vs 14.1%, $p < 0.001$) and suffer from hypoalbuminemia (13.6% vs 8.9 %, $p < 0.01$). Frail patients who received open surgical repair have larger AAA diameter (62.0mm vs 60.1mm, $p = 0.003$). Table 3-c summarises the baseline characteristics of frail patients who received open repair.

Table 3-c: Baseline Characteristics of Open Repair Cohort stratified according to frailty

Open Repair	Frail(n= 264)	Not Frail (n= 1402)	P -value
Age mean (SD)	73.1 (7.6)	71 (7)	<0.001
BMI mean (SD)	27.7 (4.8)	28(4.2)	0.5
No Comorbidity n(%)	25 (9.5)	253 (18.0)	<0.001
Diabetes n(%)	32 (12.1)	156 (11.1)	0.4
HTN n(%)	175 (66.3)	935 (66.7)	0.5
COPD n(%)	86 (32.6)	263 (18.8)	<0.001
IHD n(%)	93 (35.2)	357 (25.5)	<0.001
CHF n(%)	14 (5.3)	17 (1.2)	<0.001
CRD n(%)	52 (19.7)	123 (8.8)	<0.001
Stroke n(%)	20 (7.6)	67 (4.8)	0.04
Cancer n(%)	31 (11.7)	73 (5.2)	<0.001
PAD n(%)	41 (15.5)	82 (5.8)	<0.001
Anaemia n(%)	71 (26.9)	198 (14.1)	<0.001
Hypoalbuminemia n(%)	36 (13.6)	125 (8.9)	0.01
ASA 1 n(%)	1 (0.4)	16 (1.1)	0.2
ASA 2 n(%)	28 (10.6)	470 (33.5)	<0.001
ASA 3 n(%)	214 (81.1)	890 (63.5)	<0.001
ASA 4 n(%)	21 (8.0)	25 (1.8)	<0.001
ASA 5 n(%)	0 (0.0)	1 (0.1)	0.8
Current Smoker n(%)	71 (26.9)	341 (24.3)	0.2
Ex-smoker n(%)	156 (59.1)	862 (61.5)	0.25
Never Smoked n(%)	37 (14.)	198 (14.1)	0.5
AAA diameter (mm) mean (SD)	62 (11)	60.1 (9.1)	0.003
Creatinine mean (SD)	94.1 (35.3)	87.8 (23.0)	<0.001

BMI = Body Mass Index, HTN = Hypertension, COPD = Chronic Obstructive Pulmonary disease, IHD = Ischaemic Heart Disease, CHF = Congestive Heart Failure, CRD = Chronic Renal Disease, PAD = Peripheral Arterial Disease, ASA = American Society of Anaesthesiologists Physical Status Classification

- **Baseline Characteristics of patients who received Endovascular repair.**

As observed in the Open repair group, frail patients who received endovascular repair are older (78.0 vs 76, $p < 0.001$) and more likely to suffer from comorbidities at the time of repair. We noted that the frail patients who received EVAR are more likely to be classified as ASA 3 (79 % vs 71.3% , $p < 0.001$) or ASA 4 (9.3% vs 2.8%, $p < 0.001$). Similar to the open group, frail patients undergoing endovascular repair had larger AAA diameter (61.0mm vs 59.7 mm, $p = 0.003$) and higher mean creatinine (99.2 vs 94.1, $p < 0.002$). Table (3-d) summarises the baseline characteristics of frail patients who received endovascular repair when compared to “not frail” group.

Table 3-d: Baseline Characteristics of EVAR cohort stratified according to frailty

<u>EVAR</u>	Frail (n = 878)	Not Frail (n= 1476)	P - value
Age years mean (SD)	78.0(7.8)	75.8 (7.2)	<0.001
BMI mean (SD)	28.1 (5.1)	28.1 (4.5)	0.8
No Comorbidity n(%)	41 (4.7)	148 (10.0)	<0.001
Diabetes n(%)	186 (21.2)	227 (15.4)	<0.001
HTN n(%)	657 (74.8)	1015 (68.8)	0.001
COPD n(%)	324 (36.9)	393(26.6)	<0.001
IHD n(%)	404 (46.0)	516 (35.0)	<0.001
CHF n(%)	81 (9.2)	69 (4.7)	<0.001
CRD n(%)	169 (19.2)	167 (11.3)	<0.001
Stroke n(%)	90 (10.3)	89 (6.0)	<0.001
Cancer n(%)	95 (10.8)	156 (10.6)	0.45
PAD n(%)	67 (7.6)	77 (5.2)	0.01
Anaemia n(%)	294 (33.5)	267 (18.1)	<0.001
Hypoalbuminemia n(%)	93 (10.6)	101 (6.8)	0.001
ASA 1 n(%)	5 (0.6)	8 (0.5)	0.6
ASA 2 n(%)	95 (10.8)	374 (25.3)	<0.001
ASA 3 n(%)	695 (79.2)	1052 (71.3)	<0.001
ASA 4 n(%)	82 (9.3)	42 (2.8)	<0.001
ASA 5 n(%)	1 (0.1)	0 (0.0)	0.4
Current Smoker n(%)	143 (16.3)	245 (16.6)	0.4
Ex-smoker n(%)	592 (67.4)	983 (66.6)	0.4
Never Smoked n(%)	143 (16.3)	248 (16.8)	0.4
AAA diameter (mm) mean (SD)	61.0 (10)	59.7 (9.2)	0.003
Creatinine mean (SD)	99.2 (42.7)	94.1 (36.3)	0.002

BMI = Body Mass Index, HTN = Hypertension, COPD = Chronic Obstructive Pulmonary disease, IHD = Ischaemic Heart Disease, CHF = Congestive Heart Failure, CRD = Chronic Renal Disease, PAD = Peripheral Arterial Disease, ASA = American Society of Anaesthesiologists Physical Status Classification

Standards of Care and Cardiovascular Risk Prevention

- **Operated within 8 weeks (from MDT discussion)**

Around 2130 patients (53%) were operated within recommended waiting times (within 8 weeks from MDT discussion). Overall, frail patients were operated on within 82.6 days (95%CI 77.4 – 87.8) versus 64.8 (95%CI 62.0 – 67.5) when compared to not frail group ($p<0.05$) (Figure 3.5 and table 3-e) . Frail patients were less likely to meet waiting times SOC for both interventions. 43.2 % ($n= 114$) of the open repair frail cohort met the standards of care for waiting times compared to 57% ($n= 799$) for “not frail” group ($p<0.05$). The same findings were seen in the EVAR group. This may be due to frail patients requiring more preoperative workup and optimisation before proceeding for surgery. This is supported by the fact that frail patients in both interventions required a greater number of pre-intervention assessments in the form of either invasive cardiology investigations, referral to other speciality and/or medical optimisation (19.8% vs 13.6%, $p< 0.001$). Table 3-e presents the details of further anaesthetic investigations stratified according to procedure type and frailty status

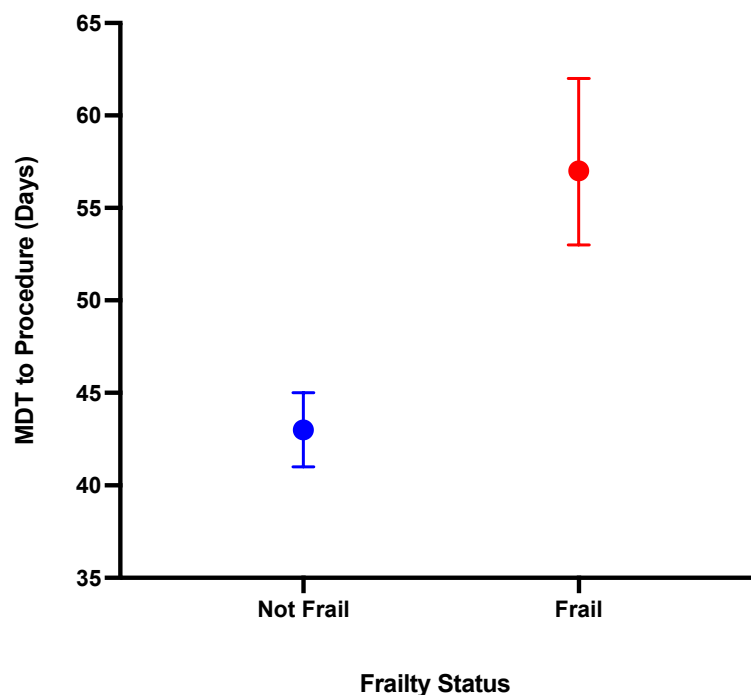


Figure 3.5 Time from MDT to Procedure for all cohort stratified according to frailty

Table 3-e Demonstration of further workup required for patients undergoing AAA repair stratified according to type of repair and frailty

	Open			EVAR		
	Not Frail	Frail	p-value	Not Frail	Frail	p-value
Further anaesthetic investigations	191 (13.6%)	56 (21.2%)	0.001	200 (13.6%)	170 (19.4%)	<0.001
Referral to speciality	109 (7.8%)	31 (11.7%)	0.02	130 (8.8%)	116 (13.2%)	<0.001
Coronary Angiogram	21 (1.5%)	3 (1.1%)	0.5	25 (1.7%)	20 (2.3%)	0.2
Optimisation Drug therapy	102 (7.3%)	34 (12.9%)	<0.001	84 (5.7%)	85 (9.7%)	<0.001

- **Cardiovascular risk prevention and receipt of SOC perioperative medications**

Only 61.3% of the overall cohort met the SOC for cardiovascular risk prevention with more pronounced difference seen in the frail cohort (57.4% vs 62.9%, $p < 0.001$). When analysed according to procedure type, frail EVAR cohort were less likely to achieve appropriate risk prevention compared to not frail cohort (55% vs 60.4%, $p < 0.05$) however that difference was not observed in the open repair cohort (65.4% vs 65.5%, $p = 0.5$) (Figure 3.6). Overall, 69.2% of patients received antibiotic prophylaxis preoperatively with no difference seen when stratified to frailty status or type of procedure. This was similarly seen in for VTE prophylaxis. (Table 3-f) summarises the SOC and cardiovascular risk prevention in both cohorts stratifying frail and not frail groups.

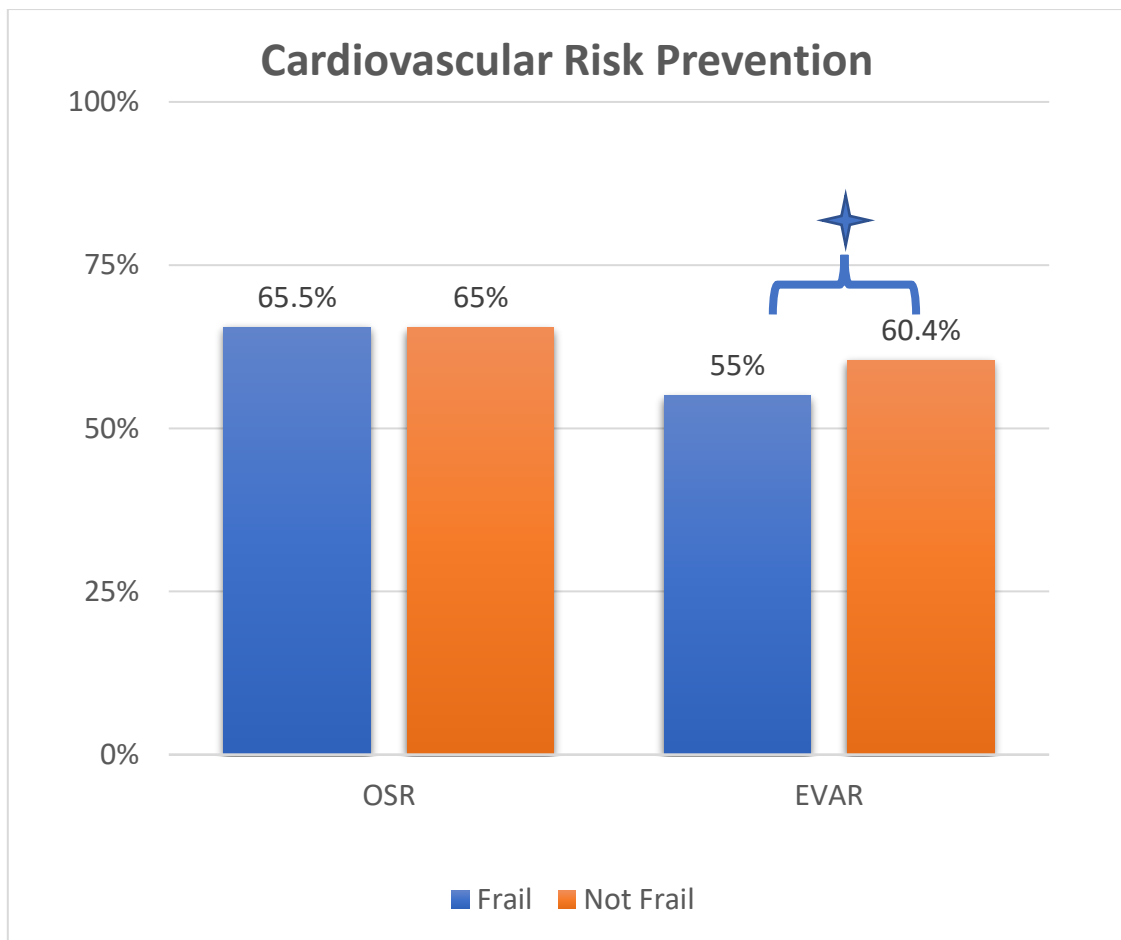


Figure 3.6 Cardiovascular Risk Prevention rates recorded in NVR stratified according to type of repair and frailty.

★ Indicates statistical significance $p < 0.05$

Table 3-f: Standards of care and cardiovascular risk prevention in patients who received elective AAA stratified by type of procedure.

	Overall (n= 4020)	OSR (n= 1666)			EVAR (n=2354)		
		<u>Not Frail</u>	<u>Frail</u>	<u>p-value</u>	<u>Not Frail</u>	<u>Frail</u>	<u>p-value</u>
Operated with 8 weeks	2129 (53%)	799 (57%)	114 (43.2%)	<0.05	810 (54.9%)	406 (46.2%)	<0.05
Cardiovascular Risk Prevention	2465 (61.3%)	917 (65.4%)	173 (65.5%)	0.5	892 (60.4%)	483 (55%)	<0.05
Anaesthetic Fitness measure	3422 (85.1%)	1272 (90.7%)	226 (85.6%)	<0.05	1230 (83.3%)	694 (79%)	<0.05
Further anaesthetic investigations	617 (15.3%)	191 (13.6%)	56 (21.2%)	<0.05	200 (13.6%)	170 (19.4%)	<0.05
Antibiotic Prophylaxis	2780 (69.2%)	1002 (71.5%)	183 (69.3%)	0.3	1010 (68.4%)	585 (66.5%)	0.2
VTE Prophylaxis	2754 (68.5 %)	989 (70.5%)	176 (66.7%)	0.1	1002 (67.9%)	587 (66.9%)	0.6

VTE= Venous Thromboembolism

p-value represent statistical significance when comparing variables to Open Vs EVAR repair

a. Length of stay and incidence of post-operative complications.

- **Post operative length of stay and ITU/HDU usage.** Table 3-g summarises the length of stay and critical care usage stratified according to type of repair and frailty

Frail patients who received open repair are more likely to stay more days in hospital when compared to not frail patients (13 days vs 10 days, $p < 0.05$) (Figure 3.7). Regarding the usage of critical care beds (HDU/ITU), there was no difference in length of stay between frail and not frail patients (3.6 days vs 3.4 days, $p = 0.7$).

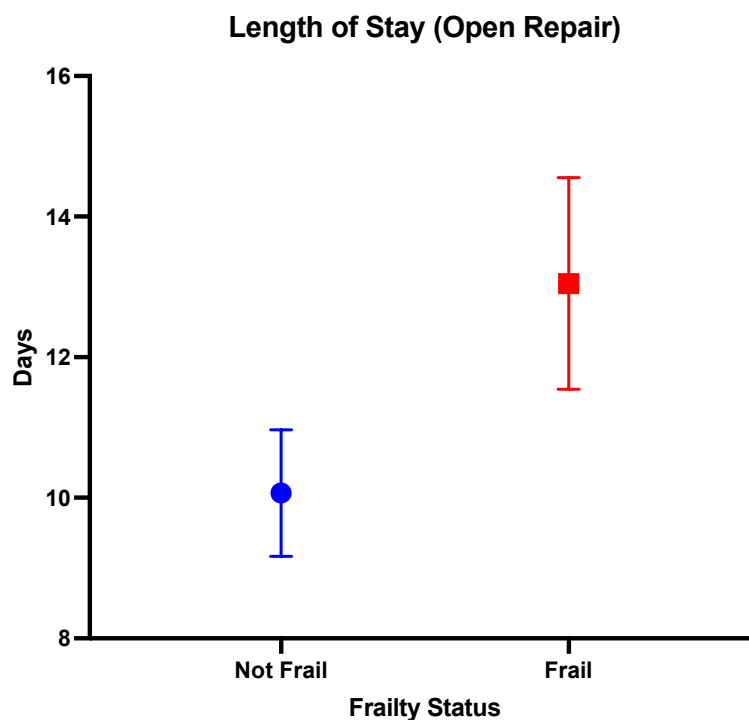


Figure 3.7: Difference in total length of stay between "Not Frail" and "Frail" patients undergoing open surgical repair (OSR)

Patients who received endovascular repair, we noted that there was no difference in total length of stay between frail and not frail. 674 patients (28.6%) required HDU/ITU stay. On further analysis of patients who required critical stay there was no significance between in the number of days between “frail” and “not frail” patients (1.35 days vs 1.24 days, $p=0.08$). In further analysis, we found that frail patients who underwent EVAR are more likely to stay in Level 2/Level3 bed post operatively (33.7% vs 22.7%, $p < 0.05$). It worth noting that some EVAR patients required Level 3 care as per NVR data.

Table 3-g: Length of stay and Critical Care usage of patients who received elective AAA stratified by type of procedure and frailty.

	OSR (n= 1666)			EVAR (n=2354)		
	<u>Not Frail</u>	<u>Frail</u>	<u>p-value</u>	<u>Not Frail</u>	<u>Frail</u>	<u>p-value</u>
Hospital Stay (days)	10 ± 17.1	13 ± 12.4	<0.05	3.3 ± 14.7	3.3 ± 14.7	0.48
Critical Care Stay (days)	3.4 ± 10.0	3.6 ± 4.0	0.7	0.3 ± 0.6	0.4 ± 0.9	<0.05
Level 2 Bed use n %	892 (63.6%)	172 (65.2%)	0.34	335 (22.7%)	296 (33.7%)	<0.05
Level 3 Bed use n %	468 (33.4%)	468 (33.4%)	0.3	28 (1.9%)	15 (1.7%)	0.4

OSR: Open Surgical Repair, EVAR: Endovascular Aneurysm Repair

- **Post- operative complications**

Frail patients who received open repair are more likely to return to theatres and be readmitted to critical care department (9.8% vs 5.8%, $p<0.05$), (6.8% vs 3.9%, $p<0.05$) respectively. We also noted that they are more likely to suffer from respiratory complications (5.7% vs 3.4%, $p<0.05$), renal failure (7.6% vs 4.6%, $p<0.05$) and post-surgery confusion (5.3% vs 1.8%, $p<0.05$). Frail patients who received open repair are also more likely to suffer from major gastrointestinal complications specifically bowel ischaemia (4.5% vs 2.4%, $p<0.05$). In regard to EVAR patients, frailty had less of an impact on post operative complications. We noted increased incidence of respiratory complications (1.9% vs 0.7%, $p<0.05$) and post-surgery confusion (0.7% vs 0.1%, $p<0.05$). Frail patients were more likely to be readmitted to hospital within 30 days after either intervention. Table 3-h summarises the incidence of complications and readmission rates for both Open Repair and EVAR stratified according to frailty status.

Table 3-h Incidence of postoperative complications following AAA repair stratified according to type of repair and frailty status

	OSR (n=1666)			EVAR(n=2354)		
	<u>Not Frail</u>	<u>Frail</u>	<u>p-value</u>	<u>Not Frail</u>	<u>Frail</u>	<u>p-value</u>
Return to theatre	81 (5.8%)	26(9.8%)	<0.05	23 (1.6%)	19 (2.2%)	0.2
Readmission to Critical Care	55 (3.9%)	18 (6.8%)	<0.05	3 (0.2%)	6 (0.7%)	0.07
Complications	344 (24.5%)	101 (38.3%)	<0.05	101 (6.8%)	87 (9.9%)	<0.05
Cardiac	48 (3.4%)	15 (5.7%)	0.06	28(1.9%)	15 (1.7%)	0.4
Respiratory	128 (9.1%)	43 (16.3%)	<0.05	11 (0.7%)	17 (1.9%)	<0.05
Stroke	5 (0.4%)	2 (0.8%)	0.3	4 (0.3%)	2 (0.2%)	0.6
Renal Failure	64 (4.6%)	20 (7.6%)	<0.05	8 (0.5%)	9 (1.0%)	0.1
Haemorrhage	15 (1.1%)	1 (0.4%)	0.3	7 (0.5%)	9 (1.0%)	0.09
Limb Ischaemia	27 (1.9%)	6 (2.3%)	0.4	8 (0.5%)	8 (0.9%)	0.2
Bowel Ischaemia	33 (2.4 %)	12 (4.5%)	<0.05	4 (0.3%)	2 (0.2%)	0.6
Post op Confusion	25 (1.8%)	14 (5.3%)	<0.05	2 (0.1%)	6 (0.7%)	<0.05
Major GI Complication	13 (0.9%)	22 (3.4%)	<0.05	0(0%)	1 (0.1%)	0.4
Readmission within 30 days	57 (4.2%)	21 (8.4%)	<0.05	59 (4.0%)	62 (7.1%)	<0.05

b. The risk of mortality and major cardiovascular events in frail patients.

The NVR dataset encompasses data regarding in-hospital mortality as well as 30-day mortality. The results of the univariate regression analysis indicate that the presence of frailty did not exhibit a statistically significant association with in-hospital mortality (OR 1.8, 95% CI 0.9 – 3.7, $p=0.1$). However, it is noteworthy that frailty did demonstrate a significant influence on 30-day mortality (OR 2.4, 95% CI 1.2 – 4.6, $p<0.05$). Upon conducting an analysis of the composite outcome encompassing major adverse cardiovascular events and mortality within a 30-days (MACED), it was observed that frail individuals who underwent open repair procedures exhibited a higher propensity for experiencing MACED comparison to their non-frail counterparts, with an odds ratio of 1.97 (95% CI 1.3 – 3.0, $p<0.05$).

A multivariable logistic regression analysis was conducted utilising a backward stepwise selection approach to evaluate the pertinent baseline characteristics and comorbidities associated with both 30-day mortality and the incidence of major adverse cardiac events (MACED). The variables that were included in the model were those that exhibited a statistically significant association, as determined by a p -value threshold of less than 0.1. The inclusion of age at surgery (>75 years), the presence of ischemic heart disease (IHD), and creatinine level ($>90\text{mcmol}$) as significant variables in the model was deemed appropriate for our study. Following the appropriate adjustments for confounding variables, it is noteworthy that frailty continues to exhibit a substantial association with both 30-day mortality and major adverse cardiac events (MACED). Table 3-i and table 3-j presents a summary of the model coefficients pertaining to frail patients who have undergone open repair.

In contrast to the findings observed within the open repair group, our analysis indicates that frailty did not exert a significant influence in the EVAR group on the 30-day mortality odds ratio (OR: 1.3, 95% [CI]: 0.5 – 3.5, $p = 0.7$) or the risk of major adverse cardiovascular and cerebrovascular events (MACED) with an odds ratio of 1.4 (95% CI: 0.8 – 2.4, $p = 0.3$) (Table 3-k, Table 3-l).

Table 3-i Odds of 30-day mortality in frail patients following open repair following backward stepwise selection

Model Coefficients – 30-day mortality

Predictor	Estimate	SE	Z	p	Odds ratio	95% Confidence Interval	
						Lower	Upper
Intercept	-4.39487	0.49311	-8.912	< .001	0.0123	0.00469	0.0324
Frail	<u>0.74651</u>	<u>0.34669</u>	<u>2.153</u>	<u>0.031</u>	<u>2.1096</u>	<u>1.06932</u>	<u>4.1620</u>
Age>75	0.19220	0.32456	0.592	0.554	1.2119	0.64151	2.2895
Creatinine	0.00368	0.00493	0.746	0.456	1.0037	0.99403	1.0134
IHD	0.58735	0.31893	1.842	0.066	1.7992	0.96296	3.3617

Note. Estimates represent the log odds of "30-day mortality = 1" vs. "30-day mortality = 0"
Odds ratio are shown with 95% confidence intervals, IHD: Ischaemic heart disease.

Table 3-j Odds of MACED in frail patients undergoing open repair following backward stepwise selection

Model Coefficients – MACED

Predictor	Estimate	SE	Z	p	Odds ratio	95% Confidence Interval	
						Lower	Upper
Intercept	-3.09321	0.29029	-10.66	< .001	0.0454	0.0257	0.0801
Frail	<u>0.59099</u>	<u>0.21031</u>	<u>2.810</u>	<u>0.005</u>	<u>1.8058</u>	<u>1.1958</u>	<u>2.7270</u>
Age>75	0.25297	0.18646	1.357	0.175	1.2878	0.8936	1.8560
Creatinine	0.00498	0.00296	1.678	0.093	1.0050	0.9992	1.0108
IHD	0.17541	0.19321	0.908	0.364	1.1917	0.8161	1.7404

Note. Estimates represent the log odds of "MACED = 1" vs. "MACED = 0"
Odds ratio are shown with 95% confidence intervals, IHD: Ischaemic heart disease.

Table 3-k Odds of 30-day mortality in frail patients following EVAR following backward stepwise selection

Model Coefficients – 30-day Mortality

Predictor	Estimate	SE	Z	p	Odds ratio	95% Confidence Interval	
						Lower	Upper
Intercept	-5.677	0.573	-9.901	< .001	0.00342	0.00111	0.0105
Frail	0.283	0.495	0.572	0.568	1.32665	0.50325	3.4973
Age>75	0.735	0.578	1.273	0.203	2.08559	0.67227	6.4702
Creatinine	0.004	0.003	1.183	0.237	1.00404	0.997	1.0107
IHD	0.302	0.491	0.616	0.538	1.35292	0.51676	3.5420

Note. Estimates represent the log odds of "30-day mortality = 1" vs. "30-day mortality = 0"
Odds ratio are shown with 95% confidence intervals, IHD: Ischaemic heart disease.

Table 3-l Odds of MACED in frail patients following EVAR following backward stepwise selection

Model Coefficients – MACED

Predictor	Estimate	SE	Z	p	Odds ratio	95% Confidence Interval	
						Lower	Upper
Intercept	-4.53876	0.34652	-13.098	< .001	0.0107	0.00542	0.0211
Frail	0.32349	0.28657	1.129	0.259	1.3819	0.78806	2.4234
Age> 75	0.08684	0.29457	0.295	0.768	1.0907	0.61232	1.9429
IHD	0.10186	0.28656	0.355	0.722	1.1072	0.63142	1.9416
<u>Creatinine</u>	<u>0.00509</u>	<u>0.00186</u>	<u>2.737</u>	<u>0.006</u>	<u>1.0051</u>	<u>1.00145</u>	<u>1.0088</u>

Note. Estimates represent the log odds of "MACED = 1" vs. "MACED = 0"
Odds ratio are shown with 95% confidence intervals, IHD: Ischaemic heart disease.

Discussion

Incorporation of frailty as a variable in the vascular surgical proformas within the National Vascular Registry (NVR) since the year 2019 has been undertaken with the objective of investigating the potential impact of frailty on various clinical outcomes. To facilitate the inclusion of various healthcare facilities employing diverse assessment tools, the NVR has devised a system of frailty categories. This system allows centres to align their respective frailty scores with the standardised NVR categories, regardless of whether they employ the Clinical Frailty Scale (CFS), Edmonton Frail Scale, or the Electronic Frailty Index.

Frailty represents a multifaceted syndrome characterised by compromised physiological reserve, thereby augmenting an individual's susceptibility to effectively recuperate from a stress-inducing event, such as a surgical procedure. Numerous validated frailty assessment tools have been documented in the existing body of literature. Nevertheless, it is noteworthy that phenotypic models, such as the Clinical Frailty Scale (CFS), have emerged as the prevailing choice within the National Health Service (NHS) hospitals and primary care settings. The adoption of the phenotypic model in evaluating frailty is of paramount significance when compared to the accumulated deficits model. This is primarily due to the former's emphasis on assessing patients' physical, mental, and social factors, as opposed to solely focusing on their comorbidities. Numerous studies have substantiated the notion that the evaluation of frailty status through phenotypic models has emerged as a distinct and autonomous prognosticator of unfavourable surgical outcomes, encompassing complications, prolonged hospitalisation, and mortality[215,216].

This study presents a real-world data analysis of the effects of frailty on outcomes subsequent to abdominal aortic aneurysm (AAA) surgery, highlighting the significance of preoperative assessment of frailty status in patients. However, it is imperative to ascertain the frailty status prior to AAA reaching the threshold size necessitating repair. This temporal allowance is anticipated to afford patients with a sufficient duration to engage in suitable interventions aimed at mitigating frailty through the enhancement of functional capacity, adherence to medications for risk prevention, and implementation of lifestyle modifications (such as smoking cessation, reduction of alcohol consumption, and dietary adjustments).

A recent survey[217] demonstrated the influence of frailty status on clinical practise of vascular units. Patient care was modified based on the individual's frailty status through various means. The predominant modalities of intervention like prehabilitation, referral to other specialities for optimisation. It also demonstrated that frailty status played an important role in shared decision making and address potential postoperative requirements needed.

The results of this study suggest a significant prevalence of frailty among patients undergoing abdominal aortic aneurysm repair. The results suggest a relationship between frailty and unfavourable outcomes subsequent to abdominal aortic aneurysm repair, particularly in the context of open surgical repair. Patients with a higher level of frailty (CFS 4-8) exhibited a greater likelihood of undergoing endovascular aneurysm repair (EVAR). Frail individuals exhibit a higher propensity for experiencing complications in both repair procedures, albeit to a comparatively lesser degree within the EVAR cohort. The absence of a correlation between frailty and mortality in the endovascular aneurysm repair (EVAR) group can likely be attributed to the relatively low level of invasiveness associated with this type of procedure. Nevertheless, the use of NVR solely captures data on mortality within the hospital setting and within a 30-day timeframe. It is important to acknowledge that the long-term survival of these patients may potentially be reduced when considering extended periods of follow-up. The findings of this study additionally indicate that frail patients who underwent open repair experienced significantly longer hospital stays, higher rates of return to theatres and increased readmission to critical care compared to the non-frail group. These results unsurprisingly highlight the strain on healthcare resources associated with caring for frail patients.

Our study showed that frail patients were more likely to die within 30- days post operatively in open surgical repair group after adjustment to covariates. This indicates frailty status can possibly be an independent predictor of mortality in this cohort and could potentially inform appropriate shared decision making in the future. These results echo previous similar studies analysing the impact of frailty. Arya et al [148] analysed the impact of frailty in around 23 207 patients who received elective AAA repair between the periods of 2005 and 2012 stratified using the modified frailty index (mFI). It demonstrated that highest frailty

score group were more likely to die in both open repair (OR: 2.3 CI 95% 1.4 -3.7) and EVAR repair (OR: 1.9 95% CI 1.2-3.0). However, our study did not show that in the EVAR frail group. This could be due to the fact that frail patients were turned down for repair. Another single centre study[218] demonstrated that there is significant positive correlation between the mFI score of 5 and both the 1- and 5-year all-cause mortality and only age and mFI – 5 contributed to predicting overall survival after EVAR.

The findings of this study elucidate potential areas of enhancement that may potentially mitigate the deleterious effects of frailty. The implementation of cardiovascular risk prevention measures was found to be suboptimal in both frail and non-frail patients, with a notable emphasis on patients who underwent endovascular aneurysm repair (EVAR). Insufficient cardiovascular risk prevention, in the form of statins, antiplatelet therapy, or smoking cessation, was observed in approximately 60% of the cohort. The significance of preventing cardiovascular events, specifically cardiovascular disease (CVD), is underscored in both national and international guidelines. Extensive evidence has shown that patients diagnosed with abdominal aortic aneurysm (AAA) experience a substantial improvement in survival rates when implementing comprehensive risk prevention strategies[49]. The vast majority of patients diagnosed with abdominal aortic aneurysm (AAA) do not necessitate immediate surgical intervention. Instead, they are typically provided with regular surveillance to monitor the growth of their aneurysm. Therefore, the inclusion of cardiovascular risk prevention within screening programmes presents a significant opportunity to provide more effective interventions for risk prevention, ultimately leading to a reduction in cardiovascular events and subsequent mortality.

Strengths and limitations

The present study sought to investigate the potential influence of frailty on elective abdominal aortic aneurysm (AAA) repairs subsequent to the implementation of a frailty metric within the National Vascular Registry (NVR). The present investigation encompasses a nationwide scope, as it encompasses elective abdominal aortic aneurysm (AAA) repairs conducted across all vascular centres in England during the year 2019. The inclusion of a substantial sample size renders it suitable for regression analysis. However, it is important

to acknowledge the limitations of this study, primarily due to its retrospective nature and reliance on prospectively collected registry data. It is worth noting that the study did not provide a precise characterisation of frailty levels, as determined by validated frailty assessment tools. The potential ramifications of this phenomenon may encompass both the attenuation and amplification of frailty's influence on various outcomes. In light of the aforementioned statement, it can be observed that individuals who were initially classified as frail were found to exhibit a Clinical Frailty Score of 4 or higher. Also, the study did not look into AAA anatomical characteristics (e.g neck length, shape and tortuosity), something could have played an important role in decision making.

Another limitation of this study pertains to our inability to analyse the patients who were declined for repair and ascertain whether their frailty status had any association with the decision-making process. As previously indicated, it is important to note that the NVR frailty index lacks validation as a frailty assessment tool, and it is plausible that inaccuracies may have occurred during the process of categorising patients according to their true frailty status. The data primarily originates from clinicians, predominantly vascular surgeons or trainees, who likely depend on frailty assessments conducted either by a preoperative assessment team or upon admission for the elective procedure. The evaluation of frailty status, particularly the utilisation of the Clinical Frailty Score, should encompass an assessment of the patient's frailty condition occurring a fortnight prior to the actual evaluation date. This aspect raises pertinent concerns regarding the precision and reliability of the frailty status depicted within the confines of this study. Lastly, the clinician biases in selection for EVAR or OSR can also overestimate or underestimate the effect of frailty on outcomes, a limitation that cannot be resolved in this study design.

Conclusion

Frailty is prevalent in patients who received elective AAA repair and is associated with increased length of stay and complications. Frail patients receiving Open surgical repair are more likely not to survive the procedure. Frailty assessment maybe a useful tool for risk stratification and inform appropriate decision making on whether performing AAA repair is in patient's best interest.

Chapter 4 : Systematic review of the feasibility and adherence of exercise programmes for patients with abdominal aortic aneurysm

Introduction

At the time of undertaking this systematic review, many recent reviews were published investigating the content and impact of prehabilitation programmes in AAA patients with. Therefore, the purpose of this review is to focus on the uptake and adherence of such programmes for both patients with small AAA and patients scheduled for AAA surgical repair.

The majority of patients undergoing AAA repair are older adults[219,220], have multiple comorbidities and are at significant risk of operative mortality and morbidity, especially for open repair[221][222]. Therefore, improving perioperative and postoperative outcomes is an important priority.

Prehabilitation, which seeks to improve overall health and well-being before surgery by enhancing functional capacity, is gaining popularity[223]. There is growing evidence which supports prehabilitation programmes in reducing postoperative complications and length of stay in cardiovascular surgeries[224]. Prehabilitation programmes can be provided in a unimodal or multimodal approach and recent reviews on prehabilitation programmes have not reached a consensus on type, dose, duration, and which patients should receive prehabilitation[225][226], describing the quality of most included studies as poor[227]. While prehabilitation programmes showed to be beneficial in older adults[228], adherence to such programmes is imperative for successful implementation.

Our aim in this review is to identify the available evidence on prehabilitation in AAA patients and evaluate the efficacy, feasibility and adherence of such programmes.

Methods

The protocol of this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO,CRD42022240928). The study methodology was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews[229].

Search strategy

An electronic search was carried out independently by two of the investigators using the following databases: Medline (1946+), CINAHL (1946+), EMBASE (1946+), and Cochrane (1946+). The search was done from October to December 2021, with an updated search done in October 2022.

The initial keywords used for the search were abdominal aortic aneurysm, repair, adherence/compliance/attendance, exercise programme, prehabilitation/preoperative exercise. A summary of the full electronic search strategy is shown in Appendix 4.1

Selection/Eligibility criteria

Studies considered for review had the following predetermined inclusion criteria:

- Adults of any age/gender with abdominal aortic pathology.
- Abdominal aortic repair – all invasive treatment modalities. Examples include open repair, endovascular repair, combined/hybrid, or staged repairs.
- Exercise programmes.
- Reported adherence or number of participants who completed the intervention.
- Primary research studies.
- English language.

Study selection (data collection and analysis)

Two reviewers independently screened the identified publications for inclusion. The first stage included screening titles and abstracts. Studies were excluded if they did not meet the predetermined eligibility criteria. Disagreements for studies to be included

were resolved through discussion and consensus between the two reviewers based on the inclusion criteria mentioned above. A third reviewer cross checked the data that were extracted from the studies.

Data extraction

The data extraction was carried out independently by two reviewers . The following data were extracted from included studies: 1) authors, year of publication and country of origin; 2) study design; 3) sample size and participant characteristics (age, gender, aortic pathology; co-morbidities); 4) type of abdominal aortic repair; 5) recruitment rates; 6) uptake and adherence rates; 7) prehabilitation details; 9) quality appraisal.

Study quality and risk of bias

The validity of included study results and findings was assessed using the Critical Appraisal Skills Programme (CASP) checklist for Randomised Controlled Trials. Three main areas are covered in this checklist: validity, results, and clinical relevance. Two reviewers independently assessed the quality of included studies, discussed any discrepancies, and agreed on a final score.

Results

We identified have 3442 studies through our search strategy (Appendix 4.1). 705 duplicate studies were removed. 2737 studies were screened and only 36 studies were assessed for full text. Eventually, 7 studies were included [195,198–201,230,231]. A meta-analysis was not possible due to the heterogeneity of the timing of prehabilitation, interval and type of exercise and reported outcomes. Figure 4.1 shows PRISMA Flow chart.

Study Characteristics

Studies included in analysis involved 463 participants in total (range 20-140). Three studies [198–200] included patients awaiting AAA repair, whilst the rest were AAA patients under surveillance. Two studies were randomised controlled studies (RCT) [199,201] Characteristics of included studies are displayed in Table 4-a. Using the CASP toolkit the quality of included studies was assessed. Blinding to treatment was not present understandably due to the type of intervention assessed in these studies. Table. 4-b summarises the quality of studies included.

Prehabilitation Intervention

Six studies[198–201,230,231] were focussed on recommending an exercise programme to patients for a specified period ranging between 2-24 weeks. Patients exercised for an average of 127 minutes per week. Four out of the seven [199,200,230,231] included studies incorporated a hospital-based exercise programme, whilst the Dronkers et al[198] was home and hospital based. Table 4-c summarises the intervention details.

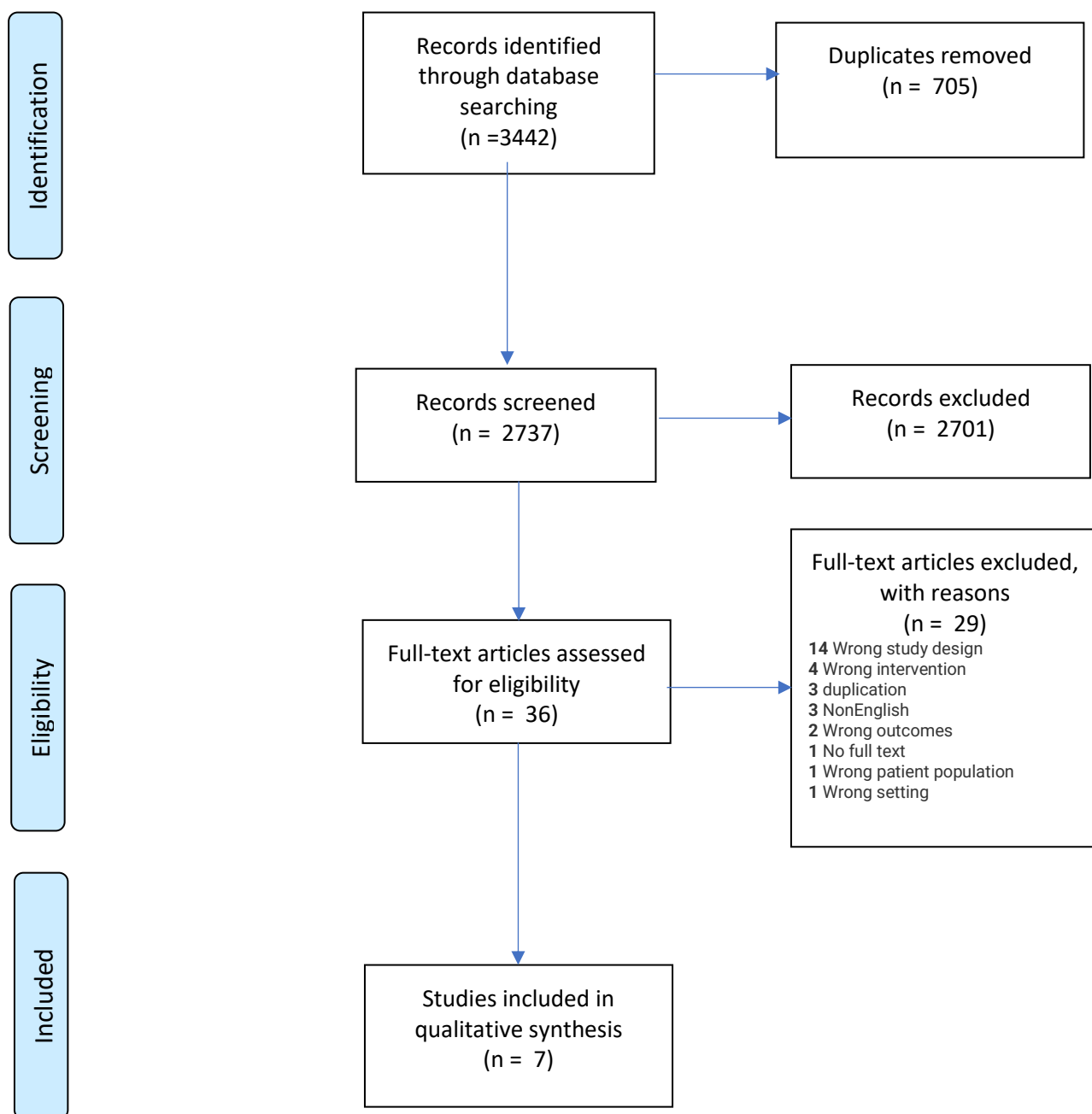


Figure 4.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 4-a Studies and participants' characteristics of a systematic review assessing the feasibility and adherence of exercise programmes in patient with abdominal aortic aneurysm.

First Author, year, Country	Study Type	n of participants(I/C)	Age (years)	Male n (%)	AAA diameter(mm)	Under Surveillance /Pending treatment
Dronkers, 2008, Netherlands	Pilot RCT	10/10	I: 70 ± 6 C: 59 ± 6	I: 2 (20%) C: 3 (30%)	NR	Pending treatment
Kothmann, 2009, UK	Pilot RCT	20/10	I: 69.5 ± 4.5 C: 69.4 ± 4	I: 13 (76.4%) C: 7 (87.5%)	I: 40 ± 0.50 C: 40 ± 0.55	Under Surveillance
Tew, 2012, UK	Pilot RCT	14/14	I: 71 ± 8 C: 74 ± 6	I: 10 (90.9%) C: 11 (78.5%)	I: 40.9 ± 7.0 C: 39.3 ± 6.4	Under Surveillance
Myers 2014, USA	Pilot RCT	72/68	I: 71.8 ± 7 C: 71.3 ± 8	I: 66 (92%) C: 63 (93%)	I: 35 ± 5.1 C: 34 ± 5.1	Under Surveillance
Barakat 2016, UK	RCT	68/68	I: 73.8 ± 6.5 C: 72.9 ± 7.9	I: 56 (90.3%) C: 61 (89.7%)	I: 6.0 ± 0.4 C: 6.3 ± 0.9	Pending treatment
Tew 2017, UK	Pilot RCT	27/26	I: 74.6 ± 5.5 C: 74.9 ± 6.4	I: 25 (92.6%) C: 25 (96.1%)	I: 6.0 ± 0.4 C: 5.8 ± 0.4	Pending treatment
Haque, 2022, UK	RCT	28/28	I: 73.3 ± 5.3 C: 72.4 ± 6.2	I: 24 (85.7%) C: 24 (85.7%)	I: 38 ± 5.0 C: 38 ± 5.0	Under Surveillance

Age and AAA diameter data are displayed in mean and standard deviation (SD). RCT: Randomised Controlled Trial, I : Intervention, C: Control, NR: Not reported, AAA: Abdominal Aortic Aneurysm.

Table 4-b CASP analysis for all studies included in the systematic review assessing the feasibility and adherence of exercise programmes in patients with abdominal aortic aneurysm.

	Is the basic study design valid for a randomised trial? Section(A)			Was the study methodologically sound Section (B)			What are the results? Section (C)			Will the results help locally Section (D)		
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Dronkers 2018	Y	Y	Y	N	N	Y	N	N	?	Y	Y	6
Kothmann 2009	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	9
Tew 2012	Y	Y	N	N	Y	Y	?	Y	Y	Y	Y	8
Myers 2014	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	9
Barakat 2016	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	10
Tew 2017	Y	Y	?	N	Y	Y	Y	Y	Y	Y	Y	9
Haque 2022	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Y	9

CASP = Critical Appraisal Skills Programme, Section A assess the validity of the basic study design, Section B assesses the methodology of the study, Section C assesses the treatment effect and reporting, Section D assesses outcomes reporting.

Table 4-c Exercise Intervention details of included studies of a systematic review assessing the feasibility and adherence of exercise programmes in patients with abdominal aortic aneurysm.

Author, year	Prehabilitation type	Setting	Intervention exercise	<i>n</i> Sessions per week	Session duration (min)	Total minutes per week	Total duration of programme n (weeks)
Dronkers 2008	Unimodal	Hospital and Home	Inspiratory muscle training	6	15	90	2
Kothmann 2009	Unimodal	Hospital	Moderate continuous exercise (Cycle)	2	30	60	6
Tew 2012	Unimodal	Hospital/ Gym	Treadmill walking and cycle ergometry	3	40	120	12
Myers 2014	Unimodal	Hospital/ Home	Moderate endurance and resistance training	3	60	180	52
Barakat 2016	Unimodal	Hospital	Cycle ergometer, resistance training, balance training	3	60	180	6
Tew 2017	Unimodal	Hospital	High intensity training (HIT)	3	45	135	4
Haque 2022	Unimodal	Gym/Home	Aerobic, resistance, stretching exercise	3	50	150	24

Efficacy of prehabilitation programmes for AAA patients

Prehabilitation for patients under “surveillance”

Four studies evaluated the effect of prehabilitation AAA patients with subthreshold aneurysms by analysing the improvement in exercise capacity measures such as peak VO₂ and AT.

Details of intervention outcomes of included studies are described below.

1. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms: a pilot study [230]

This study presents a pilot RCT conducted in the United Kingdom, aiming to assess the impact of exercise on a cohort of 20 patients diagnosed with subthreshold aneurysm who were under surveillance. The exercise intervention protocol consisted of a structured regimen comprising of 30 minutes of cycling, aimed at providing a moderate intensity exercise, with a cumulative duration of 60 minutes per week over a span of 6 weeks (comprising of 2 sessions per week). The setting of the exercise programme was supervised in-hospital setting. The primary endpoint of interest in this study was the alteration observed in the anaerobic threshold (AT) when comparing the baseline measurements to those obtained at Week 5 and Week 7 subsequent to the completion of the exercise intervention. The control arm of the study comprised a cohort of ten patients.

The present study has successfully exhibited a notable enhancement in the AT when juxtaposed with the control arm. A statistically significant improvement of 10% (1.1 mL/kg/min) was observed in comparison to the control group, with a 90% confidence interval ranging from 4% to 16% ($p < 0.05$). While the findings of the pilot RCT demonstrated a discernible enhancement in aerobic capacity (AT), it fell short of attaining the predetermined threshold for clinical significance, as established by the research cohort, which stipulated a minimum change of 2.0 mL/kg/min.

This study represents the first ever RCT analysing the impact of aerobic exercise on patients diagnosed with abdominal aortic aneurysm (AAA), with the primary objective of dispelling prevailing misconceptions surrounding the safety considerations associated with physical activity in this patient population. The intervention in question has exhibited a satisfactory level of safety. Additionally, it has been observed that patients diagnosed with abdominal aortic aneurysm (AAA) possess the capacity to enhance their aerobic threshold (AT), a metric commonly employed to evaluate the physical fitness of patients prior to surgical procedures. The authors acknowledge the potential for enhancing the proposed exercise regimen by augmenting the frequency, intensity, and duration of physical activity, with the aim of attaining substantial improvements that could potentially impact postoperative outcomes. This exercise regimen in this study only involved cycling (aerobic component) with a duration of maximum 60 minutes per week which does not meet the national guidelines of physical activity set for older adults (150 minutes of moderate – intensity activity per week)[232]. Nevertheless, it is crucial to consider the potential impact of such modifications on attrition rates and adherence to prehabilitation interventions. The requirement for participants to attend exercise sessions with greater frequency may impose financial burden on patients. Moreover, there is a possibility that only highly motivated individuals will be inclined to attend these sessions, thereby accentuating the need to incorporate a home-based component into prehabilitation programmes.

2. Endurance Exercise training in patients with small abdominal aortic aneurysm: A randomised controlled pilot study [231]

This study presents a pilot RCT conducted in the United Kingdom, aiming to assess the impact of exercise on a cohort of 14 patients versus 14 patients receiving standard clinical care diagnosed with subthreshold aneurysms who were under surveillance. The exercise intervention protocol consisted of a structured regimen comprising of 30 to 45 minutes of a mixture of treadmill walking and cycle ergometry, aimed at providing a moderate intensity exercise, with a cumulative duration of 90 - 135 minutes per week over a span of 12 weeks (comprising of 3 sessions per week). The setting of the exercise programme was supervised in-hospital setting. Main outcomes measured were the safety of exercise regime by recording adverse events related to exercising and changes to maximum AAA diameter

along with difference in CPET measures (AT, peak VO₂) between baseline and after 12 weeks of exercising.

This pilot RCT demonstrated the safety of moderate-intensity exercise in AAA with small aneurysms. No instances of adverse events related to AAA symptoms or exercise were documented. There was no difference in maximum AAA diameter (mm) (95% CI -1.5 to 1.2, $p = 0.836$ favouring exercise group). Furthermore, it is noteworthy to highlight the substantial enhancement of aerobic capacity (AT) observed in the exercise group when compared to the control group. The mean difference in AT between the two groups was 2.5 ml/kg/min, with a 95% CI ranging from 0.5 to 4.5 ml/kg/min. Importantly, this improvement exceeds the minimum clinically important difference established by the aforementioned study[230]. While there was observed enhancement in VO₂ levels, it is important to note that the observed changes did not attain statistical significance.

3. A randomised trial of exercise training in abdominal aortic aneurysm disease[195]

This was a randomised longitudinal trial analysing the effect of exercise in subthreshold AAA patients conducted in the United States. The primary outcome measured was AAA growth rates in AAA who underwent exercise trial for 3 years. The exercise was conducted either in a rehabilitation centre, home- based or a combination of both. Secondary outcome involved exercise capacity using CPET measures and energy expenditure. They successfully randomised 72 patients to the exercise arm with 68 patients randomised to control arm. Participants were asked to exercise 1 hour/day of moderate intensity at home and they were also provided the option to attend 3 weekly sessions at rehabilitation centre which involved 45-minute aerobic exercise followed by 10-minute resistance exercise.

With 81% of participants completed at least 1 years of the trial, this study demonstrated that both exercise and intervention arms had similar AAA growth rates. Most importantly, it demonstrated the safety of exercising AAA patients at home as there was no adverse events recorded.

With respect to changes in exercise capacity, the research team demonstrated notable enhancements in exercise time, with an observed increase ranging from 30% to 40%. Furthermore, the exercise group exhibited a substantial improvement in estimated metabolic energy expenditure (MET), with an average rise of 20% to 25%. The study also demonstrated that the exercise group experienced a notable rise in peak VO₂ levels after 3 and 12 months. However, it is important to note that this increase was not of the same magnitude as the observed improvement in exercise time or metabolic equivalents (METs).

The present study has provided novel insights into the functional decline observed in the control group, as evidenced by a notable decrease in peak VO₂ at the 2-year, 3-year mark in comparison to the baseline measurements. This finding potentially indicates that engaging in exercise interventions may serve as a potential preventive strategy for patients with AAA.

4. The Abdominal Aortic Aneurysm Get Fit Trial: A randomised controlled trial of exercise to improve fitness in patients with abdominal aortic aneurysm[201].

The present randomised controlled trial (RCT), which was published in 2023, was conducted in the United Kingdom. The primary objective of this study was to evaluate the efficacy of a 24-week community-based exercise intervention in individuals with subthreshold (AAA), specifically in terms of their cardiopulmonary exercise testing (CPET)-derived measures of physical fitness. The primary outcome assessed in this study encompassed the change in VO₂ in conjunction with various other CPET metrics, cardiovascular biomarkers, and a secondary outcome of health-related quality of life measurement. The exercise protocol was patient-driven and implemented either within the patients' home or at a nearby fitness facility. A cohort of 56 individuals was enlisted, with 28 participants being assigned to the exercise intervention group. The exercise protocol implemented consisted of 45–60 minutes sessions distributed throughout the week, amounting to a minimum cumulative duration of 150 minutes per week, with a focus on moderate-intensity training. The control arm received standard clinical care.

This trial has successfully showcased a noteworthy enhancement in peak VO₂ levels within the exercise intervention cohort. The mean change in peak VO₂, was found to be 1.5 (95%CI 0.5 – 2.5) after an 8-week period. Subsequently, at the 16-week mark, the exercise group exhibited a mean difference of 2.1 (95% CI 1.1 – 3.2). Finally, at the conclusion of the 24-week duration, a mean difference of 2.3 (95% CI 1.2 – 3.3) was observed. In comparison to the control group, the observed alteration in peak VO₂ following an 8-week exercise intervention did not exhibit statistical significance ($p = 0.069$). The observed measurements at 16, 24, and 36 weeks yielded statistically significant results ($p < 0.05$), indicating a deviation from the initial assumption. The patients assigned to the exercise intervention demonstrated a notable improvement in aerobic threshold (AT) levels throughout the study period. Specifically, the baseline AT measurement of 9.8 mL/kg/min (with a range of 8.9 – 10.7 mL/kg/min) exhibited a significant increase to 10.7 mL/kg/min (with a range of 9.7 – 11.6 mL/kg/min) after 8 weeks of exercise. This positive trend continued, culminating in an AT measurement of 11.3 mL/kg/min (with a 95% confidence interval of 10.3 – 12.3 mL/kg/min) at the 36-week mark.

The present study serves to corroborate the findings of Myers et al. by providing further evidence regarding the efficacy and safety of exercise training in patients diagnosed with abdominal aortic aneurysm (AAA) within a community-based setting. The clinical trial proved to be efficacious in causing improvement in peak VO₂ throughout the course of 8, 16, 24, and 36 weeks in relation to the initial baseline measurement.

The authors posit that a minimum duration of 12 weeks for an exercise programme is necessary to observe noteworthy enhancements in all cardiopulmonary exercise testing (CPET) parameters. However, it is worth noting that the most substantial enhancements in peak oxygen consumption (VO₂) and anaerobic threshold (AT) were observed after an 8-week interval, with subsequent periods showing a plateauing of improvement.

Prehabilitation for patients “awaiting surgery”.

Three studies evaluated the effect of exercise training in AAA patients who were scheduled for surgery by analysing post operative outcomes along with improvement in functional capacity.

Details of intervention outcomes of included studies are described below.

1. Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomised controlled pilot study [198]

This was randomised pilot study conducted in Netherlands aimed at investigating the effect of inspiratory muscle training for patient scheduled for AAA repair on reducing the incidence of atelectasis following repair. The “ exercise “ method used in this study focussed on enhancing the inspiratory muscles using a threshold – loading device. 10 patients were randomised to intervention arm where they asked to perform the exercise once day for 14 minutes, 6 times a week for at least 2 weeks before surgery.

The main finding of the study showed 3 patients (33.3%) in the intervention group developed atelectasis compared to 8 patients in the control group (80%). However, there was no significant difference in respiratory function metrics between two groups.

This study was published in 2008 and represent the first study to assess physical measures in order to improve outcomes in patients awaiting AAA surgery. The study was small, underpowered and it was not clear what kind of surgical intervention these patients received (Open repair/EVAR).

2. Preoperative supervised exercise improves outcomes after elective abdominal aortic aneurysm repair. A randomised controlled trial. [199]

This was a RCT study conducted in vascular tertiary unit in the United Kingdom. The main aim of the study is to investigate the impact of a structured exercise training programme for patients scheduled for either Open or endovascular repair. The exercise training programme was hospital-based composed of 3 sessions per week totalling 180 minutes of moderate intensity exercise per week for a duration of 6 weeks. The exercise session included resistance and aerobic exercises. The research team successfully recruited 62 patients to intervention arm. The primary outcomes measure was composite endpoint of cardiac, pulmonary and renal complications post operatively. Secondary outcomes measure were short term survival rates, critical care and hospital stay along with reintervention rates. A subgroup analysis was performed for those who agreed to have CPET testing on the last preoperative day.

This was the first study to assess the impact of a preoperative exercise programme on post-operative outcomes. The main findings of the study showed significant reduction in composite primary end point (cardiac, pulmonary, renal complications) in the exercise group when compared to the control arm (22.6% vs 41.9%, $p < 0.05$) with largest intervention effect seen in cardiac complication (8.1% vs 22.3%, $p < 0.05$). The authors also analysed the impact of their exercise training on EVAR patients alone and found reduction in complications in the exercise group (8.7% vs 34.8%, $p < 0.05$). Interestingly, it was also noted that intervention arm median length of stay was less than control group (7 days vs 8 days, $p < 0.05$). In regard to functional capacity metrics assessed for a subgroup of patients ($n=33$) who received exercise training, there was significant improvement in all CPET variables recorded which was unmatched in the control group.

This study showed the feasibility, efficacy and safety of implementing exercise training for patients awaiting AAA repair. However, there are some questionable findings observed when analysing treatment outcomes. For example, it was noted that EVAR patients' hospital stay in the exercise group was 4 days which does not reflect the national and international

reporting. Moreover, the incidence of complications following AAA repair was remarkably high when compared to UK National Vascular Registry data. However, this could be false conclusion as the definition of the cardiac, pulmonary and renal complications may differ which could explain the high complication rates observed in this trial.

3. Randomised feasibility trial of high-intensity interval training before elective abdominal aortic aneurysm repair. [200]

This was the only RCT to assess the feasibility of high-intensity interval training (HIT) in patients awaiting AAA repair. The experimental intervention, consisting of a sample size of 27 participants, involved implementing high-intensity interval training (HIT) conducted thrice weekly. This intervention was administered over four weeks leading up to the operative repair. In cases where the operative repair was subject to a delay, a scheduled weekly session of High-Intensity Training (HIT) was conducted. The High-Intensity Interval Training (HIT) protocol employed in this study involved eight intervals, each lasting for two minutes, during which participants engaged in vigorous cycling. These intense intervals were alternated with two-minute periods of rest, during which participants cycled at a lower intensity without any additional load. The study group consisted of 26 individuals who received the standard care treatment. The observed outcomes were evaluated with respect to their feasibility. Specifically, the exercise attendance rate was determined to be 75.8%, the recruitment rate was 22.1%, and the retention rate was reported as 91%. The anaerobic thresholds were observed and documented after the exercise training, whereas no such measurements were taken at the initial baseline stage. The initial average aerobic capacity (AT) in the exercise group was recorded at 11.7 ml/kg/min, while the control group exhibited an average AT of 11.3 ml/kg/min.

This study represents the solitary clinical trial that has investigated the effects of high-intensity exercise within a population afflicted with abdominal aortic aneurysm (AAA). Out of the total cohort of 27 individuals assigned to the exercise group, 20 participants (representing 74.1% of the sample) experienced the need to modify their exercise intensity. This adjustment was necessitated by blood pressure readings surpassing the predetermined

safety threshold of 180mmHg. In general, the observed exercise intensity exhibited a lower magnitude than initially intended, as a mere 30% of the recorded work intervals were reported to fall within the hard to very hard range, signifying the attainment of high-intensity exercise. This inquiry raises whether individuals with AAA populations can indeed endure high-intensity interval training (HIT) exercises. The patient recruitment process posed significant challenges, as 556 individuals were initially identified for potential inclusion in the study. However, upon eligibility check, it was determined that 503 patients did not meet the necessary criteria and were subsequently excluded from the study. This observation appears peculiar, considering that the patients under consideration were awaiting abdominal aortic aneurysm (AAA) repair.

Consequently, any intervention that influences the outcome of said repair must be appropriate for most patients. The observed recruitment rate indicates that the aforementioned scenario was not applicable. The quantification of fitness alterations was not undertaken in this study. Rather, the focus was on documenting the post-exercise anaerobic thresholds (ATs). Consequently, drawing significant inferences solely from these isolated numerical values becomes challenging. No discernible alterations in postoperative morbidity or mortality were observed. The findings presented in the paper suggest that High-Intensity Interval Training (HIT) may potentially enhance fitness levels as measured by Cardiopulmonary Exercise Testing (CPET). However, it is essential to note that further research in the form of a definitive trial is necessary to establish conclusive evidence in this regard. It is challenging to concur with this assertion as a dearth of empirical evidence supports the notion that Cardiopulmonary Exercise Testing (CPET) effectively captures alterations in physical fitness resulting from High-Intensity Interval Training (HIT). Moreover, based on the findings of this study, it can be inferred that Health Information Technology (HIT) may not be well-received by a significant portion of patients diagnosed with Abdominal Aortic Aneurysm (AAA) and could pose safety concerns. The current body of evidence does not provide a sufficient rationale for favouring high-intensity exercise over moderate-intensity exercise as a therapeutic approach.

Feasibility and adherence

Prehabilitation for patients “under surveillance”

Four studies [195,201,230,231] trialled exercise – focussed prehabilitation for patients with small AAA under surveillance. A total of 869 patients were found eligible and approached for recruitment. Range of participants recruited varied between 5% - 100% with total number of 254 (29.2%). One study [231] mentioned the reasons behind low recruitment rate (5%) reporting majority of them not being interested. Other reasons were because of time and travel commitment. For those who were recruited and randomised to the exercise arm, retention rates were acceptable ranging between 68%-85%. We noticed variability in the assessment used to define “adherent participants” across the four studies. Adherence rates in Meyers et al[195] was measured by the amount of metabolic equivalent of task (METs) and participants who achieved energy expenditure >1000kcal/week were defined as adherent. Adherence rates were very encouraging reporting 85% of participants being adherent and 40% achieved more than 2000Kcal/week.

One study [231] reported the number of total sessions completed (94%) but it was not clear how many participants were adherent. Table 4-d shows recruitment rates, adherence rates and dropouts.

Prehabilitation for patients “awaiting surgery”.

Three studies [198–200] were reviewed, which investigated the effectiveness of exercise prehabilitation for patients awaiting AAA repair. Two of the trials [199,200] involved participants who were scheduled for either Open repair or EVAR. One of the studies conducted by Tew et al [200], reported low recruitment rate with 78 (15.5%) eligible patients declining to participate due to work commitments or difficulty travelling. However, the retention rate was high at 89%, similar to that seen in Barakat et al [199] randomised controlled trial, which had a retention rate of 91%. The main reasons for dropouts in these two studies, were participants withdrawing from the study without providing any specific reason.

All three studies reported exercise adherence. Dronkers et al [198] reported a 100% compliance rate based on self-reported adherence in daily training diaries. Barakat et al [199] and Tew et al [200] reported that 52% and 63%, respectively, of participants completed at least 75% of the prescribed exercise sessions. Table 4-e. shows recruitment rates, adherence rates and dropout.

Table 4-d Feasibility and adherence of exercise programmes of AAA patients who were under surveillance

Author, year	Setting	Eligible	Recruitment n(%)	Retention n(%)	Reasons for drop out	Exercise adherence n(%)	Reasons for poor adherence
Kothmann 2009	Hospital	30	30 (100%)	17 (85%)	withdrew due to infection (n =1) Other surgery (n=1) Cardiac arrest (n=1)	NR	NR
Tew 2012	Hospital / Gym	545	28 (5%)	11 (78.6%)	pacemaker insertion (n=1) cancer diagnosis (n=1) chronic back pain (n=1)	94%§	NR
Myers 2014	Hospital / Home	140	140 (100%)	53 (73.6%)	NR	45 (81%)	NR
Haque 2022	Gym/ Home	154	56 (36.4%)	19 (67.9%)	too far (n=1) ill health (n = 3) no reason (n= 5)	NR	NR

§: Adherence reported as percentage of completed sessions for all participants. NR = Not reported

Table 4-e Feasibility and adherence of exercise programmes of AAA patients scheduled for repair

Author, year	Setting	Eligible n	Recruitment n (%)	Retention n (%)	Reasons for drop out	Exercise adherence n (%)	Reasons for poor adherence
Dronkers 2008	Hospital / Home	20	20 (100%)	20 (100%)	NA	20 (100%)	NA
Barakat 2016	Hospital	293	136 (46.1%)	62 (91.2%)	withdrew (n=3) small aneurysm (n=1) other urgent surgery (n=1) unfit for surgery(n=1)	51 (83.6%)	NR
Tew 2017	Hospital	240	53 (22.1%)	24 (88.9%)	withdrew (n = 2) expedited surgery (n = 1)	17 (63%)	NR

NA= Not applicable, NR = Not report

Discussion

Prehabilitation programmes are perceived to be a popular method to improve postoperative outcomes across major surgical interventions[223]. Our study results suggest that there was no consensus on the definition of adherence, with most studies relating adherence to class attendance. This is an ongoing issue on how to define and measure adherence in studies looking at participation in exercise programmes suggested that there is a need for standardization in reporting adherence [233]. The WHO guidance suggests that pre-surgery exercise programmes should aim for between 150-300 min per week of moderate exercise or 75-150 minutes of vigorous exercise per week[234]. However, the main issue is whether this amount of exercise will improve functional capacity and reduce postoperative complications in patients undergoing AAA repair. One recent RCT included in this review [201] has shown improved Cardiopulmonary exercise testing (CPET) parameters which equates to a reduction of postoperative complications. This was also demonstrated in a recent study designed to deliver a personalised home-based exercise for oesophageal cancer patients showed that 75% adherence to WHO recommendations improved patients' functional capacity and noted a reduction in the postoperative incidence of pneumonia[235]. However, there is doubt whether patients undergoing EVAR would benefit from such intervention especially that they are conducted percutaneously and under regional/local anaesthetic. Perhaps, prehabilitation may improve long term outcomes especially if patients continued with exercises following surgery.

The adherence rates of the included studies ranged from 52% to 100%. Achieving good levels of adherence to exercise programmes is variable, especially in the older population [236,237]. Elderly patients commonly suffer from frailty, falls, and chronic diseases that limit their mobility and affect their confidence to exercise.

As for the content of the prehabilitation programme, all studies in this review included an exercise only intervention. Recently, a shift has occurred in prehabilitation

programmes changing from unimodal to multimodal, including nutritional and psychosocial components. It is now recognised that an effective prehabilitation programme should contain four pillars: medical optimisation, physical exercise, nutritional support, and psychological support [238]. Cardiovascular risk reduction has proven to be suboptimal[239] and multimodal prehabilitation programmes may offer a checkpoint where patients receive continuous education and motivation to adhere to best medical therapy. Only one study[240] was identified from the literature search looking at a multimodal prehabilitation programme for AAA patients. However, this study was not included in this review as it did not report adherence levels. Nakayama's study aimed to look at AAA expansion following prehabilitation and incorporated a multimodal programme of exercise and education on lifestyle modification, dietary choices, and stress reduction. The optimisation of patients' psychological status and their nutrition should be adopted in prehabilitation programs[241]. Recent studies reported that multimodal, exercise focused pre-surgery interventions have improved functional capacity, adherence rates, and postoperative recovery compared to single component interventions, especially in sedentary patients with cancer[242,243].

Individualised or personalised provision of prehabilitation should be taken into consideration to improve adherence rates. Myers et al commented in a further publication[244] about the strategies behind such success which included participants self-monitoring, education, telephone follow up and regular encouragement. Adjuvant use of remote technologies has been shown to increase adherence in cardiac rehabilitation programs[245,246]. The inclusion of remote monitoring may be important when designing future studies in order to accurately assess adherence rates to remote prehabilitation programmes for AAA patients. However, AAA is more prevalent in the older population and barriers to using such technologies exist due to lack of knowledge of using smart devices with the presence of physical and cognitive disabilities.[247]

This review demonstrates the paucity of scientifically sound data within the field of prehabilitation of AAA patients which should encourage further trials to agree a core outcome measurement in order to formulate a consensus on who we should offer prehabilitation, duration and intensity of prehabilitation along with cost-effectiveness

analysis. The major limitation of this review is the marked variability with regards to the duration and implementation of exercise programmes which in term may have influenced adherence rates.

Conclusion

Pre-operative optimisation of AAA patients through prehabilitation programmes is gaining interest amongst healthcare professionals. However, given the quality of current evidence, it is difficult to achieve a reliable conclusion. The results of this review highlighted that adherence to exercise programmes is variable, with no standardised reporting of adherence. Future research should focus on the exploration of personalised multimodal interventions guided by behavioural change strategies to promote adherence.

Chapter 5 : Multi-centre, pilot study evaluating the feasibility, acceptability, and short-term outcomes of a tailored, virtual, home-based, prehabilitation programme in patients undergoing abdominal aortic aneurysms (AAA) repair. The PREHAB-AAA study

Introduction:

AAA are associated with a high risk of mortality in the event of rupture, accounting for around 2% of all deaths in men aged 65 and over[248] . The primary focus in improving survival in patients with AAA has been centred on the timing of surgery to prevent the consequences of rupture.

Intervention for AAA can be performed by either open or endovascular repair (EVAR) and is typically reserved for AAA of at least 5.5cm in diameter. In the UK, approximately 2800 surgical repairs are performed annually[249]. However, elective surgery carries significant risk, with thirty-day mortality rates estimated at around 3.1 % and 0.5% in patients undergoing open repair and EVAR respectively[249]. Therefore, enhancing perioperative and postoperative outcomes in individuals undergoing abdominal aortic aneurysm (AAA) repair, a significant proportion of whom exhibit comorbidities and consequently face an increased risk of mortality, represents a crucial imperative.

The existing body of research indicates that a notable proportion, ranging from 25% to 40%, of unfavourable outcomes subsequent to surgical procedures can be attributed to the existence of frailty[250,251]. Frailty, as defined within the medical context, represents a biological syndrome characterised by a diminished capacity for physiological reserve and reduced resistance to various stressors[148]. Irrespective of demographic factors such as age and gender, as well as other potential variables that may influence the results, it has been observed that individuals exhibiting frailty demonstrate notably increased rates of postoperative morbidity, mortality, and utilisation of healthcare resources. Within the realm of abdominal aortic aneurysms (AAA), extensive research has demonstrated a correlation

between higher scores on the modified frailty index (mFI) and increased rates of mortality and morbidity in individuals undergoing AAA repair procedures.

Cardiopulmonary exercise testing (CPET) is one method used to predict adverse outcome across a range of high-risk surgical procedures[252][253]. Previous research has also revealed the adverse impact of poor fitness on the outcome of patients undergoing AAA repair, with several small-scale studies further demonstrating the beneficial impact of improved physical activity levels on post-operative outcomes[254,255].

The evaluation and pre-operative optimisation of comorbidities and fitness levels is increasingly recognised as an important element of the pre-operative pathway. Prehabilitation programmes aim to reduce pre- and post-operative complications, and typically reflect a multi-disciplinary, multicomponent approach, incorporating structured exercise sessions, disease education and psychological preparation.

A recent systematic review looking at prehabilitation programmes before major abdominal surgery found that such programmes reduced overall morbidity following surgery[256]. Another systematic review, which focused solely on the role of preoperative exercise programmes in patients with AAA, found that patients who underwent EVAR had a shorter stay in hospital when a prehabilitation programme was undertaken[257]. Moreover, overall compliance with the exercise programmes was high, suggesting that such programmes are acceptable in this patient population. However, recent reviews on prehabilitation programmes have not reached a consensus on efficacy, describing the quality of the majority of included studies as poor.

Indeed, the significant heterogeneity in trials of this type (in terms of sample size, patient population, duration of prehabilitation programme and intensity of exercise) makes the results difficult to interpret. In recognition of this paucity of data, current NICE guidance recommends that further research be conducted to examine the clinical and cost-

effectiveness of prehabilitation programmes, including preoperative exercise programmes, for improving outcomes of people who are having repair of an AAA [213].

However, implementing face-to-face prehabilitation for patients with AAA may prove challenging in the post COVID-19 era, with the increased likelihood of patients (the majority of whom have multiple comorbidities) opting not to attend hospital or community settings unless absolutely necessary (e.g. for a surgical procedure only). Moreover, with many resources diverted elsewhere, there will inevitably be a large backlog of patients on the waiting list for AAA repair, thus creating a window of opportunity to address modifiable factors affecting fitness and surgery.

Telerehabilitation has gained increased recognition and is defined as the provision of rehabilitation services at a distance, using information and communication technologies. Indeed, previous research has shown that telerehabilitation programmes are feasible in a home-care setting[258]. Furthermore, there is increasing evidence to suggest that clinical outcomes in telerehabilitation programmes are similar to other, more traditional face-to-face interventions. One study demonstrated the potential of a telerehabilitation programme to improve functional ability and reduce hospital length of stay for patients undergoing cardiac surgery[259] whilst another found that a telerehabilitation programme was as effective, and more cost-effective, than convention physiotherapy in patients undergoing a total knee arthroplasty (TKA)[260]. Such telerehabilitation programmes have the possibility to be more cost-effective than traditional face-to-face programmes, with multiple studies demonstrating a significant reduction in health care expenditure using telerehabilitation compared to similar interventions[261]. However, to date, no studies have evaluated the impact of a telerehabilitation programme in patients with AAA scheduled to undergo repair.

Methods

Pilot study design

This was a prospective single-arm pilot trial based at 3 large tertiary vascular centres between September 2021 – July 2023.

Participants

Patients who were referred with threshold AAA (AAA size >5.5cm for males, or >5.0cm for females) attending vascular clinics in three vascular referral centres were screened for eligibility based on the following criteria:

Inclusion criteria:

1. Adults (aged 55 years and over) who have been diagnosed with an AAA and are scheduled to undergo Open surgical repair (OSR) or Endovascular Aortic repair (EVAR) with a wait time of at least 6 – weeks for surgery.
2. Patients with an AAA with a diameter of >5.5cm
3. Able to write, understand and communicate in English.
4. Willing and able to participate in a remote prehabilitation programme.

Exclusion Criteria

1. Thoraco-Abdominal Aneurysms
2. Connective tissue vascular disorders
3. Symptomatic aneurysms
4. Previous aortic intervention
5. Absolute contraindication to exercise
6. Inability or unwillingness to participate in trial
7. Infrarenal AAA diameter exceeding 7.0 cm
8. Symptomatic heart disease: Uncontrolled AF, Angina on minimal exertion, recent cardiac intervention (PCI, CABG)

The Research team regularly attended multidisciplinary team meetings to screen patients who meet the inclusion and exclusion criteria. After the approval of the surgical team, eligible patients were approached over the phone to check their willingness to participate in the study. A patient information sheet was then posted to patients along with consent form. A follow up call was arranged with eligible participants to confirm participation for the study. A baseline assessment date was given to participants.

Intervention

After providing written informed consent, participants were provided with information about the prehabilitation programme (described below). The following data will also be collected:

1. Discussion of the study protocol and explaining in detail the prehabilitation programme
2. Baseline demographics including age, gender sex and ethnicity.
3. Past medical and medication history
4. Frailty assessment (Clinical Frailty Score)
5. Psychological wellbeing (Well-being questionnaire W-BQ16)
6. Health – related quality of life (EQ-5D-5L AND EQ-VAS) questionnaire.
7. Disease specific quality of life questionnaires (Aneurysm TSQ , Aneurysm SRQ, Aneurysm DQol) – a validated questionnaires to assess quality of life, symptoms and treatment satisfaction in patients with abdominal aortic aneurysm[262].
8. 6-minute walk test to assess functional status [263]

Participants will be enrolled in a 6 – week remote , tailored, home- based exercise programme. Also, appropriate dietary advice (High protein/fibre diet) along with smoking and alcohol cessation.

The programme has been developed with experts in the field of sports therapy, physiotherapy and biomechanics, based on robust literature in other fields. According to participants tolerance to the 6-minute walk test using Borg Scale (Appendix 5-1), participants were assigned to a one of the pre-set exercise programmes. The course plan is

to start with 3 sessions every week for 6 weeks where participants would complete a tailored home exercise programme or until expected surgical intervention. In the first week of this programme, patient will receive three sessions with total of 150 minutes of exercise according to UK Chief Medical Officers' Physical Activity Guidelines. Participants will be offered to wear an activity tracker (Actigraph™).

After each week, via telephone, we will explore patient tolerance to the exercise regime using Borg scale. We will either increase or decrease exercise intensity according to their feedback (aiming for RPE scale 3-5) with view of increasing the number of exercise days up to 5 days with a total of 250 minutes of moderate intensity exercise.

Participants were provided with exercise plan that included aerobic, resistance, balance exercises (Appendix 5-2). Each exercise was modified according to participants tolerance to that specific exercise. Any limitations to any specific exercise were addressed and tailored to participants' feedback.

Outcomes

Primary outcomes:

1. Feasibility of recruitment
 - a. Number of participants eligible for screening
 - b. Number of participants enrolled.
 - c. Reasons for non-participation
2. Adherence
 - a. Number of sessions attended each week.
 - b. Proportion of participants who 'complete' the 6-week programme
3. Acceptability
 - a. Enjoyment of prehabilitation captured through Physical activity enjoyment scale (PACES)

- b. Reasons for drop-out will be captured.

Secondary Outcomes:

- a. Length of stay and readmission rates (30 days post-surgery)
- b. In-Hospital Complication Rate - Composite of Cardiac, Respiratory, Renal, Haemorrhage, Limb Ischaemia and Cerebral Complications, as defined by National Vascular Registry
- c. 30-day Composite Outcome: Death and Defined complication (Cardiac, respiratory, haemorrhage, limb ischaemia, renal failure)
- d. Change in 6-minute walk test (6-MWT) at end of programme, 6-weeks (Post discharge) and 3 months (Post Discharge)
- e. Change in health-related quality of life scores (using the EuroQol five-dimensional questionnaire [EQ-5D] and visual analogue scale [EQ-VAS]) at end of programme, 6-weeks (Post discharge) and 3 months (Post Discharge)
- f. Post-Operative Morbidity score (POMS)
- g. Change in aneurysm specific quality of life scores at end of programme, 6-weeks (Post discharge) and 3 months (Post Discharge)
- h. Change in Well-being questionnaire (W-BQ16) end of programme, 6-weeks (Post discharge) and 3 months (Post Discharge)
- i. Reduction in cigarettes per day at the end of programme, 6-weeks (Post discharge) and 3 months (Post Discharge)
- j. Change in weight (in kg) end of programme, 6-weeks (Post discharge) and 3 months (Post Discharge)

Sample Size

As this is a pilot study assessing feasibility, there was no formal sample size calculation.

Statistical Methods

Baseline demographics were described using independent samples t-test for any difference in continuous variables after performing Levene's test of equal variance to determine the appropriate calculation. Dichotomous variables were compared using χ^2 test or Fisher's exact test, if >20% of frequencies were <5. All significance t-test was two-tailed at a 5% level. All changes from baseline and comparisons between the groups reported as mean with associated confidence intervals (95% CI) and p values where appropriate. These analyses were undertaken in SPSS and a 0.05 significance level was assumed. All graphs, figures and tables were created using GraphPad Prism.

Results

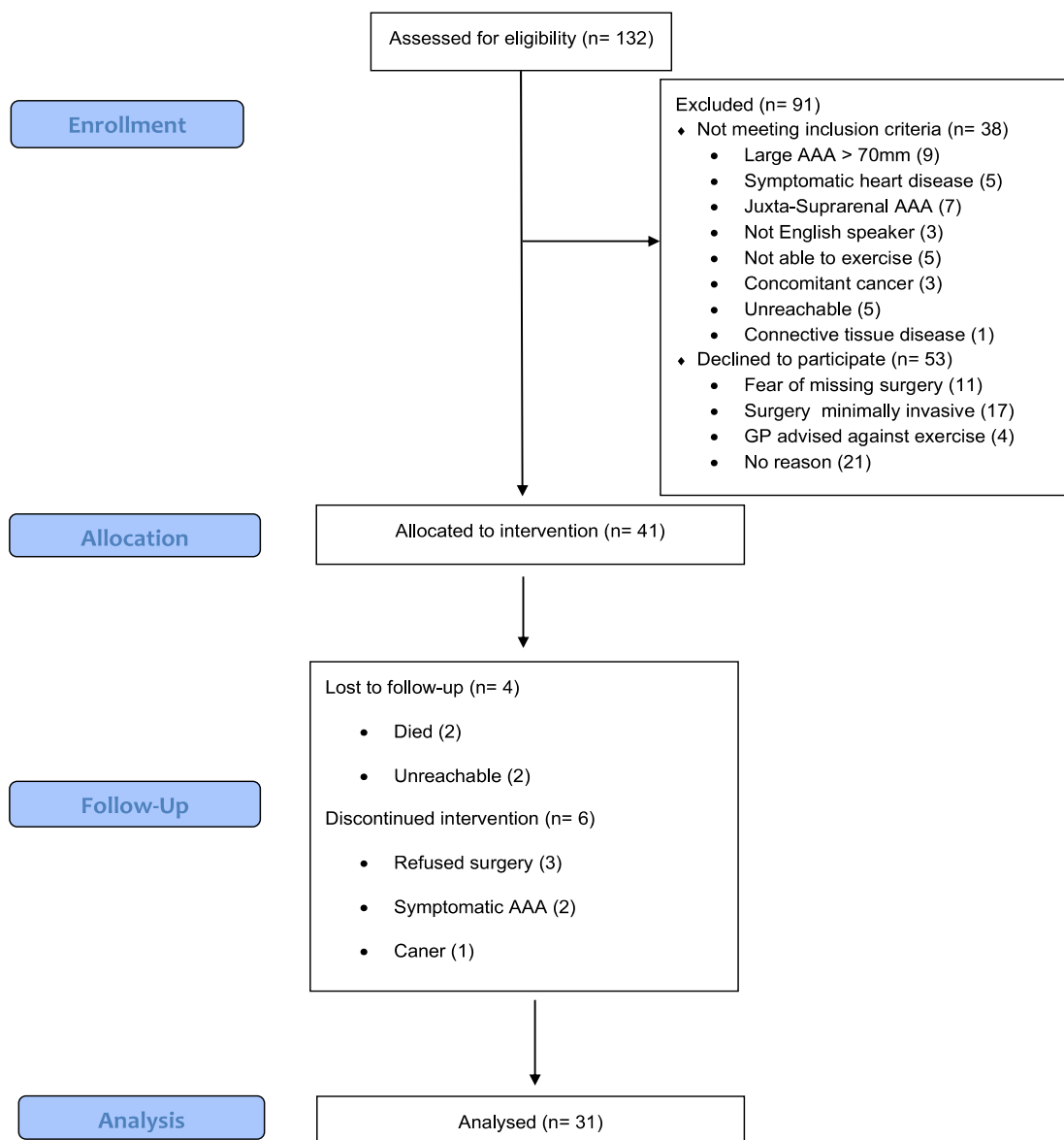
Participant flow

Recruitment

Recruitment for the study commenced in September 2021, screening process was conducted on 132 patients to determine their eligibility. 41 patients, accounting for 31.1% met the inclusion criteria, agreed to participate and attended baseline assessment. The recruitment process was finalised in June 2023, spanning a total of 21 months. This duration accounted for the necessary time spent in establishing additional sites and recovering from the constraints imposed by the COVID-19 pandemic.

After evaluation, it was found that 38 patients (28.9%), did not meet the criteria for inclusion. This was primarily due to the presence of large aneurysm size and complex anatomy (Juxta, Suprarenal AAA), as well as the presence of symptomatic heart disease that necessitated further assessment by a specialist.

Out of the total number of patients screened, a significant portion (40.2%) chose not to participate, even though they met the criteria for inclusion. 21 patients declined to provide a reason for their refusal. However, eleven patients expressed concerns about participating, as they were worried that the study might affect their scheduled surgery date. Seventeen patients were informed about the minimally invasive nature of their surgery and the likelihood of staying in the hospital for just one day. Consequently, they did not perceive any advantages in participating in this study. Some patients were advised by their general practitioner to avoid engaging in strenuous physical activity due to potential complications with their AAA.



Loss to follow up

Of the 41 participants who allocated intervention, 76% (31 individuals) successfully finished the 6-week prehabilitation programme. Three individuals who were enlisted ultimately opted out of undergoing the surgical procedure. Regrettably, two individuals died during the second week of prehabilitation, one as a result of COVID-19 and the other due to severe pneumonitis. Two participants were unable to be contacted by either the research or clinical team and were lost to follow up. A patient received a diagnosis of colorectal cancer after undergoing a colonoscopy that was scheduled during the third week of prehabilitation. Consequently, the patient was removed from the vascular waiting list. Unfortunately, two participants had to discontinue the 6-week prehabilitation programme because they were admitted with abdominal pain and back pain, which raised concerns about a possible symptomatic aneurysm. However, there were no signs of rupture or leakage observed during the surgical procedure.

Baseline Data

The study participants had a mean age of 74 years with a standard deviation of 5.1 years. The majority of the participants were men (81%) and identified as Caucasian (84%). The average size of AAA upon consent to the study was 59 mm. The average weight for participants was 81.2 kg, with a mean BMI of 27.1 kg/m². Eight participants were still smoking, while the majority of the trial participants had smoked in the past (58%).

34 participants successfully completed the 6-minute walk test at baseline, achieving an average distance of 381 metres with a standard deviation of 111 metres. Four patients declined to undergo the test without providing any reasons, while two others were unable to participate due to medical conditions (recent hip replacement and recent stroke).

Table 5-a Baseline characteristics for PREHAB-AAA participants (31 participants)

	<u>Descriptor</u>	<u>Cohort (n= 31)</u>
<u>Demographics</u>		
Age (years)	mean (SD)	74 (5.1)
Gender (male)	n (%)	25 (81)
Ethnicity (Caucasian)	n (%)	26 (84)
AAA size (mm)	mean (SD)	59 (3.8)
<u>Past Medical History</u>		
Hypertension	n (%)	29 (94)
Type 2 Diabetes	n (%)	6 (19)
Cholesterol	n (%)	23 (74)
Peripheral arterial disease	n (%)	7 (23)
Current Smoker	n (%)	8 (26)
Ex-Smoker	n (%)	18 (58)
Angina	n (%)	5 (16)
Myocardial infarction	n (%)	3 (10)
CABG	n (%)	1 (3)
Cardiac stent	n (%)	7 (23)
CVA	n (%)	3 (10)
Osteoarthritis	n (%)	10 (32)
Chronic Kidney Disease	n (%)	5 (16)
COPD	n (%)	11 (35)
Asthma	n (%)	0 (0)
Antiplatelets	n (%)	29 (94)
Statins	n (%)	30 (97)
Beta-Blocker	n (%)	16 (52)
<u>Rockwood Frailty</u>		
Fit (2)	n (%)	5 (16)
Managing well (3)	n (%)	8 (26)
Vulnerable (4)	n (%)	5 (16)
Mildly Frail (5)	n (%)	7 (23)
Moderately Frail (6)	n (%)	3 (10)
Severely Frail (7)	n (%)	1 (3)
<u>Risk assessment</u>		
Q - Mortality (%)	mean (SD)	10.2% (5.3)
<u>Clinical Examination</u>		
BMI (kg/m²)	mean (SD)	26.6 (4.2)
MUST score	mean (SD)	1
6MWT (n = 27)	mean (SD)	388 (126)

CABG: Coronary artery Bypass graft, CVA: Cerebrovascular accident, COPD: Chronic Obstructive Pulmonary Disease, BMI:

Body mass index, MUST: Malnutrition Universal Screening Tool, 6MWT: 6-minute walk test

Adherence

A total of 31 individuals successfully completed a 6-week prehabilitation programme. Seven participants, 22.6% were found to have low adherence, meaning they attended less than 80% of the minimum required three sessions per week. Various factors were documented, including personal matters such as the loss of a loved one, hospitalisation for acute cholecystitis and an infected tooth requiring surgery, advice from a general practitioner to avoid exercise, and a lack of motivation due to frequent surgery cancellations.

We analysed the adherence rates for each week by conducting weekly telephone check-ups with participants and reviewing the information recorded in their exercise diaries. On average, participants exercised 4 days in Week 1, with a small percentage (20%) exercising less than 3 days, as advised. The duration increased to 4.2 days during the second week, and we observed similar results during the third week. During weeks 4, 5, and 6, patients engaged in exercise sessions 4-5 days per week. Based on the analysis of participants' diaries, a significant majority of exercise sessions, specifically 78%, were found to be of moderate intensity. This was determined by the participants' self-reported RPE scores falling between 3-5. Figure 5.1 below summarises the mean number of days exercised by the cohort every week.

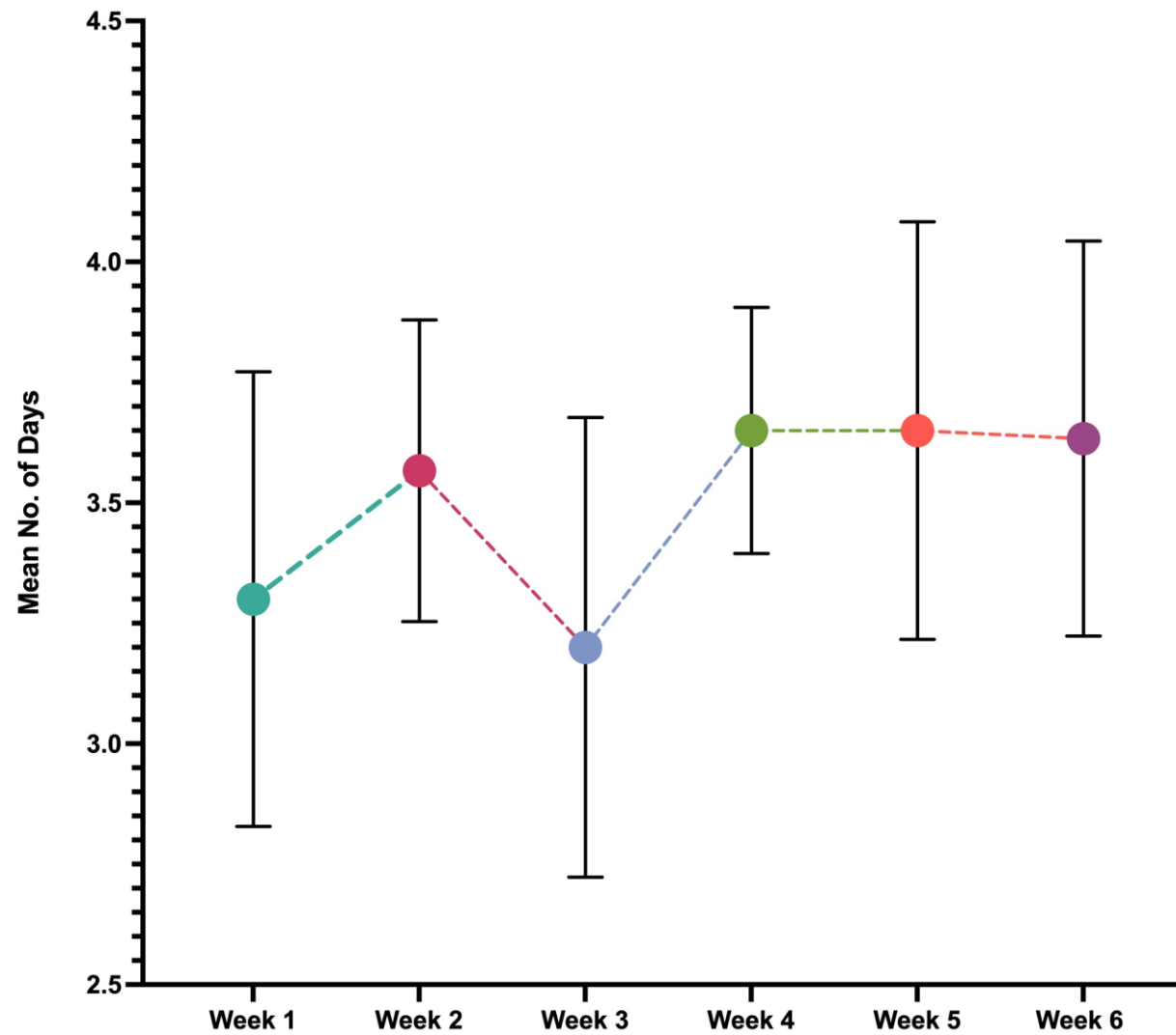


Figure 5.1 Number of days where PREHAB-AAA participants exercised stratified by each week of prehabilitation. Data presented using mean and 95% confidence interval.

Acceptability

The participants' acceptance of the prehabilitation programme was evaluated using the Physical Activity Enjoyment Scale (PACES) questionnaire. Out of the 31 participants, 25 (83.3%) successfully completed the PACES questionnaire at the conclusion of the prehabilitation programme. Five patients did not complete the questionnaire without providing a specific reason. However, most participants agreed that there is a sense of fatigue associated with the questionnaire in this study.

A significant number of participants (73.3%) reported a positive experience with the prehabilitation programme, finding it enjoyable and pleasant. Most of the participants (60%) reported experiencing a strong sense of accomplishment as a result of the study. Table 5-b summarises PACES questionnaire responses.

Table 5-b PACS questionnaire response of PREHAB-AAA participants

Item	<u>Disagree a lot</u> <u>n(%)</u>	<u>Disagree</u> <u>n(%)</u>	<u>I am not Sure</u> <u>n(%)</u>	<u>Agree</u> <u>n(%)</u>	<u>Agree a lot</u> <u>n(%)</u>
I enjoyed it	0(0)	0(0)	3(12)	18(72)	4(16)
I found it fun	0(0)	1(4)	5(20)	16(64)	3(12)
It was very pleasant	0(0)	0(0)	3(12)	17(68)	5(20)
It gave me energy	0(0)	1(4)	6(24)	13(52)	5(20)
My body feels good	0(0)	2(8)	0(0)	4(16)	19(76)
It feels good	0(0)	1(4)	5(20)	18(72)	1(4)
I got something out of it	0(0)	2(8)	3(12)	16(64)	4(16)
It was very exciting	0(0)	2(8)	8(32)	14(56)	1(4)
It gave me a strong feeling of success	0(0)	1(4)	6(24)	16(64)	2(8)
I feel bored	6(24)	12(48)	4(16)	3(12)	0(0)
I disliked it	6(24)	16(24)	3(12)	0(0)	0(0)
It made me sad	10(40)	14(56)	1(4)	0(0)	0(0)
It was not fun at all	5(20)	17(68)	2(8)	1(4)	0(0)
It frustrated me	7(28)	18(72)	0(0)	0(0)	0(0)
It was not at all interesting	7(28)	17(68)	1(4)	0(0)	0(0)
I feel as though I would rather be doing something else	9(36)	13(52)	3(12)	0(0)	0(0)

Change in 6MWT following prehabilitation program.

Baseline 6MWT was completed by 27 participants. The average distance covered by the participants was 388 metres, with a standard deviation of 124.5 metres. The 95% confidence interval for the distance ranged from 337.7 metres to 438.3 metres. After completing a 6-week prehabilitation programme, the average distance covered in the 6-minute walk test was 428.3 metres, with a standard deviation of 112.4. The 95% confidence interval for the distance ranged from 380.9 to 475.8 metres.

There was a significant rise in the distance covered during the 6-minute walk test, with an average increase of 40.5m (SD: 30.1m) (95%CI 27.8, 53.2), $p < 0.001$. Figure 5.3 displays the estimation plot of the mean difference of 6MWT distance after prehabilitation when compared to baseline.

The acceptability of conducting the 6-minute walk test (6MWT) after 6 weeks or 3 months post-surgery was found to be very low, which is why further analysis was not carried out. The primary factor was the need to travel to the appointment and a shortage of time during their usual follow-up visit.

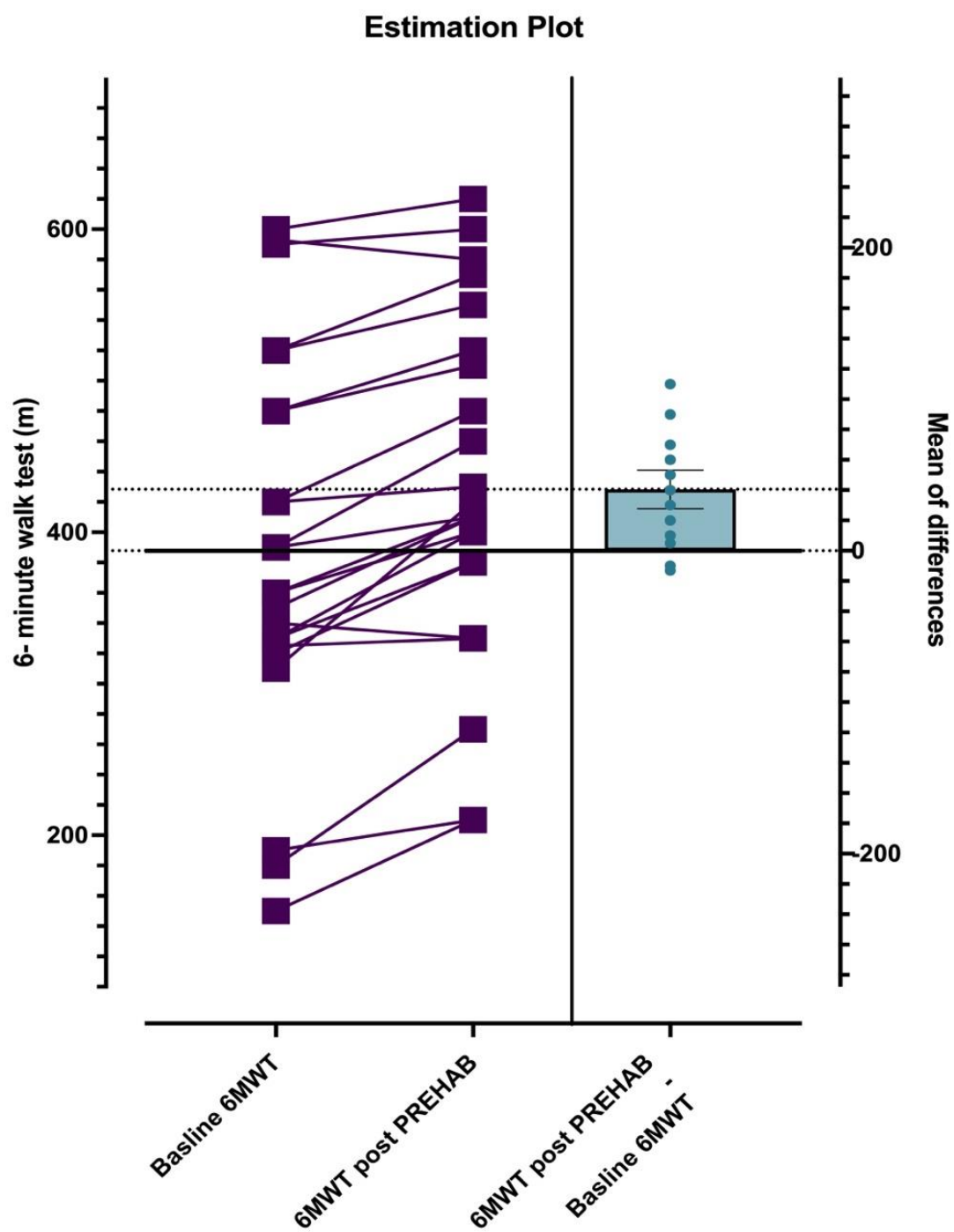


Figure 5.2 Estimation plot for the change in 6MWT after prehabilitation of PREHAB-AAA participants

Change in health-related quality of life scores (EuroQol five-dimensional questionnaire [EQ-5D] and visual analogue scale [EQ-VAS])

27 participants completed the baseline EQ-5D and EQ-VAS questionnaire. Following 6-week prehabilitation programme, 27 participants completed the questionnaire followed by 18 participants who completed 6-week post-surgery.

Around 31.1% of participants reported a problem related to either mobility, self-care, usual activities, pain/discomfort or anxiety/depression on baseline assessment. Following the prehabilitation programme and before undergoing surgery, we noted improvement of the percentage of participants reporting a problem with mobility, usual activities, pain/discomfort but not in self-care or anxiety/ depression domains. Table 5-c summarises reported EQ-5D-3L numbers and proportions reporting levels within EQ-5D-3L domains pre and post prehabilitation.

There was improvement in EQ-5D index value following prehabilitation programme, but it did not reach statistical significance (mean difference 0.02, $p = 0.194$). Participants significantly reported worse EQ-5D index value 6 weeks post-surgery when compared to both baseline and post prehabilitation. Figure 5.4 summarises reported EQ-5D index values.

There was significant improvement in reported EQ-VAS following prehabilitation programme with mean difference of 2.78 (95%CI 0.43, 5.1, $p < 0.05$). Participants reported worse EQ-VAS scores when assessed at 6 weeks post-surgery, however it did not reach statistical difference. Figure 5.5 summarises reported EQ- VAS scores.

Table 5-c EQ-5D-3L questionnaire response of PREHAB-AAA participants before and after prehabilitation

	EQ-5D-3L									
	Mobility		Self-care		Usual activities		Pain/Discomfort		Anxiety/Depression	
Severity Level	Baseline	Post Prehab	Baseline	Post Prehab	Baseline	Post Prehab	Baseline	Post Prehab	Baseline	Post Prehab
Level 1	19 (70.3%)	20 (74%)	25 (92.6%)	25 (92.6%)	22 (81.4%)	23 (85.2 %)	14 (51.9%)	18 (66.7%)	13 (48.1%)	11 (40.7%)
level 2	2 (7.4%)	5 (18.5%)	2 (7.4%)	2 (7.4%)	4 (14.8%)	2 (7.4 %)	10 (37.0%)	8 (29.6%)	12 (44.4%)	15 (55.6%)
Level 3	6 (22.2%)	2 (7.4%)	0 (0%)	0 (0%)	1 (3.7%)	2 (7.4%)	3 (11.1%)	1 (3.7%)	2 (7.4%)	1 (7.4%)
Total	27(100%)	27 (100%)	27 (100%)	27 (100%)	27 (100%)	27 (100%)	27 (100%)	27 (100%)	27 (100%)	27 (100%)
Reporting some problems	8 (29.6%)	7 (25.9%)	2 (7.4%)	2 (7.4%)	5 (18.5%)	4 (14.8 %)	13 (48.1%)	9 (33.3%)	14 (51.9 %)	16 (59.2%)
Change in numbers reporting problems	-1		0		-1		-4		2	
% change reporting problems	-3.70%		0%		-3.70%		-14.80%		7.30%	

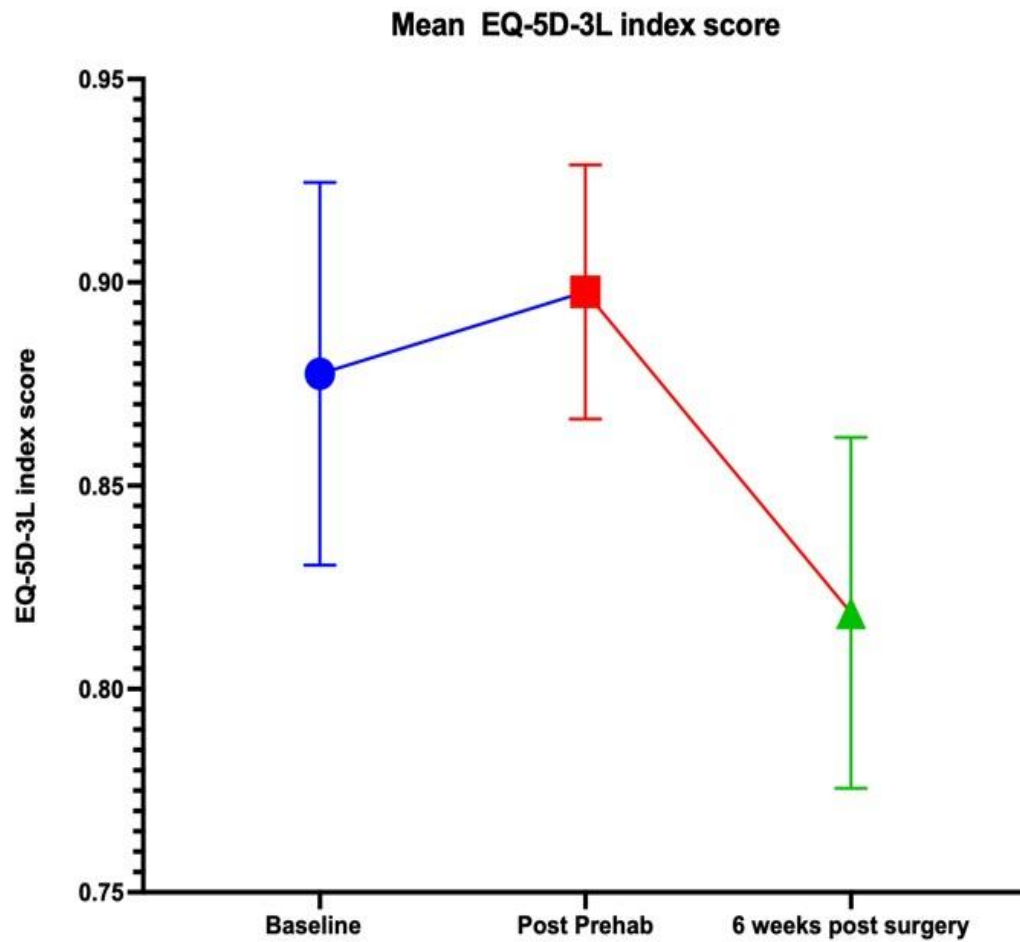


Figure 5.3 EQ-5D-3L index scores at baseline, post prehabilitation and 6 weeks following surgery. Data presented in mean and 95% confidence interval.

Descriptives

	Mean	SE	95% Confidence Interval		SD
			Lower	Upper	
Baseline	0.877	0.0229	0.830	0.925	0.1190
Post Prehab	0.898	0.0152	0.866	0.929	0.0790
6 weeks post surgery	0.819	0.0210	0.776	0.862	0.1091

Note. The CI of the mean assumes sample means follow a t-distribution with N - 1 degrees of freedom

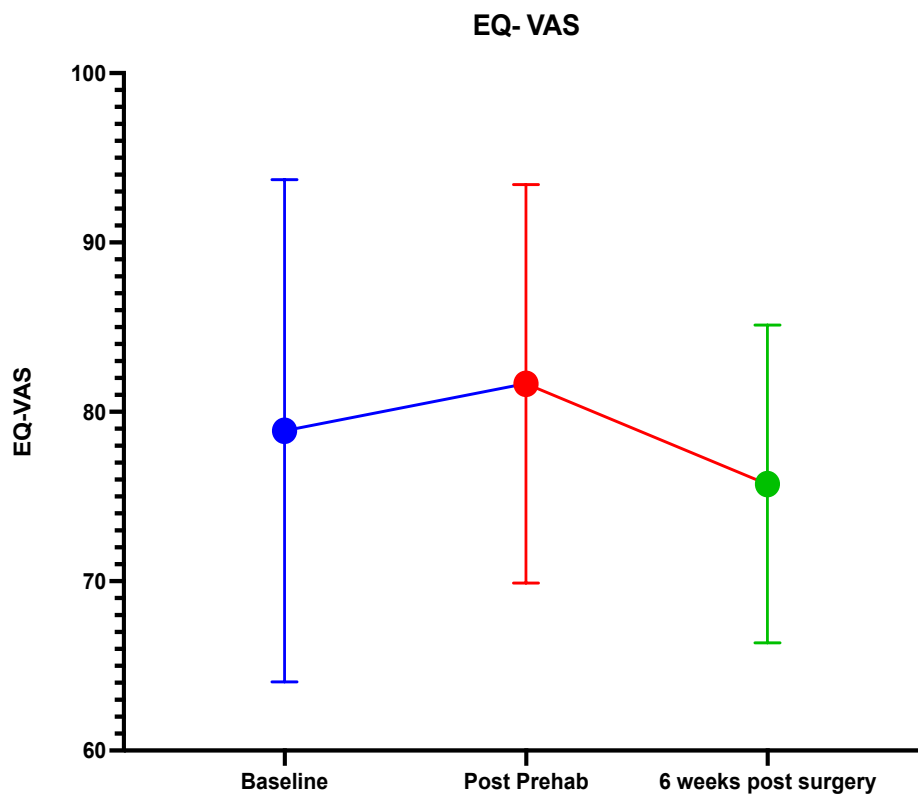


Figure 5.4 EQ-VAS scores of PREHAB-AAA participants at baseline, post prehabilitation and 6 weeks after surgery. Data presented in mean and 95% confidence interval

Descriptives

	Mean	SE	95% Confidence Interval		SD
			Lower	Upper	
Baseline	78.9	2.85	73.0	84.8	14.83
Post Prehab	81.7	2.26	77.0	86.3	11.77
6 weeks post-surgery	75.7	1.80	72.0	79.4	9.38

Note. The CI of the mean assumes sample means follow a t-distribution with N - 1 degrees of freedom

Change in Well-Being questionnaire (W-BQ16)

21 (68%) participants completed the baseline W-BQ16 questionnaire. Following completion of 6-week prehabilitation programme, 18 participants completed the questionnaire. 6 - weeks following surgery, only 12 (44%) participants reported W-BQ16 outcomes.

Mean W-B16 Generic well-being score reported at baseline assessment was 36.2 (SD: 5.9). Following 6-week prehabilitation programme, we noticed a drop in the mean score without reaching statistical significance (36.2 vs 35.4, $p = 0.4$). Mean W-BQ16 score continued to drop when assessed at 6 weeks post-surgery with mean of 34.4 (SD: 4.2) without reaching statistical significance when compared to baseline score (Figure 5-6)

On analysis of W-BQ16 Negative well-being subset, there was significant improvement following prehabilitation with mean difference 0.63 (95%CI 0.28 – 0.98, $P < 0.05$). However, there was significant deterioration 6 weeks following surgery when compared to baseline and post prehabilitation scores (Figure 5-7). There was no significant difference in Energy or Generic stress subsets of W- BQ16 questionnaire (Figure 5-8, Figure 5-9).

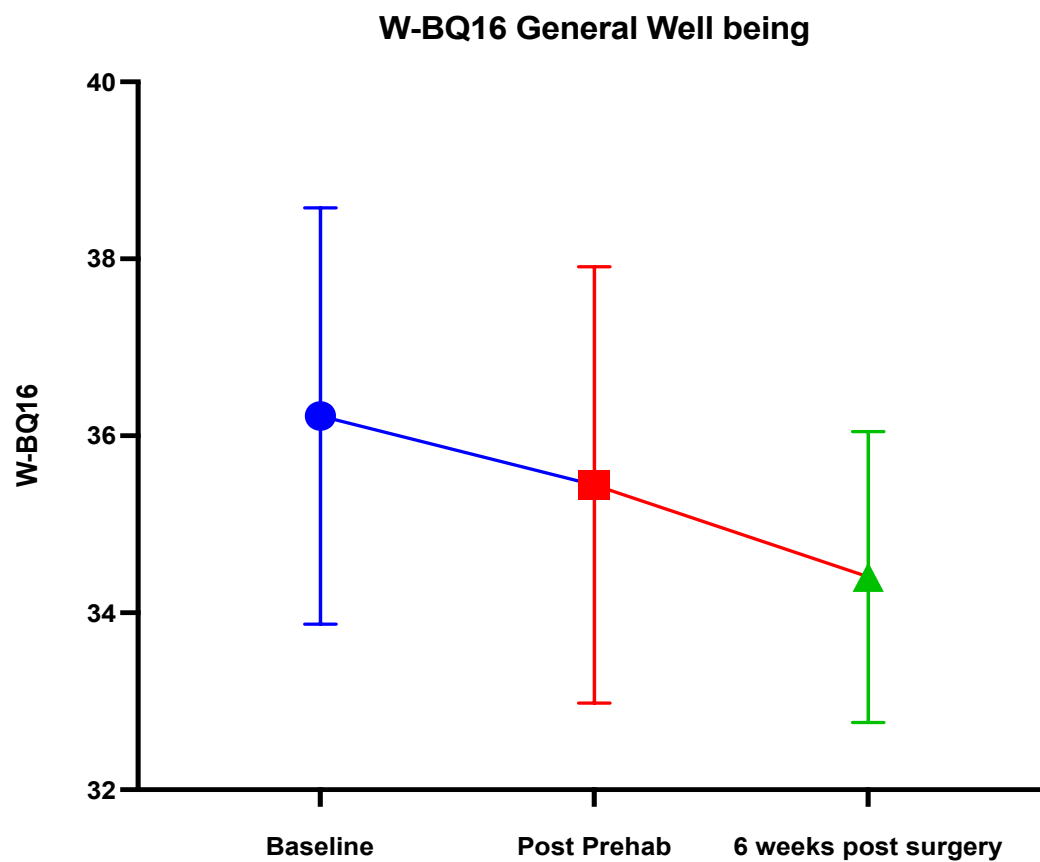


Figure 5.5 Change in W-BQ16 General Well-Being component

Descriptives

	Mean	SE	95% Confidence Interval		Median	SD
			Lower	Upper		
Baseline	36.2	1.144	33.9	38.6	37	5.94
Post Prehab	35.4	1.200	33.0	37.9	37	6.23
6 weeks post surgery	34.4	0.799	32.8	36.1	34	4.15

Note. The CI of the mean assumes sample means follow a t-distribution with N - 1 degrees of freedom

W-BQ16 Negative Well-Being Subset

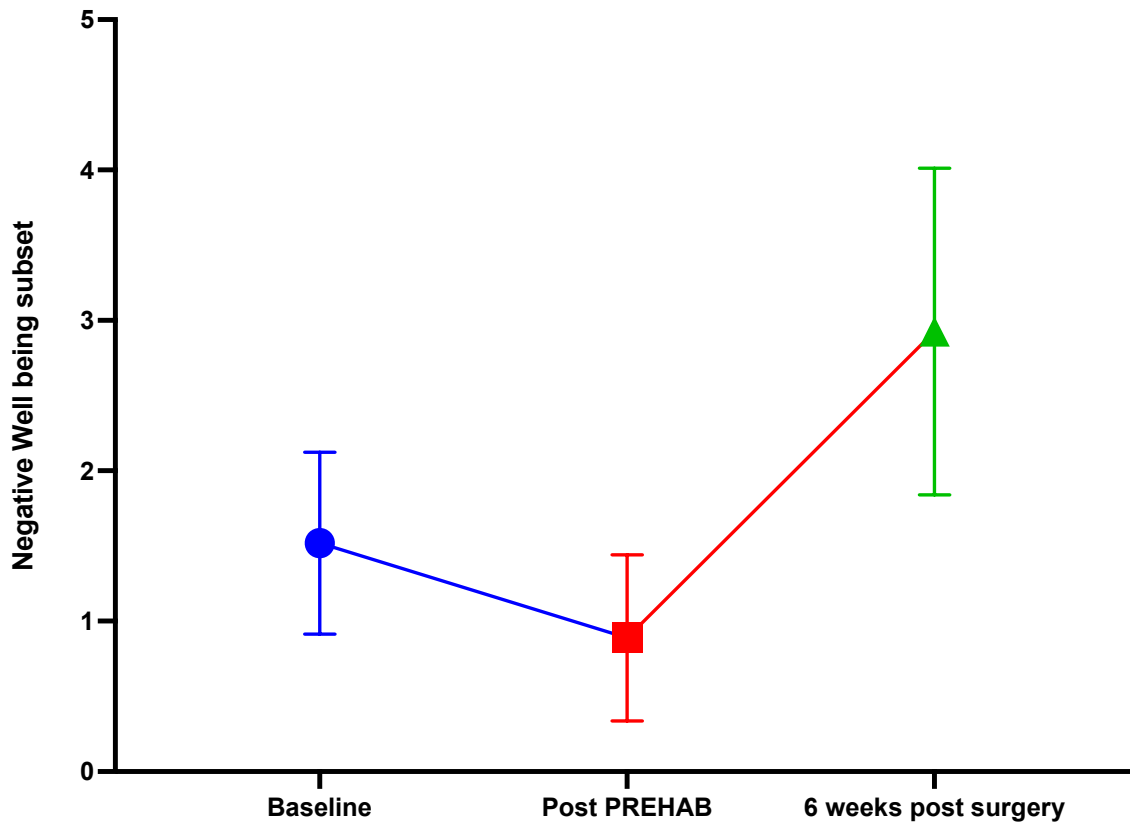


Figure 5.6 Change in Negative Well-Being subset of W-BQ16

Descriptives

	Mean	SE	95% Confidence Interval		SD
			Lower	Upper	
Baseline	1.519	0.294	0.914	2.12	1.53
Post Prehab	0.889	0.269	0.337	1.44	1.40
6 weeks post-surgery	2.926	0.528	1.840	4.01	2.74

Note. The CI of the mean assumes sample means follow a t-distribution with N - 1 degrees of freedom

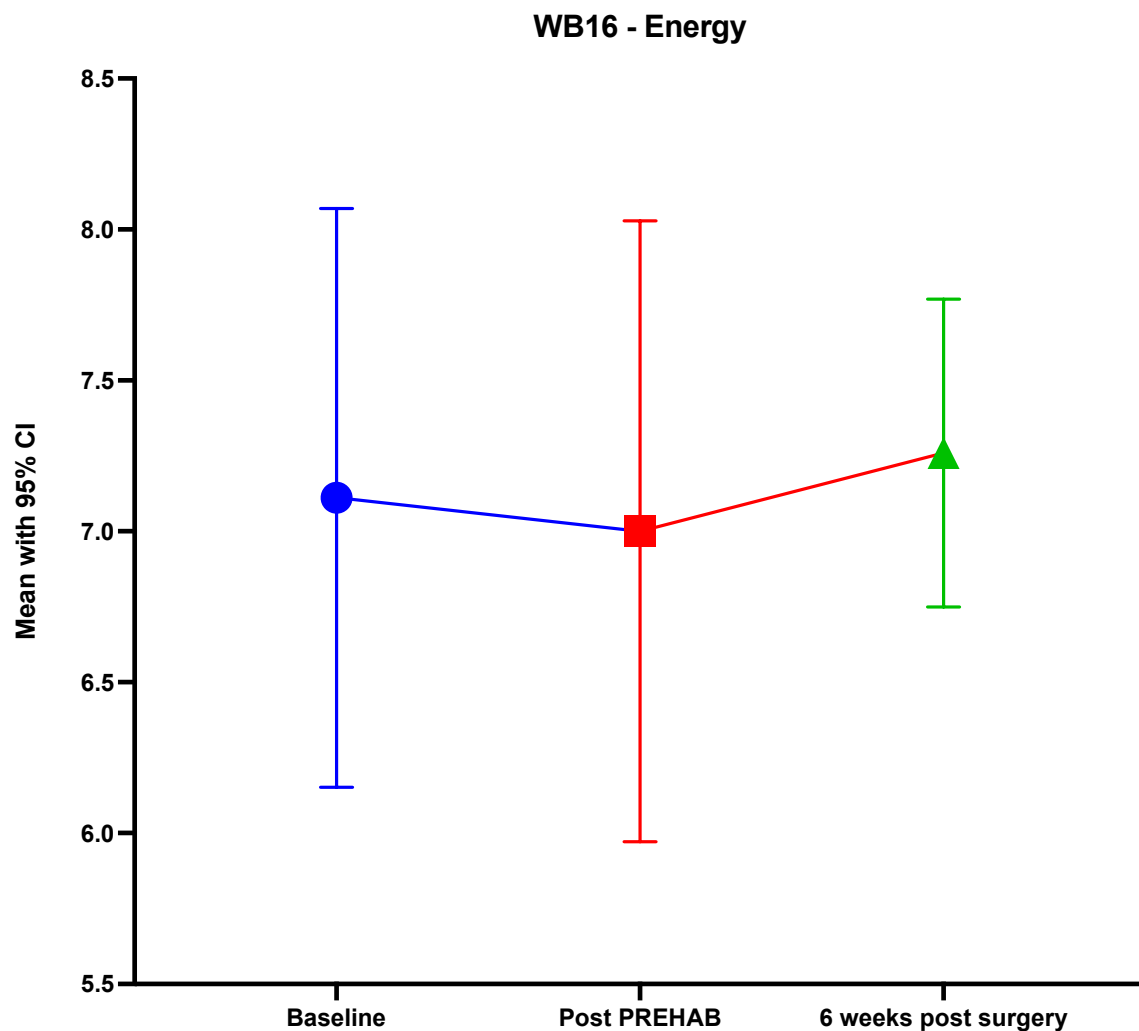


Figure 5.7 Change in Energy subset of W-BQ16

Descriptives

	Mean	SE	95% Confidence Interval		SD
			Lower	Upper	
Baseline	7.11	0.466	6.15	8.07	2.42
Post Prehab	7.00	0.501	5.97	8.03	2.60
6 weeks post-surgery	7.26	0.248	6.75	7.77	1.29

Note. The CI of the mean assumes sample means follow a t-distribution with N - 1 degrees of freedom

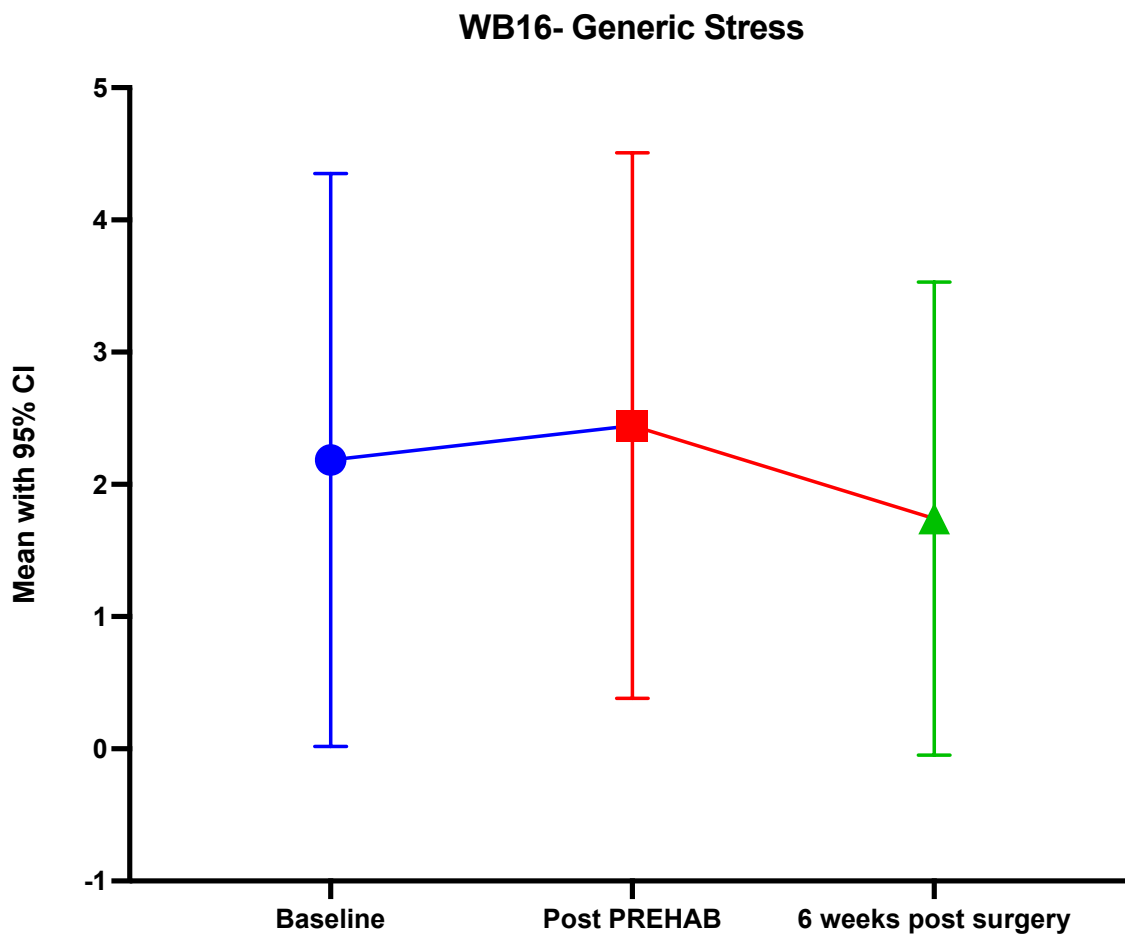


Figure 5.8 Change in Generic Stress subset of W-BQ16

Descriptives

	Mean	SE	95% Confidence Interval		SD
			Lower	Upper	
Baseline	2.19	0.417	1.33	3.04	2.17
Post Prehab	2.44	0.397	1.63	3.26	2.06
6 weeks post-surgery	1.74	0.344	1.03	2.45	1.79

Note. The CI of the mean assumes sample means follow a t-distribution with N - 1 degrees of freedom

Change in Disease related quality of life questionnaires (AneurysmTSQ, AneurysmSRQ, AneurysmDQol)

Disease related quality of life questionnaires were assessed on baseline, post prehabilitation, 6 weeks post-surgery and 3 months post-surgery. We noted that participants were not keen to fill of all the above questionnaires following surgery follow up intervals mostly due to questionnaire fatigue.

Aneurysm SRQ (Aneurysm Symptom Rating Questionnaire)

At baseline, 22 participants (73.3%) completed questionnaire while following prehabilitation, 19 participants (63.3%) did so.

The mean AneurysmSRQ score at baseline was 11.63 (95%CI 6.1 – 17.1). We noted marginal increase in mean score following prehabilitation (bothered more) however it did not reach statistical significance. Mean difference 0.38 (95%CI, -2.5 – 3.1, $p=0.9$). Figure 5-10, demonstrate mean AnuerysmSRQ with 95%CI.

AneurysmTSQ (Treatment Satisfaction Questionnaire)

At baseline , 21 participants (70%) successfully completed the questionnaire with similar percentage of participants complete AneurysmTSQ following prehabilitation. We noted significant improvement in treatment satisfaction following prehabilitation when compared to baseline. Mean difference 2.4 (95%CI 0.2 – 4.6, $p<0.05$). Figure 5-11 below demonstrate mean AneurysmTSQ with 95%CI.

AneurysmDQol (Dependant Quality Of Life)

At baseline , 19 participants completed AneursymDQol while only 12 participants (40%) completed it following prehabilitation. There was improvement in dependant quality of life scores recorded following prehabilitation however it did not reach statistical significance. Mean difference 0.4 (95%CI, -0.4 – 1.2, $p=0.3$). Figure 5-12 below demonstrate mean AnueysmDQol when assessed at baseline and post prehabilitation.

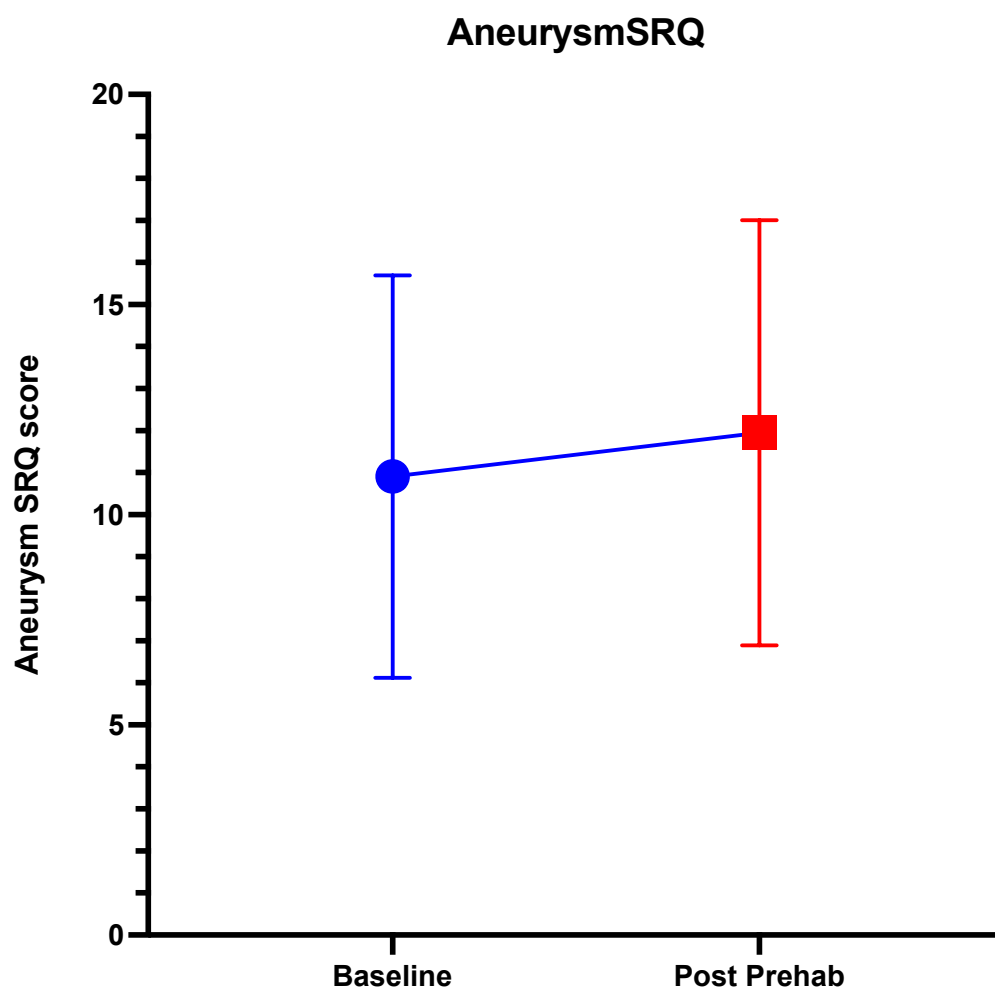


Figure 5.9 Change in Aneurysm SRQ score of PREHAB-AAA participants at baseline and after prehabilitation

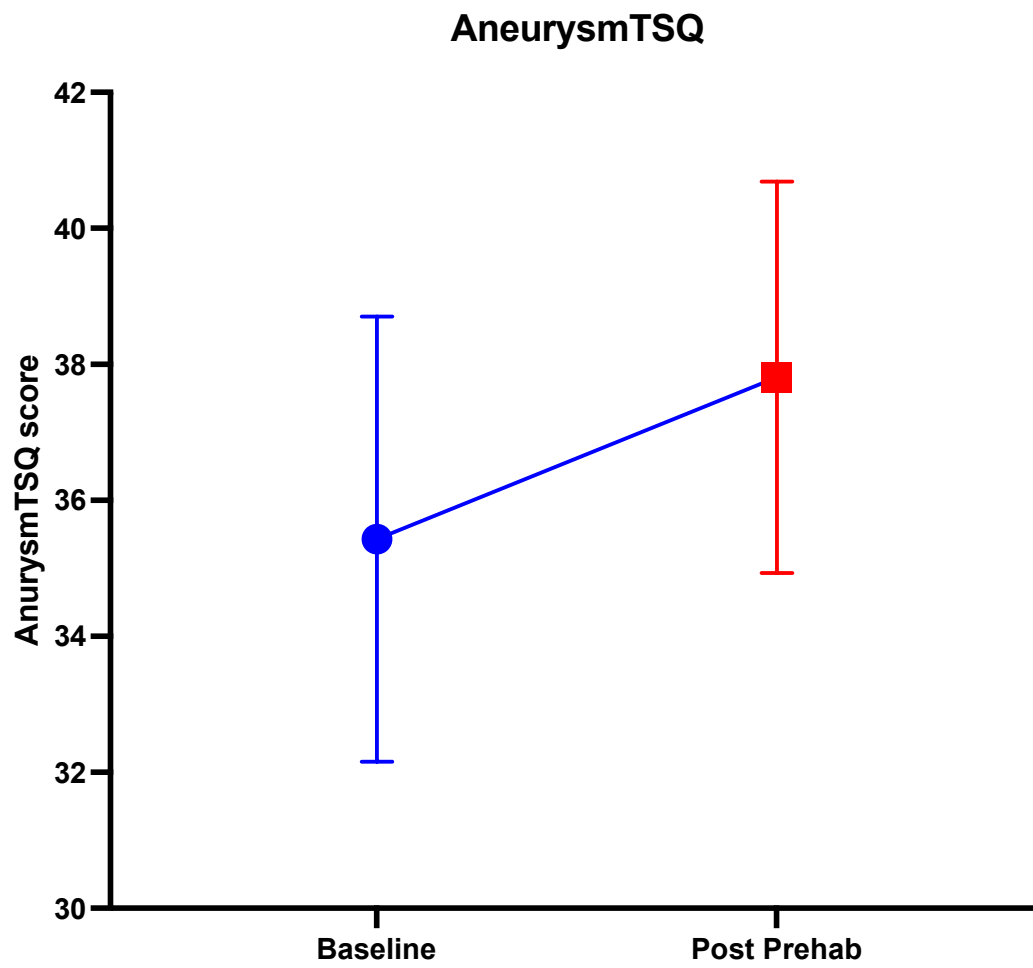


Figure 5.10 Change in AneurysmTSQ score in PREHAB-AAA at baseline and following prehabilitation.

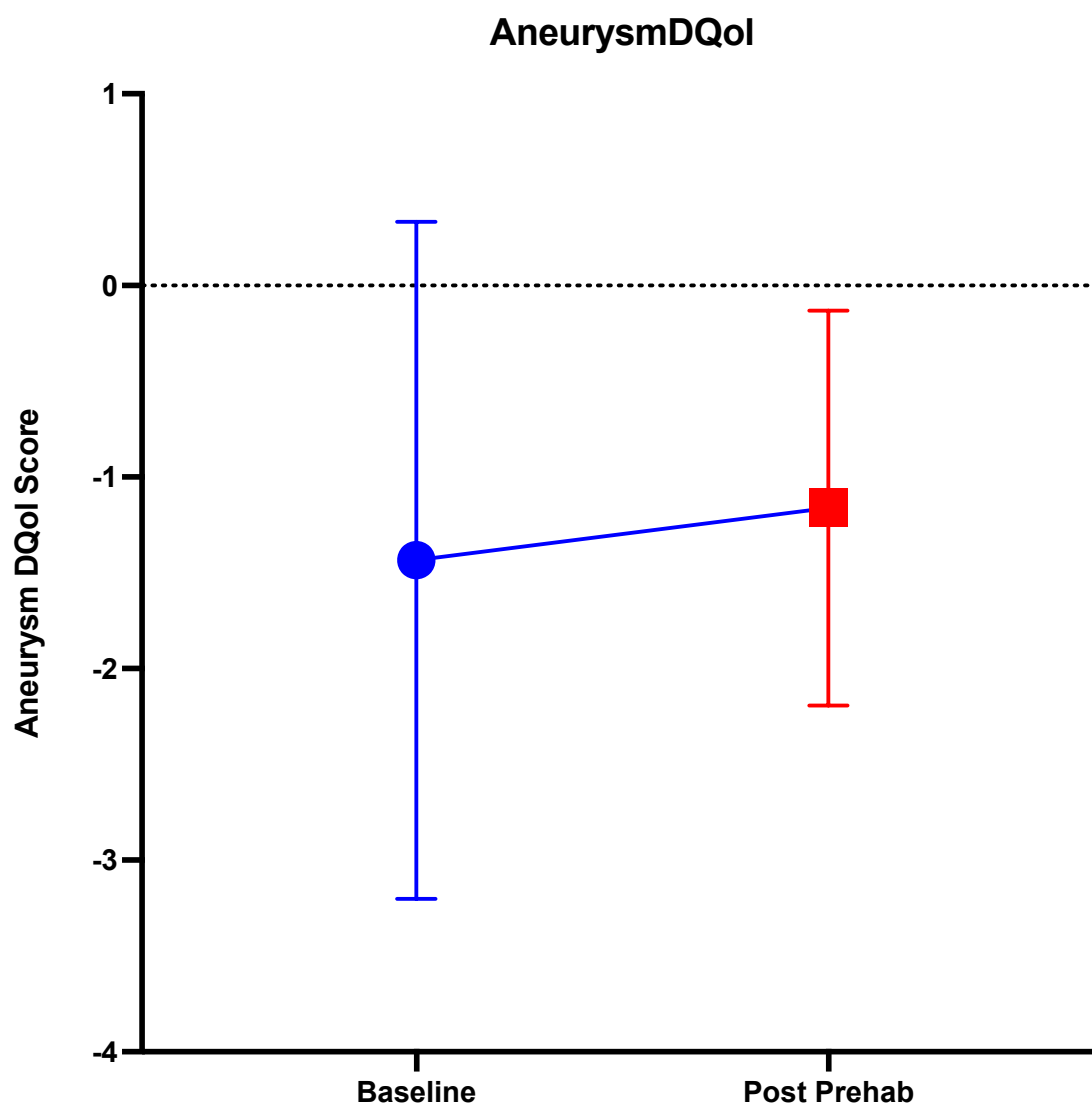


Figure 5.11 Change in AneurysmDQol score in PREHAB-AAA participants at baseline and following prehabilitation

Postoperative outcomes

Length of stay, Critical care use and discharge destination

17 participants who completed the 6-week prehabilitation program underwent open AAA repair with mean total hospital stay of 17 days. While 13 participants underwent EVAR with average hospital stay of 1.8 days.

On analysing critical care use, Open repair participants had an average of 7.4 days while EVAR group needed 0.6 days on average of critical care stay. 61.5% (n= 8) who underwent EVAR needed critical care bed postoperatively.

Majority of patients (83.3%, n= 25) were discharged to their residence. Two participants were discharged to a rehabilitation facility while two participants died in hospital. One participant was readmitted within 30 days.

Post operative complications.

58.8% of participants who received Open repair had a complication throughout their hospital stay with respiratory complication being the most common (41.1%, n = 7). The second most common complication was renal (29.4%, n = 5). Two patients needed return to theatres due to limb ischaemia. None of the patients had intraoperative death.

Two patients died during their hospital stay. Death recorded due to multiorgan failure.

Discussion

This study has successfully assessed the feasibility and the acceptability of a remote personalised prehabilitation programme for patients scheduled for elective AAA repair. Recruitment rate was 31.1% of all participants who were screened. However, 43% of patients who met the inclusion criteria were recruited with dropout rate of 26.8%.

A key finding of the research involves documenting the factors that deterred individuals from participating, which will prove valuable in shaping the design of future trials. A significant number of patients who declined participation believed that undergoing endovascular repair for their AAA did not necessitate prehabilitation. This discovery raises doubts about the practicality of providing prehabilitation for patients awaiting EVAR. Frequently, individuals awaiting EVAR tend to be older and experience a significant degree of frailty in comparison to those undergoing open repair. This helps to explain their lack of motivation to engage in prehabilitation. It is worth noting that our observation revealed that 41% of participants who completed a 6-week prehabilitation programme underwent EVAR, which is lower to what the national practise. One might reasonably question the potential advantages of providing prehabilitation to this particular group, considering the limited impact it has on improving outcomes for patients undergoing EVAR in terms of complication rates and length of hospital stay. Nevertheless, there is a debate regarding the provision of such intervention to patients who have undergone EVAR. This intervention could potentially stimulate a desire to maintain an active lifestyle post-surgery, leading to potential benefits such as improved overall survival rates, reduced risk of cardiovascular events, and decreased dependency.

We noted that another reason for not participating in this pilot study, is fear of missing surgery despite reassurance that this pilot study will not interfere with the ongoing plan provided by the surgical team. None of the participants dropped out of the 6-week prehabilitation programme due to surgery. This should be considered when designing large trial and emphasis should be made that proposed intervention will not affect surgery date. We believe this was a crucial point in the design of this trial making it a more acceptable intervention and perhaps the percentage of participation decline would have been higher if

this prehabilitation programme interfered with surgery date. It is crucial to acknowledge that the commencement of this pilot study coincided with the COVID-19 restrictions, which could potentially account for the limited recruitment of eligible patients. Consequently, the recruitment rates observed may not accurately reflect what would be expected in larger-scale studies. Nevertheless, a recent trial[201] investigating the effect of prehabilitation in AAA under surveillance, demonstrated a recruitment rate of 38.3% which is comparable to the recruitment rate observed in this study.

This pilot study has shown that patients who agreed to participate have achieved satisfactory adherence rates, with an attrition rate of 22.3%. There is a debate surrounding the participants of this study, suggesting that they are individuals who are highly motivated and lack physical constraints when it comes to exercising or making lifestyle changes. Participants provided explanations for their inability to maintain adherence rates, indicating their active involvement in the process. However, external circumstances hindered their ability to continue adhering to the programme, which is a common occurrence among elderly patients.

This pilot study has also successfully demonstrated the acceptability of such intervention which was reflected with positive results from PACES questionnaire. Almost all participants found the programme enjoyable and useful. This was also demonstrated in the cohort with low adherence rates, which may demonstrate the reason behind not exercising is motivational rather than fatigue. Acceptability of prehabilitation programmes is crucial in influencing the uptake rates of such programmes and ultimately affecting its successfulness. Remote prehabilitation may possibly hold better acceptability when compared to in hospital prehabilitation programmes as it allows participants to exercise anytime during the day without being restricted to prespecified appointments. Another advantage for the use of remote prehabilitation, is the reduction of transport financial commitments that can burden AAA patients which is one of the main barriers in achieving adequate adherence rates. A recent systematic review investigating the barriers and facilitators to participation in prehabilitation in people undergoing major surgery has identified “Physical opportunity” as a main component affecting the success of a prehabilitation programme[264]. This component includes “limited financial capacity and “ transportation and parking limitations”

as one of the main barriers that can be facilitated using a tailored home based prehabilitation.

The study has demonstrated that there is significant improvement in distance covered during 6MWT with an average increase of 40.5 metres from baseline which indicate significant improvement in functional capacity of participants. This demonstrates the potential efficacy of this prehabilitation programme. The significance of this finding on post operative outcomes is difficult to interpret as this is a single-arm exploratory study. 6MWT is a reliable, cheap and simple measure of functional capacity and easy to interpret. A recent study[265] investigating 574 patients' disability-free survival after major surgery, has demonstrated that the use of 6MWT test as risk assessment tool is comparable with cardiopulmonary exercise testing (CPET) for all predictive assessments. As a result, theoretically, this may have an impact in reducing all-cause mortality which has impact on improving outcomes following AAA repair.

We observed notable improvement in physical aspect of health-related quality of life scores at the end of the prehabilitation program when compared to baseline. However, this finding was not observed in the psychological component. This could be explained possibly due to the overall feeling of stress and anxiety towards surgery itself as the majority of participants reported feeling of enjoyment and feeling of achievement during prehabilitation. This possibly indicate that "psychological support" component of this prehabilitation was lacking and requires improvement. Preoperative psychological optimisation is increasingly being recognised in multimodal prehabilitation programmes, emphasising the importance of reducing anxiety/stress before surgery and possibly could affect adherence to such programmes.

Participants also reported questionnaires "fatigue" as they found them repetitive, exhaustive and sometimes irrelevant to their disease or to the prehabilitation programme. This was evident in the disease-specific questionnaires, where significant number of participants did not respond to questionnaires following surgery which should be considered when designing a future trial on a broader scale. Albeit there has been improvement in all of its domains when compared to baseline scores.

Overall, the findings of this exploratory study have shown promising results in the feasibility of applying remote prehabilitation for patients awaiting AAA surgery. The model of weekly tailoring exercise prescription was highly rated by participants and was described as “motivational”. Other aspect these weekly follow up calls provided a reassurance regarding issues surrounding the surgery itself. However, integrating such a prehabilitation programme into normal practise require cost-effectiveness analysis.

Conclusion

Remote 6-week prehabilitation programme for patients awaiting AAA surgery is feasible with acceptable recruitment rates. It also improves the functional capacity of such high-risk patients associated with improvement in health-related and disease specific quality of life measures. Participant feedback shows that it is reasonable to implement such a programme in the regular practice of AAA surgery. However, this pilot study has demonstrated that open surgery patients are more accepting to the idea of prehabilitation. As a result, this justifies a large scale, national randomised controlled study to assess the effectiveness of remote, tailored prehabilitation programme in improving AAA outcomes.

Chapter 6 : The impact of adherence to outcomes measured in PREHAB-AAA study. Ancillary analysis.

The main objective of this chapter is to demonstrate the difference in outcomes between adherent and non-adherent participants on outcomes measured.

Introduction

AAA are associated with a high risk of mortality in the event of rupture, accounting for around 2% of all deaths in men aged 65 and over[248] . The primary focus in improving survival in patients with AAA has been centred on the timing of surgery to prevent the consequences of rupture.

Intervention for AAA can be performed by either open or endovascular repair (EVAR) and is typically reserved for AAA of at least 5.5cm in diameter. In the UK, approximately 2800 surgical repairs are performed annually[249]. However, elective surgery carries significant risk, with thirty-day mortality rates estimated at around 3.1 % and 0.5% in patients undergoing open repair and EVAR respectively[249]. Therefore, enhancing perioperative and postoperative outcomes in individuals undergoing abdominal aortic aneurysm (AAA) repair, a significant proportion of whom exhibit comorbidities and consequently face an increased risk of mortality, represents a crucial imperative.

The existing body of research indicates that a notable proportion, ranging from 25% to 40%, of unfavourable outcomes subsequent to surgical procedures can be attributed to the existence of frailty[250,251]. Frailty, as defined within the medical context, represents a biological syndrome characterised by a diminished capacity for physiological reserve and reduced resistance to various stressors[148]. Irrespective of demographic factors such as age and gender, as well as other potential variables that may influence the results, it has been observed that individuals exhibiting frailty demonstrate notably increased rates of postoperative morbidity, mortality, and utilisation of healthcare resources. Within the realm of abdominal aortic aneurysms (AAA), extensive research has demonstrated a correlation between higher scores on the modified frailty index (mFI) and increased rates of mortality and morbidity in individuals undergoing AAA repair procedures.

Cardiopulmonary exercise testing (CPET) is one method used to predict adverse outcome across a range of high-risk surgical procedures[252][253]. Previous research has also revealed the adverse impact of poor fitness on the outcome of patients undergoing AAA repair, with several small-scale studies further demonstrating the beneficial impact of improved physical activity levels on post-operative outcomes[254,255].

The evaluation and pre-operative optimisation of comorbidities and fitness levels is increasingly recognised as an important element of the pre-operative pathway. Prehabilitation programmes aim to reduce pre- and post-operative complications, and typically reflect a multi-disciplinary, multicomponent approach, incorporating structured exercise sessions, disease education and psychological preparation.

A recent systematic review looking at prehabilitation programmes before major abdominal surgery found that such programmes reduced overall morbidity following surgery[256]. Another systematic review, which focused solely on the role of preoperative exercise programmes in patients with AAA, found that patients who underwent EVAR had a shorter stay in hospital when a prehabilitation programme was undertaken[257]. Moreover, overall compliance with the exercise programmes was high, suggesting that such programmes are acceptable in this patient population. However, recent reviews on prehabilitation programmes have not reached a consensus on efficacy, describing the quality of the majority of included studies as poor.

Indeed, the significant heterogeneity in trials of this type (in terms of sample size, patient population, duration of prehabilitation programme and intensity of exercise) makes the results difficult to interpret. In recognition of this paucity of data, current NICE guidance recommends that further research be conducted to examine the clinical and cost-effectiveness of prehabilitation programmes, including preoperative exercise programmes, for improving outcomes of people who are having repair of an AAA [213].

However, implementing face-to-face prehabilitation for patients with AAA may prove challenging in the post COVID-19 era, with the increased likelihood of patients (the majority of whom have multiple comorbidities) opting not to attend hospital or community settings unless absolutely necessary (e.g. for a surgical procedure only). Moreover, with many resources diverted elsewhere, there will inevitably be a large backlog of patients on the

waiting list for AAA repair, thus creating a window of opportunity to address modifiable factors affecting fitness and surgery.

Telerehabilitation has gained increased recognition and is defined as the provision of rehabilitation services at a distance, using information and communication technologies. Indeed, previous research has shown that telerehabilitation programmes are feasible in a home-care setting[258]. Furthermore, there is increasing evidence to suggest that clinical outcomes in telerehabilitation programmes are similar to other, more traditional face-to-face interventions. One study demonstrated the potential of a telerehabilitation programme to improve functional ability and reduce hospital length of stay for patients undergoing cardiac surgery[259] whilst another found that a telerehabilitation programme was as effective, and more cost-effective, than convention physiotherapy in patients undergoing a total knee arthroplasty (TKA)[260]. Such telerehabilitation programmes have the possibility to be more cost-effective than traditional face-to-face programmes, with multiple studies demonstrating a significant reduction in health care expenditure using telerehabilitation compared to similar interventions[261].

The PREHAB-AAA study is a single-arm proof of concept study examined the feasibility of introducing a 6-week remote prehabilitation programme for patients scheduled for AAA repair. We here present the impact of adherence on outcomes measured in PRHEAB – AAA.

Methods

PREHAB – AAA study design

This was a prospective single-arm pilot trial based at 3 large tertiary vascular centres between September 2021 – July 2023. Detailed methodology to prehabilitation programme has been explained in the previous chapter.

For the purpose of this ancillary analysis, we performed comparative analysis between adherent and non-adherent participants. Baseline demographics were described using independent samples t-test for any difference in continuous variables after performing Levene's test of equal variance to determine the appropriate calculation. Dichotomous variables were compared using X2 test or Fisher's exact test, if >20% of frequencies were <5. All significance t-test was two-tailed at a 5% level. All changes from baseline and comparisons between the groups reported as mean with associated confidence intervals (95% CI) and p values where appropriate. These analyses were undertaken in SPSS and a 5 % significance level was assumed. All graphs, figures and tables were created using GraphPad Prism.

Results

31 participants were included in the final analysis. 7 participants were deemed not adherent according to the threshold set previously in the PREHAB-AAA protocol.

Difference in 6-minute walk test

A total of 24 participants performed 6MWT at baseline and after finishing the prehabilitation programme of which 18 (75%) participants were deemed adherent. The mean baseline distance covered in the adherent group was 406.4 (95%CI 344-469) metres compared to 337.9 (95%CI 247-428) metres in the non-adherent group which was not significant ($p = 0.2$).

Following the prehabilitation programme, the adherent group significantly improved in their distance covered (48.7m, 95%CI 34.2 – 63.1) when compared to the non-adherent group (15.8m, 95%CI -3 – 34.7) ($p= 0.005$). Figure 6.1 below demonstrates the mean difference between two groups in 6MWT.

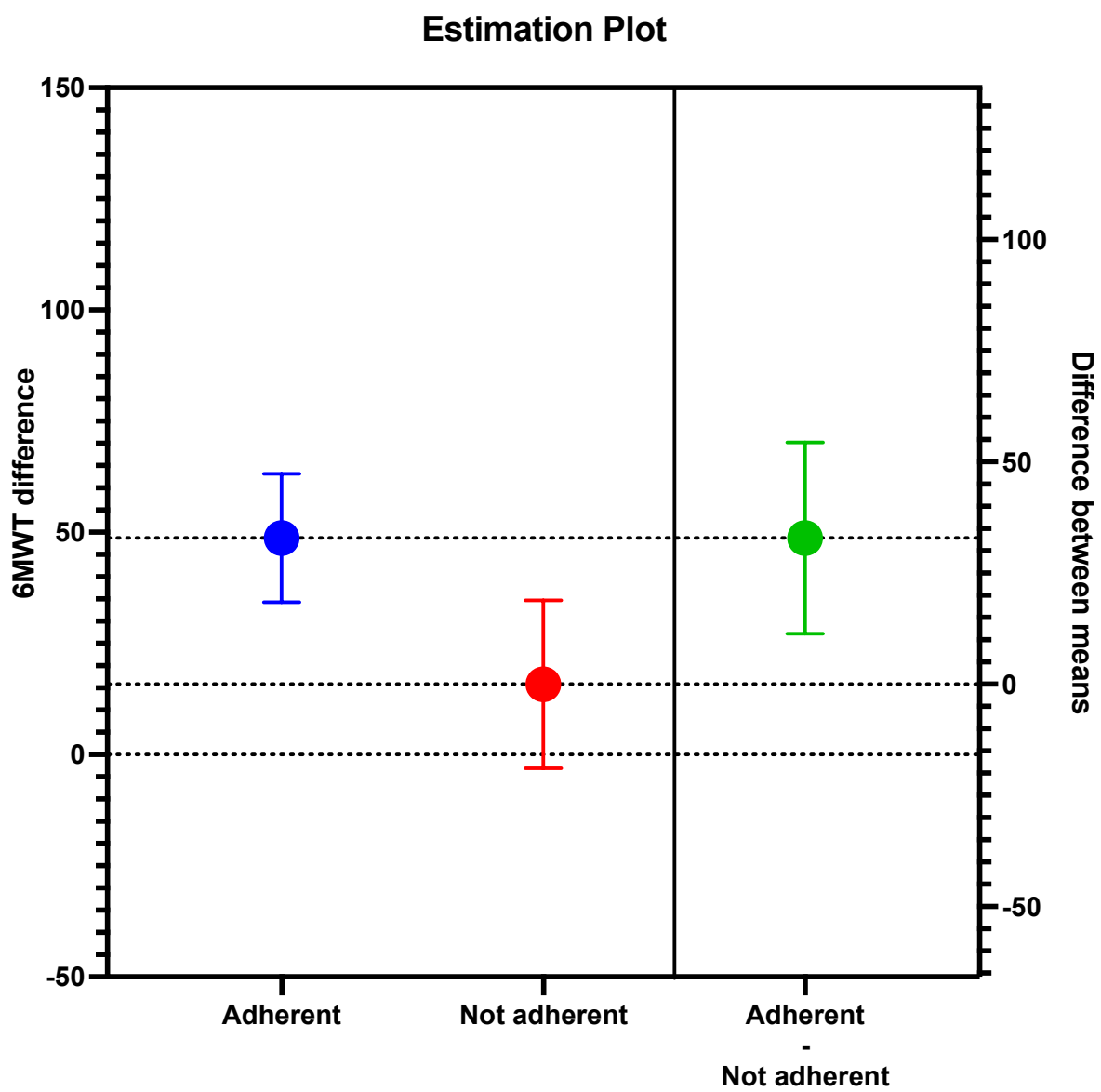


Figure 6.1 Mean difference in 6MWT distance stratified according to adherence.

Change in Well-Being questionnaire (W-BQ16)

A total of 26 participants fully completed the W-BQ16 questionnaires at baseline and following the prehabilitation programme of which 20 (76.9%) participants were deemed adherent.

There was no difference in W-BQ16 scores recorded at baseline between the adherent or non-adherent group (35.7 vs 34.6). As we mentioned before there was a decline in W-BQ16 in the whole cohort, however the non-adherent group reported greater decline when compared to the adherent group (-2.7 vs -0.4) without reaching statistical significance ($p = 0.43$). Figure 6.2 demonstrates the mean difference between the two groups.

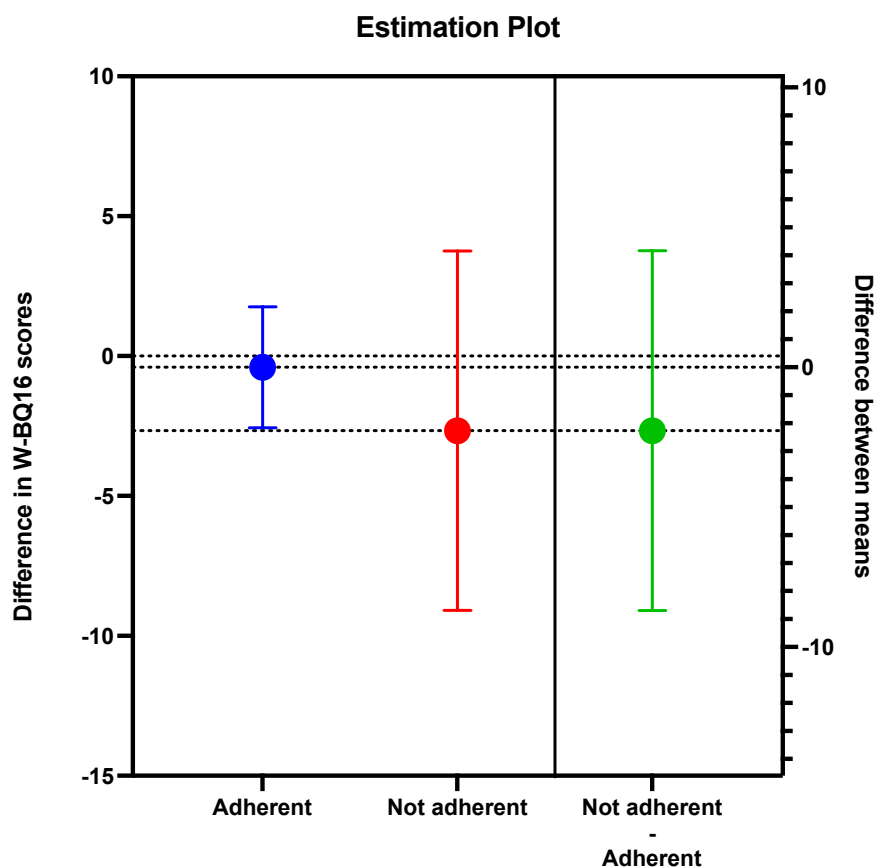


Figure 6.2 Mean difference in W-BQ16 scores stratified according to adherence.

Change in Disease related quality of life questionnaires (AneurysmTSQ, AneurysmSRQ, AneurysmDQol)

There was no difference between the baseline score of disease related quality of life questionnaires between adherent and non-adherent groups. Following finishing the prehabilitation programme, there was no significance difference between both groups across the three questionnaires. Figure 6.3 below demonstrate the Aneurysm TSQ, AneurysmSRQ and AneurysmDQol scores between adherent and non-adherent groups.

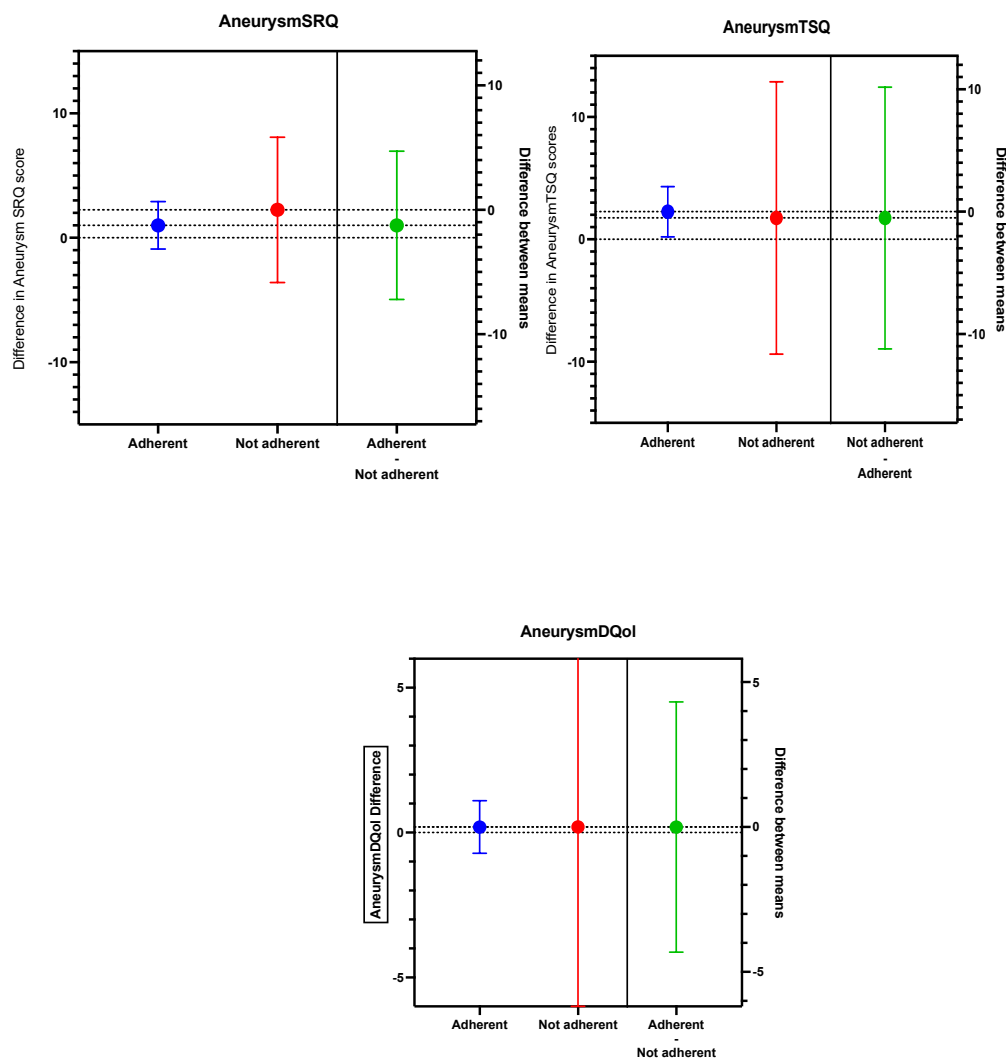


Figure 6.3 Difference in AneurysmSRQ, AneurysmTSQ and AneurysmDQol scores of PREHAB-AAA participants stratified according to adherence.

Difference in post operative outcomes

Open repair cohort

A total of 17 participants underwent open repair. 12 (71%) participants were deemed adherent. Although the adherent group has less hospital stay when compared to non-adherent group, it did not reach statistical significance (16.5 days vs 19.6 days). Figure 6.4 demonstrates the mean hospital stay with 95%CI across both groups.

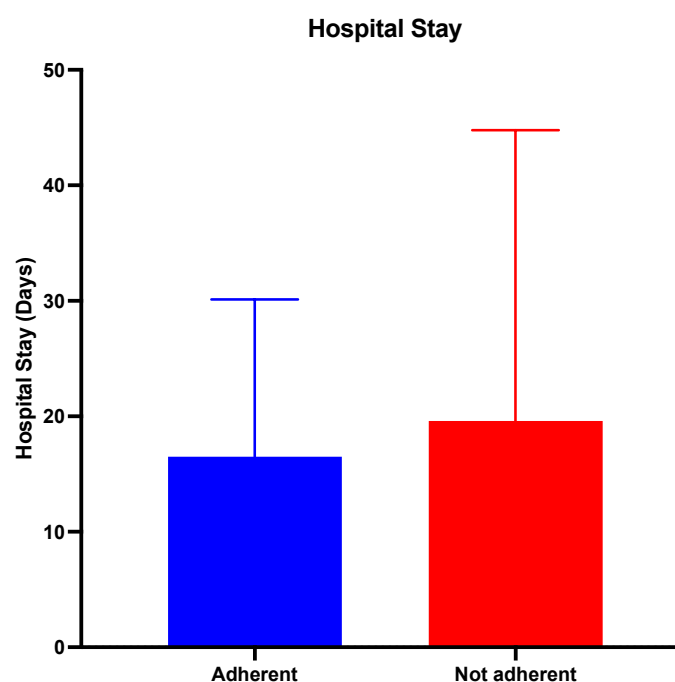


Figure 6.4 Hospital stay of PREHAB-AAA participants who underwent Open repair stratified according to adherence.

This was similarly seen in total ITU stay. The mean ITU stay in the adherent group was 6.1 days, compared to 9.8 days in the non-adherent group ($p=0.6$).

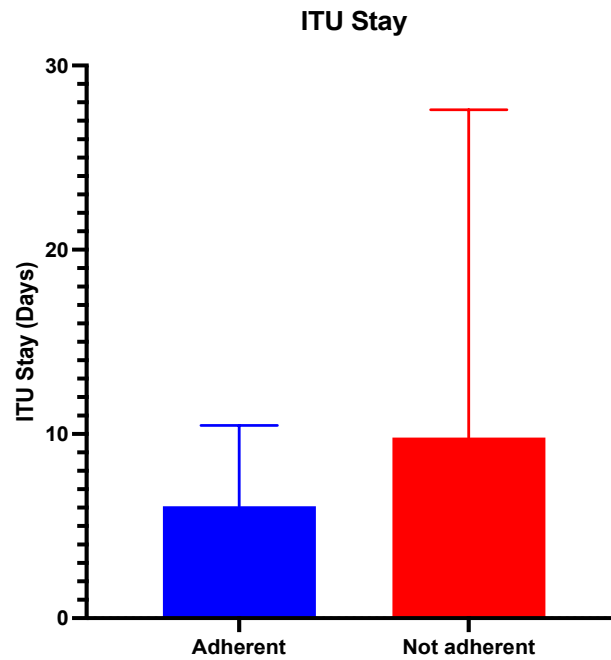


Figure 6.5 Critical care stay of PREHAB-AAA participants who underwent Open repair stratified according to adherence

Regarding incidence of complications , there was no difference between both adherence group (58.3% vs 60%, $p=0.94$).

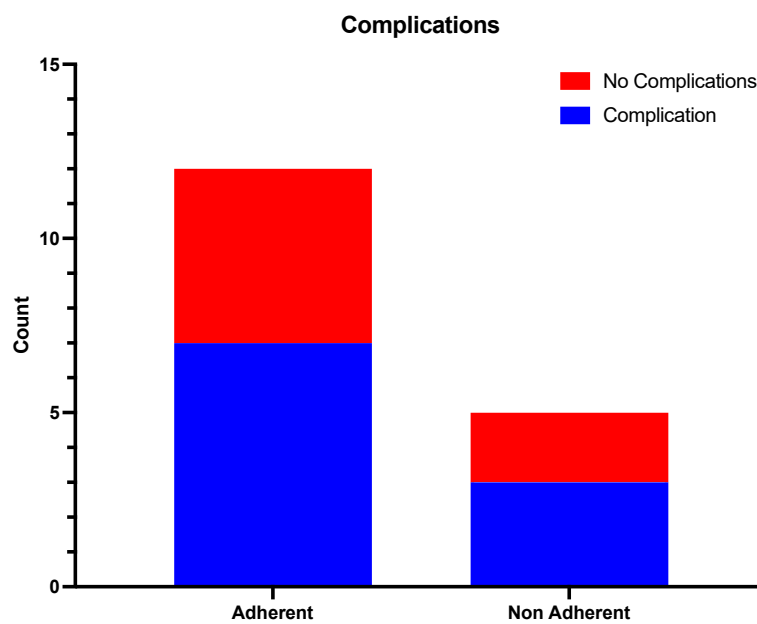


Figure 6.6 Incidence of complications in PREHAB-AAA participants who underwent Open repair stratified according to adherence

EVAR Cohort

A total of 14 participants underwent EVAR repair for which 8 participants (57%) were adherent. There was no difference in mean days of total hospital stay between adherent and non-adherent group (1.8 vs 2.0 , $p=0.76$). The critical care usage in EVAR patients was low and there was no difference between both groups. There were no recorded complications in the EVAR cohort.

Discussion

The PREHAB-AAA is a single arm study, and the purpose of this ancillary analysis is to explore the impact of adherence of outcome measures. The results demonstrated in this ancillary analysis should be interpreted with caution due to the small number of participants involved in the comparative groups which makes it susceptible to type 2 error , missing the benefit effect of prehabilitation on outcomes. However, it does demonstrate that there may be an improvement in the functional capacity of patients who were adherent to the 6 – week prehabilitation group. An improvement was observed in the non-adherent group, as they have exercised in a lesser extent but not sufficient to be deemed adherent.

Although there was a tangible improvement in the functional capacity of the adherent group, this was not reflected in reducing total hospital significantly nor in reducing incidence of complications in participants who underwent open repair. This can be explained by the small sample size and perhaps if this prehabilitation programme explored in a large scale, significant reduction in ITU and total hospital stay may be observed which will have enormous effect in improving outcomes of AAA.

In the other hand, as mentioned in the previous chapter, if the purpose of a prehabilitation programme is to reduced hospital stay and reduce complications, implementing such programme in EVAR patients should be questioned. As demonstrated, the incidence of a complication following EVAR was not existent. Similarly, the hospital stay observed in the EVAR group in this study was between 1-2 days and margin for improvement is small. Also,

EVAR patients were less likely to adhere to this prehabilitation programme which also question the cost-effectiveness of implementing such programme. However, this pilot study did not examine the long-term impact of prehabilitation, something EVAR frail patients may benefit in improving their overall survival.

Conclusion

The impact of adherence in PREHAB-AAA study showed better functional capacity demonstrated by significant improvement in 6MWT distance covered by the adherent group. Adherent participants who received open repair demonstrated reduction in ITU and total hospital stay but it did not reach statistical significance. Due to the small size of the study, the results should be interpreted with caution. However, the results justify exploring PREHAB-AAA programme in large, randomised study.

Chapter 7 : Data recorded from activity monitor (Actigraph™) for participants enrolled in PREHAB-AAA pilot study. A case series

Introduction

Wearable devices provide a non-invasive approach to gather patient-specific data through the measurement and storage of clinically relevant biomarkers. The emergence and utilisation of wearable technology in the healthcare sector have created substantial prospects for ongoing health surveillance, prompt disease identification, and tailored care delivery. The recent COVID-19 epidemic acted as a crucial alert for healthcare providers, underscoring the fragility of healthcare systems and catalysing a wave of innovative solutions to tackle the challenges associated with an ageing population.

The application of wearables in vascular surgery has seen a notable rise, particularly in tracking the activities of patients suffering from peripheral vascular disease. The initial approach for managing patients with claudication involves supervised exercise therapy, as regular mobility for individuals with peripheral vascular disease is essential in mitigating disease progression. Nonetheless, only a limited number of facilities within the NHS offer this service, primarily due to constraints in infrastructure and staffing. Consequently, wearable devices are increasingly utilised to track and customise exercise therapy according to patients' preferences, which should logically enhance adherence. Nevertheless, wearables can provide accurate data on whether patients are improving in their distance or not adhering to the exercise prescription at all.

PREHAB-AAA is a pilot study assessing the feasibility of remote prehabilitation for patients awaiting AAA repair. To ensure that the exercise prescription provided to PREHAB-AAA participants meets the required intensity and to verify adherence, we supplied random group of participants with activity monitors. We present the data collected by Actigraph™ activity monitor and correlate it with the diaries reported by participants.

Methods

Wearable device – Actigraph™ (wGT3-BT)

The wGT3X-BT is a Actigraph's flagship activity monitor, used by researchers around the world to capture and record continuous, high resolution physical activity and sleep/wake information. The device is body worn and intended for use in applications where quantifiable measurement and storage of physical movement is desired.

The device activity monitors contain a 3-axis MEMS accelerometer with a dynamic range of +/- 8 G. Acceleration data are sampled by a 12-bit analogue to digital converter at user specified rates ranging from 30Hz to 100Hz and stored in a raw, non-filtered/accumulated format in the units of gravity(G's). Data are stored directly into a non-volatile flash memory. The advantage of using this device specifically in monitoring physical activity is the long battery life which can actively record physical activity up to 27 days in single charge. This specification was crucial as we wanted to minimise the burden of regularly charging the battery in a population such as AAA patients, who may find this not tolerable.

ActiGraph™ is one of the most common physical activity monitoring used in research for various populations[266,267]. A recent systematic review[268] examined the criterion validity of ActiGraph™ in older adults which demonstrated acceptable validity.

The research team successfully acquired five activity monitors despite the constraints of limited resources. According to the study protocol, the use of the activity monitor was optional, and participants had the freedom to discontinue wearing the monitor at any point during the study. Participants have been asked to wear the device for one week prior to commencing the prehabilitation programme. This will help establish a baseline of their activity levels, allowing us to measure the impact of the programme on their daily activities.

Results

A total of 9 participants agreed to wear ActiGraph™ wearable. We herein present each participant data provided from the activity monitor.

Case 1:

This participant was a 67-year-old scheduled for open AAA repair. According to the participant reported diary, the participant was adherent and was reporting exercise at least 5 days a week for 6 weeks, all being in moderate intensity as per RPE scale provided. The data for which the device started recording was from 17/10/2022 – 09/01/2023. The participant stopped exercising around surgery time. Participant baseline 6MWT was 310 metres. During the control week, the device recorder a total of 230 minutes of moderate intensity exercise equating to 3.9% of device wear time. During the first week of prehabilitation, this participant exercised a total of 1289 minutes in moderate intensity, equating to 13% of device wear time. The participant continued to exercise with noticeable increase in total number of minutes in the following weeks until surgery date. Participant 6MWT increase to 410m (from 310m). Figure 7.1 below demonstrates the change in minutes exercise throughout the prehabilitation programme.

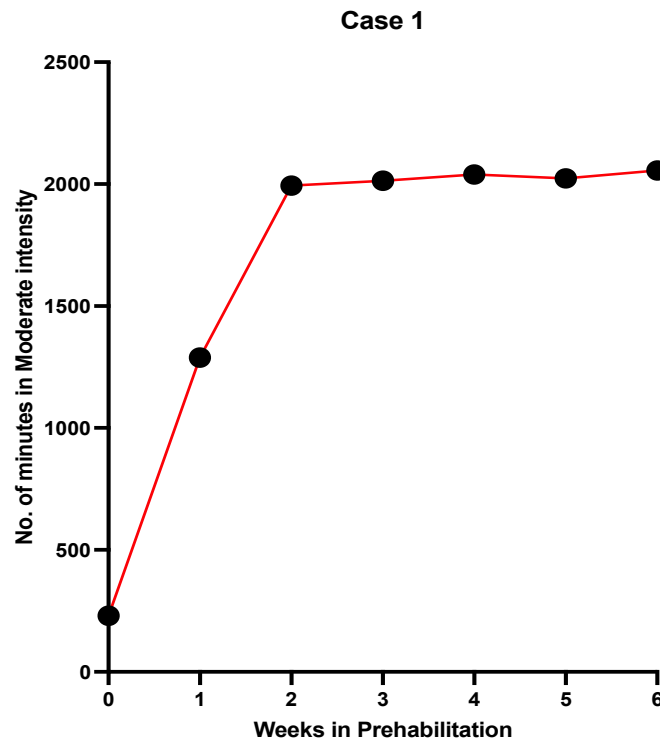


Figure 7.1 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 1

Case 2:

This participant was an 84-year-old male with 6.5cm AAA scheduled for open AAA repair. His baseline 6MWT was 390 meters. According to participant exercise diary, he was exercising 3 days a week which then increased to 5 days a week as tolerated. He did report moderate to vigorous intensity as per RPE scale. During the weekly follow up, we tailored his exercises to reduce its intensity to make more tolerable. During the control week, the device recorded a total of 93 minutes of moderate intensity exercise equating to 1.5% of device wear time.

During the first week of his prehabilitation, participant exercised a total of 924 minutes equating to 11.6% with noticeable reduction in his sedentary time. In the second week, participant reported fatigue, as a result the exercise regime was tailored to make sure it lies within moderate intensity. Patient completed the 6-week prehabilitation with adequate adherence. His 6MWT has increased significantly to 460 meters. Figure 7.2 demonstrates the total number of minutes spent in moderate intensity throughout the prehabilitation programme.

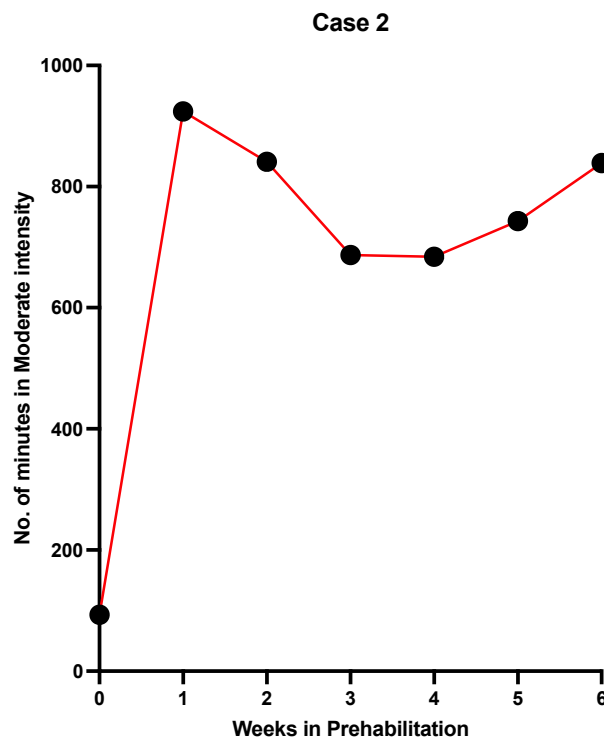


Figure 7.2 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 2

Case 3:

This participant was a 62-year-old male, actively working as a handyman scheduled for EVAR repair. During his work up for AAA repair, his echocardiogram demonstrated severe aortic valve stenosis and consequently underwent aortic valve repair before his AAA repair. Due to the uncertainty of the safety of conducting a remote prehabilitation programme with patients suffering from severe aortic stenosis, decision was made to start prehabilitation following the cardiac surgery. The prehabilitation programme was offered to participant while he is undergoing cardiac rehabilitation, which he did not attend regularly. The prehabilitation programme was prescribed to the participant after he was deemed fit for exercise following his cardiac surgery.

Unfortunately, patient did not document his exercise session in the provided diary, however, he did confirm doing the exercises with appropriate moderate intensity verbally during the weekly follow up calls. When he was provided the activity monitor, he did

confirm wearing the device in the first couple of weeks but then he did not carry on wearing the activity monitor which made it difficult to assess his adherence to the prehabilitation programme. Nevertheless, his performance in the first two weeks when compared to the control week showed significant increase in the number of minutes spent in moderate intensity. Figure 7.3 below summarise the data recorded from this participant.

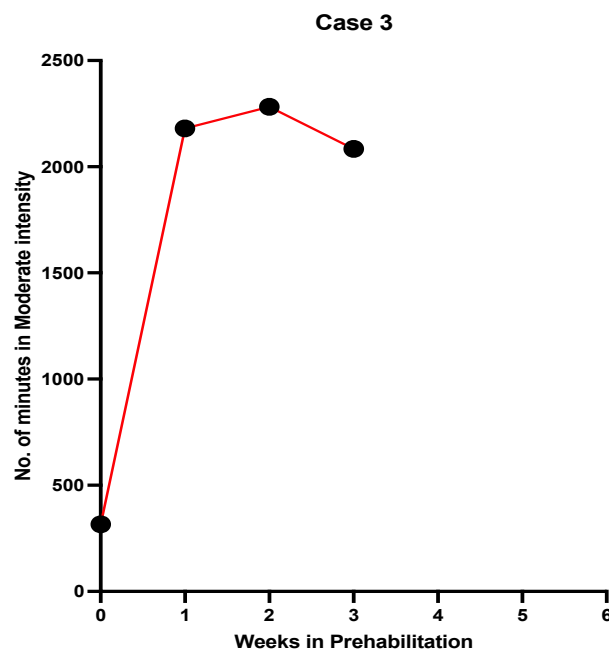


Figure 7.3 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 3

Case 4:

This participant was a 78-year-old male, scheduled for open AAA repair. His baseline 6MWT was 480 meters. Participant successfully finished 6-week prehabilitation programme. His 6MWT has increased by 70 metres reaching 550 meters. Participant however reported in exercise diary that he did reduce the number of days spent exercise during surgery week but achieved the minimum number of days of exercise (3 days a week).

Figure 7.4 demonstrate the change in number of minutes spent in moderate intensity.

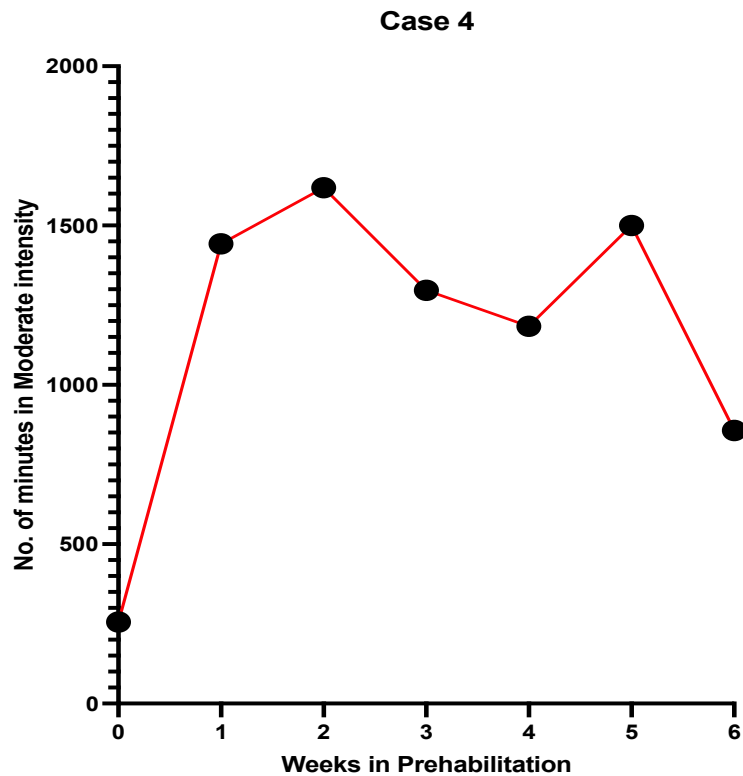


Figure 7.4 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 4

Case 5:

This a 72-year-old male, who was scheduled to have an open AAA repair for a 6.0cm aneurysm. He performed well in his baseline 6MWT reaching 520 metres. He successfully completed the prehabilitation programme and carried on exercising with same intensity until his surgery which was postponed due to theatre capacity. Post 6-week prehabilitation 6MWT increased by 90 meters reaching 610m. During the control week, the device recorded a total of 1153 minutes of moderate intensity activity equating to 12.3% which then increased significantly to an average of 31% during the prehabilitation programme. We noted that this participant is an active golfer which explains the relatively high number of minutes spent in moderate intensity in control week.

Figure 7.5 summarise the change in minutes spent exercising in moderate intensity during the prehabilitation programme.

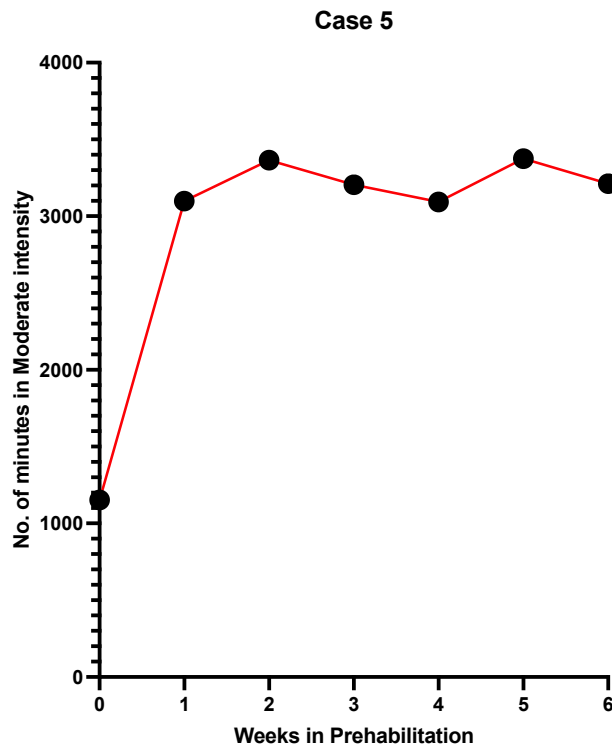


Figure 7.5 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 5

Case 6:

This was a 75-year-old female with 5.6cm AAA scheduled for EVAR repair. Her baseline 6MWT was 250 meters and she unfortunately was found not to be adherent to the prehabilitation programme despite regular follow up calls to motivate this participant to exercise. The reasons behind not exercising recorded were due to family reasons and being admitted to hospital with acute cholecystitis. Participant reported that she was trying her best to follow prehabilitation programme and while wearing the activity monitor, however, on analysing the data captured from the device, we found that only one week of exercise was recorded along with control week. Figure 7.6 summarises the data captured from the activity monitor.

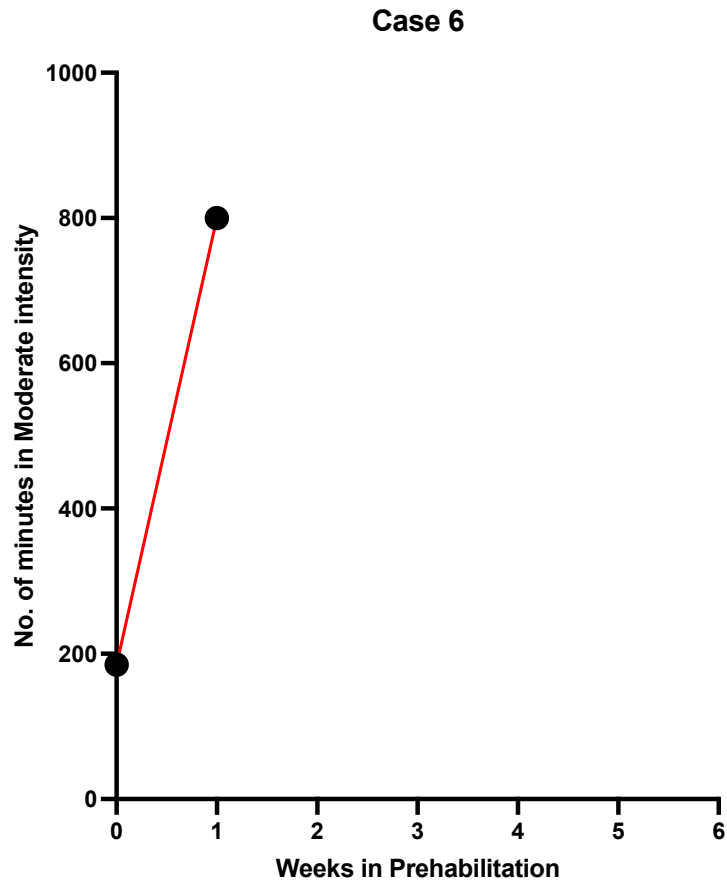


Figure 7.6 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 6

Case 7:

This is a 68-year-old female who was scheduled for Open AAA repair for a 6cm aneurysm. Her baseline 6MWT was 325m. She completed successfully the 6- week prehabilitation programme with noted improvement in her 6MWT reaching 390 meters. Participant reported that she did not exercise as much during week 5 to week 6 due to illness. Nevertheless, participant continued exercising after finishing the 6- week prehabilitation programme and elected to keep the activity monitor to record her performance. Figure below demonstrate the minutes spent in moderate intensity during 8 weeks of wearing the activity monitor

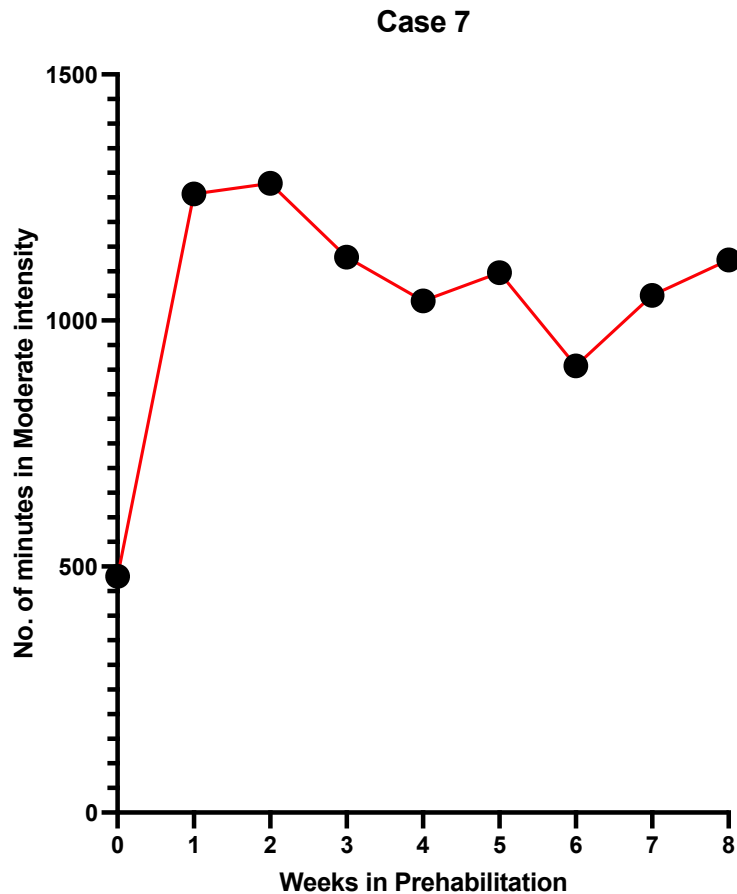


Figure 7.7 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 7

Case 8:

This is a 78-year-old male with a 6.5cm AAA with background of peripheral vascular disease requiring lower limb angioplasty in the past. He denied any symptoms of intermittent claudication. Patient elected not to undertake 6MWT on baseline assessment. He successfully finished the prehabilitation programme and carried on exercising until surgery date. During the weekly follow up calls, and after finishing the prehabilitation programme, participant reported pain in his calf when he was performing the daily prescribed walks. As a result, the research team have flagged this complaint to the responsible clinical team and participant was attended to urgently. Further investigations revealed that he had a thrombosed popliteal aneurysm which was not known before. He underwent an urgent surgical bypass and recovered from surgery with no complications. Patient elected to carry

on with prehabilitation when was deemed fit to exercise by the surgical team. Figure 7.8 below demonstrate change in minutes spent with moderate intensity exercise.

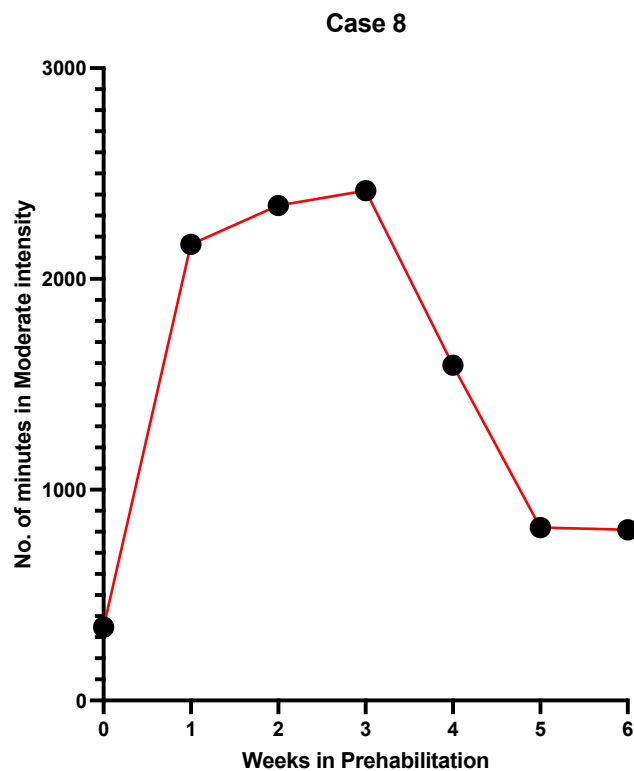


Figure 7.8 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 8

Case 9:

This is a 75-year-old male who has a 6.1 cm aneurysm scheduled for EVAR repair. He has a background of COPD for which he is taking inhalers and known to have atrial fibrillation on anticoagulation. His baseline 6MWT was 390 meters. Participant reported adequate adherence to exercise programme during its 6-week course as reported on his exercise diaries. The activity monitor successfully recorded his first four weeks of exercise activity, however for some reason, not reported to the research team, patient did not wear the device in the last two weeks. 6MWT post prehabilitation has demonstrated increase in his distance to 410m with increase of 20 meters. Figure 7.9 demonstrates the decline in minutes spent in moderate intensity activity reaching to nearly baseline which may indicate

that patient was not adherent to exercise from week 3 onwards contrary to what was document in the exercise diary.

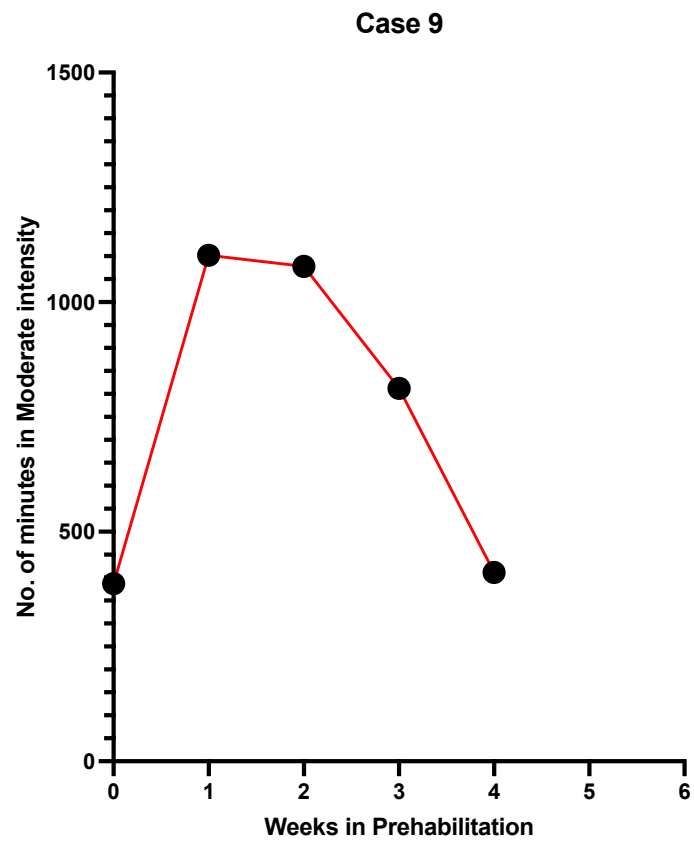


Figure 7.9 Trend in moderate intensity exercise minutes during PREHAB-AAA study for Case 9

Discussion

This case series has successfully demonstrated that adherent participants undertaking remote prehabilitation while awaiting their AAA repair have achieved adequate level of exercise intensity “moderate intensity” exceeding the expected minimum number of minutes to achieve adherence (>250 min of moderate intensity exercise per week). Participants who were adherent to exercise prescription showed significant increase in the total number of minutes spent in moderate intensity activity which reflected in improvement in functional capacity demonstrated in the increase of 6MWT distance covered.

The introduction of activity monitors in the PREHAB-AAA pilot study was designed to rigorously assess the accuracy of the exercise prescription in achieving the intended exercise intensity, as compared to the participants' exercise diaries. As previously stated, there was an instance where a participant indicated exercising 5-7 days a week in their diaries, which was not supported by the data collected from the activity monitor. This important finding might explain the reasons behind certain participants, despite reporting sufficient adherence, not showing improvement in their 6-minute walk test distance. In the design of a large-scale trial, it may be beneficial to utilise activity monitors for recording exercise activity. This approach could ensure a more precise identification of adherent participants, leading to a clearer understanding of the effects of prehabilitation on outcomes after AAA surgery. Relying on exercise diaries might be less effective, as they can be overwhelming for patients to fill out, particularly after completing their exercises. Furthermore, it could potentially pinpoint the cohort of individuals who are less likely to engage in physical activity (such as those undergoing EVAR), thereby conserving resources that would otherwise be allocated to their recruitment in a large-scale study.

In this case series, we chose to utilise the 3D accelerometer while disabling the heart rate monitoring feature, as it would deplete the device's battery in under a week. Participants assigned to wear activity monitors indicated that the device was not intrusive and appreciated its user-friendly design, particularly the convenience of not needing to charge it frequently. This presents a benefit of utilising this device, particularly among a cohort of

patients who may not be familiar to such technology.

One advantage of monitoring participants' heart rates is the ability to calculate the metabolic equivalent of task (MET), a commonly utilised metric for evaluating exercise intensity, where moderate intensity exercise corresponds to 3-6 METs. Several studies have examined the threshold values of vector magnitude derived from accelerometers that correspond to the METs necessary for attaining moderate intensity exercise. The algorithm employed by Actilife™ software for analysing vector magnitude data and calculating the duration of participant engagement has undergone validation, demonstrated minimal variance when compared to analyses conducted using MATLAB[269]. In contrast, certain studies have shown that the moderate intensity reported by Actigraph may be overestimated, particularly in devices worn on the wrist. This could account for the unexpectedly high total minutes recorded for PREHAB-AAA participants.

Conclusion

This case series has shown that patients with AAA can reach the minimum target of 250 minutes of moderate intensity exercise per week when they adhere to the Prehab-AAA prehabilitation programme. Wearable devices have the potential to significantly enhance the accuracy of adherence tracking, especially when contrasted with patient-reported diaries, leading to more reliable data on the outcomes of prehabilitation.

Chapter 8 : Neuromuscular Electrical Stimulation for Rehabilitation after general and vascular surgery (NMES - REHAB) - a pilot randomised clinical study.

Introduction

Rehabilitation after surgery is an essential process to achieve an optimal surgical outcome. Over 320 million major surgeries are performed each year around the world[270], and the increase in the aging population and co-morbidities requires comprehensive peri-operative care.

Prospectively gathered in-house data collected at Imperial College Healthcare NHS Trust, suggests that length of stay (LOS) after vascular surgery is a median of 17 days, in patients aged 63-78 with an average Rockwood Frailty Score of 3, which equates with a “managing well” frailty level. This indicates that there is room for improvement in rehabilitation as these patients should have significant capacity for recovery. NHS general ward bed costs are significant, with an estimated cost of £586.59 per day[271], compounded by a considerable deficit in rehabilitation beds.

Current best postoperative recovery practice is intensive physiotherapy and occupational therapy to return patients to a pre-morbid independence level[272]. However, due to patient fatigue and resource constraints, especially outside of the working week, such rehabilitation is necessarily limited. Early discharge not only reduces NHS costs, but also lowers the risk of hospital acquired complications[273], and, most importantly, returning to normal life is a key factor in improving the quality of life for all patients after surgery.

Neuromuscular electrical stimulation (NMES) utilises electrical impulses to cause involuntary contraction of the target muscle groups. NMES has been shown to be beneficial in improving symptoms in claudication and venous disease and is the subject of a multi-centre National Institute for Health Research (NIHR) randomised study[274,275]. Studies have also demonstrated that NMES improved recovery after orthopaedic surgery, stroke and intensive

care stay[276–278]. NMES is safe[279], low cost and user-friendly technology that can provide an effective alternative for early postoperative intervention.

The aim of this study is to investigate the acceptability and safety of NMES as an adjunct for rehabilitation after vascular and general surgery and assess the impact of using NMES in postoperative recovery in terms of activity, frailty, independence and quality of life (QoL) levels.

Methods

Patient recruitment

This study was a prospective, single-centre, single-blind, parallel group, randomised controlled trial conducted in a secondary care setting (Charing Cross Hospital and St Mary's Hospital, Imperial College London NHS Healthcare Trust, London, UK), between July 2021 and January 2022. Ethical approvals were provided by London-Harrow Research Ethics Committee and the Health Research Authority (Ref: 21/PR/0250), and the trial protocol was registered on clinicaltrials.gov (NCT04784962). The protocol has been published [280].

Patients over 18 years old undergoing vascular, colorectal or urology surgery (excluding day surgery) with Rockwood Frailty Score of above 3 were recruited from the outpatient department and admission lounge by the research team. Patients were excluded if they had an implanted electrical device such as pacemaker or defibrillator, acute deep vein thrombosis (DVT), or were pregnant. A urine pregnancy test was performed in women of childbearing potential on admission.

Following written informed consent, baseline information, including demographic characteristics, medical history and medication was collected. EuroQoL Five-Domain Utility Index and Visual Analogue Scale (EQ5D5L+VAS)[281] were also completed by each participant at baseline. The patients were then randomised on a 1:1 ratio with block randomisation by the research team, using a web-based randomisation service (www.sealedenvelope.com) to either the intervention group (Group A) or the placebo group (Group B), (Figure 8.1).

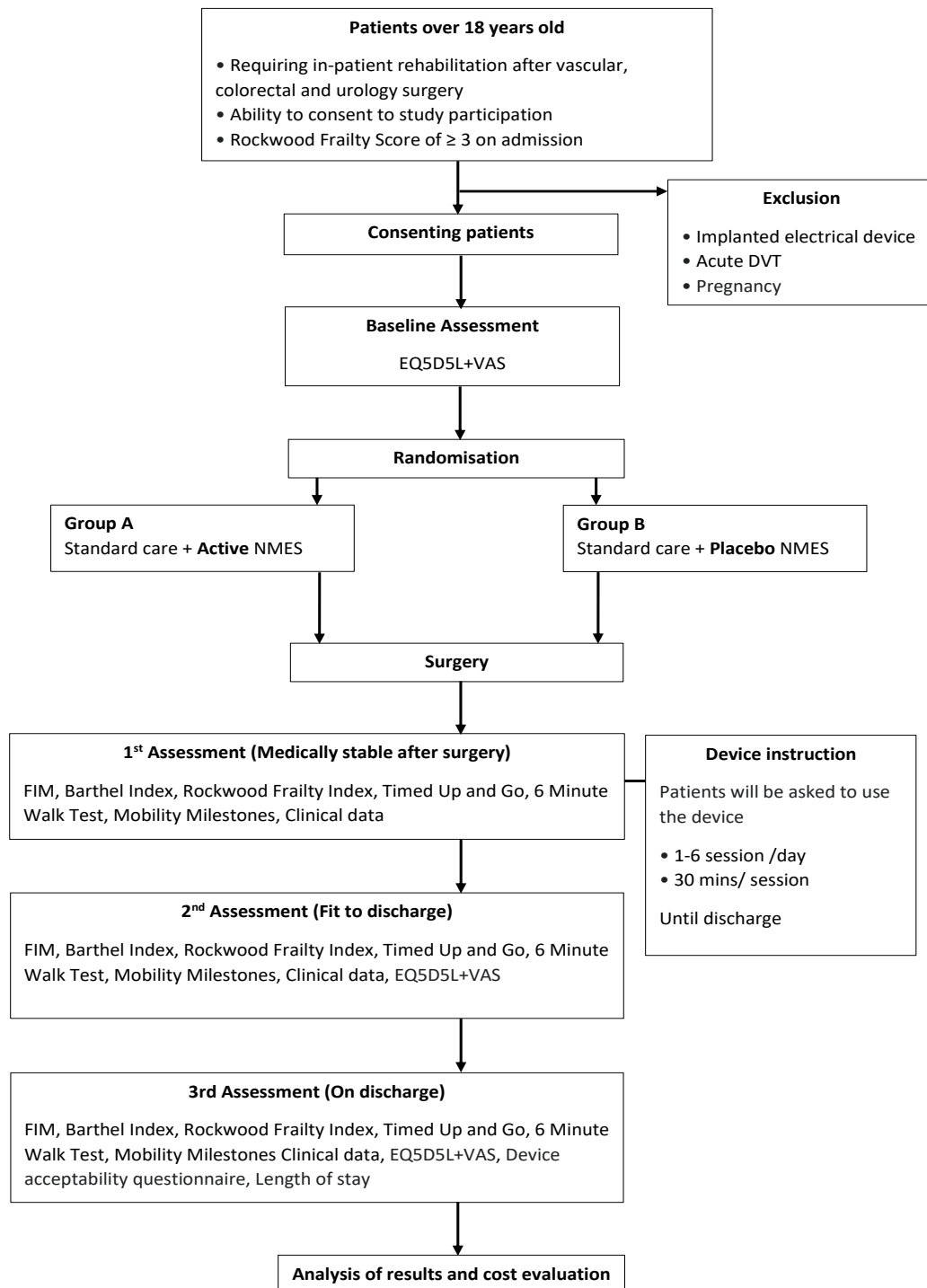


Figure 8.1 Trial flowchart. EQ5D5L: Five-Domain Utility Index, VAS: Visual Analogue Scale, FIM: Functional Independence Measure, DVT: Deep Vein Thrombosis, NMES: Neuromuscular Electrical Stimulation.

Sample Size

As this was a pilot trial, power calculation was not performed. However, a pragmatic study to assess acceptability and early trends was planned. This required 100 patients - 50 in each group.

The neuromuscular electrical stimulation (NMES) device: REVITIVE Medic®

The device used (REVITIVE Medic®, Actegy Health Ltd) is a class IIa medical device, CE marked to treat disorders of the lower limb (Figure 8.2). The device was used in the seated position, with the users' bare feet placed on a pair of conductive footplate electrodes (Figure 8.3). Electrical impulses are delivered to the muscles and nerves of the feet, which cause foot and calf muscle contraction. Direct contact between skin and electrodes is required for stimulation, precluding the use of compression stockings. Both feet have to be placed on the conductive footplates for the device to work.



Figure 8.2 NMES Device (Revitive Medic) – Courtesy of Actegy

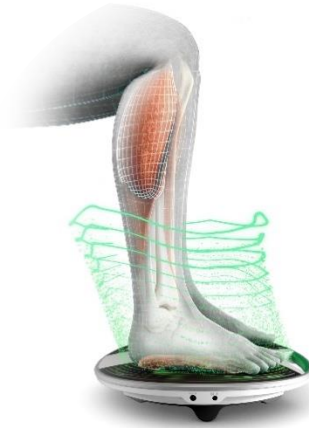


Figure 8.3 How to use the device – Courtesy of Actegy

Participants in both groups were blinded and asked to use the device 1-6 sessions daily (30mins per session) after surgery in addition to standard NHS rehabilitation care with occupational therapists (OT), physiotherapists (PT) and rehabilitation physicians. Device instruction was given by trained registered healthcare professionals upon the first assessment (when medically stable post operatively as defined by the clinical team). Participants were asked to use the device until discharge. The investigators were not blinded to the allocation as they were required to deliver different device instructions to each group.

Active device (Group A)

The device runs a 30-minute programme of NMES consisting of 15 different waveform patterns, each with varying electrical output characteristics. The intensity of stimulation ranges from 1-99 units, delivering a maximum current of 15mA (r.m.s., root mean square) at 500 Ω resistance. Stimulation intensity is increased by the subject until visible contraction is seen. Patients were advised to use the highest intensity that was comfortable for them.

Sham device (Group B)

The sham device looks identical to the active device. It delivers a very mild sensory stimulation, but no effective electrical impulses are delivered to contract the muscles. Participants in Group B were asked to select intensity 25, not to adjust the intensity. Hence, it simulated the effect of sitting still for 30 minutes. Patients were blinded as they were not informed which group they were allocated to and had never used NMES previously.

Outcome assessments

There were four assessment timelines in this study. Baseline assessment was performed on recruitment before surgery; the first assessment when patients were medically stable post-operatively as defined by the clinical team; the second assessment was when patients were medically fit for discharge as defined by the clinical team; the third assessment was on the day of discharge from hospital.

The primary outcome measures were acceptability, safety and adherence of NMES as an adjunct for rehabilitation, assessed by device acceptability questionnaire, medical records and device usage diary recorded by a registered healthcare professional.

The secondary outcome measures were to compare the two groups with respect to: Rockwood Frailty Index[282], Functional Independence Measure[283], Barthel Index[284], Timed Up and Go Test[285], 6 Minute Walk Test[286], Mobility Milestones tests (if patients are able to sit for >5 minutes, stand for >1 minute, walk >50m), EQ-5D-5L Health Related Quality of Life (HRQoL) and Visual Analogue Score (VAS), Assessments were conducted by trained registered healthcare professionals between the baseline and the third assessment. The details of assessments on each timeline are illustrated in Figure 8.1 previously.

Statistical Analysis

Data was analysed using SPSS version 28 (IBM, Armonk, NY, USA) on an intention-to-treat (ITT) basis. Intergroup comparison of categorical variables was analysed using the chi-square

or Fisher exact test. Parametric data were analysed using *t* test statistics. Non-parametric data were analysed using the Wilcoxon test for paired and Mann–Whitney test for non-paired data. In all analyses, $p < .05$ was considered statistically significant.

For continuous data, if the data were normally distributed mean and standard deviation (SD) were presented, whereas median and interquartile range (IQR) were presented if the data were not normally distributed. For categorical data, frequencies and percentages were presented. T tests were conducted if the data were normally distributed, whereas the Mann Whitney U test was performed if data were not normally distributed. Chi-squared tests were performed to compare treatment group proportions. Missing data were handled with complete-cases analysis.

Study feasibility

Study feasibility was assessed by number of participants enrolled, number of participants withdrawn, follow-up response rates, missing data from questionnaires and assessments, time spent using the NMES device.

Cost Effectiveness Analysis

HRQoL was estimated in the study using the EQ-5D instrument at baseline and second assessment (medically fit for discharge). It was not appropriate to calculate quality-adjusted life years (QALYs) in this context because the study was conducted in a hospital setting, and longer duration of hospital stay is not an indicator of greater benefit for the patient.

The time from baseline to assessment of being fit for discharge, and total length of hospital stay, was collected from hospital notes. The duration of sessions provided by rehabilitation professionals was measured using the NMES usage diary completed by patients.

The NMES device acquisition cost was £249.99 per unit (manufacturer's list price), and it was assumed the device could be reused for 50 patients. A 10-minute training session by a nurse was imputed for each patient. The unit cost of physiotherapists and occupational therapists was estimated from Personal Social Services Research Unit (PSSRU 2019) as £1.90 per minute. The cost of the hospital stay was estimated from NHS reference costs (ref) as £459 per day.

Discounting was not applied as the time horizon was less than one year. The price year used was 2020/2021. The health economic analysis was conducted from the perspective of the UK NHS. The cost and HRQoL data were analysed using a seemingly unrelated regression (SUR), which conducts a joint analysis of two correlated dependent variables. In this case, the dependent variables were cost per patient and the HRQoL at second assessment, adjusting for baseline demographic and clinical covariates (age, gender, BMI, smoker and alcohol consumption status, pathology, ethnicity, and baseline QOL).

Results

Participants Flow Diagram

This pilot randomized controlled trial recruited a total of 103 participants and randomly assigned them to either the active device group (n=55) or the sham device (control) group (n=48). Four participants in the active group and five participants in the Control group did not receive the allocated intervention as per the randomisation. The flow of participants throughout the study can be visualized in CONSORT diagram (Figure 4)

CONSORT 2010 Flow Diagram

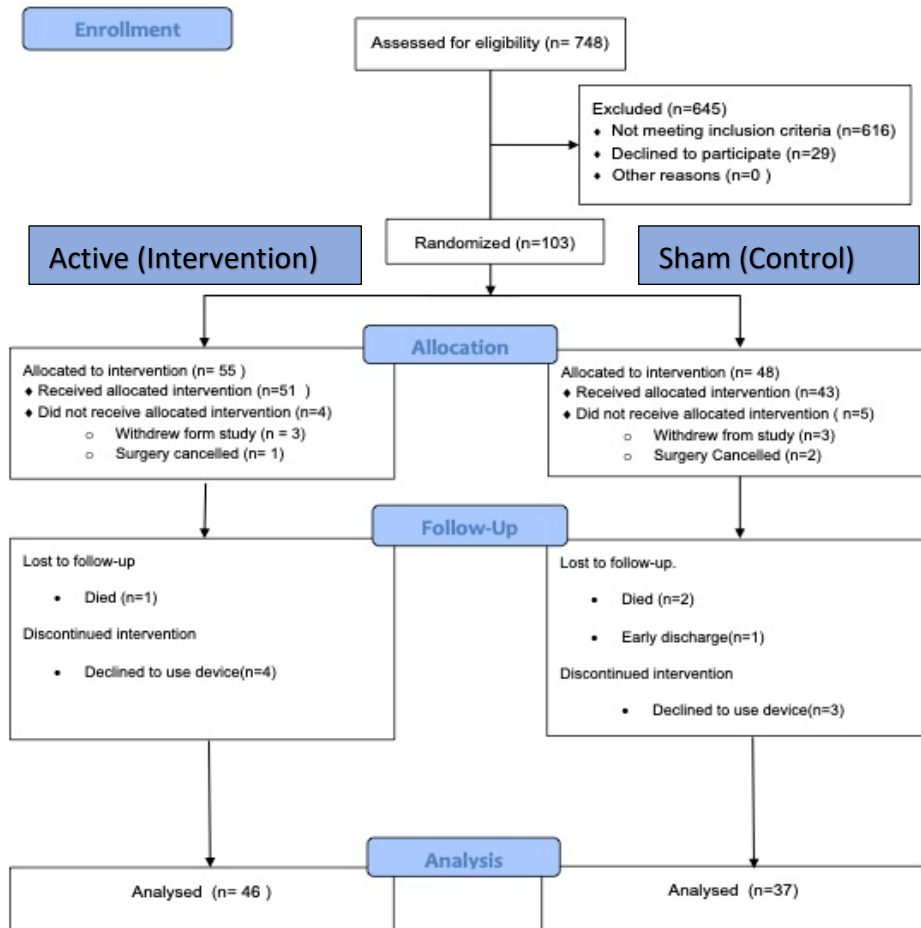


Figure 8.4 CONSORT Flowchart for NMES trial

Baseline Data

A total of 83 participants were included in the analysis. The mean age of the participants was 62.6 years with a standard deviation of 13.2 years. The majority of participants were male (71.1%) and white Caucasians (65.1%). Using the frailty index by Rockwood, 46 participants (55.4%) had a score of 3, indicating they were “managing well”. There were no significant differences in baseline characteristics between the active and sham device groups as shown in Table 8-a.

Table 8-a Baseline characteristics of 103 patients enrolled in the pilot randomised controlled study assessing Neuromuscular Electrical Stimulation (NMES) for rehabilitation after general and vascular surgery

	Overall (n= 103)	Active (n=55)	Control (n= 48)	p-value*
Patient Characteristics				
Age - years, mean (SD)	63.6 ± 13.5	63.0 ± 13.7	64.2 ± 13.4	0.653
Sex (Male) n (%)	75(72.8%)	39(70.9%)	36(75.0%)	0.664
Ethnicity (White) n (%)	69(67.0%)	38 (69%)	31(64.6%)	0.678
BMI – kg/m ²	27.4 ± 5.4	26.9 ± 5.8	27.9 ± 4.9	0.34
Past Medical History				
Hypertension n (%)	57(55.3%)	29(52.7)	28(58.3%)	0.835
Type 2 Diabetes n (%)	16(15.5%)	7(12.7%)	9(18.8%)	0.694
Hypercholesterolemia n (%)	52(50.5%)	28(50.9%)	24(50%)	0.992
Current Smoker n (%)	20(19.4%)	11(20%)	9(18.8%)	0.537
Ex-Smoker n (%)	44(42.7%)	26(47.3%)	18(37.5%)	0.328
Stroke n (%)	3(2.9%)	2(3.6%)	1(2.1%)	0.893
Type of Procedure				
Colorectal n (%)	34(33%)	18(32.7%)	16(33.3%)	0.557
Vascular n (%)	32(31.1%)	20(36.4%)	12(25%)	0.286
Urology n (%)	37(35.9%)	17(30.9%)	20(41.7%)	0.306
Laparotomies n (%)	30(29.1%)	18(32.7%)	12(25%)	0.515
Rockwood Frailty				
3(Managing well) n (%)	57(55.3%)	31(56.3%)	26(54.1%)	0.845
4(Vulnerable) n (%)	32(31.1%)	18(32.7%)	14(29.2%)	0.431
5(Mildly Frail) n (%)	11(10.7%)	3(5.5%)	8(16.7%)	0.064
6(Moderately Frail) n (%)	3(2.9%)	3(5.5%)	0(0%)	0.148
Health related quality of life				
EQ-5D-5L index value, mean (SD)	0.63 ± 0.18	0.66 ± 0.18	0.6 ± 0.18	0.107
EQ-VAS, mean (SD)	62.4 ± 19.2	60.1 ± 18.5	65.0 ± 20.0	0.2

BMI = Body Mass Index, EQ-5D-5L = EuroQol Five-Domain Utility Index, EQ-VAS = EuroQol Visual Analogue Scale

Primary Outcomes:

Safety:

In this study, participants were evaluated daily for the incidence of any adverse events related to the use of the NMES device or procedure- or disease-related complications. Two patients in the intervention group who underwent femoral-femoral arterial bypass surgery experienced groin bleeding on postoperative Day 1, 30 minutes after using the device. The patients required surgical intervention, and the cause of the bleeding was determined to be a suture line bleed, which was not related to the device.

One episode of in-hospital mortality was identified in the intervention group. The patient had undergone a major vascular intervention in the form of aortic reconstruction and deteriorated after surgery, with no relation to the use of the NMES device. The patient passed away on the 11th post-operative day.

Adherence:

The participants in this study were asked to use the device at least once a day from the day they were declared clinically stable. Sufficient adherence to NMES device usage was defined as completion of at least 75% of intended sessions, with at least one session per day. In the intervention group, this level of adherence was achieved in 54.3% (n=25) of patients, while in the sham group, it was achieved in 48.6% (n=18) of patients (p=0.384).

Acceptability:

Patient satisfaction data were collected before hospital discharge. 74.4% (n=32) of participants randomized to the intervention group found it to be "acceptable" to use the device in a hospital setting. 77.8% (n=35) of the active device group expressed confidence in using the device, however we noticed that most participants required encouragement to use the device. Twenty-seven patients (60%) believed that the active NMES device aided their recovery. A detailed analysis of the patient satisfaction questionnaire is outlined in Table 8-b. Overall, satisfaction in the intervention group was significantly higher compared to the control group (6.75 vs 5.59, p<0.05).

Table 8-b Patient satisfaction questionnaire for 83 patients enrolled in the pilot randomised controlled study assessing Neuromuscular Electrical Stimulation (NMES) for rehabilitation after general and vascular surgery

Patient satisfaction	Active (n= 46)	Control (n=37)	p- value
Is the device active (Yes)	42(91.3%)	13(35.1%)	<0.05*
Is the device acceptable (Yes)	32(74.4%)	19(54.2%)	0.053
Likeness (Liked)	32(71.1%)	19(52.8%)	0.071
Effort to use (Huge effort)	8(17.8%)	4(11.1%)	0.303
Help in recovery (Agree)	19(43.2%)	11(30.5%)	0.177
Interfered with priorities (Disagree)	25(55.6%)	16(44.4%)	0.221
Confident in using device (Confident)	35(77.8%)	24(66.7%)	0.193
Confident to aid recovery (Confident)	26(57.8%)	15(42.9%)	0.136
Recommend to a friend (Yes)	31(68.9%)	18(51.4%)	0.087
Purpose of use makes sense (Yes)	35(77.8%)	27(77.1%)	0.578
Overall satisfaction (out of 10)	6.76 ± 2.7	5.39 ± 2.7	<0.05*

Data are presented as *n* (%)

*The *p* value refers to univariable comparison between active device and control group.

Secondary Outcomes:

Summary of secondary outcomes findings are shown in Table 8-c.

Functional Independence measure (FIM) and Barthel Index

Motor, cognitive, and total FIM scores were recorded at the first, second, and third assessments. It was noted that there was poor recording for these scores in the third assessment due to the short period of hospital stay between the second and third assessments. There was no significant difference between the intervention group and the control group in terms of FIM scores (105.6 vs 104.2, $p=0.41$). Similar findings were noted in Barthel Index across points of assessment. There was no significant difference between two arms (17.9 vs 17.4, $p = 0.28$).

Timed up and Go (TUG) and 6-minute walk test (6MWT)

During the study, it was observed that participants were not motivated to perform the Timed Up and Go (TUG) test and the 6-Minute Walk Test (6MWT) at the first assessment (medically stable) due to the impact of having recently undergone a surgical intervention. The number of participants who completed TUG at the first assessment were 16(35%) in the active device group and 13(35%) in the sham device group. The number of participants who completed 6MWT at the first assessment were 10(22%) in the active device group and 13(35%) in the sham device group. On the second assessment (medically fit for discharge), there was no statistically significant difference between the two groups in TUG or 6MWT ($p=0.224$, $p=0.458$)

Table 8-c Secondary outcomes observed in the 83 patients enrolled in the pilot randomised controlled study assessing Neuromuscular Electrical Stimulation (NMES) for rehabilitation after general and vascular surgery

	Active (n=46)	Control (n=37)	p-value
Motor FIM			
1st assessment	50 ± 16.8	50.5 ± 17.0	0.453
2nd assessment	78.07 ± 18.3	79.7 ± 13.7	0.33
3rd assessment	75.3 ± 17.1	83.0 ± 8.8	0.108
Cognitive FIM			
1st assessment	33.0 ± 6.2	32.2 ± 7.7	0.31
2nd assessment	30.91 ± 9.67	31.0 ± 9.8	0.483
3rd assessment	25.44 ± 14.0	32.0 ± 8.8	0.118
Total FIM Score			
1st assessment	81.89 ± 20.3	82.05 ± 22.1	0.486
2nd assessment	105.64 ± 28.6	104.2 ± 30.8	0.415
3rd assessment	111.75 ± 17.5	115.4 ± 14.9	0.29
Barthel Index			
1st assessment	9.85 ± 5.17	10.0 ± 5.5	0.44
2nd assessment	17.95 ± 3.34	17.44 ± 4.7	0.287
3rd assessment	16.8 ± 4.4	18.0 ± 3.8	0.229
Timed Up and Go			
1st assessment	26.0 ± 16.8	26.5 ± 15.6	0.463
2nd assessment	25.6 ± 35.1	19.4 ± 12.4	0.224
3rd assessment	17.6 ± 16.8	22.8 ± 13.6	0.29
6MWT			
1st assessment	193.7 ± 88.3	134.4 ± 84.1	0.058
2nd assessment	198.7 ± 102	201.8 ± 97.6	0.458
3rd assessment	212.4 ± 102.1	150.7 ± 116.7	0.208
Mobility Milestones (able to sit for 5 min)			
1st assessment	37(80.4%)	30(81.1%)	0.435
2nd assessment	44(95.7%)	37(100%)	0.439
3rd assessment	44(95.7%)	37(100%)	0.439
Mobility Milestone (able to stand for 1 minute)			
1st assessment	27(58.7%)	22(59.5%)	0.5
2nd assessment	44(95.7%)	37(100%)	0.439
3rd assessment	44(95.7%)	37(100%)	0.439
Mobility Milestone (able to walk for 50 metres)			
1st assessment	8(17.3%)	8(21.6%)	0.491
2nd assessment	36(78.3%)	32(86.5%)	0.373
3rd assessment	44(95.6%)	34(91.9%)	0.301
Length of stay (days)	11.1 ± 12.7	9.4 ± 7.5	0.467

Abbreviations: FIM = Functional Independence Measure, 6MWT = 6-minute walk test

Subgroup analysis according to specialty

Colorectal surgery group had 17 participants in the active arm and 15 participants in the sham group. The active group had a significantly shorter length of stay (8.41 days vs 14.1 days, $p = 0.02$). This was not observed in the urology or vascular group. Detailed subgroup analysis of different specialties is shown in following tables (8 -d, e, f)

We performed a non-planned subgroup analysis for participants who received laparotomies. 18 (32.7%) participants in the intervention arm had laparotomies compared to 12(25%) in the placebo group. There was no difference in length of stay between two groups (13.1 days vs 11.6 days, $p=0.71$).

Table 8-d Colorectal Surgery Subgroup analysis

	Active Device(n=17)		Control (n=15)		p-value
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
Motor FIM					
1st Assessment	17	46.9 ± 15.4	15	46.9 ± 15.6	0.495
2nd Assessment	17	78.9 ± 20.8	14	77.1 ± 17.0	0.395
3rd Assessment	3	78.3 ± 12.9	3	80.3 ± 10.1	0.421
Cognitive FIM					
1st Assessment	17	33.1 ± 6.8	15	30.9 ± 9.7	0.231
2nd Assessment	17	28.4± 12.2	14	30.9 ± 10.1	0.277
3rd Assessment	2	20.5 ± 19.1	3	34.3 ± 0.58	0.132
Total FIM Score					
1st Assessment	17	77.6 ± 18.5	15	76.5 ± 23.5	0.444
2nd Assessment	17	104.2 ± 33.5	14	100.6 ± 32.9	0.385
3rd Assessment	12	118 ± 9.1	13	108.6 ± 21.2	0.22
Barthel Index					
1st Assessment	17	8.4 ± 5.2	15	8.7 ± 6.3	0.451
2nd Assessment	17	18.5 ± 2.4	15	17.1 ± 5.1	0.16
3rd Assessment	12	18.3 ± 2.9	13	16.4 ± 5.9	0.292
Timed up and Go (seconds)					
1st Assessment	7	30.8 ± 19.7	6	29.7 ± 15.6	0.456
2nd Assessment	16	21.1 ± 18.0	6	14.8 ± 4.7	0.211
3rd Assessment	2	31 ± 22.6	4	20.3 ± 9.4	0.211
6MWT (metres)					
1st Assessment	3	218.2 ± 74.8	6	124 ± 53	0.032
2nd Assessment	15	216.4 ± 101.8	6	233.5 ± 107.5	0.455
3rd Assessment	2	185.3 ± 92.8	4	172 ± 137.8	0.735
Length of stay (days)	17	8.41 ± 6.1	15	14.1 ± 8.9	0.021*
Total time with Device (min)	17	239.2 ± 230.9	15	156 ± 85.8	0.099

* denotes statistically significant change compared to control

Abbreviations: FIM = Functional Independence Measure, 6MWT = 6-minute walk test

Table 8-e Urology surgery subgroup analysis

	Active Device(n=12)		Control (n=15)		p-value
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
Motor FIM					
1st Assessment	12	49.6 ± 14	15	55.7 ± 18	0.17
2nd Assessment	10	74.2 ± 18.9	15	83.7 ± 6.9	0.044*
3rd Assessment	5	77.2 ± 12.6	4	86 ± 2.16	0.108
Cognitive FIM					
1st Assessment	12	31.25 ± 8.4	15	34.7 ± 1.0	0.062
2nd Assessment	10	34.5 ± 1.6	15	31.1 ± 9.8	0.148
3rd Assessment	4	35	4	35	1
Total FIM Score					
1st Assessment	12	79.8 ± 21.0	15	90.5 ± 18.2	0.085
2nd Assessment	10	111.7 ± 14.7	15	107.1 ± 30.0	0.328
3rd Assessment	5	112.2 ± 12.6	4	121 ± 2.2	0.108
Barthel Index					
1st Assessment	12	9.75 ± 4.3	15	11.5 ± 5.2	0.185
2nd Assessment	10	17.1 ± 3.6	15	18.5 ± 2.2	0.116
3rd Assessment	5	16.4 ± 3.2	4	19.0 ± 1.4	0.09*
Timed up and go					
1st Assessment	4	31.0 ± 17.9	6	23.3 ± 17.8	0.262
2nd Assessment	6	13.2 ± 5.5	11	17.8 ± 11.2	0.18
3rd Assessment	2	9.0 ± 4.26	1	11	0.383
6MWT					
1st Assessment	2	279.5 ± 36.1	7	143.2 ± 107.4	0.067
2nd Assessment	6	156.7 ± 106.8	11	208.2 ± 95.7	0.162
3rd Assessment	1	140	1	161	-
Length of stay					
	12	12.4 ± 19.7	15	6.3 ± 4.8	0.126
Total time with Device					
	12	218.3 ± 253.4	15	154 ± 112.1	0.193

* denotes statistically significant change compared to control

Abbreviations: FIM = Functional Independence Measure, 6MWT = 6-minute walk test

Table 8-f Vascular surgery subgroup analysis					
	Active Device(n=17)		Control (n=7)		p-value
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
Motor FIM					
1st Assessment	17	53.4 ± 19.9	7	47.0 ± 15.1	0.225
2nd Assessment	17	79.5 ± 15.8	7	76.4 ± 17.0	0.339
3rd Assessment	3	69.0 ± 29.9	3	81.7 ± 14.5	0.272
Cognitive FIM					
1st Assessment	17	34.2 ± 2.9	7	29.9 ± 10.3	0.059
2nd Assessment	17	31.3 ± 9.2	7	31.0 ± 10.58	0.473
3rd Assessment	3	16.0 ± 16.5	3	25.7 ± 16.2	0.254
Total FIM Score					
1st Assessment	17	87.6 ± 21.3	7	75.9 ± 23.8	0.123
2nd Assessment	17	103.53 ± 30.4	7	105.1 ± 32.3	0.454
3rd Assessment	3	102.7 ± 32.1	4	118.3 ± 12.2	0.202
Barthel Index					
1st Assessment	17	11.35 ± 5.5	7	9.9 ± 4.0	0.261
2nd Assessment	17	17.94 ± 4.1	7	15.9 ± 7.4	0.191
3rd Assessment	3	15.3 ± 8.1	4	19.0 ± 2	0.258
Timed up and go (seconds)					
1st Assessment	5	15.2 ± 4.3	1	27	0.07
2nd Assessment	7	45.3 ± 62.8	4	30.8 ± 18.4	0.334
3rd Assessment	1	-	1	-	-
6MWT(metres)					
1st Assessment	5	144.6 ± 85.4	0	0	0
2nd Assessment	5	196.2 ± 103.3	4	136.8 ± 76.8	0.186
3rd Assessment	1	-	1	-	-
Length of stay (days)					
	17	14.29 ± 12.7	7	6.1 ± 2.7	0.056
Total time with Device (min)					
	17	145.6 ± 115.0	7	142.1 ± 150	0.476

Abbreviations: FIM = Functional Independence Measure, 6MWT = 6-minute walk test

Cost effectiveness

The cost-effectiveness analysis was conducted in 61 patients with complete data (32 in intervention and 29 in control), that is, patients who completed assessments of HRQoL using the EQ5D-5L at baseline and at second assessment and provided data on the resource use in hospital (length of stay and physiotherapy or occupational therapy).

HRQoL in both groups measured using the EQ-5D-5L decreased between the baseline and the second assessment. There appears to be a trend towards a positive benefit for the intervention group (a lower decrease in QoL over the study period compared with the control group) but the effect is statistically insignificant (difference 0.0465, $p=0.49$) after adjusting to covariates. Regression analysis demonstrated in Table 8-g below.

Table 8-g Difference in EQ5D between baseline and 2nd assessment			
	Estimate	SE	p-value
Intercept	0.0802	0.2400	0.7397
<u>Treatment arm (Active)</u>	<u>0.0465</u>	<u>0.0664</u>	<u>0.4864</u>
Age	0.0029	0.0024	0.2284
Gender (Male)	0.0387	0.0817	0.6382
BMI	-0.0099	0.0062	0.1179
Smoker (Current)	0.1474	0.0837	0.0846
Alcohol (Never)	0.0685	0.0759	0.3708
Group (Ref. Vascular)			
Colorectal	0.0587	0.0823	0.4792
Urology	0.0317	0.1033	0.7607
Ethnicity (Ref. White)			
Asian	-0.1430	0.0950	0.1390
Black	0.4259	0.2589	0.1064
Other	-0.0738	0.1768	0.6783
Baseline QoL	-0.4064	0.1150	0.0009 *

**Denotes statistical significance*

The unadjusted difference in cost between the intervention and control was £1181.70, $p = 0.40$. This arose because of the longer mean length of stay in the intervention group (Table 8-h).

Table 8-h Costs incurred by each patient by treatment for active and control groups

Source of costs	Active device	Control device	p-value
NMES	4.99	0.00	0.0000
Nurse costs	9.38	0.00	0.0000
Stay costs	5436.281	4336.759	0.4043
PT/OT	228.0000	160.1897	0.3840
Total	5 678.65	4 496.95	
Difference		1181.70	0.3958

Abbreviations: NMES: Neuromuscular electrical stimulation, PT: Physiotherapy, OT: Occupational therapy

The longer length of stay is due to a small number of outliers specifically in vascular and urology surgery groups. However, after adjusting for baseline covariates, the difference in mean cost between the groups was small and statistically insignificant (cost £116, $p = 0.94$) (Table 8-i).

Table 8-i Regression analysis of costs incurred with adjusting to covariates

	Estimate	SE	p-value
Costs			
Intercept	-7176.26	5719.54	0.2157
<u>Treatment arm (Active)</u>	<u>116.11</u>	<u>1581.23</u>	<u>0.9418</u>
Age	89.38	56.94	0.1231
Gender (Male)	901.37	1946.49	0.6454
BMI	143.56	147.89	0.3366
Smoker (Current)	-1750.85	1993.54	0.3842
Alcohol (Never)	2688.26	1807.99	0.1436
Group (Ref. Vascular)			
Colorectal	-1224.47	1961.53	0.5354
Urology	-1704.02	2462.33	0.4922
Ethnicity (Ref. White)			
Asian	-2572.14	2264.55	0.2617
Black	-3863.39	6168.03	0.5340
Other	1238.95	4213.71	0.7700
Baseline QoL	4144.29	2740.90	0.1371

Discussion

This pilot randomised controlled trial aimed to determine the feasibility and acceptability of using NMES devices in patients undergoing colorectal, vascular and urology interventions as an adjunct for inpatient rehabilitation.

This study has demonstrated the safety and acceptability of using such devices as evidenced by rapid recruitment and low dropout rate. There were no adverse events related to NMES usage. While there were two instances of postoperative bleeding after femoral bypass surgery in the group using the active device, these were due to a recognised complication of the procedure itself[287] and not caused by the usage of NMES. One participant experienced muscle fatigue and dropped out of the study.

In this pilot randomised controlled trial, approximately half of the participants (54.3%) in the intervention group utilizing the active NMES device achieved sufficient adherence, defined as utilizing the device for greater than 75% of the sessions. Participants who did not adhere to the treatment regimen reported fatigue, pain, sickness, and limited mobility related to their surgery as the main reasons for non-compliance. The study found that participants required regular verbal encouragement and support for adherence to the treatment regimen. The research team observed that most patients required reminders to use the device daily or assistance with device setup. Despite this, most participants (77.8%) in the intervention group reported confidence in their ability to utilise the device.

Overall, in this non-powered trial, there was no significant difference in functional improvement observed between the intervention group and the placebo group. The characteristics of the participants, the types of procedures they underwent, and their level of frailty were similar in both groups. Upon performing subgroup analysis, a significant decrease in hospital stay was observed in the intervention group among the participants who underwent colorectal surgery (8.4 days vs 14.1 days, $p=0.02$). However, this effect was not observed in the vascular or urology subgroups. The possible explanation for this difference may be due to the nature of the procedure undertaken, as it was found that participants in the intervention arm had a high rate of laparotomies (32.7 % vs 25%), which may have influenced the length of hospital stay. It may be that those undergoing laparotomies are the patients who benefit from the NMES rehab pathway. With the minimal cost increment seen in this study this may offer the opportunity for significant improvements at low cost.

Another potential explanation for the lack of significant difference in functional improvement between the intervention and placebo groups may be the variable usage of the NMES device among the participants in terms of the intensity selected. Although the study recommended a minimum daily usage of the device (30 minutes per session, one session per day), only half of the participants achieved this. A recent systematic review [288] suggests that to achieve optimal treatment effects in quadriceps strength, the device should be used daily at a frequency of greater than 50Hz at the maximum tolerable intensity. It is possible that this level of usage was not achieved in the intervention arm, as the average frequency used was 30Hz. We also need to bear in mind the possibility that the device is not effective in producing any difference in outcomes.

Following surgery, secondary sarcopenia develops by the lack of physical activity due to fatigue and post operative pain[289]. Returning to baseline function following surgery is a challenge for both patients and healthcare providers. Longitudinal studies demonstrated that patients hospitalised due to critical illness tend to suffer from functional and pervasive impairments at least one to five years after discharge [290–292]. Therefore, early intervention after surgery is crucial to prevent long-term complications. A recent Cochrane review [293] studied the effectiveness of NMES devices in 933 participants with muscle weakness due to chronic diseases. They reported improvement in muscle strength in NMES compared to controls, however, the quality of RCTs included were low. In their recommendation, they highlighted the need for further research to examine NMES as an adjuvant treatment to enhance rehabilitation. Similar findings were reported in a review[294] focusing on the benefits of NMES in sarcopenic critically ill patients. Furthermore, the positive effect of NMES on lower limb venous blood flow[295,296], reflected a recommendation on thromboprophylaxis by National Institute for Health and Care Excellence (NICE) for high-risk individuals that are unable to use other form of prophylaxis [297].

Based on the results of this pilot study, we have identified several areas for improvement when planning future studies. We found that the functional and quality of life assessments were poorly completed postoperatively. In future studies, we recommend conducting assessments preoperatively, at discharge, 2 weeks, 3 months, 6 months, and 1 year to avoid data duplication and questionnaire fatigue. Participants reported that they did not see the need to complete quality of life questionnaires at the third assessment (at discharge) as they had already completed similar questionnaires at the second assessment (when they were medically fit for

discharge). Additionally, we observed high attrition in performing functional assessments (6-minute walk test and timed up and go test) at the first assessment (postoperatively). We recommend conducting functional assessments preoperatively and on discharge in future studies. Finally, it appears the group most likely to benefit would be patients undergoing laparotomy, suggesting a targeted recruitment strategy.

This study has several limitations, primarily the fact that it was a single-blinded randomised controlled trial. As the participants in the intervention and placebo groups required different instructions, it was not possible to blind the investigators. Additionally, this study only investigated the effects of NMES during hospital stay and did not assess the long-term effects on clinical outcomes and quality of life. Another limitation is that it was difficult to blind the participants, even though we recruited patients who had never used an NMES device before, and a sham device was utilised. Participants may have been able to deduce their group allocation based on the activity or inactivity of the device.

Conclusion

In summary, this pilot randomized controlled trial has demonstrated the safety and feasibility of utilising NMES as an adjunct for rehabilitation in patients undergoing major general and vascular surgery. Results also showed a trend towards improvement in quality of life and shorter length of hospital stay. Future larger randomised controlled trials should focus on the effectiveness and cost-effectiveness of NMES for rehabilitation in patients following laparotomy with longer term follow-up.

Chapter 9 : Critical appraisal and summary of findings

This chapter provides a brief overview of the findings from the studies included. This thesis consists of three primary studies utilising various methodologies to address specified aims. In order to evaluate the effectiveness of achieving these specific goals, it is crucial to thoroughly evaluate the studies that have been included.

The impact of frailty on treatment outcomes for non-ruptured abdominal aortic aneurysms. A National Vascular Registry cohort study – critical appraisal

This study conducted a comprehensive analysis of nationally collected data (NVR) spanning from January 2019 to March 2020. Requesting data prior to January 2019 will not align with the intended objective, as the NVR dataset does not include frailty scoring. Another method for accessing pre-2019 data is by utilising the Clinical Practice Research Datalink (CPRD). Nevertheless, the implementation of capturing frailty index in primary care took place in 2018. Unfortunately, due to financial constraints, it was not possible to obtain the requested data for this unfunded study. In addition, it is important to note that the CPRD data may not offer comprehensive information on the post-operative outcomes of patients who have undergone AAA repair, as outlined in the NVR. We chose to exclude any data beyond March 2020 due to the significant influence of Covid-19 on AAA practice nationwide.

One of the primary concerns with utilising NVR data to address the specified aim is the potential for inaccurate data imputation, particularly when it comes to assessing frailty levels. We previously noted that the NVR frailty scoring has not been validated, and the levels of frailty were categorised into four groups. The prevalence of frailty in AAA patients may have been either underestimated or overestimated. In addition, NVR is a registry audit database that focusses on procedures rather than long-term data. One drawback of utilising NVR data is its limited scope, as it only includes patients who underwent surgery. Consequently, it becomes impossible to determine the total number of patients with frailty who did not undergo surgery, thus hindering the study's ability to provide a complete

picture. While there is existing literature on the prevalence of frailty in patients with AAA, no published study has yet examined real-world national registry data to assess the impact of frailty on patients undergoing surgical repair of AAA.

The primary objective of this study is to examine the effects of frailty on mortality rates during hospitalisation and the occurrence of significant cardiovascular complications. The data provided by the sources were adequate for investigating these objectives. The findings will provide valuable insights into the effects of frailty and how it can be addressed to enhance surgical results in patients at high risk. This may involve implementing prehabilitation measures to optimise patient outcomes.

Regarding the methodology used in this study, the data provided by the NVR team included patients who had both elective and non-elective repairs, as well as complex and infrarenal AAA repairs. This was despite the clear request for only elective infrarenal AAA repairs with documented frailty scores. Nevertheless, we conducted thorough data cleaning to incorporate precise procedural codes that are pertinent to the research question. Although extensive data cleaning and validation were conducted, it is possible that procedural errors occurred, resulting in some missing data. We have noted that approximately 20% of the data provided was excluded due to the absence of a documented frailty score. This exclusion may raise concerns about potential selection bias. Nevertheless, we have verified with data providers that the data in question consists of consecutive patient records who underwent surgery prior to January 2019. Due to the limited number of patients in the moderate and severe frailty category, we made the decision to group all frail patients together and compare them to patients who were not frail. This approach may have introduced sampling bias.

Upon examining the patient demographics in this study, it was observed that a significantly higher number of patients underwent EVAR, which is in line with the standard practice in the UK. It is not surprising to find that EVAR patients tend to be older and have comorbidities. After examining the levels of frailty in both interventions, it became evident that patients who are not frail are more inclined to undergo Open repair. This may raise concern whether the impact of frailty on outcomes following open repair is not fully

powered and be interpreted as type 1 error. Again, this could not be resolved within the context of study period.

Examining the standards of care in this study was crucial for identifying areas where the care of AAA patients could be improved. It also suggested that preoperative optimisation could be incorporated, particularly for frail patients. Nevertheless, it would be misleading to draw such a conclusion without considering the potential risks of delaying treatment (rupture risk), which cannot be determined from the information provided in this registry.

The statistical methodology used to evaluate the impact of frailty on outcomes was deemed appropriate and validated by an experienced statistician. A validated model has been developed using multivariable logistic regression to evaluate the impact of frailty on outcomes. This model takes into account factors such as age, creatinine levels, and the presence of comorbidities. Based on the findings, it can be concluded that frailty plays a significant role in predicting poorer outcomes after open surgical repair. This was not clearly shown in the EVAR group. It is not unexpected to see these results when only considering outcomes within a 30-day timeframe after the intervention. However, since AAA repair is centralised, it is possible that these patients may have been readmitted to other hospitals due to cardiovascular complications, which would not be captured in the registry data provided.

The findings of this study are robust and indicate that the presence of frailty, as classified by the NVR system, has a detrimental effect on postoperative outcomes after AAA repair, particularly in the open repair group. This finding has important implications and warrants further investigation into methods to enhance outcomes in this group.

Multi-centre, pilot study evaluating the feasibility, acceptability, and short-term outcomes of a tailored, virtual, home-based, prehabilitation programme in patients undergoing abdominal aortic aneurysms (AAA) repair - Critical appraisal

This is a proof-of-concept study that is prospective and multicentre in nature, with the objective of determining whether it is possible to conduct a remote prehabilitation program for patients who are due to undergo AAA repair. In accordance with the recommendations made by NICE, which highlighted this subject as a priority[213], the population of interest was effectively recruited to participate in the study, and this provides an additional piece of evidence towards the implementation of such programs in order to improve clinical outcomes following AAA repair.

The research was carried out between 2021 and 2023, involving patients who were scheduled for AAA repair from three different regions: West London, Essex, and Cambridge. It included individuals who were scheduled for open or endovascular repair. The data obtained from this study provides an accurate representation of the clinical care pathways for patients with AAA who are awaiting surgical repair on a national scale.

It is crucial to acknowledge that the study was conducted during the COVID-19 period, and we must not underestimate the influence it had on recruitment and acceptability. As previously mentioned, the waiting times for AAA repair during that period may have been prolonged due to a significant number of patients awaiting treatment. In addition, it is important to take into account that certain individuals who could have potentially participated in the pilot study may have regrettably passed away to COVID-19. In contrast, the recruitment rates mirrored those of previous prehabilitation interventions[197]. It is conceivable that this pilot study could have attained greater recruitment rates if it were carried out in the current era.

The primary objective of this study is to assess the feasibility of introducing a remote prehabilitation program for patients who are awaiting AAA repair. This intervention has not been previously explored, making it a novel area of investigation. The primary outcome was divided into three main parts, with a focus on the feasibility of recruitment, adherence, and acceptability. This will lay the foundation for a larger and more definitive research study. The

study's structure was strong and aligned with the established recommendations for feasibility studies that concentrate on exercise intervention[298].

One possible criticism of the study's design is the lack of a control group. Including a control group would have allowed for a comparison of the percentage of participants who completed the preoperative functional assessments (such as the 6MWT) and quality of life assessments. Nevertheless, establishing a control arm for exercise interventions poses a significant challenge, if not an insurmountable one. This is due to the potential for performance bias, where the knowledge of the intervention could potentially influence the outcomes. In addition, individuals in the control group have the option to engage in an exercise routine outside of the study, potentially reducing the potential advantages of the exercise intervention being examined in the study.

The research team diligently screened patients for the study, ensuring a high recruitment ratio. They attended regular multidisciplinary meetings and maintained regular communication with clinicians responsible for patient care. However, it is possible that some patients who may have met the criteria were overlooked. The study was not funded, and the research team from Imperial College faced logistical challenges in capturing all patients, despite their best efforts. This is evident in the relatively low number of patients assessed for eligibility, which was 132. In addition, the AAA care pathway varied among the three centres in this multicentre study, primarily due to the adjustments made to the pathway during the COVID-19 pandemic. This played a crucial role in capturing patients who were eligible for the study prior to their scheduled surgery.

Adherence rates were measured through regular weekly phone calls, participants' diaries, and, to a lesser extent, wearables. The study clearly outlined the criteria for success in adherence, with 80% of the prescribed sessions being the benchmark. There are valid concerns about the accuracy of capturing adherence rates through the proposed methodology, as it relies on participants and may be influenced by non-response bias or social-desirability bias. Some participants may have found it challenging to keep track of the intensity and frequency of each exercise component. This problem will persist in evaluating the compliance of exercise programs offered through remote means. One possible solution that has been explored in this study is the utilisation of wearables. Our study revealed that individuals who received a

wearable device exhibited a non-wear time of 20%. Furthermore, these participants yielded more precise outcomes concerning exercise intensity compared to those who relied on exercise diaries. Nevertheless, it can be debated whether the reported "moderate intensity" of the device truly aligns with the prescribed RPE scale of 12-14. Additionally, there may be financial considerations when providing each participant with such devices during the design of a large, randomised trial.

While the study has effectively shown that remote prehabilitation is safe for AAA patients, there are some concerns about the accuracy of assessing the acceptability of these interventions using the PACES questionnaire. This is also a matter of concern for the quality of life and disease-specific questionnaires, as they may potentially be inaccurate due to questionnaire fatigue or non-response. Nevertheless, the questionnaires utilised in the study have undergone validation in previous studies involving the UK population[262,281] and have been extensively employed to assess similar outcomes.

The proposed prehabilitation program is exercise-focused and has been designed in consultation with specialists in the field of exercise and prehabilitation. The intervention can be provided and monitored by a wide range of healthcare professionals. This indicates that this intervention has the potential to be replicated on a national level, which is crucial when planning a comprehensive study. The remote nature of the intervention allows participants to have flexibility in their exercise schedule, enabling them to choose the most convenient time during the week. This personalised approach aims to improve tolerability and accommodate individual preferences. Nevertheless, it is crucial for prehabilitation programmes to adopt a comprehensive approach, encompassing various modalities and addressing additional factors such as nutrition, lifestyle modification, and psychological interventions, as needed. Unfortunately, this study did not effectively explore these aspects. Regrettably, evaluating a multimodal prehabilitation program at the pilot stage necessitates the incorporation of other disciplines, such as nutritionist, which was not feasible in a limited, unfunded study.

The inclusion and exclusion criteria utilised in this study were deemed suitable and are representative of the patient population undergoing AAA repair in the UK. It is possible that excluding complex AAA was unnecessary in the context of a feasibility study but including them in a large-scale trial may not be feasible due to the complexity of repair.

This feasibility study has effectively presented the findings regarding screening, recruitment, and adherence rates. The study also provided a clear explanation for the exclusion of certain participants and the factors contributing to non-participation or non-adherence to the proposed prehabilitation program. It is important to consider a particular finding when designing a large-scale trial: the observed low participation and adherence rates in patients awaiting EVAR.

In this study, the researchers utilised the six-minute walk test as a means of evaluating the functional capacity of patients and assessing the effectiveness of the prehabilitation program. The results were presented in a manner consistent with reporting standards, utilising mean difference with 95%CI and p-value. However, there is a notable concern regarding the participation rate of individuals during the follow-up period, specifically at 6 weeks and 3 months after the surgical procedure. The reasons for this finding were primarily attributed to a lack of participant interest in travelling for study assessment only. The research team anticipated conducting the 6MWT during their routine follow-ups with the clinical team, which, unfortunately, had to be done through telephone follow-up due to the impact of COVID-19, which made the 6MWT assessment impossible.

There are concerns about using the 6MWT to assess the functional capacity of patients with AAA. CPET is widely regarded as the gold standard for evaluating functional capacity and predicting outcomes in major surgical procedures and AAA repair specifically. However, as discussed in the study's discussion section, CPET necessitates significant infrastructure and resources. Out of the three centres, only one incorporated CPET as a standard preoperative functional assessment. In addition, the 6MWT is not only cost-effective, but it has also demonstrated a positive correlation with CPET measurements[267]. The positive outcome of the exercise program should be taken into consideration when evaluating the effectiveness of prehabilitation, based on the improvements observed in the 6MWT distance.

The study findings are backed by the study results. Prehabilitation for patients awaiting AAA repair can be done remotely, and it has been found to be feasible and acceptable with reasonable adherence rates. The secondary outcomes of this study have demonstrated encouraging improvements in the functional capacity of participants. However, the implications

of these improvements on postoperative outcomes remain uncertain. This study has the potential to lay the foundation for a comprehensive nationwide randomised controlled study.

Neuromuscular Electrical Stimulation for Rehabilitation after general and vascular surgery - a pilot randomised clinical study - Critical appraisal

This study was conducted in a single centre and followed a prospective, single-blind, pilot randomised controlled trial design. The time frame of the study spanned from July 2021 to January 2022, aligning with the current state of clinical practice. Given the innovative nature of this intervention, it would be best to conduct a pilot randomised controlled trial (RCT) to investigate the acceptability and safety of this approach. The utilisation of neuromuscular electrical stimulation as an additional tool for rehabilitation following orthopaedic surgery, as well as in stroke and critical care patients, has demonstrated significant benefits. Exploring the potential of incorporating this adjunct into rehabilitation after vascular and general surgery could potentially enhance outcomes, making it an intriguing area of study.

The primary goal of this study is to establish a foundation and gather preliminary data to support a comprehensive and conclusive randomised controlled trial. The pilot study was conducted to assess the feasibility of randomisation and evaluate safety, acceptability, and adherence in utilising NMES as the primary outcome measure. This study is suitable for a pilot RCT that aims to investigate a new intervention in a clinical setting. Secondary outcomes also encompassed functional outcomes measured and cost-effectiveness analysis, which were sufficient to investigate the suitability of utilising these measures in a large-scale trial.

A computerised randomisation method was used, which is widely accepted as a robust method for randomisation. It could be argued that each speciality surgery should have been randomised separately to determine the feasibility of randomisation across different specialities. Nevertheless, since this study focused on evaluating the practicality of utilising the device in surgical patients within a hospital environment, the randomisation process was appropriate for addressing the intended inquiry.

The research team, in collaboration with device manufacturers, made every effort to ensure that patients were unaware of which group have they been assigned to. It was not feasible to blind the assessors due to the need for continuous instructions in the "active" group, such as increasing intensity, which was not required in the "control" group. In addition, the participants in the study were informed about the potential effects of the device on muscle contractions, which could have provided a clue about their assignment to the "active group." The results clearly demonstrated a significant difference between the two groups, with 91% of participants in the "active" group perceiving the device as active, compared to only 35% in the "control" group. Therefore, there is a debate about the feasibility of conducting a blinded RCT with this device.

Concerns may be raised about the feasibility of randomisation due to the high number of participants excluded from the study, which accounts for approximately 90% of the screened participants. The reason for this finding is the inclusion of patients who have a Rockwood frailty score of more than 3, indicating frailty. The rationale for this inclusion criteria is to identify patients who are particularly vulnerable to extended hospital stays due to their frailty. In addition, we were interested in investigating the practicality of implementing a device in a population of individuals who are typically elderly and may have reservations about using technology. However, the impressive recruitment rates indicate that these patients can be successfully enrolled in this study.

To ensure effective compliance with device usage, participants were required to utilise the device daily. However, during the randomisation process, participants were advised to use the device between 1 and 6 times per day. Even though the requirements for successful adherence were not very demanding, only 54% of the individuals in the intervention group were able to meet them. It is important to consider this when planning future trials, as we discovered that patients needed consistent reminders and support. One possible explanation for the participants' lack of interest in using the device is the challenge of sitting out in a chair, which can be quite overwhelming for frail patients recovering from recent surgery. In order to ensure satisfactory adherence rates, it is crucial to provide patients with proper education on how to use the device. Additionally, it would be beneficial for future trials to introduce the device prior to surgery, rather than on the day of surgery.

The reporting of secondary outcomes was presented with difference of means and p-values for illustrative purposes, and it should be interpreted with caution as this study is not powered. Nevertheless, the positive outcomes observed in the participants of the colorectal surgery study may suggest potential advantages in expediting patient recovery, as demonstrated in a comprehensive and well-designed trial.

The health economics analysis was conducted by an expert in the field, although its scope was constrained due to the study's design. A total of 61 out of 103 participants were included in the analysis as they did not respond to the HRQoL questionnaire. After adjusting to the baseline covariants, the observed variation in average costs between the groups was not statistically significant. The participants needed frequent reminders to use the device, which was not considered in the cost-effectiveness analysis, a factor that could question the reliability of the cost-effectiveness analysis and perhaps should be factored in the design of future trials.

The applicability of NMES device as a supplementary tool for rehabilitation shows promise, and the participants in the study correspond to current practices. The use of NMES devices can offer significant benefits in improving the recovery of frail patients who have undergone major surgery, potentially leading to reduced resource costs. If the device's effectiveness is confirmed, it could be seamlessly incorporated into the treatment of not just vascular patients, but also individuals undergoing significant surgical procedures such as cancer patients.

Chapter 10 Future work

The studies demonstrated in this thesis has provided new evidence in the field of frailty and prehabilitation in the effort of improving outcomes of patients undergoing AAA repair. It also has set grounds for the use of technology in such cohort of patients. However, more work required to establish Level 1 evidence in order to implement these interventions in clinical practice if proven to be effective. We herein present the design of future studies.

Study 1: Multi-centre randomised controlled study of a multimodal remote tailored 6-week prehabilitation programme to improve short- and long-term outcomes of patients scheduled for abdominal aortic aneurysm repair.

Population

Any patient scheduled electively for AAA repair (AAA size < 7cm) and able to participate in a prehabilitation programme with the involvement of as many vascular centres in UK as possible.

Intervention

A multimodal , remote, tailored, 6-week prehabilitation programme for patients scheduled for AAA repair with follow up at end of prehabilitation programme and then 6 weeks, 12 weeks, 24 weeks, 36 weeks following surgery. Functional capacity assessment using 6-minute walk test performed at baseline, end of prehabilitation programme and then 6 week, 12 weeks following surgery to assess long term effect of prehabilitation.

Comparison

Standard clinical care for patients undergoing AAA repair.

Outcomes

- Primary outcome : 30 -days major cardiovascular events (MACE)
- Secondary outcomes:
 - Change in 6-minute walk test
 - HDU/ITU and total length of stay
 - 1, 3, 5-year freedom from cardiovascular events
 - 1, 3, 5-year overall survival

- Change in health-related and aneurysm-specific quality of life assessments
- Cost effectiveness

Study 2: Randomised controlled trial to assess the effectiveness of using neuromuscular nerve stimulator(NMES) in improving outcomes following AAA repair

Population

Any patients who underwent open AAA repair and able to use neuromuscular nerve stimulator.

Intervention

Patients who underwent from open AAA repair and able to sit out in chair will be advised to use NMES device 3 times a day while they are admitted. Follow up will be at the time of discharge and then 6 weeks, 12 weeks following surgery.

Comparison

Patients who underwent open AAA repair and able to sit out in chair will be advised to use a “Sham” NMES device 3 times a day while are admitted

Outcomes

- Primary outcome: Length of stay following surgery
- Secondary outcomes:
 - Change in health related and aneurysm specific quality of life assessment
 - Cost effectiveness
 - Change in 6MWT
 - Postoperative complication
 - Change in Frailty score measured using Clinical Frailty Scale

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Appendix

Appendix 3.1: HRA assessment for the requirement of ethical approval for Frailty in AAA study – (Chapter 3)

04/01/2021

Result - NOT Research

Go straight to content.



Is my study research?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:
Impact of frailty on patients undergoing abdominal aortic aneurysm repair

IRAS Project ID (if available):

You selected:

- **'No'** - Are the participants in your study randomised to different groups?
- **'No'** - Does your study protocol demand changing treatment/ patient care from accepted standards for any of the patients involved?
- **'No'** - Are your findings going to be generalisable?

Your study would NOT be considered Research by the NHS.

You may still need other approvals.

Researchers requiring further advice (e.g. those not confident with the outcome of this tool) should contact their R&D office or sponsor in the first instance, or the [HRA](#) to discuss your study. If contacting the HRA for advice, do this by sending an outline of the project (maximum one page), summarising its purpose, methodology, type of participant and planned location as well as a copy of this results page and a summary of the aspects of the decision(s) that you need further advice on to the HRA Queries Line at Queries@hra.nhs.uk.

For more information please visit the [Defining Research](#) table.

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Appendix 4.1 Search strategy for the systematic review of the feasibility and adherence of exercise programmes for patients with abdominal aortic aneurysm

	Ovid MEDLINE(R) ALL <1946 to October 26, 2022> Search date 26 October 2022	
1	exp Aortic Aneurysm/	60392
2	exp Aneurysm, Ruptured/	19727
3	exp Aorta, Abdominal/	22144
4	AAA*.ti,ab.	19240
5	(aneurysm* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort*)). ti,ab.	45704
6	(aort* adj3 (balloon* or dilat* or bulg*)). ti,ab.	12342
7	(abdom* adj3 (balloon* or dilat* or bulg*)). ti,ab.	1177
8	(aneurism* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort*)). ti,ab.	514
9	or/1-8	113832
10	exp Exercise/	239346
11	exp Exercise Therapy/	61516
12	Preoperative Exercise/	348
13	"home based train*". ti,ab.	312
14	"interval train*". ti,ab.	3853
15	"physical activit*". ti,ab.	140832
16	"physical train*". ti,ab.	6512
17	"physical therap*". ti,ab.	27054
18	exercis*. ti,ab.	341077
19	physiotherapy. ti,ab.	22929
20	prehabilitat*. ti,ab.	1155
21	pre-habilitation. ti,ab.	75
22	"physical fitness". ti,ab.	11606
23	prehab. ti,ab.	55
24	or/10-23	597914
25	9 and 24	913

	Embase <1974 to 2022 October 26> Search date 26 October 2022	
1	exp aortic aneurysm/	27473
2	exp aneurysm rupture/	20704
3	exp Aorta, Abdominal/	24431
4	AAA*. ti,ab.	26262
5	(aneurysm* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort*)). ti,ab.	60555
6	(aort* adj3 (balloon* or dilat* or bulg*)). ti,ab.	19873
7	(abdom* adj3 (balloon* or dilat* or bulg*)). ti,ab.	2002
8	(aneurism* adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort*)). ti,ab.	727
9	or/1-8	136719
10	exp exercise/	435657
11	exp kinesiotherapy/	99554
12	preoperative exercise/	890
13	"home based train*". ti,ab.	428
14	"interval train*". ti,ab.	4971
15	"physical activit*". ti,ab.	190845
16	"physical train*". ti,ab.	9791
17	"physical therap*". ti,ab.	42883
18	exercis*. ti,ab.	476836
19	physiotherapy. ti,ab.	41952
20	prehabilitat*.ti,ab.	1810
21	pre-habilitation.ti,ab.	183
22	"physical fitness".ti,ab.	15172
23	prehab.ti,ab.	135
24	or/10-23	848016
25	9 and 24	1772

	CINAHL via EBSCO Search date 26 October 2022	
S24	S8 AND S23	757
S23	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22	481,153
S22	TX prehab	57
S21	TX "physical fitness"	23,362
S20	TX pre-habilitation	28
S19	TX prehabilitat*	527
S18	TX physiotherapy	62,092
S17	TX Exercis*	237,751
S16	TX "Physical Therap*"	152,260
S15	TX "Physical train*"	1,673
S14	TX "Physical activit*"	97,275
S13	TX "Interval Train*"	2,567
S12	TX "home based train*"	134
S11	MH "Preoperative Care+"	23,050
S10	MH "Therapeutic Exercise+"	59,206
S9	MH "Exercise+"	122,192
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	18,646
S7	TX (aneurism* N4 (abdom* or thoracoabdom* or thoraco-abdom* or aort*))	57
S6	TX (abdom* N3 (balloon* or dilat* or bulg*))	261
S5	TX (aort* N3 (balloon* or dilat* or bulg*))	3,271
S4	TX (aneurysm* N4 (abdom* or thoracoabdom* or thoraco-abdom* or aort*))	10,119
S3	TX AAA*	5,453
S2	MH "Aorta, Abdominal"	1,500
S1	(MH "Aortic Aneurysm+")	8,521

Appendix 5-1: Borg Scale

Borg Scale	Rating of Perceived Exertion (RPE)	Breathing Response
0	Nothing at all, seated rest	No change, normal
0.5	Extremely Weak	
1	Very Light	Slight Increase
2	Light	
3	Moderate	Lightly puffing, able to hold conversation
4	Somewhat Hard	Noticeable puffing, can only hold a BROKEN conversation
5	Hard	Laboured
6		
7	Very Hard	Short of Breath
8		
9	Extremely Hard	Out of Breath
10	Maximum Effort	Gasping

The Borg Perceived Exertion Scale gives you an idea of how hard your exercise feels.

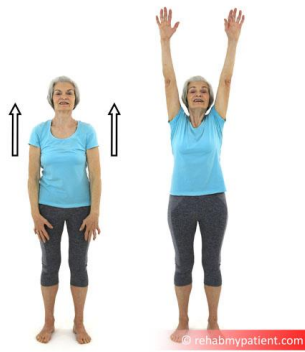
If the exercise feels light (less than 2), you should **increase** the pace of your exercise.

If the exercise feels hard (5 or greater), you need to **slow** the pace.

Exercise should feel somewhat hard (3-4).

Appendix 5-2: Example of exercise prescription provided to PREHAB-AAA participants

Imperial College research project		Email: majd.rawashdeh12@imperial.ac.uk	
Exercise plan: Level 3 extended	Patient: M S(CUH)	Date: 17th Oct 2022	Practitioner: Majid Rawashdeh
		Lumbar Rotation Lie on a bed or the floor. Bend your knees and keeping your feet flat on the bed or floor, rotate your hips to one side creating a rotation through your lower back. Only go as far as feels comfortable, you do not need to get your knees to the floor. Return to the opposite side. This is an excellent lower back mobility exercise, especially if you have lower back pain or disc problems. Remember to keep breathing! Progression: Take your knees further over. Sets: 2 Repetitions: 10 Both sides Video: http://youtu.be/UxORTXzuU9E	
		Ankle Circles Sitting Sit down, and move your ankles around in circles both anti-clockwise and clockwise. This is a great mobility exercise to the ankle, and very useful for ankle stiffness, making you ready for other exercises. Progression: Raise your foot higher before circling your ankle. Sets: 2 Repetitions: 10 Both sides Video: http://youtu.be/6XX3R9ibBfw	
		Wrist Circles Draw circles with your hand and wrist. Move in one direction first, and repeat to the opposite direction. This exercise will help mobilise a stiff wrist. Progression: Hold a small weight (for example a tennis ball or a small food tin) in your hand while circling your wrist. Sets: 2 Repetitions: 10 in each direction Both sides Video: https://youtu.be/wRSk1_C6yOM	



Shoulder Flexion Standing

Stand upright with good posture. Lift both arms gently in front of you. Take your arms as far as feels comfortable. If you cannot get your arms above your head, just take your arms to your comfortable end of range. Slowly lower your arms. This will help mobilise your shoulders and upper back, and strengthen your arms.

Progression: When you feel steady, go up on to your toes, stretching up with your arms.

Sets: 2 | Repetitions: 10

Video: <https://youtu.be/Ws7mfNoVazg>



Standing Rotations

Stand upright with good posture and your feet shoulder width apart, toes pointing forwards. Cross your arms in front of your body. Twist your upper body around towards the left as far as is comfortable, keeping your hips facing forwards. Slowly return to the centre then repeat to the right. This exercise helps improve mobility to the pelvis and spine, but also helps balance.

Progression: If you are confident with your balance, do this exercise with your eyes shut.

Sets: 2 | Repetitions: 10 | Both sides

Video: <https://youtu.be/3-LyyoRtauU>



Back Side-Flexions Standing

Stand upright with good posture. Stand with your feet shoulder width apart, and your hands resting by your sides. Gently bend your spine to the left side running your arm down the outside of your leg. Slowly return to the centre and repeat to the right side. This will help stretch your spine and improve your balance.

Progression: Hold in the stretched position for 2-3 seconds.

Sets: 2 | Repetitions: 10 | Both sides

Video: <https://youtu.be/bvzL2CfodxU>



Two-arm Side Circles

Draw gentle circles with your arms to the side of your body. Move your arms clockwise and anti-clockwise. This exercise will actively mobilise stiff shoulders.

Progression: make bigger circles with your arms.

Sets: 2 | Repetitions: 10 in each direction

Video: <https://youtu.be/GinxXNiyHFA>



The Football Supporter

Take a scarf, hand towel or dowel rod, and grasp both ends. Lift it above your head, and slowly move the scarf from side-to-side as if you were waving a football scarf. This exercise will help improve mobility to the shoulder, but if your shoulder is stiff, start gently as it can be uncomfortable.

Progression: increase your speed.

Sets: 2 | Repetitions: 10

Video: <https://youtu.be/fi73pRbWiXI>



Marching Climb a Rope

Stand upright with good posture, next to a wall or table just in case you need support. March on the spot. Keep your knees up, and using your arms, imagine you are pulling a rope downwards from the ceiling. Try to stay in exactly the same spot throughout your march. This exercise is good for knee mobility, endurance, balance and co-ordination.

Sets: 2 | Repetitions: 10

Video: <https://youtu.be/DyxD-D51zpU>



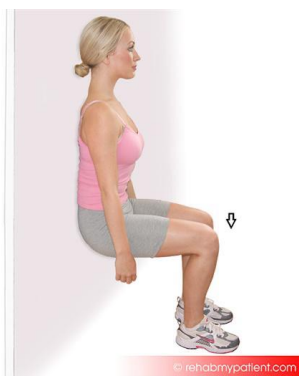
Sidestep Big

Stand upright with good posture with some clear space around you. Take a large step to the side with one foot, and then join with the other foot. Repeat with the opposite leg leading this time to come back to the start position. This exercise improves strength and co-ordination in the legs.

Progression: For extra challenge do this exercise more quickly..

Sets: 2 | Repetitions: 5 | Both sides

Video: <https://youtu.be/H47KMfgw9Fs>



Full Wall Squat

Open your legs slightly wider than shoulder width, stand with your back resting against a wall, and bend your knees to the full squat position (90 degrees). Make sure you keep the middle of your knee-cap in line with the middle toes of your foot. Always keep your feet flat on the ground, do not let your heels raise from the floor. This exercise will help to strengthen your quadricep muscles, knee joints and legs.

Progression: Increase the time in the squat position to build more strength.

Sets: 2 | Repetitions: 5 | Time: 2-5 seconds

Video: <https://youtu.be/dXkL0muKCLo>



Shoulder Push

Grasp a light dumbbell (or object such as a water bottle) in each hand, and gently lift the dumbbell above your head with one arm, and then the other. Only go as far as feels comfortable. This exercise strengthens the deltoid muscle group.

Progression: use a heavier weight.

Sets: 2 | Repetitions: 8 | Both sides

Video: <https://youtu.be/pOG9JgHh8Yk>



Wall Press-Up

Stand upright with good posture, position yourself in front of a wall in a press-up position with your arms straight and palms flat on the wall. Drop your chest towards the wall by bending your elbows. Hold this position for 1-2 seconds. Return to the start position by pushing through your arms. This is a chest, back and shoulder strengthening exercise.

Progression: You can make the exercise harder by standing further back from the wall.

Sets: 2 | Repetitions: 5

Video: <https://youtu.be/ox18YHnWTsU>



Hip Abduction with Band

With an exercise band secured around your ankle, and the other end anchored to a fixed object to your side, move your straight leg (abduct) away from your body to create resistance in the band. This exercise predominantly strengthens your outer hip and gluteal (buttock) muscles, but also improves balance on your opposite leg.

Progression: Do more slowly.

Sets: 2 | Repetitions: 5 | Both sides

Video: <http://youtu.be/mH631V-5K6s>



Single Leg Balance Standing with Support

Stand on one leg, and try to keep your balance. Be careful and hold on to a wall or table for support when you first start this exercise. A single leg balance exercise such as this is an enormously valuable exercise, and its benefits including strengthening the muscles and ligaments around the ankles and knees, and improving balance.

Sets: 2 | Repetitions: 5 | Time: 10-30 seconds | Both sides

Video: <https://youtu.be/3j0O6jRe8uY>



Step Up and Downs Unsupported

Stand upright in front of the bottom step of your staircase. Step up onto the first step with one leg, and bring the other leg to the step to meet it. With control, lower this same foot back to the floor, followed by the other. Tip: Keep your knee tracking over your toes.

Progression: Do this exercise more slowly for extra challenge.

Sets: 2 | Repetitions: 5 | Both sides

Video: <https://youtu.be/FBaTE2EpdXQ>



Sit to Stand - Bottom Touch

Sit upright with good posture. Place your arms across your chest. Gently lean forwards and use as much leg and core strength as you can to push yourself up. If you get stuck, use one or both arms to assist. Once upright, stand up straight. When you feel comfortable, slowly sit back down, ideally with your arms across your chest. However, if you need some guidance then use your arms to assist the sitting. Touch your bottom on the chair, and then repeat the first part by standing up again. Try to keep a straight spine during the sitting rather than let your back round forwards too much. This exercise will strengthen your legs and core. Easier option: Start off with a cushion on the chair, if you find this exercise hard initially.

Sets: 2 | Repetitions: 5

Video: <https://youtu.be/Hwmn2pLpkeU>



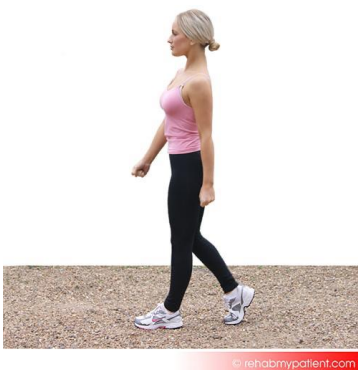
Supine Bridge Medium

Lie flat on your back with your arms across your chest, and with your knees bent. Squeeze your bottom muscles and lift your body upwards. Make sure you maintain good posture (do not over-arch your lower back) and contract the deep abdominal muscles by squeezing your tummy towards your spine. This exercise helps to strengthen the abdominal, lower back, gluteal and hamstring muscles.

Progression: Hold the bridge position for 2-5 seconds.

Sets: 2 | Repetitions: 5

Video: <http://youtu.be/wFYhfbFYzZI>



Walking

Maintain a good upright posture and make sure you keep your head up, with your eyes on the horizon line. The aim is to be slightly breathless but still able to hold a conversation. Ideally, walk with a friend to make it more fun.

You can replace this walking with fast-paced walking or jogging.

Aim to do that 5 times a week

Sets: 1 | Time: 30 mins (5 times per week)

Video: <https://youtu.be/VomnFAuHb60>

End of Thesis