THE EFFECTIVENESS OF A SHORT-TERM REHABILITATION PROGRAMME OF PREOPERATIVE HIGH INTENSITY EXERCISE AND INSPIRATORY MUSCLE TRAINING TO IMPROVE POSTOPERATIVE RECOVERY IN CANCER PATIENTS UNDERGOING SURGICAL LUNG RESECTION

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It has been said that it takes a community to raise a child and in that sense, it has taken a community to reach this point in the Doctoral journey. For the last 2 years this thesis has been my child, requiring attention and nurture to develop and grow into a work that I am immensely proud of and grateful for the opportunity to complete. I am so proud of the tenacity and commitment that I have given this study but wholeheartedly acknowledge that this would not have been possible without the important support network around me, and they deserve my sincere thanks. Firstly, to my colleagues at the University Hospital of North Midlands NHS Trust for the drive and passion to trust in the development of services that can shape quality healthcare delivery in the future. To my Supervisor Professor Roozbeh Naemi who has provided expertise and consistent guidance throughout these years of study. To my wonderful husband, Alex who has shown great patience and provided much needed motivation and encouragement in times when mine began to waver. To my amazing Mum, Sister Leisa and Brother-in-Law Ajith who have always believed in me and appreciated the sacrifices required to commit to academic study. Together they have been my biggest champions throughout. Finally, to my adorable, brilliant and beautiful Niece Florence who has provided the many moments of hilarity, honesty and perspective that has proven to be the light-hearted relief of immeasurable importance throughout this journey.

Abstract

Introduction: Patients with operable lung cancer may be elderly, frail and multi-morbid, presenting with debilitating symptoms that can increase the risk of postoperative pulmonary complications and result in extended hospital length of stays. It was hypothesised that a 2-4 week preoperative rehabilitation programme consisting of high-intensity interval training (HIIT) and inspiratory muscle training (IMT) could improve preoperative pulmonary function to optimise postoperative recovery. The twice weekly face-to-face programme was supervised by a qualified physiotherapist or exercise physiologist within a community gym setting and the virtual programme consisted of recorded videos and live online exercise sessions for patients to access at home. The aim of this study was to investigate the efficacy of the two modes of preoperative rehabilitation programmes in improving patient outcomes in comparison with standard care (no rehabilitation) in patients awaiting surgical resection for lung cancer.

Methods: A case-control cohort design evaluated the effectiveness and feasibility of preoperative HIIT and IMT for lung cancer patients delivered through the expansion of an existing Cardiac Rehabilitation Service. The preoperative rehabilitation programme was delivered either face-to-face or virtually and was compared to standard care. A total sample of 444 patient records were evaluated; standard care (n=166), face-to-face rehabilitation (n=142) and virtual rehabilitation (n=136). Groups were matched on age, BMI, ASA classification and extent of surgical resection undertaken. Patient data from a 3-year period was accessed to

review hospital length of stay, incidence of pulmonary complications and 12-month survival. Pre and post intervention pulmonary function tests and health-related quality of life were measured alongside patient uptake, programme completion, HIIT attainment and patient or clinician reported adverse events in both rehabilitation groups.

Results: PiMAX improved significantly pre and post virtual rehabilitation, mean increase 1.312 cmH_20 (p=0.001, 95% CI 0.535-2.089cmH_20) and pre and post face-to-face rehabilitation, mean increase 1.144cmH_20 (p<0.001, 95% CI 0.558-1.730cmH_20). Face-to-face rehabilitation significantly increased preoperative FEV1, mean difference 0.064 litres (p<0.001, 95% CI 0.032-0.096 litres), percentage predicted FEV1 2.79% (p<0.001, 95% CI 1.599-3.978%) and preoperative FVC 0.083 litres (p<0.001, 95% CI 0.045-0.121 litres). Virtual rehabilitation achieved non-significant increases in these pulmonary function measures and significantly increased percentage predicted FVC 2.74% (p=0.021, 95% CI 0.331-3.858%). Postoperative complication severity was significantly lower with virtual rehabilitation in comparison to standard care (p=0.002) but was not statistically different to face-to-face rehabilitation. Virtual rehabilitation had a significantly lower proportion of positive radiological findings at 20.6% compared to face-to-face rehabilitation 33.8% (p=0.013). Despite significant improvements in pulmonary function and some improvement in postoperative complications with rehabilitation, hospital length of stay (mean ±SD) for virtual rehabilitation (8.13 days ±6.45) or face-to-face rehabilitation (9.75 days ±9.61) was not significantly different to standard care (8.27 days ±5.47) (p=0.114). Mean length of high

dependency care was also not statistically different between groups (p=0.561). Preoperative rehabilitation groups did not differ statistically from standard care for antimicrobial therapy prescription, high flow oxygen requirement, tracheostomy insertion or chest drain duration. All factors indicative of postoperative pulmonary complications were associated with significantly increased risk of mortality 12 months post-surgery; postoperative tracheostomy insertion HR 8.19 (p<0.001, 95% CI 4.25-15.77), high flow oxygen requirement HR 3.90 (p<0.001, 95% CI 2.17-7.00), positive radiological findings HR 2.62 (p<0.001, 95% CI 1.58-4.35), positive sputum culture HR 2.44 (p=0.002, 95% CI 1.41-4.25) and antimicrobial therapy prescription HR 2.33 (p=0.002, 95% CI 1.38-3.94). Virtual or face-to-face rehabilitation did not influence 12-month survival although a poorer baseline physical activity status was associated with a significantly increased risk of mortality at 12-months HR 1.92 (p=0.001, 95% CI 1.33-2.77). No serious adverse events occurred with intervention and programmes had 100% uptake and high completion rates; virtual rehabilitation 76.5% and face-to-face rehabilitation 73.2%. 43% of patients in either mode of delivery were unable to achieve 80% HRR HIIT targets in the programme. Waiting time to surgery (mean ±SD) was significantly longer in face-to-face rehabilitation (23.48 days ±11.39) in comparison to virtual rehabilitation (19.92 days ±12.12) (p=0.033, 95% CI 0.23-6.89) and standard care (18.45 days ±19.92) (p<0.001, 95% CI 2.07-7.98).

Conclusion: A 2-4 week combined HIIT and IMT programme as a preoperative rehabilitation strategy can improve pulmonary function for patients awaiting surgical lung resection but improvements may not influence hospital length of stay,

incidence of postoperative pulmonary complications or 12-month survival. Virtual rehabilitation appears to be a superior mode of delivery to influence clinical severity of postoperative complications and provide timely intervention in comparison to face-to-face rehabilitation. Cardiac Rehabilitation programmes could be a viable referral pathway for lung cancer patients to access rehabilitation programmes in the future but further research is needed to establish the cost effectiveness of these interventions prior to implementation.

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Chapter 1. Introduction

1.1. Lung Cancer Aetiology and Global Prevalence and Mortality Statistics

Lung cancer, medically termed carcinoma, occurs when cells within lung tissue divide uncontrollably. This uncontrolled cell growth results in tumour formation, causing inflammation and obstruction within affected regions of the lung. Lung cancers can be categorised as either non-small cell lung carcinomas (NSCLC) or small cell carcinomas. National lung cancer statistics identify that NSCLC is notably the most prevalent form of lung cancer, and currently accounts for 80-85% of all known lung cancer cases (Bareschino et al., 2011). Small cell carcinoma is a more aggressive form of carcinoma, it divides, mutates and spreads more rapidly than NSCLC but, according to current statistics, appears to be far less prevalent. The overall prevalence of lung cancer worldwide is staggering and is reflected in statistics compiled for the American Cancer Society indicating that lung cancer remains the leading cause of cancer-related mortality worldwide, with 25% of cancer deaths directly attributable to lung carcinoma (Siegel et al., 2018). This individual percentage is higher than the combined deaths related to colon, breast and prostate cancers. NSCLC cancers can be sub-divided further into squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Current evidence suggests that adenocarcinomas account for 30% of NSCLC cases, these cancers are formed within the lining of lung surfaces and are usually present on the outer regions of the lungs (Zappa and Mousa, 2016; Cancer Treatment Centres of America, 2021). A further 30% are attributable to squamous cell carcinomas and these affect the

respiratory tract and airways (Zappa and Mousa, 2016). The specific location of tumour growth and the associated inflammation and obstruction within the respiratory tract and surrounding lung tissue results in often unpleasant and distressing symptoms experienced by patients diagnosed with lung cancer.

The most common symptoms associated with lung cancer include persistent coughing, expectorant containing blood flecked sputum, chest and bone pain, breathlessness, hoarse voice, unintentional weight loss and fatigue (Corner et al., 2005; Hamilton et al., 2005). These symptoms are not exclusive to lung cancer, they can be associated with many different medical conditions alongside the natural progression of ageing and this non-specificity of signs and symptoms, may result in detrimental delays in diagnosis and treatment in this patient population. Theoretically the lack of symptom specificity may result in patients with lung cancer seeking medical attention when symptoms are prolonged, extensive and present a greater symptom burden, and this ultimately arises within the later stages of disease progression. This could, in part, explain the higher mortality rate in lung cancer cases worldwide.

1.2. Lung Cancer Staging and Survival

Lung cancer survival varies greatly depending upon how early patients are diagnosed, the cancer staging and overall condition of the patient. Staging of lung cancer is particularly pertinent to survival. Lung cancer is categorised into four stages with 1 being the earliest and 4 being the latest stage. Current evidence

indicates that 55% of lung cancer cases will survive for five years or more if caught and treated at stage 1 (Cancer Research UK, 2021). This compares with just 5% of cases surviving at five years when treated at stage 4 (Cancer Research UK, 2021). This highlights the importance of early recognition and rapid implementation of management pathways for this patient population. Treatment options available to these patients are dependent upon the type and spread of the cancer alongside the robustness and wider health status of the individual. Since symptoms are non-specific, can be gradual in onset, slow to present themselves and occur most frequently in elderly populations it is likely that this also contributes significantly towards the devastating prognosis and survival rates evident in lung cancer worldwide. Clinically, patients undergoing adjuvant therapy, such as radiotherapy or chemotherapy or surgical procedures, often present at the time of treatment with significant symptom burden, poor health-related quality of life and significant comorbidities which can negatively impact upon overall prognosis and recovery.

1.3. Lung Cancer and Associated Risk Factors

The British Lung Foundation (2021) report stated that 85,000 people residing in the United Kingdom currently have a diagnosis of lung cancer and this prevalence has increased by 23% since 2004. Based on extensive and consistent epidemiological evidence, smoking has long been considered the greatest risk factor associated with lung carcinoma, and this is largely attributable to the toxic substances inherent within tobacco products. These harmful cancer-causing agents are known as

carcinogens and are present within cigarette smoke. The inhalation of this smoke exposes the lung tissue to carcinogenic material, damaging the lung cells and subsequently altering cell structure and function, resulting in abnormal mutations and cell growth. The impact of smoking in lung cancer is overwhelming. The Centres for Disease Control and Prevention (2021) highlighted smokers are fifteen to twenty times more likely to develop lung cancer than non-smokers. Similarly, Cancer Research UK (2021) considers that 80% of confirmed lung cancer diagnoses are a direct result of smoking. Considerations regarding advancing age also seem particularly pertinent in lung cancer diagnosis, further statistics by Cancer Research UK highlight that out of 46,800 new lung cancer diagnosis made in a year, approximately 45% of these are in those aged 75 years and over (Cancer Research UK, 2021). This report also noted that prevalence of lung cancer was slightly higher in male populations with 24,900 new cases diagnosed in males as opposed to 23,100 in females in the UK in 2017.

Incidence of lung cancer has also been reported to be over 80% greater in areas of high deprivation suggesting that standards of living and environmental factors may also impact upon disease aetiology and progression (Centres for Disease Control and Prevention, 2021). Carcinogens and toxic substances are found in an array of pollutants, these may also be related to housing or work environments within working class communities and highly industrialised and poorer areas. Extensive public health campaigns have been employed to highlight the adverse health effects related to smoking (Public Health England, 2018). The effectiveness of these campaigns and their impact upon the disease and healthcare burden, may not be

evident in lung cancer screening and prevalence for the foreseeable future, as evidenced through the increasing prevalence of lung cancer diagnosis annually. Recently a higher incidence of chronic respiratory conditions, such as Chronic Obstructive Pulmonary Disease (COPD) have been observed in lung cancer, with researchers suggesting that this factor may warrant inclusion in early identification screening tools (Mouronte-Roibas et al., 2016; Carr et al., 2018). A causative association between these chronic respiratory conditions and their aetiology in lung cancer has not been comprehensively established within the literature. However, a history of smoking, higher levels of deprivation and exposure to environmental pollutants have consistently been identified as causative factors that lead to chronic respiratory conditions such as COPD (Global Initiative for Chronic Obstructive Lung Disease, 2022) and the link between chronic respiratory diseases and lung cancer may therefore be one of associated precipitating risk factors.

A significant proportion of previous research has focused on the epidemiological evidence to identify causative agents linked to lung cancer and pioneering scientific work has commenced to identify key biomarkers that could be used to screen and prevent the devastating morbidity and mortality statistics attributable to late-stage lung cancer (Chu et al., 2018; Seijo et al., 2019; Sears and Mazzone 2020). Identifying lung cancer at an earlier stage could enable more patients to undergo curative adjuvant therapy or surgical interventions and instigating this process at an earlier stage may also negate some of the adverse physical effects of prolonged symptom burden. Currently surgical removal of cancerous lung tissue remains the

primary curative treatment for NSCLC patients. NHS England (2019) has set out clear ambitions in lung cancer management within The NHS Cancer Programme and NHS Long Term Plan for Cancer. This, coupled with current identification, screening and lung cancer pathways has resulted in an elderly, frail and multimorbid patient presenting for complex surgical procedures. Identifying strategies to optimise functional capacity and preparation for the insult of surgery continues to receive increasing attention within the literature and clinical teams. Consensus on the most effective management strategy is yet to be fully determined and therefore a comprehensive preoperative strategy for these patients is yet to be embedded into clinical practice.

1.4. Operable Lung Cancer and Surgical Risk

Surgery for lung cancer consists of removal or resection of the tumour and excursion of affected lung tissue. Dependent upon the location and extent of lung tissue to be resected this may require the removal of a defined wedge, a complete segment, lobe or entire lung and respectively these procedures are termed wedge resection, segmentectomy, lobectomy and pneumonectomy. Approximately 2400 lobectomies and 500 pneumonectomies are undertaken in the United Kingdom annually, with in-hospital mortality rates reported to be in the region of 2-4% and 6-8% for each group respectively (Rasheed and Govindan, 2012). Global mortality rates have been reported to be as high as 11% for pneumonectomy; the most extensive lung resection performed in thoracic surgery (Rasheed and Govindan,

2012). The prognosis for lung cancer patients with advanced disease or that of an inoperable nature is undoubtedly poor, but significant morbidity and mortality risk is also associated with surgical procedures within the thoracic cavity requiring direct removal of lung tissue, since this type of surgery can significantly impact respiratory function in both the immediate and long term. Rasheed and Govindan (2012) highlighted that a primary aim of preoperative pulmonary assessment was to identify those patients presenting with the highest risk of perioperative complications and thus most likely to result in long term disability, with the fewest tests possible. This essentially includes determining whether the tumour is appropriate for resection, whether the patient has adequate respiratory reserve to tolerate removal of lung tissue, and whether there are any major medical contraindications to anaesthesia and surgery; referred to as an assessment of anatomical, physiological and operational resectability. Thoracic surgery results in several pulmonary physiological effects including changes in lung volume, lung compliance and pulmonary blood flow. Evidence suggests that even without removal of actual lung tissue a persons' vital capacity would decline by 25% in the early postoperative period, with a gradual improvement to baseline over the course of weeks (Lyrd and Burns 1975; Bolton and Weiman, 1993). In the context of patients requiring removal of lung tissue or those with underlying lung disease, this degree of reduced vital capacity through thoracic surgery and associated pulmonary complications may result in respiratory failure or death.

In the hours prior to surgery patients must fast and limit fluid intake. This can lead to a drying of mucus membranes, particularly in the oral cavity. The membranes of

the respiratory tract are further insulted by encountering anaesthetic particles during the procedure. Modern anaesthetic gases are usually a combination of hydrofluorocarbons sevoflurane and desflurane, the chlorofluorocarbon isoflurane and nitric oxide (Charlesworth and Swinton, 2017). The potency of the drugs required to keep patients sedated during procedures can cause inflammation and damage to mucosal linings. The epithelium of the respiratory airways contains cilia; small hairlike projections that move within a sol and gel fluid layer. The cilia trap potentially harmful particles and move them to the larger airways where they can be expelled by the body through coughing or swallowing. This muco-ciliary escalator is an important defence mechanism preventing particles reaching the smaller sensitive airways and respiratory surfaces directly involved in gas exchange. Once particles reach these areas, they can cause further inflammation and inflammatory exudate, and this affords pathogens an environment and opportunity to multiply. The function of the muco-ciliary escalator is impaired postoperatively due to the reduced hydration, drying of mucous linings and inflammation affecting cilial action. This can further impede gas exchange but can also lead to postoperative respiratory infections with an increase in pulmonary secretions (Gamsu et al., 1976; Main and Denehy, 2016). Adequate secretion clearance is dependent upon cough effectiveness. The cough has three components, it requires sufficient respiratory muscular strength to increase lung volume, closure of the glottis to hold air under pressure and finally sufficient abdominal muscular strength to forcibly contract and expel air at high velocity (Main and Denehy, 2016). Failure in any one of these components can result in an inability to clear secretions and

subsequently impair alveolar-capillary gas transfer. It has been established that cough pressure is reduced to 30% of the preoperative value in postoperative patients and this figure only increases to 50% one-week post-operation (Rasheed and Govindan, 2012). Altered biomechanics, increased accessory respiratory muscle use, increased metabolic demand, fatigue and postoperative pain are all likely to contribute to these poor percentages.

1.5. National Lung Cancer Guidelines and Determinants of Surgical Risk

The National Institute for Health and Care Excellence (NICE) has established a lung cancer diagnosis and management pathway that incorporates the management of individuals with cancer at different stages with a range of prognostic outcomes. The guideline was introduced in 2005 and was updated in 2011 and 2019 respectively, with the intention to improve outcomes for lung cancer patients by ensuring prompt and effective investigations and treatments are accessible to patients (NICE, 2019). The guidance is intended for healthcare professionals, commissioners, service providers and people diagnosed with lung cancer and their loved ones. It is this spectrum of key stakeholders that can help to realise the aims set out within this guidance. An important aspect is centred around communication and ensuring individuals diagnosed with lung cancer are provided with the knowledge of their condition, an opportunity to discuss tests and treatment options with specialists and with the support of family, loved ones and carers. The need to provide patients and their families with access to specialist lung

cancer nurses throughout the entire process for education and ongoing support is a clear recommendation running throughout the document. The guideline stipulates that any information provided should be both accurate and understandable for patients, with tests and treatment options explained within the context of survival, side effects and anticipated symptoms (NICE, 2019). It also highlights end of life and palliation decisions should not be left until the terminal stages of the disease process but instead be incorporated throughout all stages of treatment planning (NICE, 2019). Fundamental to this process is shared decision-making and the ability of patients to make informed decisions about their treatment plan and any advancements within that plan, in collaboration with healthcare specialists and with a clear understanding of the implications and value of the options available to them.

Communication also refers to that taking place between healthcare organisations and a range of healthcare specialists who may be well-placed to support patients throughout this process and help to establish and deliver a comprehensive management plan. The specifics regarding the healthcare services that would provide this comprehensive plan is not explicitly outlined within the guidance and therefore the implementation, across a multitude of services nationally, is open to interpretation and significant disparity in current practice. Therefore, providing patients with information and services encompassing the aspects of management available to them, is likely to vary across healthcare organisations depending upon decision-making and commissioning priorities at a local level. Unsurprisingly, NICE (2019) does reference the importance of early referral to any intended

organisations and relevant members of the multidisciplinary team. However, other than referencing the chest physician, the specific members of the multidisciplinary team remain largely unidentified within the guidance. NICE (2019) also considers the need for fast-track or rapid access clinics for lung cancer patients and this is indicative of the overall pathway objectives; namely that timely and early diagnosis and interventions have a direct impact on the likelihood of survival and reduction in anxiety for these patients. Irrespective of the healthcare professional the patient is being referred to, and in the absence of specifics regarding the possible interventions that could prove beneficial across a multidisciplinary team, it is clear referrals should be acted upon with urgency once agreed upon in clinical practice.

The guideline focuses attention on recommendations for NSCLC patients undergoing potentially curative surgical resection. It is recommended that patients receive smoking cessation input and be informed of the pulmonary surgical complications that may be associated with continuing to smoke in the preoperative period. It is clearly stipulated however, that surgery should not be postponed whilst patients are referred to or attempting to stop smoking (NICE, 2019). This indicates that whilst there is a recognised and increased risk of postoperative complications with ongoing smoking, the greater risk would be associated with delayed surgical intervention. It is unclear within the recommendation how smoking cessation should be implemented for this patient group and whether this should fall into referral to external organisations or be integrated into lung cancer services. In current practice, there are several differing methods and commissioning routes for implementing smoking cessation programmes and this

could result in a complicated and delayed referral pathway for patients requiring this intervention. Smoking has been highlighted previously as a known carcinogenic agent for the development of lung cancer and the available evidence compiled by NICE (2019) suggests that it also has a role in worsening outcomes and delayed recovery following surgical procedures.

The need for adequate risk factor management prior to surgery is addressed within the guidance. Cardiac and pulmonary function should be included within perioperative assessment, with the recommendation that a specific score to measure mortality risk should be used prior to surgery (NICE, 2019). Scoring systems to imply the risk associated with surgery in clinical practice include Thoracoscore and the American Society of Anaesthesiologists ASA Physical Status Classification, which incorporate physical functioning alongside disease severity. The local NHS Trust uses the American Society of Anaesthesiologists (ASA), commonly referred to as ASA classification. This is a six-point classification of 1 to 6 with a higher score allocated to patients if their disease is of greater severity, limits physical activity levels to a higher degree and the disease is considered an imminent and direct threat to life. The ASA classification has been in clinical use for more than sixty years across all disciplines related to anaesthesia and is a useful tool designed to communicate medical morbidities prior to anaesthesia (ASA, 2020). The American Society of Anaesthesiologists caveat that this tool alone does not predict the risks during surgery and highlight that surgery type, frailty and level of conditioning should also be interpreted within the context of the ASA classification (ASA, 2020). NICE (2019) recommends that patients receive specialist

Cardiologist review if they present with significant cardiac history or have suffered an acute event within the last month. Patients needing to undergo myocardial revascularisation procedures, either percutaneously or through invasive cardiac bypass grafting, is one of the only medical status' to be highlighted as an appropriate reason to delay surgery for lung cancer by NICE (2019). This in turn suggests the significant additional risk associated with acute cardiac history in patients presenting for lung cancer resection and the importance of early surgical intervention wherever possible.

Patients undergoing lung resection must withstand the physiological disadvantage that is derived from the removal of lung tissue, including some removal of healthy lung tissue involved in gas exchange, to ensure an adequate margin of clearance is achieved. Since this would have significant effects on respiration it is perhaps unsurprising that an assessment of preoperative lung function is recommended prior to decisions regarding eligibility for surgery. Objective respiratory assessment via spirometry testing including the measure of transfer factor (TLCO), a measure of gas diffusion capacity for carbon monoxide, in patients considered for treatment for lung resection should be established prior to decisions regarding surgical intervention (NICE, 2019). The guidance further suggests that those patients achieving a forced expiratory volume in one second (FEV1) within normal limits and presenting with a good exercise tolerance should be offered the option of surgery. The guidance suggests that those patients with an FEV1 or TLCO below 30% could be offered the option of surgical resection if they understand and accept the risk of short and long-term complications (NICE, 2019). Those risks include ongoing

dyspnoea or dysfunctional breathing that can have associated long-term restrictions in physical functioning, self-care tasks and independence with other activities of daily living. The potential negative impact on postoperative physical functioning also highlights the importance of optimising lung function prior to surgery, given that those with poorer lung function should be counselled with caution on the increased likelihood of disability and complications following surgery. Those individuals with higher levels of respiratory functioning, as indicated through spirometry testing, present with lower surgical risk and are unlikely to experience the same level of physiological deficit following the removal of lung tissue. This highlights the importance of identifying effective strategies to preoperatively manage those with poorer preoperative lung function.

The current NICE guideline does not provide clear recommendations regarding the interventions to improve lung function prior to surgery but consideration for preoperative exercise testing has been included. NICE (2019) recommends that a shuttle walk can be used to further assess the exercise capacity of those individuals at moderate to high risk of postoperative dyspnoea, whereby achieving a distance of 400 metres or more, would be indicative of adequate physical functioning to undergo the surgical procedure. The shuttle walk is a pragmatic test for use in clinical practice, it is essentially a submaximal field test that can provide an estimation of aerobic capacity and requires little equipment. Cardiopulmonary exercise testing is a maximal laboratory-based exercise test that can accurately measure aerobic capacity by identifying the maximum volume of oxygen consumed per kilogram of body weight per minute (ml/kg/min) achieved by an individual ($V0_2$

max). It is commonly performed through a treadmill or cycle-based exercise test and therefore some eligible patients may be unable to perform the test due to existing comorbidities. NICE guidance considers that this test should be undertaken to assess function in those of moderate to high risk, as determined by initial spirometry, and that a V02 max of 15ml/kg/min should be used as an indication of sufficient function to withstand the surgical procedure and loss of lung tissue (NICE, 2019).

1.6. Enhanced Recovery Programmes to Lower Surgical Risk

Upper and lower abdominal surgery, such as upper gastrointestinal and colorectal surgery to remove cancerous tissue present in the upper and lower gastro-intestinal tract, have well-established enhanced recovery programmes. Enhanced recovery programmes in this field provide specialist and targeted preoperative input addressing counselling, nutrition, pharmacology and rehabilitation needs prior to surgery, to improve or enhance the trajectory of patient postoperative recovery. Thoracic surgery performed to treat cancer in the thoracic cavity, as opposed to the abdominal cavity, has not received comparable attention or funding in clinical practice. Therefore, enhanced recovery programmes for patients with lung cancer are not currently common practice. Instead, preoperative management for lung cancer remains primarily under the jurisdiction of thoracic surgeons, oncologists and specialist lung cancer nurses. Enhanced recovery programmes have a wide array of specialist staff from multiple disciplines including psychologists,

dieticians, physiotherapists, smoking cessation advisors and pharmacists in addition to nursing and medical professionals to optimise a patients preoperative health status. Systematic reviews of enhanced recovery after surgery 'ERAS' programmes which include preoperative rehabilitation protocols for colorectal, bariatric, gastrointestinal, pancreatic and vascular surgery have consistently demonstrated clinical effectiveness and significant in-hospital cost savings attributed to a faster recovery, reduced morbidity and fewer complications (Rawlinson et al., 2011; Stowers et al., 2015). Implementing preoperative physiotherapy, and specifically rehabilitation including increased physical activity and preoperative exercise, would theoretically achieve similar benefits in thoracic patient groups as enhanced recovery programmes have achieved for abdominal surgery patients. There are fewer thoracic operations performed in the United Kingdom in comparison to gastrointestinal operations. The infrastructure and staffing costs of setting up an enhanced recovery programme would undoubtedly be significant, due to the specialist expertise required and diverse multidisciplinary approach needed to realise the potential benefits of these services. This cost would theoretically have greater justification in gastrointestinal surgery where case numbers are much higher than in thoracic surgery. Despite caseloads being smaller in thoracic surgery the pragmatics of the enhanced recovery programme would still require a range of health professionals that may prove both resource and labour intensive. Thoracic surgery is a smaller discipline in many United Kingdom hospitals and therefore resources can be scarce and specialist professionals fewer in number and this may, in part, explain why such enhanced recovery programmes have not

been routinely implemented or fully funded to the same extent in this small but vital healthcare discipline.

In the United Kingdom, thoracic surgery often resides under the broader Cardiothoracic specialty. Although some surgeons will perform either cardiac surgery or thoracic surgery exclusively there are some surgeons within this field that will perform both. Furthermore, on admission and during the recovery period patients undergoing thoracic surgery will often follow the same patient flow through hospital wards and theatres as those receiving cardiac surgery. That is, they are admitted onto the same preoperative ward, are operated on in the same theatres and return to the same recovery bays and postoperative wards. During the hospital stay, from admission to hospital discharge, the care of thoracic surgery mirrors that of cardiac surgery. Patients will share nurses and therapists and follow similar early respiratory physiotherapy protocols to aid secretion clearance, increase lung volumes and will be assisted to achieve similar ambulatory targets prior to discharge. A striking difference between patients undergoing cardiac and thoracic surgical procedures is that cardiac patients have an additional pathway to access outpatient rehabilitation programmes. Cardiac Rehabilitation programmes have clear National guidelines including NICE guidance for Acute Coronary Syndromes (NICE, 2020) and The British Association of Prevention and Cardiac Rehabilitation core components and standards (BACPR, 2023). Cardiac Rehabilitation programmes present a well-established and evidenced strategy reducing cardiovascular mortality and hospital readmissions in patients with coronary heart disease (Anderson et al,. 2016; Rauch et al., 2016; Long et al, 2018)

and are integrated into cardiology and cardiac surgery pathways in the United Kingdom. Cardiac surgery is only rarely performed for cancerous tissue on the heart such as myxomas and is instead usually performed for coronary artery bypass grafts, valve replacements or a combination of the two. This may explain the current difference in access to rehabilitation programmes between cardiac and thoracic surgical patients despite the similarities in their hospital admission pathways.

According to annual National figures collated in the National Audit for Cardiac Rehabilitation (NACR), Cardiac Rehabilitation programmes consistently have patient uptake rates of approximately 50% within their intended priority cardiovascular patient groups (NACR, 2018; NACR, 2019; NACR 2020). The cardiovascular priority groups for Cardiac Rehabilitation include myocardial infarction, angina, revascularisation procedures and heart failure (Dalal et al., 2015; Sager et al., 2015; Long et al., 2018). These consistently low uptake rates across programmes would account for up to 50% of patient slots potentially being unused by cardiovascular patients per annum. In clinical practice it was therefore hypothesised that Cardiac Rehabilitation programmes, already a specialist support service within the broader Cardiothoracic discipline, could facilitate the additional capacity within their existing services to accommodate high-risk preoperative lung cancer patients. It is this concept that formed the basis for the local Acute NHS Trust Cardiac Rehabilitation programme to trial referrals from the Cardiothoracic Specialty for high-risk preoperative lung cancer patients. Theoretically using the existing Cardiac Rehabilitation Service, with established referral and treatment

pathways would prove a cost-effective option that would not require the level of funding, or incur the same costs, that would be required to set up a new and independent lung cancer preoperative rehabilitation programme for the NHS Trust. Cardiac Rehabilitation programmes benefit from core standards outlined in BACPR (2023) guidance and this affords these services a clear infrastructure for staffing requirements, programme delivery and facilities. This infrastructure is well aligned to the requirements needed for a preoperative programme preparing lung cancer patients for surgical intervention and shares similarities with that of the enhanced recovery programmes. Furthermore, cardiovascular disease is a common comorbidity in lung cancer patients (Kravchenko et al., 2015), unsurprising since a history of smoking has been recognised as a major risk factor in the aetiology of both disease processes. Therefore, utilising the existing Cardiac Rehabilitation pathway was considered an appropriate service expansion within the current skillset of the existing workforce. The BACPR guidelines outline the need for Cardiac Rehabilitation programmes to be staffed by a comprehensive multidisciplinary team capable of addressing key lifestyle risk factors, primarily associated with cardiovascular disease. This includes strategies to address smoking, weight management, nutrition, alcohol and substance abuse, physical inactivity and poor mental health and wellbeing (Rice and Stead, 2008; Roest et al., 2010; Dong et al., 2020; Cowell et al., 2021). These risk factors also reflect those addressed by enhanced recovery programmes and required for preoperative optimisation including smoking cessation, improved nutrition, optimising physical function and exercise tolerance and supporting mental health in preparation for surgery. It is

unclear within the existing literature whether preoperative rehabilitation programmes have utilised existing outpatient Cardiac Rehabilitation service models within the research protocols and methodology. The existing research predominantly states the type and mode of exercise delivery and the healthcare specialist prescribing the intervention without alluding to the service model specificities and this is particularly apparent in the systematic reviews and meta-analysis within this field.

1.7. Intended Study Aims and Objectives

Current literature suggests that enhanced recovery programmes that include preoperative rehabilitation strategies may improve postoperative outcomes in patients with operable cancer (Rawlinson et al., 2011; Stowers et al., 2015). Lung cancer patients deemed operable undergo the thoracic surgical procedure of lung resection and are commonly assessed and treated within the Cardiothoracic Specialty. Existing outpatient Cardiac Rehabilitation programmes within the United Kingdom may prove an effective referral pathway for lung cancer patients awaiting surgical resection within the Cardiothoracic Specialty. The aim of this study was to investigate the efficacy of a preoperative rehabilitation programme in improving patient outcome in comparison with standard care (no rehabilitation) in patients with lung cancer awaiting surgical resection. The study had four main objectives, listed below and outlined in detail in Chapter 3.

Objective 1: To determine whether there was a difference in postoperative recovery with preoperative rehabilitation in comparison to standard care.

Objective 2: To determine whether preoperative rehabilitation influenced postoperative survival time in comparison to standard care.

Objective 3: To determine the effectiveness of preoperative rehabilitation programmes in the optimisation of patient pulmonary function and health-related quality of life in preparation for surgical lung resection.

Objective 4: To determine the feasibility of preoperative rehabilitation delivery based on patient uptake, completion and ability to achieve intended exercise prescription parameters.

1.8. Quality Improvement Service Evaluation

This study evaluated the effectiveness of an improvement initiative that had been developed and trialled within the Cardiac Rehabilitation service over a three-year period. It was considered a summative evaluation culminating in a review of the body of existing clinical data to inform decisions regarding sustaining or improving service delivery and patient care. Summative outcome evaluations are focused on the overall impact of an initiative and any improvement initiative should be aligned with the wider strategy defined by the organisation (Langley at al., 1996). Within the NHS Trust the Cardiothoracic Speciality had been highlighted as an area for development and additional funding opportunities, as part of the Trust Quality

Improvement Strategy. Quality Improvement is an important Directive within the NHS aimed to harness the power within individual departments to achieve wider Directive operational goals. The overall strategy for this initiative was to reduce costs by judicious resource allocation, reduce length of stay and provide quality care to service users, and therefore reflected the balance between optimising costs and maximising quality care. The Rehabilitation Department initiative to expand service delivery to preoperative rehabilitation of lung cancer patients sat comfortably within the wider NHS Trust Directive and Cardiothoracic Department strategy. Therefore, undertaking appropriate service evaluation to understand the impact of service initiatives through systematic assessment and rigorous design was of paramount importance and key to clinical decision-making.

Chapter 2. Literature Review and Background

2.1. Lung Cancer Patient Presentation and Symptomology

Lung cancer is currently the third most common cancer in the United Kingdom and accounts for 13% of all new cancer cases (Cancer Research UK, 2021). It is associated with significant symptom burden including pain, fatigue and dyspnoea which can be very debilitating for patients and concerning for loved ones. The incidence of lung cancer is highest in people aged 85 to 89 years old and currently 44% of new cases are diagnosed in those over 75 years of age (NICE, 2019; Cancer Research UK, 2021). The advanced age, coupled with some of the comparable aetiology between lung and cardiovascular disease, can result in this patient population presenting with a high degree of frailty and extensive comorbidities. There are numerous management strategies available depending upon the type and stage of lung cancer, but for those deemed eligible for surgical resection, this complex multimorbid status would evidently increase their risk of developing postoperative complications, in accordance with ASA classification. From an anatomical perspective, patients undergoing thoracic surgery for lung resection are at particular risk of developing postoperative pulmonary complications. Current research suggests that postoperative complications are between 19% and 59% within this patient group (Wang et al., 1999; Garcia-Miguel et al., 2003; Licker et al., 2006). The large variability in these figures may be due to differences in possible surgical approaches in lung resection including invasive open thoracotomy or video assisted surgery and the differing amount of lung tissue removed from wedge to an

entire lung removal. The incidence of postoperative complications following upper abdominal surgery has been reported to be between 16% to 17% and this incidence is reduced further still for lower abdominal surgery which is estimated to be between 0% and 5% (Garcia Miguel et al., 2003). These figures suggest that surgical location is a significant factor in the development of pulmonary complications postoperatively, with those surgical approaches performed close to or within the thoracic cavity presenting with higher pulmonary complications following surgery.

Interestingly, the incidence of postoperative pulmonary complications in cardiac surgery, where procedures are also performed within the thoracic cavity, is also lower than the figures associated with lung surgery. Pulmonary complications have been reported to range from 3% to 16% after coronary artery bypass grafting and 5% to 7% following valve surgery (Rock and Rich, 2003; Weissman, 2004). Therefore, factors additional to surgical location must influence the incidence of postoperative pulmonary complications. Abdominal surgery and lung surgery are both frequently performed for the removal of cancerous tissue whilst cardiac surgery is performed predominantly to improve vascularisation and cardiac insufficiency. The physical deconditioning and frailty of patient presentation preoperatively may differ significantly between these patient groups and account for some variance.

2.2. Pulmonary Complications and Management following Lung Surgery

Research highlights that the postoperative pulmonary complications in patients following lung resection surgery are associated with impaired diaphragmatic mobilisation, altered thoracic cage biomechanics, an increase in respiratory loading and evidence of inspiratory muscle fatigue (Takazakura et al., 2007; Miserochi et al., 2010; Brocki et al., 2018). In these studies, improvement in lung function only occurred after two weeks and onwards from the postoperative period. Clinically, the majority of patients undergoing lung resection are discharged within the first week following this type of surgery. This is consistent with the National Lung Cancer Audit from the Royal College of Physicians (RCP) (2019) reporting that NHS Trusts currently performing lung resection surgery in the United Kingdom, have median hospital length of stays ranging between four to seven days. The report also highlighted that there does not appear to be any correlation between length of stay following initial surgery and readmission rates (RCP, 2019). These figures suggest that either not all patients experience these physiological alterations, or that some patients have effective compensatory mechanisms to overcome the potential deleterious effects associated with them. The surgical approach, anaesthesia, removal of lung tissue and alterations in respiratory mechanics can precipitate the onset of atelectasis and sputum retention and clinically this can lead to a greater requirement for ventilatory support, antibiotic prescription and supplemental oxygen therapy (Agostini et al., 2010). The need for additional resources and supportive therapy can ultimately lead to both longer stays in high dependency level care and increased hospital stays. Currently these complications are managed

reactively in the early postoperative inpatient stay. A randomised clinical trial by Reeve et al. (2010) aimed to investigate the effectiveness of postoperative physiotherapy regimes on reducing the incidence of pulmonary complications following lung surgery, but the limited incidence of complications within the overall sample prevented any inference of this nature. Since routine postoperative chest physiotherapy during an inpatient stay following lung surgery is embedded into clinical practice, well-controlled prospective controlled trials within this area are limited. Typically, postoperative management would include medical, nursing and physiotherapist input to manage pain, antimicrobial therapy, breathing exercises, nebulisers and early ambulation. These postoperative approaches can be labour and resource intensive and impact upon wider hospital systems regarding bed flow and theatre planning. It is widely reported within the literature that improving cardiopulmonary fitness prior to surgery can favourably influence postoperative recovery and reduce hospital length of stay. A significant amount of research, of varying quality, has focused on the preoperative optimisation of lung cancer patients through exercise and this strategy is commonly referred to within the literature as 'prehabilitation'. Current systematic reviews evaluating the effectiveness of prehabilitation programmes have predominantly focused on moderate intensity aerobic exercise (Pouwels et al., 2015; Sebio-Garcia et al., 2016; Cavalheri and Granger, 2017; Steffens et al., 2018; Sanchez-Lorente et al., 2018; Gravier et al., 2022; Vacchi et al., 2022) inspiratory muscle training and chest physiotherapy (Rosero et al., 2019; Pu et al., 2021). The specifics regarding mode, frequency and delivery of interventions are poorly described and significant

heterogeneity exists between included studies, limiting meaningful pooling of data and statistical analysis. Despite these significant limitations, systematic reviews in this area have largely been supportive of preoperative exercise-based training interventions, whereby the most positive results indicate that preoperative rehabilitation could more than halve the risk of patients developing postoperative pulmonary complications (Cavalheri and Granger, 2017; Steffens et al., 2018; Rosero et al., 2019; Pu et al, 2021; Gravier et al., 2022).

2.3. Preoperative Respiratory Muscle Training in Surgical Populations

Inspiratory muscle training (IMT) has received increasing attention as a preoperative rehabilitation strategy. This technique uses a light handheld device, whereby patients inhale and exhale through a mouthpiece. The device has a one-way valve that provides controlled resistance to load the respiratory muscles during inhalation, this resistance can be set at increasing intensities to produce a training effect over time. It is a form of strength and endurance training targeting the inspiratory respiratory muscles, commonly recruited during quiet tidal breathing. These muscles include the diaphragm and external intercostal muscles. The technique also has an ability to train and load those muscles that may be recruited to aid inhalation during times of increased loading and additional respiratory effort, including sternocleidomastoid and scalene muscles. Typically, these muscles are recruited during exertion related to exercise and physical activity, but these muscles may also be employed to overcome the deleterious effects on ventilation

following surgical interventions. The effectiveness of IMT to reduce postoperative pulmonary complications has been most widely studied in cardiac and abdominal surgery populations. Mans et al. (2015) included cardiac, thoracic and upper abdominal surgery in a systematic review and meta-analysis of eight randomised controlled trials and 295 participants. In this review IMT halved the risk of postoperative pulmonary complications developing, with a relative risk 0.48 (95% CI, 0.26 – 0.89). The maximum inspiratory pressure (piMAX) achieved by patients increased significantly within the group receiving IMT training, with an average increase of 15cmH_20 and it was inferred that these gains were, to some extent, maintained in the early postoperative period. Theoretically the ability to achieve and maintain higher maximum inspiratory pressures may enable patients to remain above a theoretical threshold that if fallen below would predispose a patient to developing pulmonary complications. Of particular interest in this study was the high compliance rates in the IMT groups suggesting that IMT may be a feasible and well-tolerated preoperative modality for surgical patients. However, there was no significant difference in hospital length of stay between those groups receiving or not receiving IMT, which may limit the operational and economic impact of these findings. Katsuri et al. (2015) identified similar findings in a larger systematic review of twelve trials and 695 participants. This review focused on cardiac and major abdominal surgery and preoperative IMT was compared with standard care. In this review, preoperative IMT was associated with a significant reduction in the development of postoperative atelectasis relative risk 0.53 (95% CI, 0.34-0.82) and pneumonia relative risk 0.45 (95% CI, 0.26-0.77). IMT did not however impact upon

30-day mortality and, similarly to Mans et al. (2015) did not achieve significance in reducing hospital length of stay in comparison to standard care. Despite the lack of significance, the authors noted a general trend towards a lower length of hospital stay in favour of the IMT group. The review by Karanfil and Moller (2018) also found inconclusive results for the effectiveness of preoperative IMT in reducing length of stay but identified similar reductions in the development of postoperative atelectasis and pneumonia in their IMT training groups. Two out of the three studies within this review showed significant reductions in these complications, with IMT groups having an incidence of atelectasis of 14.2% and 18.7%, in comparison to standard care groups with an incidence of 50% and 43.2% respectively. Similar positive findings were identified in pneumonia, whereby two studies out of five identified postoperative incidence in IMT groups of 6.5% and 5.3% in comparison to standard care group incidence of 16.1% and 12.3%. Karanfil and Moller (2018) restricted their review to 29 randomised controlled trials and acknowledged that some studies did not produce results of statistical significance at reducing either atelectasis or pneumonia, despite some positive findings. Most recently a systematic review by Pu et al. (2021) focussed specifically on IMT with and without aerobic exercise in preoperative lung cancer management where the pooled results from ten studies found a mean reduction in postoperative length of stay 3.44 days (95% CI 2.75-4.14 days) with preoperative intervention. The review also identified a reduced incidence in pneumonia, odds ratio 0.37 (95% CI 0.18-0.75) and wider pulmonary postoperative complications, odds ratio 0.37 (95% CI

0.21-0.65) despite no significant differences in pulmonary function or health related quality of life with IMT in combination with aerobic exercise.

Encouragingly, whilst the participants included in these reviews included a wide range of surgical patients, with only the reviews by Pu et al, (2021) and Mans et al. (2015) including thoracic patients, the preoperative training was implemented for a minimum of two weeks, suggesting that pulmonary function can be enhanced within the period available prior to lung resection. Despite these reviews including randomised or quasi-randomised trials, the grading of included studies showed that few were of moderate quality and the majority were considered low to very low quality. There was significant disparity amongst these studies with regards to duration of intervention and the training intensities of IMT with settings between 15% and 40% of patients' maximum inspiratory load capacity across the studies included in Karanfil and Moller (2018). The amount and type of supervision provided across the studies also varied and this would potentially impact on the performance, participant technique and motivation. Whilst the meta-analysis conducted within these reviews often included postoperative pulmonary complications, specifically atelectasis and pneumonia, the outcome measures to determine these differed significantly across individual studies. Studies used any combination of radiological evidence, antimicrobial prescription, microbiological evidence from sputum samples or expert medical opinion to determine postoperative pulmonary complications. The lack of consistency with diagnostic determination and significant variation in outcome measures used across studies makes accurate interpretation problematic and therefore, despite positive findings

that IMT may halve the risk of pulmonary complications, results remain inconclusive, and the most effective training protocol has yet to be established. This lack of specificity in training approach, coupled with the questionable impact on length of stay, may explain why IMT has yet to be adopted into routine clinical practice in many surgical populations.

2.4. Respiratory Muscle Training in Chronic Respiratory Disease

COPD has been identified as an independent risk factor for postoperative complications in patients undergoing lung surgery and therefore the tolerance of IMT in this patient population should be considered. Neves et al. (2014) included five studies with a total of 111 COPD participants in a review of both IMT and expiratory muscle training (EMT). There was large variation in the training approaches with respiratory loads ranging from 10 to 60% of maximum pressures and treatment times between fifteen and thirty minutes. The largest difference was in treatment duration that ranged between five to forty weeks of device usage. Clearly, these time frames are well beyond the limited preoperative window available prior to lung resection. These timescales do, however, suggest that there is a high compliance with longer term muscle training via hand-held devices for COPD patients and this is encouraging. The study demonstrated significant changes in maximum inspiratory and expiratory pressures following training with the respiratory device. Mean maximum expiratory pressure increased by 31.98cmH_20 (95% CI, 26.93-37.03cmH_20) and mean maximum inspiratory pressures increased

by 27.98cmH20 (95% CI, 20.10-35.85cmH20) (Neves et al., 2014). There were no significant differences demonstrated with dyspnoea scores or functional exercise tolerance as measured by the six-minute walking test. It is also not clear whether the increased maximal inspiratory or expiratory pressures would be sufficient to overcome the effects and respiratory compromise within a surgical environment, but the review demonstrates that COPD patients with severe disease are able to achieve improvements in pulmonary measures through this training mode. Beaumont et al. (2018) also identified similar improvements in a large systematic review of IMT and pulmonary rehabilitation in COPD patients, including forty-three studies for review with thirty-seven of the studies allowing for meta-analysis. This enabled a large sample with 642 participants within the IMT and rehabilitation intervention group. This large review identified comparable improvements in maximal inspiratory pressures and in addition found improvements in dyspnoea, quality of life and exercise capacity with greater distances achieved over the six-minute walking test in intervention groups. The authors of this review cautioned that these improvements were comparable across IMT combined with pulmonary rehabilitation and pulmonary rehabilitation alone and therefore whether IMT affords any additional benefit beyond exercise training remains uncertain.

Systematic reviews evaluating the use of preoperative IMT in thoracic surgery have often incorporated this device alongside a variety of exercise approaches, including aerobic and resistance exercise training. Cavalheri and Granger (2017) included five randomised controlled trials and 167 participants, undergoing lung resection for NSCLC, within their review. Preoperative exercise training with or without IMT was

compared to non-exercise groups that were considered standard care. In this review, only four studies allowed for pooled meta-analysis, where preoperative exercise training resulted in a 67% reduced risk of developing postoperative complications in comparison to non-exercise groups risk ratio 0.33 (95% CI, 0.17-0.61). More specifically the review identified that preoperative exercise training was associated with a 3.33 day reduction in the duration of chest drain insertion (95% CI, 1.30-5.35 days) and a 4.24 day reduction in hospital length of stay (95% CI, 3.06-5.43 days). Preoperative training improvements were noted in six-minute walking distance, with an average increase of 18.23 metres (95% CI, 8.50-27.96 metres), whilst improvements in lung function tests achieved mixed results. Forced vital capacity increased by 2.97% of predicted values in those receiving preoperative exercise training in comparison to the non-exercise group (95% CI, 1.78-4.16%) but no differences between FEV1 were identified between groups. There was also limited data on dyspnoea, fatigue or postoperative mortality across the studies used in this review.

A large systematic review by Li et al. (2019) also found inconsistent differences in pulmonary function between preoperative exercise and non-exercise control groups. This review included seven randomised controlled trials with 404 participants awaiting lung resection and provided further analysis of those with or without COPD. The review included a range of respiratory training including IMT, breathing exercises and incentive spirometry in addition to aerobic exercise. The review did demonstrate improvements comparable to the Cavalheri and Granger (2017) review in pulmonary complications and reductions in hospital length of stay

for preoperative exercise in non-COPD patients. In this group, exercise was associated with a lower risk of pulmonary complications, odds ratio 0.44 (95% CI, 0.27-0.71) with the exception of pneumonia. Patients in the exercise group also achieved a reduced mean length of hospital stay of 4.23 days (95% CI, 2.32-6.14 days). This suggests that a combination of approaches used in clinical practice may be beneficial. Specifically for COPD patients, the data was less conclusive, and the exercise group did not achieve statistical significance for a protective effect of preoperative training for postoperative pulmonary complications, odds ratio 0.44 (95% CI, 1.18-1.08). Preoperative exercise did not significantly alter pulmonary function but did show improvements in six-minute walking distance and maximum oxygen peak, indicating some improvement in exercise capacity. The studies included in this review varied in exercise prescription from three times per week for one week and up to five times per week for four weeks. The trials included in the systematic reviews predominantly included patients with mild to moderate COPD. It is likely to be those patients with more severe disease and at greater risk of developing postoperative complications that may experience greater gains from participation in a preoperative training intervention. The studies also included patients who underwent open thoracotomy or minimally invasive video-assisted thoracic surgical approaches. It has been considered within the literature that the incidence of pulmonary complications is two to six times greater in open thoracotomy approaches in comparison to video-assisted surgery, with estimations of between 4 and 15% (Agostini et al., 2010). Therefore, the pooling of different

surgical procedures is likely to have impacted on the incidence of postoperative complications within these studies and any inference for clinical practice.

Determining the effectiveness of preoperative interventions for COPD is particularly important, partly because it is a recognised independent risk factor for patients undergoing lung surgery but also because the prevalence of COPD in lung cancer patients is so high. It has been estimated that 40% to 70% of lung cancer patients have COPD (Dela Cruz et al., 2011). Identification of effective preoperative management strategies for high-risk groups undergoing lung surgery should be a priority for future research. Despite some inconsistencies within the existing literature for IMT the simplicity, convenience and low expense of the device make it an attractive option for widespread use within clinical practice if growing evidence can establish where it can be used to best effect.

2.5. Exercise as a Preoperative Rehabilitation Strategy in Thoracic Surgery

A large number of systematic reviews that have investigated preoperative exercise strategies have focused on studies evaluating moderate intensity exercise (Pouwels et al., 2015; Sebio Garcia et al., 2016; Cavalheri & Granger, 2017; Steffens et al; 2018; Gravier et al., 2018; Vacchi et al., 2022). Despite some positive results, all reviews concluded that there was a dearth of large randomised controlled trials within this area, and this was imperative to clearly define the mode, frequency, and dose of preoperative exercise interventions to evaluate their comparable effects and facilitate appropriate statistical analysis. Traditionally, Cardiac Rehabilitation

programmes in the United Kingdom commonly prescribe continuous moderate intensity exercise in management strategies within clinical practice. Lung cancer patients are typically operated on within two to three weeks of their diagnosis once operability has been established. NICE (2019) lung cancer management recommends surgery should be performed within twenty-eight days of confirmation for surgery. Therefore, any preoperative intervention should be time sensitive with the ability to provide rapid physiological changes, improving physical and respiratory function sufficiently to influence postoperative results. Despite the positive findings of existing reviews, current scientific and laboratory-based testing indicate that physiological adaptations from moderate exercise would takes several months to occur. It is on this premise that, high intensity interval training (HIIT) is emerging as a potentially more effective strategy for rehabilitation in this patient population.

Scientific evidence in non-patient populations has provided convincing evidence that changes can occur to muscle structure and oxidative capacity, mitochondrial mass and exercise performance within weeks when using a HIIT approach (MacInnis and Gibala, 2017; Blue et al., 2018; Fransson et al., 2018; Hostrup et al., 2019). These studies have included healthy populations and those engaging in sporting pursuits such as sub-elite and elite football players. The transference of these physiological adaptations to patient populations has received growing attention in healthcare research. Systematic reviews evaluating HIIT have focused on coronary heart disease (Gomes-Neto et al., 2017; Hannan et al., 2018; Wewege et al., 2018), heart failure (Aruaujo et al., 2019; Gomes-Neto et al., 2018) and diabetes (Da Silva

et al., 2019; Lora-Pozo et al., 2019) and all have indicated that this approach could be safe and effective when used in patient populations. Wewege et al. (2018) analysed twenty-three studies with 1117 participants, where 547 participated in HIIT in comparison to 570 completing moderate continuous aerobic exercise. One significant cardiovascular event, two minor cardiovascular events and three musculoskeletal complaints occurred following HIIT in comparison to two non-cardiovascular events occurring with moderate intensity exercise. This equated to one significant event per 17083 exercise sessions and the authors considered this a sufficiently low rate in cardiac populations for HIIT to be plausibly applied within Cardiac Rehabilitation settings (Wewege et al., 2018). Similarly, the review by Hannan et al. (2018) analysed seventeen studies and 953 participants where there were no deaths or serious adverse events requiring hospitalisation reported in either the moderate intensity or HIIT groups.

Interestingly, there were more adverse events during exercise reported in the moderate intensity group than HIIT overall, with nine and five events in each group respectively. Furthermore, HIIT resulted in significantly improved cardiorespiratory fitness with a standardised mean difference of 0.34 ml/kg/min (95% CI, 0.2-0.48ml/kg/min) within this review, but sessions were over six weeks duration, with the greatest improvements seen at seven to twelve weeks duration. This is typical of the duration of programmes in Cardiac Rehabilitation and analysis did not allow for inference of potential gains within two to three weeks of initiation. In a further testament to the potential safety of HIIT, a review by Gomes-Neto et al. (2018) of thirteen studies and 411 participants compared moderate intensity exercise and

HIIT in heart failure patients with reduced ejection fraction. In accordance with the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) risk stratification in Cardiac Rehabilitation these patients would be considered to be of high risk for adverse events during exercise (AACVPR, 2012). The AACVPR stratification algorithm outlines the highest risk of events occurs in patients with left ventricular ejection fraction of less than 40%, congestive heart failure, complex dysrhythmias, low functional exercise capacity of less than five metabolic equivalents and clinically significant depression or depressive symptoms (AACVPR, 2012). The review by Gomes-Neto et al. (2018) found improvement in peak oxygen consumption in heart failure patients of 1.35 ml/kg/min (95% CI, 0.03-2.64ml/kg/min) following HIIT but no difference in quality of life measured by the Minnesota Living with Heart Failure Questionnaire. Large systematic reviews and meta-analysis investigating HIIT in lung cancer or specifically preoperative lung cancer patient populations are currently lacking but these reviews in high-risk cardiovascular populations suggest that it is a safe strategy that could be worthy of consideration in preoperative lung cancer populations.

2.6. High Intensity Training for Preoperative Rehabilitation in Lung Cancer

Small randomised controlled trials utilising HIIT as a preoperative rehabilitation strategy for patients with lung cancer are emerging within healthcare literature. A small randomised controlled trial by Licker et al. (2017) demonstrated preoperative HIIT reduced postoperative complications in lung resection surgery, with the most

notable effect on respiratory complications, risk ratio 0.54 (95% CI, 0.33-0.88), but the preoperative intervention had little impact on other cardiac and surgical complications, risk ratio 0.72 (95% CI, 0.55-1.05). There was also no difference between postoperative hospital length of stay, with the usual care group admitted for a mean length of nine days and HIIT intervention group for ten days. Length of time spent in high dependency level care did however favour preoperative HIIT intervention with this group having a twelve hour mean reduction in high dependency level care in comparison to the usual care group. However, with such a small sample size generalisation is limited and the difference in high dependency stay could have resulted from influential outliers and impedance from ward bed flow. Particularly relevant for clinical practice the participant adherence to preoperative HIIT programmes did appear favourable across several trials investigating HIIT in preoperative patients with lung cancer, with studies averaging 90% adherence to HIIT intervention (Stefanelli et al., 2013; Sommer et al., 2016; Vagvolgyi et al., 2018; Bhatia & Kayser, 2019). This is encouraging when considered within the context of recent reports from the National Audit of Cardiac Rehabilitation (NACR) and the National Asthma and COPD Audit Programme (NACAP) indicating registered Cardiac and Pulmonary Rehabilitation programmes within the United Kingdom currently have between 50% and 54% patient adherence rates (NACR, 2019; NACAP, 2020). This suggests that HIIT could be a viable rehabilitation strategy, although it is worth noting that there was significant variation in actual training intensities achieved by participants in comparison to

programme targets and many participants did not achieve the higher target heart rate ranges during the intervention.

Importantly, the studies did not report any serious adverse events associated with preoperative HIIT intervention in patients with lung cancer. Sommer et al. (2016) outlined patient reported reasons for non-adherence to preoperative HIIT sessions and these included lack of motivation, unpleasant side effects from adjuvant chemotherapy treatments and non-intervention related hospitalisation and death. Licker et al. (2018) also found that timings between study enrolment and date of surgery did not differ between intervention and usual care groups, with a median of 25 and 26 days respectively. This is significant as it suggests surgery was not delayed for patients to participate in the preoperative rehabilitation programme. Karenovics et al. (2017) and Sommer et al. (2018) both considered the long-term impact of preoperative intervention and included one year follow-up to review quality of life. Karevonics et al. (2017) showed favourable results for HIIT intervention for health-related quality of life and symptoms measured by EORTC, FACT-L scores, and MRC dyspnoea scores. Unfortunately, in the trial by Sommer et al. (2018) the preoperative aspect of the programme was not considered viable due to the fast-track surgical system bringing lung cancer patients through for surgery at the earliest opportunity. Therefore, the data analysed and presented in this trial predominantly related to HIIT performed within the postoperative period and unfortunately any preoperative programme data obtained during the study was not reported separately.

Two trials investigating the effectiveness of preoperative HIIT for patients awaiting lung cancer surgery identified that six-minute walking distance increased following intervention. 238 participants were included in a randomised controlled trial by Vagvolgyi et al. (2018) and 86 of these were allocated to preoperative HIIT, where mean walking distance increased from 378.3 metres to 441.3 metres following rehabilitation. Similarly, the trial by Licker et al. (2017) discovered walking distance increased by a mean 66 metres following intervention for the 74 participants who received HIIT intervention, in comparison to a reduction in mean walking distance of two metres in the 77 participants receiving standard care. Several trials have focused on post training improvements in exercise capacity with preoperative intervention and Licker et al. (2017) identified significant improvements in peak V02 by 2.9ml/kg/min (95% CI, 1.1-4.2ml/kg/min) with HIIT intervention preoperatively, whilst peak V02 reduced by a mean of 1.5 ml/kg/min in the standard care group. Similar results were demonstrated in a trial by Stefanelli et al. (2013) where lung cancer participants undergoing preoperative HIIT training achieved significant improvements in peak V02 from a pre-training mean of 14.9ml/kg/min to a post training mean of 17.8ml/kg/min. This trial also found a corresponding reduction in peak V02 from 14.8ml/kg/min to 14.5ml/kg/min in the standard care group over the same time period. This suggests that short term HIIT intervention conducted over two to three weeks in the preoperative phase can elicit physiological improvements and prevent decline in physical capacity in lung cancer patients awaiting surgery.

It is unclear whether these improvements are sufficient to protect against postoperative pulmonary complications and favourably influence overall hospital length of stay. There is also substantial disparity in the description of HIIT within the literature and correspondingly the exercise prescription protocols used. Few study methodologies followed the stipulations to classify exercise as HIIT based on target heart rate ranges and oxygen consumption and this heterogeneity limits implementation in practice. There is however a growing number of published protocols outlining clear HIIT interventions in pending clinical trials and this will inevitably add to a growing evidence-base in this field.

2.7. Patient and Public Involvement to Influence Design and Delivery

Prior to the NHS Cardiac Rehabilitation Service implementing the preoperative initiative to include high risk operable lung cancer patients into the existing community-based rehabilitation programme, the West Midlands Research Design Service supported a bursary application made by the researcher. The West Midlands Research Design Service awarded the researcher £285 to facilitate a PPI event for patient involvement to inform the practice and evaluation. 8 patients who had previously undergone lung resection surgery in the last 12 months were invited to a one-hour focus group with the researcher and a member of the NHS Trust Research and Innovation Team. Patients received a £20 shopping voucher for their participation along with reimbursement of travel and parking expenses incurred to attend the event. Participants were invited to comment on the inspiratory muscle

trainer and HIIT including broader areas around any psychological or lifestyle impact in undergoing preoperative training. This event was intended to inform the viability of rehabilitation and the appropriateness of the preoperative interventions for this patient group and ultimately their likely adherence to the programme prior to service implementation.

The group clarified that there was a desire to be well prepared for surgical interventions and the group would have been very receptive to lifestyle and rehabilitation interventions had this been available prior to their own procedures. They understood that being well prepared for surgery was an important part of the process and whilst they were willing to participate in a rehabilitation programme, where increasing physical activity was an integral component, they were unanimous that they would be most confident to do this under the direct supervision of a qualified health professional such as a physiotherapist. The group did not appear concerned by the need for additional contact and visits to complete the preoperative supervised intervention and for the majority of the group this had become part of their routine with the necessary health investigations that had already been a course of their management for some time in both the preoperative and early postoperative period. This suggested that adherence to supervised programmes at community locations may be high within this patient group. The group also expressed a desire for the intervention not to be termed intense exercise within the patient resources or literature as they felt that both terms may be off putting for some patients who were awaiting procedures. They considered that 'preoperative activity' or 'strengthening' or 'rehabilitation' would be more

agreeable terms to patients. The group also recollected that the breathlessness and fatigue associated with exertion in the preoperative period may impact upon their ability to achieve the training intensities independently. They felt that appropriate guidance from an appropriate professional would mitigate some of this apprehension. The group were particularly supportive of the hand-held inspiratory muscle trainer, they liked that it was light, small and easy to use. The group trialled the use of the equipment directly within the meeting and realised that it needed little instruction and they felt confident that they would be able to use this aspect of the intervention independently at home without the need to perform this under direct supervision. They felt that using the device for 10-15 minutes at a time would be manageable but more frequently would become more onerous. All participants in the group wished to take these devices with them and continue to use them independently. Interestingly, the group also reflected that they continued to experience unpleasant symptoms 12 months after surgery, including thoracic and shoulder discomfort, reduced range of movement and a reduction in exercise tolerance. Many of the group muted that rehabilitation was something that they would be open to attending at this late stage in their recovery. This aspect was outside the scope of this preoperative initiative and evaluation but was an interesting self- initiated discussion amongst the participants and reassured the researchers that long term follow up was an appropriate and worthwhile inclusion into the evaluation.

2.8. SARS-CoV-2 Pandemic Influence on Remote Rehabilitation Delivery

The SARS-CoV-2 pandemic has posed many challenges to healthcare services and particularly pertinent to those patients awaiting surgery has been the operational planning for acute healthcare services to reduce theatre and elective surgical high-dependency bed capacity and facilitate staff redeployment in anticipation of high numbers of hospitalised SARS-CoV-2 cases during peaks within the pandemic. This has resulted in delayed treatment and prolonged waiting times across elective surgery patient populations. It has been estimated that 38% of surgery for cancer have been cancelled worldwide during peak times within the pandemic (Negopdiev et al., 2020). This not only acted to preserve acute resources, particularly those surrounding airway management and respiratory support for the worst affected cases but also limited virus transmission across the hospital in high-risk populations. SARS-CoV-2 has had devastating respiratory complications across vulnerable groups and high-risk cancer patients, including those awaiting lung resection, and these patients were considered at risk of high morbidity and mortality should they contract SARS-CoV-2 in either the preoperative or early postoperative period. The surgical procedure impairs lung function in already vulnerable groups and the surgical procedure would expose clinical teams to high aerosolised viral loads through bronchoscopy, intubation and possible lung leaks and therefore thoracic surgery was considered a particularly high-risk procedure during the pandemic. This led to published guidance from Thoracic Surgery Outcomes Research Network (2020) outlining appropriate triage processes for cancer cases. There was a recommendation within the guidance that small or earlier stage lung cancer may

be offered alternatives to surgical intervention during the pandemic including ablative therapy and cryotherapy, which were deemed at lower risk and less impact on acute bed capacity. However surgical resection has been established as the primary curative treatment available in lung cancer patients and therefore this approach warranted caution since it could impact significantly on longer term survival. In a large systematic review and meta-analysis, Johnson et al. (2020) pooled 2,533,355 patients and found that delaying surgery for 12 weeks in breast, lung and colon cancers during the pandemic may decrease overall survival within these groups. Specifically, for lung cancer the hazard ratio 1.04 (95% CI, 1.02-1.06) for these patients was identified from a pooled sample of 236,199 patients and the majority of this sample was lower grade stage 1 or 2 cancer. Ultimately the true impact of delayed timescales and risks associated with clinical decisions and triage processes of surgical cases during the pandemic remain relatively unknown.

The overall guidance by Thoracic Surgery Outcomes Research Network (2020) suggested that surgery should continue to be performed on patients where survivorship would be compromised with delays of up to 12 weeks, during periods of low numbers of hospitalised SARS-CoV-2 cases. Whereas treatments for lung cancer patients should relate only to the management of emergency complications during times of peaks in SARS-CoV-2 hospital admissions. This would relate to emergencies such as tumour-associated infection and haemorrhage that could not otherwise be managed by non-surgical approaches. Fraser et al. (2021) established that whilst SARS-CoV-2 infection significantly increased morbidity and mortality in patients undergoing lung resection it could be safely performed if appropriate

precautionary measures were employed. The multi-centre cohort study across thoracic surgical units in London during 2020 identified that with preoperative isolation, screening and SARS-CoV-2 swabs prior to surgery it was able to continue operating on these patients safely. 61.7% of thoracic surgery was performed through minimally invasive procedures during this period in comparison to 54.8% pre-pandemic. Interestingly, the median length of hospital stay was six days and thirty-day post-operative survival was 98.3% which was comparable to pre-pandemic figures of six days and 98.4% respectively (Fraser et al., 2021). Early evidence from China suggested a 20% mortality rate in surgical patients who later developed SARS-CoV-2 infection (Lei et al., 2020). Incidentally, only 2% of patients were diagnosed with SARS-CoV-2 in the study by Fraser et al. (2021) and mortality in those affected was 28.5%, but these figures are based on very small numbers contracting the virus.

The pandemic had an unprecedented impact on healthcare services generally and surgical specialties specifically. It also provided unexpected opportunity to re-imagine service provision and this has been evident within outpatient rehabilitation services. The need for National and Local Lockdowns and the shielding of vulnerable patient groups has required these services to think differently about how they implement programmes and provide important resources remotely and comprehensively. The Lockdown strategy and closure of public and community services such as leisure centres resulted in the suspension of centre-based rehabilitation service delivery and provided a catalyst for the expansion of services to develop home-based and telehealth modes of provision. Ramachandran et al.

(2022) reviewed the effectiveness of home-based telerehabilitation for coronary heart disease patients who would previously have been eligible for traditional outpatient Cardiac Rehabilitation classes. Fourteen randomised controlled trials of 2869 participants were included in the systematic review comparing home telerehabilitation with centre-based rehabilitation and usual care. The review found that home-based rehabilitation showed significant improvement in functional capacity assessed by six-minute walking distance with a mean improvement of 25.58 metres (95% CI, 14.74-36.42 metres) following intervention and an increased mean daily step count of 1.05K steps (95% CI, 0.36 -1.75K steps) (Ramachandran et al., 2022). Positive differences in depression scores, quality of life assessed by the Short-Form mental component and physical component summary were also observed within this review. A systematic review of telerehabilitation programmes in heart failure patients found similar benefits, Cavalheiro et al. (2021) pooled seventeen studies and 2206 patients and found telerehabilitation programmes provided improvements in six-minute walking distance, with a mean increase in walking distance with intervention of 15.86 metres (95% CI, 7.23-24.49metres) and peak $V0_2$ increased by a mean 1.85ml/kg/min (95% CI, 0.16-3.53ml/kg/min) with corresponding improvement is quality of life. Importantly to clinical practice, no adverse events were reported during exercise completed remotely through telerehabilitation within the studies included for review. Since heart failure patients are considered a particularly high-risk group for experiencing unpleasant side effects and events during exercise, this is particularly encouraging.

Unfortunately, during the early stages of the pandemic, it has been estimated that almost half of outpatient Cardiac Rehabilitation services were suspended within the first wave with a corresponding rapid impetus to adopt technology into practice and reinstate service provision at the earliest opportunity (O'Doherty et al., 2021). This is an exciting area within outpatient rehabilitation services, with many programmes rapidly evolving to incorporate remote telehealth within existing programmes and this hybrid approach has been included within updated Cardiac Rehabilitation guidance from the Exercise Professionals Group (BACPR, 2020). It is likely that there will be an increasing volume of research emerging investigating the effectiveness of remote rehabilitation programmes in comparison to traditional centre-based models in future years, with particular focus on the practicalities of implementation and how telerehabilitation can be most appropriately employed within existing services. Clinically, the addition of a telerehabilitation approach has the potential to increase the capacity and reach of traditional rehabilitation models. Evaluating the effectiveness of these approaches to inform practice is imperative for effective service delivery. The outpatient Cardiac Rehabilitation at a local NHS Trust successfully employed a remote telehealth mode of programme delivery during the pandemic and this provided a further opportunity to explore telerehabilitation within this service evaluation.

Chapter 3. Rationale and Aims

3.1. Rationale for a Preoperative Rehabilitation Strategy in Lung Cancer

Postoperative pulmonary complications and increased length of hospital stay can be distressing for patients and result in extensive additional healthcare costs and operational delays in bed flow and operating theatre capacity. Patients presenting with pulmonary complications postoperatively often require higher levels of medical support, lengthy admissions to high dependency level care, increased ventilatory support with higher levels of supplemental oxygen, increased pharmacotherapy needs and greater levels of clinical supervision during their hospital stay. Therefore, evaluating the effectiveness of preoperative interventions to reduce postoperative complications in high-risk patient groups has the potential to inform clinical practice, reduce the labour and resource costs associated with managing complications and provide a future direction for research into the most effective preoperative strategies to optimise patients for surgery. Inspiratory muscle training (IMT) and high intensity interval training (HIIT) have received extensive attention in cardiac and abdominal preoperative patient populations but remain poorly understood as a preoperative intervention for operable lung cancer. Current evidence suggests that lung surgery has the highest rates of postoperative pulmonary complications in comparison to cardiac and abdominal surgeries and therefore identifying effective preoperative strategies for this patient population should be a priority with the potential for the most significant gains. Patients with lung cancer who present with poor preoperative lung function and reduced

exercise capacity are at greatest risk of experiencing postoperative pulmonary complications, that can be of greater severity and result in longer hospital lengths of stay. A strategy to improve patient preoperative lung function through a preoperative rehabilitation programme, combining IMT and HIIT could have a significant protective impact on the development of postoperative pulmonary complications and reduce hospital length of stay following surgery.

The National Institute for Health and Care Excellence (NICE) established a lung cancer management pathway to improve outcomes and ensure prompt and effective treatments are accessible to patients with lung cancer (NICE, 2019). Clinically, lung cancer screening, classifications and the updated management guidelines have provided a significant challenge for health professionals within the field of thoracic surgery. The operable patient group can be frail, elderly with multiple morbidities, which can present additional risks for postoperative morbidity and mortality. The preoperative preparation of patients undergoing surgery in this population warrants further research to help determine successful strategies to minimise postoperative complications and optimise both short and long-term postoperative recovery. The SARS-CoV-2 pandemic has also provided greater uncertainty for NHS service provision with many non-urgent appointments cancelled and outpatient Rehabilitation Services temporarily suspended. The combination of a new cancer diagnosis, a period of enforced lifestyle restrictions during National and Local Lockdowns and the uncertainty of whether the provision of potentially curative treatments would be negatively impacted during the pandemic has placed a greater importance on the need for effective preoperative

strategies to appropriately support patients in navigating such difficult times. The need for remote and digital delivery methods has been paramount to the ongoing provision of outpatient services during the SARS-CoV-2 pandemic and there is a consensus within digital health and NHS bodies that the gains afforded by digital modes of delivery should be incorporated and expanded in future healthcare provision planning. Therefore, establishing the services with high levels of patient uptake and adherence and the patient populations who may benefit the most will help clinical decision-making in allocating resources appropriately and capitalising on digital opportunities.

3.2. Aims of a Preoperative Rehabilitation Strategy in Lung Cancer

The best outcomes for patients with lung cancer are linked to the early removal of cancerous tissue through surgical resection; an intervention that can result in thoracic pain and altered rib cage mechanics in the early postoperative period. Following surgery patients can experience dyspnoea, reduced lung volumes and retained secretions that can predispose patients to atelectasis and respiratory infections, these complications can result in the patient requiring prolonged chest drain insertion, longer high dependency or critical level care and prolonged overall hospital stays. Patients completing exercises designed to strengthen muscles, including those used for ventilation, before their operation, could help to better prepare patients to withstand this type of surgery, recover quickly and have fewer

complications. Patients are operated on within two to three weeks once the patient has been deemed a candidate for surgery and informed consent gained.

An evaluation of a preoperative rehabilitation strategy should also be considered in the context of the lung cancer standard set, which has been established for research involving newly diagnosed lung cancer patients treated through curative surgery or palliation and includes both small cell and non-small cell lung cancer (Mak et al., 2016). The standard set recommends the inclusion of 12-month survival data, a quality of life (QOL) measurement to include the domains of pain, cough, dyspnoea and data that could establish whether the intervention had resulted in a delay to proven curative interventions (Mak et al., 2016).

This study focused on a preoperative IMT and HIIT rehabilitation strategy for operable patients diagnosed with NSCLC and considered at high-risk of postoperative pulmonary complications and will add to the existing body of research in this area that is currently limited to small, randomised trials with limited follow up post hospital discharge. This study intended to add to current knowledge with a large sample, focussing on patients at high risk of postoperative complications with a clearly defined HIIT prescription that will include measures of pre and post training lung function, health-related quality of life and 12-month survival following surgery. Inclusion of outcome measured recommended by the standard set has the intention of ensuring consistency in the outcome measures used across studies in the field and it is hoped that this work can be pooled with the wider evidence base.

3.3. Study Scope and Boundaries

This work aimed to compare standard care for patients scheduled to undergo lung resection with preoperative rehabilitation, using a combined approach of independent IMT and twice weekly HIIT guided by a trained respiratory physiotherapist or exercise physiologist for two to three weeks prior to surgery, delivered on either a face-to-face or virtual platform. A combined approach incorporating both IMT and HIIT was utilised because it was most representative of the 'package of care' model delivered within clinical practice, whereby multiple modalities may be offered and used in patient management. The combined approach used in this study would prevent the extrapolation of the relative effects of the individual rehabilitation modalities, however this was designed to be a pragmatic evaluation to determine clinically relevant outcomes of the current interventions and to maximise the impact of research in clinical practice. The isolation of the relative effectiveness of each individual modality was not considered a primary aim of this study and was considered outside of the scope of this evaluation. The application of this study focused on those patients who had lung resection surgery through an open thoracotomy incision with the intention to identify effective preoperative strategies specifically for this type and surgical approach, findings were not intended to be extrapolated for lower risk and minor thoracic surgery or non-cancerous thoracic surgery.

3.4. The Aim and Objectives of the Study

3.4.1. Aim

The aim of this study was to investigate the efficacy of two modes of preoperative rehabilitation programme, delivered either face-to-face or virtually, in improving the patients' outcome in comparison to standard care (no rehabilitation) in patients with lung cancer awaiting surgical lung resection.

3.4.2. Objective 1: Postoperative Recovery

The first objective of this study was to determine if there was a difference in postoperative recovery with a preoperative rehabilitation programme combining HIIT and IMT, delivered face-to-face or virtually in comparison to standard care. Specifically, to identify if preoperative rehabilitation could reduce the incidence and severity of postoperative pulmonary complications and reduce the length of high dependency level care and overall hospital length of stay including the extent of subsequent hospital admissions within a 12-month follow up period.

3.4.3. Objective 2: Post-Surgery Survival

The second objective was to determine if there was a difference in survival with preoperative rehabilitation combining HIIT and IMT, delivered either face-to-face or virtually in comparison to standard care and if preoperative rehabilitation could influence survival time in lung cancer patients undergoing surgical resection. This objective specifically focused on determining patient survival status at 6-month and 12-month intervals post-surgical resection.

3.4.4. Objective 3: Efficacy of Preoperative Rehabilitation

The third objective was to determine if there was an improvement in preoperative lung function and health related quality of life following preoperative rehabilitation programmes, combining HIIT and IMT, delivered face-to-face or virtually, to prepare patients for surgical lung resection. To determine whether piMAX, FEV1 and FVC measures improved with rehabilitation programmes and whether there was a difference in the efficacy of mean improvements in these preoperative measures between programmes.

3.4.5. Objective 4: Feasibility of Preoperative Rehabilitation

The fourth and final objective of this study was to determine the feasibility of a preoperative programme for lung cancer patients awaiting surgical resection delivered through an existing Cardiac Rehabilitation programme. Specifically, to determine whether lung cancer patients were able to adhere to a face-to-face or virtual programme of combined HIIT and IMT in the preoperative period, establish whether patients were able to achieve the target heart rate required for HIIT and identify patient or clinician reported side effects during the programmes.

3.5. Context in Relation to Practical Implications in Clinical Practice

HIIT is a relatively new concept in patient populations and therefore patient safety was also considered a clinically relevant objective. In accordance with the lung cancer standard set the investigation included whether participation in the

preoperative rehabilitation programme delayed the time from diagnosis to surgical intervention, the degree of health pre and post intervention incorporating patient reported outcomes of pain, fatigue, dyspnoea, social, emotional and cognitive functioning.

Ultimately the outcome of this study was to determine whether HIIT and IMT were viable preoperative rehabilitation strategies for future inclusion into lung cancer patient care pathways and ascertain whether there was a superior mode of delivery regarding adherence and efficacy to inform future service delivery and resource allocation. Pragmatically, the service model to expand the existing outpatient Cardiac Rehabilitation programme to accept high-risk preoperative lung cancer patients into the Service through the Cardiothoracic Specialty could also showcase this approach as a potential referral pathway into rehabilitation for preoperative lung cancer patients.

Chapter 4. Methodology

4.1. Ethical Approval for the Study

This study was accepted as a service evaluation by UHNM NHS Trust Research and Innovation Department and was approved and registered with the NHS Trust under Clinical Audit, registration number: CA18124. To comply with NHS Trust Information Governance and data protection the study was also approved by UHNM NHS Trust Data, Security and Protection department with correspondence and approvals shown in Appendix 1. This study was approved as a service evaluation by the Staffordshire University Review Ethics Committee; the original form is shown in Appendix 1. The initial form was signed off by the Principal Supervisor and submitted on 4th March 2021. On the 10th March 2021 the committee approved the study with minor flaws, the committee comments were subsequently addressed by the researcher and an amendment form submitted to the panel. Full approval for the study was given by the University Ethics Committee on 25th May 2021 to allow implementation and data collection for the purposes of audit and service evaluation.

4.2. Participants

4.2.1. Study Population and Sample

The study sourced retrospective patient data from the Thoracic Surgery Department and Cardiac Rehabilitation Department at the University Hospital of

North Midlands NHS Trust for comparison. The study population was patients over the age of 18 years undergoing lung resection surgery, through an open thoracotomy incision during the period of February 2018 to April 2021. This data was readily available to the researcher and actively collated for service evaluation and developmental purposes as part of their existing clinical managerial role. This anonymised data was pooled and analysed retrospectively for this study.

The researcher initially collected and reviewed a total of 485 patient records over the period February 2018 – April 2021 and these were matched based on identifiable risk factors associated with poorer postoperative outcomes, with the intention to provide an estimated 150 subjects within three retrospective groups. These were Group 1. Standard Care (February 2018-February 2019), Group 2. Face-to-face HIIT and IMT Intervention (March 2019-March 2020) and Group 3. Virtual HIIT and IMT Intervention (April 2020-April 2021). The researcher determined the study population and sample size based upon the total number of appropriate lung resection surgery cases during the study period; information gained from the NHS Trust Clinical Audit Team.

4.2.2. Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they met the criteria stipulated below:

- Patient was at least 18 years of age
- Patient had a diagnosis of operable NSCLC and consented to surgical resection

- Reduced preoperative lung function identified through FEV1 less than 80% of predicted values or significant respiratory past medical history
- Patient underwent lung resection surgery to remove cancerous tissue through an open thoracotomy incision
- Patient was identified by a Thoracic Surgeon as high risk for surgery and appropriate for the preoperative intervention
- Patient had the mental capacity to consent to and follow preoperative rehabilitation instructions to undertake the IMT and HIIT intervention

Patients were excluded from the investigation if they met any of the exclusion criteria stipulated below:

- Patient was under 18 years of age
- Patient had an inoperable lung cancer diagnosis
- Patient had an operable NSCLC diagnosis who declined surgical resection
- Patient underwent biopsy or lung resection through minimally invasive video-assisted thoracic surgery or mini-thoracotomy
- Presence of contraindications to perform IMT intervention (undrained pneumothorax, tracheal stenosis, ruptured eardrum, pulmonary hypertension, large bullae, desaturation below 94% during or immediately following IMT, acute or uncompensated heart failure)
- Presence of contraindications for HIIT intervention (unstable angina pectoris, acute uncompensated heart failure, recent myocardial infarction, recent coronary artery bypass grafting, complex ventricular arrhythmias or heart block, uncontrolled hypertension severe neuropathy)

- Evidence patient performed HIIT or IMT prior to case identification
- Patient did not have capacity to consent to or follow preoperative instructions to participate with the intervention

4.3. Study Design

4.3.1. Rationale and Defence of Study Approach

The case-control study fell under the umbrella of service evaluation. There was no direct participant prospective involvement therefore additional NHS ethics was not required. The underlying principles of service evaluation encapsulated the needs of the researcher who primarily holds a clinical managerial role within the Rehabilitation department, reporting to and engaging with a range of stakeholders. Evaluation has been described as the systematic assessment of a programmes' implementation or impact, ascertaining the value of the initiative by gathering information in a rigorous design, to make better informed decisions (Langley et al., 1996). Service evaluations are practical in nature and are intended to be of use to those individuals who require information to make decisions and implement actions and it is these aspects of the service evaluation approach that appealed to the researcher. The systematic and rigorous design required for well executed service evaluations provided assurance that the study would be reliable, valid and repeatable. Primarily the service evaluation and outcomes were clinically important to determine the value of a preoperative rehabilitation initiative for lung cancer patients' undergoing surgery within the local NHS Trust and the outcomes would

be of interest to key stakeholders. The evaluation of a large service data set was a pragmatic and efficient approach to influence and shape service delivery. Service evaluations can be derided as predominantly displaying a local influence with limited generalisation to wider populations. However, since this initiative was both an innovative and relatively under-researched area of practice, with no large sample trials investigating combined IMT and HIIT in this specific patient population, there remains potential for this study to have a greater impact than one restricted to Departmental decisions and this will be considered by the researcher on dissemination of findings.

4.3.2. Case-Control Design

The study utilised a case-control cohort design, whereby the researcher compared data from the three distinct groups. Group 1: The Standard Care Control Group, Group 2: The face-to-face IMT and HIIT intervention group and Group 3: The virtual IMT and HIIT intervention group. Case-control design was considered an appropriate approach to reduce the impact of potential confounders by ensuring equal distribution of variables known to affect the outcome across all groups under study (De Graaf et al., 2011). The retrospective approach had the clinical and pragmatic advantage of access to and analysis of data for a large cohort of patients. Dey et al. (2020) considered an added advantage of case-matched designs was that they are economical to perform, design and implement.

In the first instance, baseline characteristics were analysed through IBM SPSS statistical software to establish whether the three groups were sufficiently similar

to negate the requirement of individual subject case-matching. The three sample groups were matched to eliminate the potential effect of confounding variables, known to influence postoperative recovery, according to baseline characteristics and demographics routinely collected and audited for all preoperative lung cancer patients referred to the NHS Trust. Matching variables should only consist of those that are known to be associated with the outcome and should be restricted to as few as possible to ensure that the study does not produce spurious results or fail to provide any information (Dey et al., 2020). Therefore, whilst statistical analysis was undertaken across a range of baseline characteristics to determine overall similarity across the three groups, decision-making regarding sample-matching was focused on the independent risk factors associated with poorer outcomes following lung resection surgery identified in the Thoracic Guidelines and current research. These were age, respiratory conditions, Body Mass Index (BMI), extent of surgical resection, ASA classification and pulmonary function. Preoperative physical activity status has not been established as an independent risk factor but is incorporated within the ASA classification and is measured by the Eastern Cooperative Oncology Group (Oken et al., 1982). The specific classifications related to ASA classification and ECOG score are outlined in Table 4.3.2.a and Table 4.3.2.b respectively for further detail.

Table 4.3.2.a. American Society of Anaesthesiologists ASA classification (ASA, 2020)

ASA Classification	Definition
1	A normal healthy patient
2	A patient with mild systemic disease
3	A patient with severe systemic disease
4	A patient with severe systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive without the operation
6	A patient who has been declared brain-dead and organs are being removed for transplant

Table 4.3.2.b. Eastern Cooperative Oncology Group Score System (Oken et al., 1982)

ECOG Score	Descriptor For Score
0	Asymptomatic fully active, able to carry out all pre-disease activities without restriction
1	Symptomatic but completely ambulatory. Restricted in physical strenuous activity. Able to carry out work of a light or sedentary nature
2	Symptomatic less than 50% of time in bed during the day. Ambulatory and capable of self-care
3	Symptomatic more than 50% of time in bed. Capable of only limited self-care activities
4	Bedbound unable to carry out self-care. Confined to bed or chair

4.4. Interventions

4.4.1. Standard Care (Data set from February 2018 - February 2019)

Patients received standard care which consisted of attending a pre-assessment clinic with an NHS Cardiothoracic Nurse and a Junior Doctor on rotation within the Cardiothoracic department during this period. The clinic consisted of the completion of the anaesthetic checklist in accordance with ASA guidance, an explanation of the planned surgery and the completion of preliminary consent forms. The nurse recorded objective measurements of the patients' height and weight and these figures were used to calculate BMI. Patients were referred for pulmonary function testing during the preoperative period upon the request of the Thoracic Surgeon. All patients were required to answer questions on their current lifestyle that would be pertinent to determining anaesthetic risk and subsequent postoperative management, this included current smoking status, alcohol intake in units per week and average physical activity levels. This information was recorded within the ward care plans in preparation for their in-hospital patient stay. Throughout the preoperative process patients had access to a Specialist Lung Cancer Nurse to provide care and support to patients and their carers in an outpatient capacity during this period and this may have included home visits or telephone support.

4.4.2. Face-to-Face Rehabilitation (Data set from March 2019–March 2020)

Patients received the standard care outlined in Group 1 and in addition patients also attended an outpatient clinic with a physiotherapist where pulmonary function

tests were completed using the Micro 1 Handheld Portable Spirometer. The physiotherapist used this device in accordance with manufacturer guidance to perform Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC) respiratory manoeuvres. The device is durable and portable and therefore an appropriate choice for use in an outpatient Rehabilitation Service. The Spirometer was purchased through additional NHS funding supporting the expansion of the Cardiac Rehabilitation Service. At the clinic patients were given a hand-held Philips Respironics inspiratory muscle trainer model HS730010 (Philips Respironics, 2022) as shown in Figure 4.4.2.a. The physiotherapist demonstrated and instructed patients how to breathe in and out through the device mouthpiece in accordance with Manufacturer's instructions for use by Philips Respironics included with the device. The physiotherapist set the resistance on the inspiratory muscle trainer at the clinic and this was identified by measuring the patients' maximum inspiratory pressures (piMAX) using the portable spirometer. The inspiratory muscle trainer was set at 60-70% of patient piMAX at the initial clinic appointment. Patients were advised to use the device independently at home, twice a day for fifteen minutes every day until the day of their operation. PiMAX was re-assessed after one week and the resistance adjusted to ensure that the trainer was still achieving a resistance of 60-70% of the patients' piMAX. This ensured that the treatment continued to be effective at the intended pressure and reflected any training effect that may have taken place during this period. The physiotherapist completing the initial outpatient clinic, performing spirometry and demonstrating the use of the inspiratory muscle trainer was an experienced NHS

advanced respiratory physiotherapist, qualified for 15 years and trained in adult spirometry in accordance with the Association for Respiratory Technology and Physiology (ARTP).

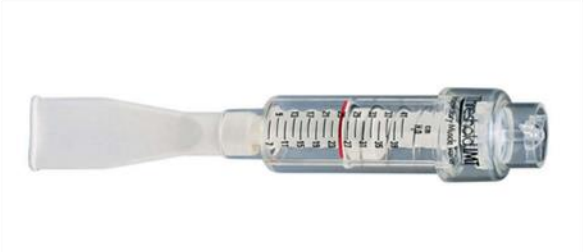

Figure 4.4.2.a. Philips Respironics Threshold Inspiratory Muscle Trainer

At the end of the clinic patients were booked in to attend Cardiac Rehabilitation exercise sessions, up until their operation date, at a community gym currently hired for the existing Cardiac Rehabilitation programme. Patients were offered the choice of nine different gym venues across the region. There was no gym membership cost for patients as they were entered into the existing NHS Rehabilitation scheme alongside the patients referred for cardiac conditions. Patients exercised under the direct supervision of an NHS and Healthcare Professions Council registered physiotherapist or NHS exercise physiologist employed within the Cardiac Rehabilitation Service. All employees had a minimum of six years of experience working within the Cardiac Rehabilitation Service and prior experience of working with postoperative lung cancer patients in a ward environment within the Therapies Department. Physiotherapists and exercise physiologists within the Service were trained to at least Bachelor of Science Degree level in either Physiotherapy or Exercise Science and in addition had current

training in Level 4 BACPR Cardiac Specialist Exercise Instructor and or Level 4 in Cancer and Exercise Rehabilitation.

Exercise prescription for patients consisted of a ten-minute warm-up period, ten-minute HIIT period and a five-minute cool down period as shown in figure 4.4.2.b. Patients wore heart rate monitors during the exercise and at the time that was midpoint through each of the exercises, patients were asked to give their rating of perceived exertion using the Borg scale. The Borg scale, shown in Figure 4.4.2.c, provides descriptors for the effort patients sense during exercise with a verbal rating between 6 and 20 (Borg, 1998). The Borg Scale is in routine clinical use within outpatient rehabilitation services and is recommended to monitor and prescribe exercise within cardiovascular rehabilitation literature (BACPR, 2017). Rehabilitation for preoperative thoracic surgery has not yet been established into routine practice and therefore there is a lack of clarity in guidelines for specifics regarding implementation of exercise. Since preoperative patients with lung cancer were incorporated into the existing Cardiac Rehabilitation programme, for the purposes of this study, using the Borg scale already in routine practice for cardiac patients within the service, was considered an appropriate and pragmatic approach. HIIT was achieved when patients reached 80% of their heart rate reserve (HRR) as monitored by their heart rate monitor, supplemented by a rating of perceived exertion (RPE) between 15-18, which equated to a patient perception that the exercise was ‘hard’ or ‘very hard’.

Figure 4.4.2.b Example picture of the face-to-face rehabilitation programme

Borg RPE	
Score	**Level of exertion**
6	No exertion at all
7	
7.5	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Figure 4.4.2.c Borg Scale Rating of Perceived Exertion (Borg, 1998)

Heart rate and RPE were monitored and documented on patient's exercise profiles and an example copy of the patient's exercise profile is shown in Appendix 2. Patients would complete exercise on a selection of static exercise bikes, rowing machines, treadmills and use hand-held dumbbell weights. This was to allow variety and facilitate patient preference, technique and take in to account any additional limiting morbidities. Patients would exercise at high intensity for one minute and recover for thirty seconds at a time. Patients were asked to discontinue or reduce the exercise intensity if an RPE greater than 18 was reported.

4.4.3. Virtual Rehabilitation (data set from April 2020–April 2021)

Patients attended their clinic appointment with the physiotherapist by either telephone consultation or a video consultation through the Attend Anywhere digital platform. This platform was piloted, endorsed and procured by NHS England and was rapidly upscaled for National use in healthcare during the pandemic. Local Commissioners supported the use of digital and remote modes of delivery during the pandemic and patients were posted the Phillips Respironics inspiratory muscle trainer and a portable finger pulse oximeter during this period. Patients had been guided in their use by the NHS physiotherapist during their telephone or video consultation. During the SARS-CoV-2 pandemic, pulmonary function testing utilising portable spirometry, was considered a high-risk aerosol generating procedure and was a suspended practice at times during this study period. The physiotherapist guided patients to adjust the resistance pressures on the

inspiratory muscle trainer based on patient reported feedback of exertion where piMAX was unable to be used to establish training intensity objectively.

Patients accessed education material through audio podcasts and recorded exercise sessions within an online patient library commissioned to support the digital transformation of the Cardiac Rehabilitation programme during the pandemic. The online library was provided via the 'RecapHealth' platform, this was owned by a local business and had been piloted by the NHS Trust Heart Failure Service prior to the pandemic. The physiotherapist was made an administrator of this platform through the Cardiac Rehabilitation Service. The physiotherapists and exercise physiologists uploaded the specific and relevant content for individual patients for accurate prescription. The platform provided a digital count of when content had been accessed and completed by patients. Patients were advised to complete the exercise sessions twice a week and each individual session was of thirty minutes duration. Patients also had the opportunity to participate in live online sessions, which were carried out once a week and set for the same duration as the recorded sessions, guided directly by the physiotherapist. The recorded and live sessions were devised by the team to be comparable to the programme intensity set in the face-to-face rehabilitation group as shown in figure 4.4.3.a.

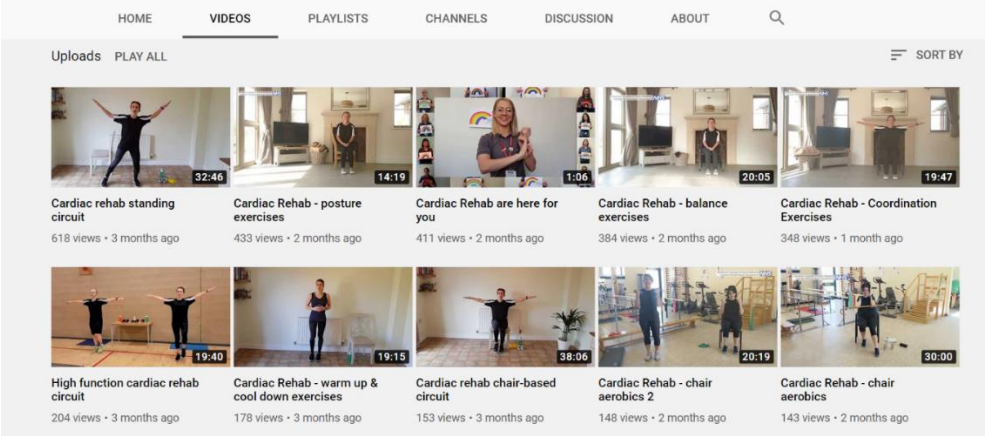

Figure 4.4.3.a. Example of instructor-led exercise videos for the virtual rehabilitation programme

The portable finger pulse oximeters enabled patients to self-assess and report heart rate measures throughout their sessions and the Borg scale was displayed on the screen throughout the sessions for patients to review and document their RPE at midpoint through the exercise and the physiotherapist or exercise physiologist alerted patients to this point in the recorded and live sessions. Patients with home gym equipment were able to make use of this equipment during their sessions, otherwise regular household items were used to replicate the face-to-face programme. This included steps and stair climbing, food tins, water bottles and bags filled with weighted objects. Patients were asked to discontinue or reduce the intensity of the exercise if they reported an RPE of greater than 18.

4.5. Data Collection

4.5.1. Access to Hospital Systems

The patient outcome data was accessible to the researcher for retrospective data collection and evaluation within their clinical and managerial role and access was granted by the Quality, Safety and Compliance Department at the NHS Trust. The researcher accessed all relevant patient case data through the electronic NHS Trust Hospital Systems; Iportal and Medisec, the departmental Cardiac Rehabilitation Excel database, Cardiac Rehabilitation paper patient records stored within the department and the Quarterly Commissioning Reports of Service Key Performance Indicator Dashboards. The data collected from each source was inputted into the researcher-produced data collection Microsoft Excel spreadsheet that would subsequently be imported to IBM SPSS version 2.7 software on completion.

4.5.2. Data Collection for Baseline Characteristics

Baseline descriptive data on age, gender, BMI, current smoking status including smoking pack years and alcohol units consumed per week were obtained through the Cardiac Rehabilitation Departmental Database and inputted directly into the data collection spreadsheet. The Cardiac Rehabilitation paper records were accessed to identify patient medical conditions and inputted into the spreadsheet under the classifications of respiratory, cardiovascular, neurological, musculoskeletal, renal or gastric conditions. The Medisec electronic system provided access to relevant clinic letters, discharge letters and key medical tests. The surgeon clinic letter was accessed to determine operability and listing for lung

resection surgery and relevant past medical history. The pre-assessment notes were accessed to establish ASA classification and physical activity status. The hospital discharge letter provided a further opportunity to establish relevant medical conditions. The operation notes and hospital discharge letter confirmed the type of surgery undertaken and the extent of the lung resection; categorised as wedge resection, segmentectomy, lobectomy or pneumonectomy.

4.5.3. Data Collection for Objective 1

The Iportal electronic system provided the hospital admission date for surgery, date of surgery, date the patient was transferred to the ward from high dependency or critical level care and the date the patient was deemed medically fit for discharge following surgery. These dates were inputted into the data collection Excel spreadsheet to generate high dependency length of stay and overall hospital length of stay in days. The Iportal electronic system also provided 12-month follow up information relating to the number of hospital admissions within the 12-months following surgery and the date of admission and discharge of each hospital admission during that period. This information was inputted into the spreadsheet to determine the total number of hospital admissions and the cumulative number of hospital bed days over the 12-month follow-up period. The Medisec electronic system provided access to the lung resection operation notes and hospital discharge letter and this highlighted postoperative management and aided the identification of postoperative pulmonary complications. This included reporting of postoperative chest x-rays, results of sputum samples and prescription of oxygen

therapy, antimicrobial therapy, tracheostomy requirement and chest drain removal dates.

4.5.4. Data Collection for Objective 2

The Iportal electronic system alerts confirm the deceased status of the patient and, where appropriate, the date of death and this information was used by the researcher to calculate 6-month and 12-month survival status and the total number of days survived post-surgery at the 12-month follow up period and this data was inputted, in days, into the data collection spreadsheet. The oncology and surgical follow-up clinic letters were also reviewed on the Medisec system related to the 12-month following surgery to identify whether the patient had undergone radiotherapy or chemotherapy at any point within their management and whether a confirmed positive SARS-CoV-2 had been reported.

4.5.5. Data Collection for Objective 3

The Medisec system was accessed for preoperative pulmonary function tests for patients who had undergone standard care and would not therefore have spirometry undertaken in a Cardiac Rehabilitation clinic appointment. The paper records held within the Cardiac Rehabilitation Department provided pre and post training pulmonary lung function tests that consisted of FEV1, FVC and piMAX and pre and post training health-related QOL scores, as assessed by the EORTC-QLQ-C30 questionnaire (Aaronson et al., 1993), for patients receiving either face-to-face or virtual rehabilitation and this information was used to further populate the data collection spreadsheet.

4.5.6. Data Collection for Objective 4

The Cardiac Rehabilitation Department database provided information on the mode of rehabilitation delivery, to determine whether patient data related to group 2 or 3, referral date into the rehabilitation programme, the date of the initial clinic appointment within the programme, the frequency of attendance to rehabilitation sessions and the total number of rehabilitation sessions attended and this information was used to populate the data collection spreadsheet. Finally, the Departmental database also provided information on discharge status from the rehabilitation programme, including the completion or cancellation status and the patient-reported reason for cancellation, if known, and this was coded and inputted in the data collection spreadsheet. Rehabilitation programme patient specific information regarding patient achievement of HIIT level training as determined by achieving 80% HRR in at least one exercise station within a session and an RPE rating of between 15-18, the reporting of serious adverse events and patient reported outcomes of side effects were obtained by the researcher through individual review of patient paper records held within departmental secure files.

4.6. Patient Consent for Data Use

Patients with lung cancer attending the Cardiac Rehabilitation programme for preoperative intervention consented to their data being used for service evaluation and developmental purposes before commencing within the programme and an example of the patient information sheet outlining this is included in Appendix 3.

Prior to data being included for this analysis the NHS hospital numbers of all cases identified across all three groups were entered into the Data Warehouse system, this data cleansing system was actioned within the NHS Trust in 2020 and the system highlighted the NHS numbers where patients had declined the use of their data for research or auditing purposes. This additional step in the data collection process provided further assurance that the cases included for this study continued to consent and approve their data usage. All patient information was accessed by the researcher on the NHS Trust site and specifically within the Cardiac Rehabilitation Department. The data was collated onto the Excel spreadsheet, created by the researcher, for the purpose of data collection only. All patient information was anonymised at the point of entry onto the spreadsheet and held confidentially in line with NHS Trust and Staffordshire University Ethics guidance.

4.7. Study Process to Protect Patient Confidentiality

All patient data collated for the study was stored electronically on Microsoft Excel and IBM SPSS spreadsheets on the researchers privately-owned laptop. The laptop was password protected with a password that was known only to the researcher and the laptop was exclusively used by the researcher. The laptop was kept in a locked filing cabinet within the researchers' home when it was not in use. There was a single key to this cabinet and this key remained in the researchers' possession throughout. The laptop was used by the researcher within the workplace, for data collection purposes, and remained in their possession throughout. No paper

patient profiles left the workplace. Patient paper profiles were accessed and reviewed by the researcher within the Cardiac Rehabilitation department and these records were returned to a locked filing cabinet within the Department, as per the current NHS Trust stipulated storage requirements for patient records. All data was anonymised at the point of electronic entry onto the Excel or SPSS spreadsheets using coding and individual identifier codes. The researcher maintained their own record of the unique identifier codes for reference purposes during data entry, this list was kept securely and destroyed after data entry was checked for accuracy.

The NHS Trusts electronic systems and Cardiac Rehabilitation departmental databases required signed permission from NHS Information Technology Services and NHS Cardiology Directorate level Management to access through unique log in and password codes. The researcher had existing permission to access these electronic systems in their current role for the purposes of clinical audit, service evaluation and service improvement. The NHS Cardiology Directorate gave their permission for this access to be used for the purposes of this study and the letter of permission from the Directorate Manager is shown in Appendix 4. The NHS Trust Quality Assurance and Audit Department also provided their written permission for the researcher to utilise the relevant patient records relating to the study period and explicitly for the purposes of the study, as shown in Appendix 5. All currently employed Cardiac Rehabilitation administrative and clinical staff have access to the NHS Trust systems Medisec, Iportal and the Cardiac Rehabilitation departmental databases that hold the patient identifiable raw data for the purposes of their NHS work. Only the researcher and the Staffordshire University Supervisory Team for

this study had access to the non-identifiable patient data that had been collated from these systems and inputted onto the researcher-produced spreadsheets to create data sets for selected cases. These spreadsheets were shared with the University Principal Supervisor through email and Microsoft OneDrive shared resources. The researcher will follow current guidance for data storage and the raw data held on the Departmental databases and paper records will be held securely for eight years and after this period destroyed securely through confidential waste, as per the current Government guidance. The data sets created by the researcher on the researchers' personal laptop will be held for ten years in accordance with Staffordshire University research policy for post-graduate study. This affords an appropriate duration to facilitate future study publication and assist in researcher recollection to answer questions relating to any possible publications. Once this period has passed the laptop files will be wiped clean using professional software.

4.8. Objective 1-4 Continuous and Categorical Variables

4.8.1. Objective 1 Variables

The continuous variable hospital length of stay was considered the ultimate primary outcome of this study and was measured in total number of days. Thoracic Surgeons currently employed at the NHS Trust collectively agreed that a mean reduction in overall hospital length of stay by two days, due to a preoperative intervention, would be of clinical significance and this was incorporated into the analysis and interpretation of findings. There was no agreement in a clinically

significant reduction in high dependency level care days between the Thoracic surgeons, but this was considered an important component of hospital stay for inclusion. Comparison of the mean total number of readmissions and the cumulative number of days hospitalised during the 12-month follow up period was a longer-term variable included to indicate potential differences in recovery.

The presence of pulmonary postoperative complications and the severity of postoperative complications was also considered an important primary outcome measure to determine any significant impact from the preoperative intervention. Postoperative pulmonary complications were measured by the documented evidence of any one or more of the following categorical variables; prescription of antimicrobial therapy during the admission due to a confirmed or suspected respiratory infection, diagnostic evidence of respiratory infection or atelectasis on a postoperative chest x-ray and confirmed by the radiological report, requirement of additional ventilatory support or significant supplemental oxygen support that included invasive and non-invasive ventilation including bi-phasic (BIPAP) or continuous (CPAP) positive airway pressure support or high-flow oxygen therapy through either face mask or nasal delivery and need for a tracheostomy postoperatively for ventilatory support or secretion clearance. The continuous variables to determine postoperative pulmonary complications were the number of days that intercostal chest drains remained in situ postoperatively with greater mean duration indicative of postoperative pulmonary compromise, and this was calculated from the postoperative management report on discharge letters. Postoperative complication severity was classified by the validated Clavien-Dindo

classification (Dindo et al., 2004). The researcher graded the complications once inputted into the data collection spreadsheet. The Clavien-Dindo classification is a standardised system that aims to grade the severity of a complication in a reproducible manner. This classification informs healthcare professionals on clinically significant complications, therefore indicating they are of sufficient severity to result in a deviation from anticipated milestones in the course of a patient's postoperative recovery. Additionally, the classification incorporates the level of therapy required to manage a complication within the grading system (Dindo et al., 2004). Therefore, allowing some inference to be made regarding the potential resource cost of treating complications, although economic evaluation was not the aim of this study.

4.8.2. Objective 2 Variables

Survival following lung resection was also considered a primary outcome of this study since current studies investigating preoperative rehabilitation in lung cancer have rarely included a long term follow up within their design. A comparison of survival was undertaken with both categorical and continuous data across the three sample groups, with categorical data indicating survival up to 6-month and 12-months post-surgery and the continuous data comparing mean days of survival following surgery. Categorical variables from baseline characteristics, objective 1 and the additional collection of SARS-CoV-2 status and adjuvant therapy requirement were also used to further explore 12-month survival patterns and hazard ratios across the full sample, whereby the type of preoperative care was

analysed for any potential effect between standard care, face-to-face rehabilitation and virtual rehabilitation.

4.8.3. Objective 3 Variables

Pre and post rehabilitation pulmonary function tests were collated and used as potential explanatory outcomes for any differences in objective 1 and 2. The continuous variables FEV1, percentage predicted FEV1, FVC, percentage predicted FVC and piMAX were measured at baseline prior to intervention and following intervention at two to three days prior to surgery for individual comparison of a possible training effect in the face-to-face rehabilitation sample and the virtual rehabilitation sample. Degree of patient health-related quality of life was also evaluated with pre and post training EORTC QLQ-C30 scores from questionnaires given to patients pre and post intervention and these were individually compared across face-to-face and virtual rehabilitation samples independently. A specimen EORTC QLQ-C30 questionnaire is shown in Appendix 6.

4.8.4. Objective 4 Variables

Waiting time was determined by the length of time from diagnosis of operable lung cancer to surgical resection, in days. This continuous variable was based on the outpatient clinic appointment with the Thoracic surgeon and date of admission to the Cardiothoracic ward for surgery used to compare mean waiting times for surgical resection across the three groups.

Pragmatics related to the feasibility of service delivery were determined by categorical variables. This consisted of proportion of samples attending the clinic

and completing the programme alongside patient-reported reasons for cancellation. Categorical variables of HIIT attainment were established with the proportion of samples with documented evidence of HIIT attainment at training zones at 80% HRR during at least one exercise station within a session. Number of reported serious adverse events and side effects associated with the intervention delivered either face-to-face or virtually were also reviewed and reported.

Chapter 5. Data Analysis

5.1. Data Handling to Establish Sample Groups

5.1.1. Sample Size

The initial data collection yielded 142 patients who received face-to-face rehabilitation intervention and 136 patients who had received rehabilitation through virtual delivery. Patients who had undergone lung resection through a thoracotomy approach and received standard care resulted in 206 potential cases identified for the standard care sample. The initial yield of 206 potential cases for standard care included patients of low surgical risk in addition to those with comparable presentations to the two intervention groups. Cases were retained for the standard care group when a complete data set was available that included preoperative pulmonary function tests; FEV1, percentage predicted FEV1, FVC and percentage predicted FVC. These results were important baseline measures to compare homogeneity across the three groups, since a higher lung function is clinically indicative of less respiratory deficit and a reduced likelihood of developing postoperative pulmonary complications. Patients would be unlikely to be referred for preoperative pulmonary function testing, that may delay surgery, if the surgeon had sufficient confidence through clinical assessment that a patient had adequate respiratory function to withstand the anaesthetic and respiratory compromise associated with lung resection. The approach to include only patients who had preoperative pulmonary function tests performed removed the lowest risk patients from the standard care sample that would have otherwise positively skewed results

in the favour of no intervention. This approach removed 40 cases and resulted in the initial 206 cases being filtered to a final sample size of 166 cases in the standard care group for comparison with the intervention groups.

Clinically, it was also theorised that preoperative spirometry was requested when the patient history and presentation suggested increased surgical risk. Surgical risk has been linked with advanced age, known respiratory conditions, current smoking status, significant and numerous comorbidities, high BMI, poor baseline physical activity and lower preoperative FEV1 in lung resection surgery (Stephan et al., 2000; Agostini et al., 2010; Agostini et al., 2018). These characteristics would also identify eligible patients for referral for preoperative rehabilitation intervention as indicated by the inclusion criteria. Therefore, filtering cases for standard care by the presence of relevant preoperative pulmonary function tests was also a pragmatic approach to increase homogeneity across the three groups for a range of risk factors.

5.1.2. Baseline Characteristics

Baseline descriptive sample characteristics for standard care (n=166), face-to-face rehabilitation (n=142) and virtual rehabilitation (n=136) are outlined in table 5.1.2.a with means and standard deviations included to two decimal places. On initial inspection the three sample groups appear largely consistent across means but understanding of their individual distributions would guide further statistical analysis.

Table 5.1.2.a. Descriptive Statistics for the Three Groups

Characteristic		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation
Gender	*Male (n)*	39% (64)	51% (73)	40% (54)
	Female (n)	61% (102)	49% (69)	60% (82)
Activity Status (ECOG)	*1 (n)*	30% (50)	29% (41)	39% (53)
	2 (n)	52% (86)	43% (61)	52% (71)
	3 (n)	18% (30)	28% (40)	9% (12)
ASA Classification	*1 (n)*	0.6% (1)	1% (2)	2% (3)
	2 (n)	26% (43)	17% (24)	22% (30)
	3 (n)	69% (114)	78% (111)	74% (101)
	4 (n)	4% (7)	4% (5)	2% (2)
	5 (n)	0.6% (1)	0% (0)	0% (0)
Type of Surgery	*Wedge Resection (n)*	1% (1)	1% (2)	1% (1)
	Segmentectomy (n)	52% (87)	52% (74)	48% (66)
	Lobectomy (n)	46% (77)	47% (66)	49% (67)
	Pneumonectomy (n)	1% (1)	0% (0)	2% (2)
Smoking Status	*Non-Smoker (n)*	22% (36)	15% (21)	24% (33)
	Smoker (n)	28% (46)	38% (54)	34% (46)
	Ex Smoker (n)	50% (84)	47% (67)	42% (57)
Smoking Pack Years	*Mean (SD)*	28.03 (26.69)	37.27 (37.61)	25.82 (27.65)
Cigarettes Per Day	*Mean (SD)*	3.60 (6.91)	5.18 (7.56)	4.15 (6.33)
Alcohol Intake (unit per week)	*Mean (SD)*	6.24 (11.14)	9.16 (16.84)	6.07 (10.08)
Age (years)	*Mean (SD)*	69.89 (11.68)	69.96 (10.17)	68.52 (12.02)
Body Mass Index	*Mean (SD)*	27.94 (5.61)	28.02 (6.19)	28.04 (6.08)
Number of Comorbidities	*Mean (SD)*	2.07 (1.35)	2.15 (1.48)	2.36 (1.51)
Totals	*n*	166	142	136

5.1.3. Data Handling of Samples for Normality Distributions

Determining the normality of a distribution is a pre-requisite for further statistical testing and is often an underlying assumption for parametric testing (Pallant, 2020). Each group had an individual sample size over 100 and therefore the Kolmogorov-Smirnov test was used to statistically analyse normality of the distribution in favour of the Shapiro-Wilk test, as recommended in statistical guidance (Mishra et al., 2019). A non-statistically significant result would allow acceptance of the null hypothesis and indicate normality in distribution statistically (Pallant, 2020). The normality of the distribution was further analysed by reviewing the kurtosis and

skewness statistics. Skewness and kurtosis statistic values that fell within -1 to +1 were considered reflective of equal distribution (Kim, 2013. The z-score was calculated with scores between -3.29 and +3.29 indicative of a normally distributed sample in accordance with statistical literature on sample size (Ghasemi and Zahediasl, 2012; Kim, 2013). The researcher visually inspected histogram and Q-Q plots, as recommended by Pallant (2020) to negate situations where statistical tests of normality can be overly or under sensitive. Tabachnik and Fidell (2013) reflected that skewness and kurtosis statistics can be overly sensitive with large sample sizes and in these circumstances visual inspection of normality distribution plots should be undertaken.

5.1.4. Normality of Baseline Characteristics between Groups

The continuous variables of interval or ratio level; age, BMI, cigarettes smoked per day, smoking pack years, alcohol consumption and relevant comorbidities were analysed and Kolmogorov-Smirnov tests were statistically significant in all baseline characteristics except BMI within the standard care group as shown in appendix 7. Cigarettes smoked per day, smoking pack years and weekly alcohol unit consumption demonstrated the greatest skew and kurtosis, with statistics some distance from the desirable parameters. Histograms shown in Appendix 7 suggest that this is largely be due to non-smoker or teetotal inclusion creating an early peak within the data and this same pattern was evident across standard care, face-to-face and virtual rehabilitation groups. Histogram and Q-Q plots visually presented uni-modal distributions across BMI, age and comorbidity variables.

5.1.5. Normality Interpretation of Preoperative Pulmonary Function

Preoperative piMAX measures were taken in the intervention groups. All three groups, including standard care also underwent preoperative pulmonary function testing that consisted of FEV1, percentage predicted FEV1, FVC and percentage predicted FVC and the mean and standard deviations to two decimal points are shown in table 5.1.5.a.

Table 5.1.5.a. Baseline Preoperative Pulmonary Function Tests for the Three Groups

Preoperative Lung Function		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation
FEV1	*Mean (SD)*	2.16 (0.75)	2.00 (0.84)	2.20 (0.79)
	min-max	0.91-4.67	0.58-5.04	0.76-5.08
Percentage Predicted FEV1	*Mean (SD)*	89.14 (22.39)	77.00 (22.54)	86.81 (20.25)
	min-max	44-154	31-139	38-143
FVC	*Mean (SD)*	3.18 (1.00)	3.16 (1.01)	3.16 (1.01)
	min-max	1.32-6.45	1.11-6.55	1.09-6.38
Percentage Predicted FVC	*Mean (SD)*	103.45 (22.01)	97.72 (22.07)	98.00 (17.59)
	min-max	44-165	35-169	60-160
Totals	*n*	166	142	120

Predicted percentage FEV1 and percentage predicted FVC demonstrated statistical inference of normal distribution across all groups and this was supported with histogram and Q-Q plots as shown in Appendix 8. Normal distribution was not inferred statistically for PiMAX and absolute values for FEV1 and FVC although visual inspection of the respective histograms and Q-Q plots for all pulmonary function tests did not suggest a significant deviation from the uni-modal bell-shaped curve associated with a normal distribution. Normality was also indicated by skewness and kurtosis statistics and z-scores within acceptable parameters for the majority of preoperative pulmonary function tests (Ghasemi and Zahediasl,

2012; Kim, 2013). FEV1 was the only measure to fall outside of these parameters for all three study groups.

5.1.6. Choice of Test to Determine Homogeneity based on Data Distribution

Normal distribution was inferred statistically in preoperative spirometry and was supported graphically with the general appearance of normality across the preoperative spirometry variables. Baseline characteristics demonstrated some deviation from normality, however the study benefitted from large sample sizes and therefore, only extreme deviation from normality from either statistical testing or visual inspection of histograms would have warranted non- parametric testing of baseline characteristics. Pallant (2020) highlighted with sample sizes of greater than 30 or 40 that some violation of normality would not impact upon subsequent statistical analysis and parametric tests may be appropriately used. The Kolmogorov-Smirnov test has also been criticised in statistical literature as particularly sensitive to few extreme values (Kim, 2013) and since the normality graphs reflected bell-shaped curves and a closeness to expected lines of best fit overall, with sample sizes over 100 across all three groups, it was considered appropriate that variance between group variables be analysed through parametric Analysis of Variance (ANOVA) testing. ANOVA is considered a statistically robust test that can withstand deviations from normal distribution with minimal risk of type 1 errors (Pallant; 2020; Laerd, 2022).

5.2. Homogeneity in Baseline Variables for the Three groups

5.2.1. Statistical Tests for Homogeneity

Baseline characteristics were statistically analysed to determine any significant heterogeneity between the three groups that would bias any further analysis if compared as independent samples. ANOVA testing was used to compare means within and between groups for continuous level data and Chi-square test of independence was used for categorical variables except where expected cell frequency was less than 5 and Kruskal Wallis testing was used. All baseline data was analysed but particular focus for determining homogeneity between groups statistically, was placed on the known independent risk factors associated with postoperative pulmonary complications in patients with lung cancer undergoing surgical resection. Agostini et al. (2018) indicated that advanced age, comorbidities including presence of COPD, high BMI, higher ASA classification, extent of surgical excision and poor preoperative lung function were the strongest independent risk factors for postoperative pulmonary complications following multivariate analysis and therefore these factors were considered most important to establish homogeneity across the three groups.

5.2.2. Homogeneous Variables

Visual inspection of baseline characteristics and referenced in table 5.1.2.a suggested that groups were closely matched overall with a high visual level of homogeneity across the three groups for all the characteristics and although there were large standard deviations across the continuous variables age and BMI,

neither were considered statistically significant. ANOVA testing showed no significant difference between standard care, face-to-face rehabilitation and virtual rehabilitation for age (f=0.486, p=0.772), BMI (f=0.011, p=0.989) or the number of comorbidities (f=1.535, p=0.216) and specifically respiratory conditions (f=1.764, p=0.172).

From a surgical perspective there was also no significant difference in ASA classification, indicating that surgical risk was similar across groups (h=2.396, p=0.302). Groups were also closely matched for type and extent of surgery performed, and all three groups had comparable proportions of wedge resection, segmentectomy, lobectomy and pneumonectomy procedures (h=0.729, p=0.650). The mean values of preoperative piMAX were consistent across groups, with no significant difference identified by ANOVA (f=0.192, p=0.662). The absolute values for preoperative FEV1 (f=2.310, p=0.100) and FVC (f=0.015, p=0.985) were also not statistically significant.

Additionally, there was no significant difference in smoking status and weekly alcohol consumption across groups with comparable cigarettes smoked per day (f=2.548, p=0.280) and alcohol intake in units per week (f=2.585, p=0.077). There was also a similar proportion of current, previous and non-smokers across the groups (χ^2=7.080, p=0.132). Smoking pack years were of statistical significance (f=5.504, p=0.004), where post-hoc testing with Games-Howell, showed that mean pack years smoked in the face-to-face rehabilitation group (37.27) was significantly higher than the mean values in virtual rehabilitation (25.82) (p=0.011, 95% CI 2.149

– 20.761) and standard care (28.03) (p=0.040, 95% CI 0.337 – 18.139), whilst virtual rehabilitation and standard care were not statistically different (p=0.761). Calculation of pack years incorporated an individuals past history of smoking as opposed to current status and therefore greater emphasis was given to the homogeneity shown in current smoking status and cigarettes smoked per day between the three groups.

5.2.3. Heterogeneous Variables

ANOVA was statistically significant for both predicted percentage FEV1 (f=12.768, p<0.001) and predicted percentage FVC (f=3.665, p=0.026). Post hoc statistical testing with Games-Howell showed that mean percentage predicted FEV1 in the face-to-face rehabilitation group (77%) was statistically different from mean percentage predicted FEV1 in both the virtual rehabilitation group (86.81%) (p=0.001, 95% CI -16.04 to -3.57) and the standard care group (89.14%) (p<0.001, 95% CI -18.20 to -6.09), whilst the virtual rehabilitation and standard care groups did not significantly differ from each other (p=0.628). The lower percentage predicted FEV1 in the face-to-face rehabilitation group could indicate greater severity in respiratory dysfunction, despite comparability in the presence of respiratory conditions across all three groups. Post-hoc testing revealed a significant difference between the mean percentage predicted FVC in the standard care group (103.5%) in comparison to face-to-face rehabilitation (97.72%) (p=0.049, 95% CI 0.02-11.45) whilst there was no significant difference with virtual rehabilitation (98.00%) (p=0.085) and the lower mean values in the intervention

groups did not significantly differ from each other (p=0.999). The standard care group demonstrated the highest mean percentage predicted FVC and mean percentage predicted FEV1, whilst the face-to-face rehabilitation group had the lowest mean values for both measures.

Baseline preoperative ECOG scores where lower scores were indicative of better physical activity status were statistically different between the three groups (χ^2=18.326, p=0.001). The virtual rehabilitation group had a significantly higher proportion of lower ECOG scores than the face-to-face rehabilitation group (χ^2=17.245, p<0.001) and standard care (χ^2=6.317, p=0.042), with no significant difference between the face-to-face and standard care groups (χ^2=4.728, p=0.094). Physical activity status helps to determine ASA classification, which interestingly did not differ significantly between the groups.

The proportion of males and females also showed some statistical difference between the groups (χ^2= 6.036, p=0.049). Further statistical testing identified that gender differed significantly between face-to-face rehabilitation and standard care groups (χ^2=5.121, p=0.021) whilst there was no significant difference between standard care and virtual rehabilitation (χ^2=0.042, p=0.838) or between the two rehabilitation groups (χ^2=3.834, p=0.051). The face-to-face rehabilitation group had 51% males and 49% females and this compared to 39% males and 61% females in the standard care group. Gender has not convincingly been established as an independent risk factor associated with poorer recovery following lung resection surgery.

5.2.4. Interpretation of Homogeneity of Characteristics for Data Analysis

The three groups were comparable for variables established as independent risk factors for poor recovery following lung resection as shown in table 5.2.4.a. Gender, smoking pack years, preoperative activity status and percentage predicted FEV1 and FVC were the only baseline variables showing a statistically significant difference across the groups. Gender and prior history of smoking have not been established as clear independent risk factors for developing postoperative pulmonary complications following lung resection surgery. Whilst physical activity status has been considered within the literature as an important clinical assessment measure that informs the overall ASA classification (ASA, 2020), it has not yet been established as an independent risk factor. The literature currently suggests ASA classification is an independent risk factor (Agostini et al., 2018) and therefore the non-statistical difference between groups for ASA classification was given greater emphasis than physical activity to determine homogeneity across groups.

The differences across groups for pulmonary function should be recognised as face-to-face rehabilitation had the lowest means in both percentage predicted FEV1 and FVC whilst standard care had the highest, as referenced in table 5.2.4.a. FEV1 and FVC percentage predicted values of less than 80% would be considered the diagnostic threshold to determine respiratory deficit of clinical significance (British Thoracic Society, 2013). All three groups demonstrated mean values higher than 80% predicted values for predicted FVC and only the face-to-face rehabilitation group had a mean value below this 80% threshold for percentage predicted FEV1.

The small degree of heterogeneity in these two lung function measures was not considered sufficient to warrant individual case matching, given that homogeneity had been established with most baseline characteristics. Additionally, case-matching individual patients across the three groups based upon baseline characteristics would have resulted in a significant loss of sample size across both standard care and face-to-face rehabilitation groups. Therefore, individual sample sizes were retained across the three groups. Retaining the larger samples across the groups added strength and statistical power beyond that achieved with individual case matching. The larger sample size, in part determines the precision and level of confidence in sample estimates and reduces the margin of error.

Table 5.2.4.a. Homogeneity of Baseline Characteristic Variables

Variable Type	Characteristic		Standard Care (SC)	Face-to-Face Rehabilitation (F2F)	Virtual Rehabilitaton (VR)	Sample Significance	Post-Hoc Comparison
Categorical	Gender	*Male (n)*	39% (64)	51% (73)	40% (54)	*χ2=6.036 p=0.049**	*SC & F2F χ2=5.121 p=0.021** *SC & VR χ2=0.042 p=0.838 (NS)* *F2F &VR χ2=3.834 p=0.051 (NS)*
		Female (n)	61% (102)	49% (69)	60% (82)		
	Activity Status (ECOG)	*1 (n)*	30% (50)	29% (41)	39% (53)	*χ2=18.326 p=0.001**	*SC & F2F χ2=4.728 p=0.094* *SC & VR χ2=6.317 p=0.042* *F2F & VR χ2=17.245 p<0.001**
		2 (n)	52% (86)	43% (61)	52% (71)		
		3 (n)	18% (30)	28% (40)	9% (12)		
	ASA Classification	*1 (n)*	0.6% (1)	1% (2)	2% (3)	*h=2.396 p=0.302 (NS)*	NA
		2 (n)	26% (43)	17% (24)	22% (30)		
		3 (n)	69% (114)	78% (111)	74% (101)		
		4 (n)	4% (7)	4% (5)	2% (2)		
		5 (n)	0.6% (1)	0% (0)	0% (0)		
	Tye of Surgery	*Wedge Resection (n)*	1% (1)	1% (2)	1% (1)	*h=0.729 p=0.650 (NS)*	NA
		Segmentectomy (n)	52% (87)	52% (74)	48% (66)		
		Lobectomy (n)	46% (77)	47% (66)	49% (67)		
		Pneumonectomy (n)	1% (1)	0% (0)	2% (2)		
	Smoking Status	*Non-Smoker (n)*	22% (36)	15% (21)	24% (33)	*χ2=7.080 p=0.132 (NS)*	NA
		Smoker (n)	28% (46)	38% (54)	34% (46)		
		Ex Smoker (n)	50% (84)	47% (67)	42% (57)		
Continuous	Smoking Pack Years	*Mean (SD)*	28.03 (26.69)	37.27 (37.61)	25.82 (27.65)	*f=5.504 p=0.004**	*SC & F2F p=0.040** *SC & VR p=0.761 (NS)* *F2F & VR p=0.011**
	Cigarettes Per Day	*Mean (SD)*	3.60 (6.91)	5.18 (7.56)	4.15 (6.33)	*f=2.548 p=0.280 (NS)*	NA
	Alcohol Intake (unit per week)	*Mean (SD)*	6.24 (11.14)	9.16 (16.84)	6.07 (10.08)	*f=2.585 p=0.077 (NS)*	NA
	Age (years)	*Mean (SD)*	69.89 (11.68)	69.96 (10.17)	68.52 (12.02)	*f=0.486 p=0.772 (NS)*	NA
	Body Mass Index	*Mean (SD)*	27.94 (5.61)	28.02 (6.19)	28.04 (6.08)	*f=0.011 p=0.989 (NS)*	NA
	Number of Comorbidities	*Mean (SD)*	2.07 (1.35)	2.15 (1.48)	2.36 (1.51)	*f=1.535 p=0.216 (NS)*	NA
	piMAX (cmH_20)	*Mean (SD)*	NA	81.51 (17.68)	80.28 (17.92)	*f=0.192 p=0.662 (NS)*	NA
	FEV1	*Mean (SD)*	2.16 (0.75)	2.00 (0.84)	2.20 (0.79)	*f=2.310 p=0.100 (NS)*	NA
	% Predicted FEV1	*Mean (SD)*	89.14 (22.39)	77.00 (22.54)	86.81 (20.25)	*f=12.768 p<0.001**	*SC & F2F p<0.001** *SC & VR p=0.628 (NS)* *F2F & VR p=0.001**
	FVC	*Mean (SD)*	3.18 (1.00)	3.16 (1.01)	3.16 (1.01)	*f=0.015 p=0.985 (NS)*	NA
	% Predicted FVC	*Mean (SD)*	103.45 (22.01)	97.72 (22.07)	98.00 (17.59)	*f=3.665 p=0.026**	*SC & F2F p=0.049** *SC & VR p=0.085 (NS)* *F2F & VR p=0.999 (NS)*

NA - Not Applicable NS - Non significance *significance

5.3. Statistical Approach to Continuous Variables

5.3.1. Normality of Distribution in Objective 1 Variables

Overall statistical analysis and graphical representation would suggest some violation in normality of distribution for the continuous variables for objective 1; Length of hospital stay (days), duration of high dependency level care (days), duration of postoperative chest drains (days), and number and cumulative length

of hospital readmissions (days) with statistical significance in Kolmogorov-Smirnov testing for all three individual samples, standard care ($p<0.001$), face-to-face rehabilitation ($p<0.001$) and virtual rehabilitation ($p<0.001$) and the collective total sample ($p<0.001$). Histograms and Q-Q plots also indicated positively skewed peaked distributions as shown in Appendix 9. This was further supported by skewness and kurtosis statistics and their respective z-scores for length of hospital stay, duration of high dependency level care, duration of chest drain insertion and hospital readmissions exceeding permitted parameters for normality.

5.3.2. Normality of Distribution in Objective 2 Variables

Normality in distribution was not statistically inferred for the continuous variable for objective 2; Survival days within a year (days) with statistical significance on Kolmogorov-Smirnov testing in standard care ($p<0.001$), face-to-face rehabilitation ($p<0.001$), virtual rehabilitation ($p<0.001$) and the collective total sample ($p<0.001$). Skewness and kurtosis statistics and their respective z-scores all exceeded permitted parameters for normality. Visually, the individual and collective sample histograms and Q-Q plots also reflected a negatively skewed high-peaked distribution that deviated from expected values in normally distributed data as shown in Appendix 10.

5.3.3. Normality of Distribution in Objective 3 Variables

The continuous variables for objective 3; pre and post intervention piMAX (cmH_20), FEV1 (litres), FVC (litres) and percentage predicted values (%) and EORTC-QLQ-C30

scores (%) largely indicated normally distributed data. The preoperative pulmonary spirometry measures were previously analysed for normality in section 5.3.

The Shapiro-Wilk test was used to analyse normality for post intervention FEV1 and FVC values in virtual rehabilitation where the sample was limited to 53 and was not significant for the post intervention variables percentage predicted FEV1 ($p=0.829$), percentage predicted FVC ($p=0.128$) and FVC ($p=0.395$). Kolmogorov-Smirnov testing was also not statistically significant for the face-to-face rehabilitation sample post intervention variables percentage predicted FEV1 ($p=0.200$) and percentage predicted FVC ($p=0.200$). Skewness and kurtosis statistics and respective z-scores were also within accepted parameters and the histogram and Q-Q plots reflected normally distributed data.

Kolmogorov-Smirnov testing was significant in the face-to-face rehabilitation variables; FEV1 ($p=0.001$), FVC ($p=0.016$), piMAX ($p<0.001$) and the virtual rehabilitation variables; piMAX ($p<0.001$) and FEV1 ($p=0.029$). Skewness, kurtosis statistics and respective z-scores were within permitted parameters for all of these variables suggesting some closeness to normality and this was supported by histogram and Q-Q plots as shown in Appendix 11.

Normality in distribution was inferred for pre intervention EORTC-QLQ-C30 in the virtual rehabilitation sample ($p=0.667$) and post intervention EORTC-QLQ-C30 scores, face-to-face rehabilitation ($p=0.117$), virtual rehabilitation ($p=0.073$). Only preintervention EORT-QLQ-C30 scores were statistically significant in the face-to-

face rehabilitation sample (p=0.003). Skewness and kurtosis statistics and their respective z-scores were also close to 0 and histograms visually reflected normally distributed data across all sample data.

5.3.4. Normality of Distribution in Objective 4 Variables

The continuous variable for objective 4; Waiting time from referral to surgery (days) was significant on Kolmogorov-Smirnov testing for all 3 individual samples, standard care ($p<0.001$), virtual rehabilitation ($p<0.001$) face-to-face rehabilitation ($p=0.001$) and the collective total sample ($p<0.001$). Their respective histograms indicated a mild positive-skew and high-peaked distribution, shown in Appendix 12.

5.3.5. Decision for Choice of Statistical Test for Continuous Variables

Statistical literature highlights that violation of the normality assumption will not impact upon statistical analysis through parametric testing in large samples (Tabachnik and Fidell, 2013; Pallant, 2020). Therefore, parametric ANOVA statistical testing was employed to compare means between the three groups. ANOVA testing is statistically robust to violations in the normality assumption with large samples (Tabachnik and Fidell, 2013; Pallant, 2020; Laerd, 2022). All continuous variables for objective 3 showed statistical normality or sufficient closeness to normality on skewness and kurtosis analysis and therefore pre and post pulmonary function and HRQOL measures were analysed by parametric paired samples T-Test. This test is also considered sufficiently robust to be unaffected by mild deviation in normality of distribution.

5.4. Statistical approach to Categorical Variables

5.4.1. Objective 1 Variables

The categorical variables for objective 1; radiological evidence of atelectasis or pneumonia, positive sputum culture, prescription of microbial therapy, prescription of high-flow oxygen therapy, postoperative tracheostomy insertion were reported as 'yes' or 'no' if this was required during the hospital stay. These variables correspond with typical outcome measures used to determine postoperative pulmonary complications within the existing literature for lung resection surgery (Stephans et al., 2000; Agostini et al., 2010; Agostini et al., 2018; Li et al., 2019). All cells had values greater than 5 and therefore were analysed using Chi-square test of independence. Clavien-Dindo classification for severity of postoperative complications had expected cell frequencies lower than 5 for a number of classifications and was therefore analysed with Kruskal-Wallis testing.

5.4.2. Objective 2 Variables

Categorical data for objective 2 established frequency counts of patients' survival status at 6 months and 12 months using 'yes' if the patient was alive or 'no' if deceased at 182 or 365 days for the three individual samples. All cells had values greater than 5 and were analysed using Chi-square test of independence. Cox regression analysis was also performed on the collective sample and hazard ratios (HR) established for 12-month postoperative mortality using the independent categorical variables included within initial data collection. HR that were non-significant and close to 1 were not considered to be associated with increased risk

of mortality. Statistically significant HR less than 1 were considered to have a protective effect associated with a reduced risk of 12-month mortality and greater than 1 were considered as associated with an increased risk of 12-month mortality following surgery. Multivariate analysis was undertaken with variables that achieved statistical significance with univariate analysis. Kaplan-Meier plots were used to display 12-month survival outcomes for those variables of statistical significance. Given the large number of categorical variables in the initial data collection multivariate analysis was undertaken in three stages; significant factors available preoperatively, in the acute postoperative period and finally within the 12-months follow up period post-surgery. This enabled a maximum of five variables to be included in multivariate analysis. The final multivariate analysis included factors from all three stages that remained statistically significant to establish predictive modelling of increased risk of 12-month mortality.

5.4.3. Objective 4 Variables

Frequency counts were established for the categorical variables for objective 4; uptake (attendance to first clinic appointment), completion of rehabilitation programme, HIIT attainment and serious adverse events. These were categorised as 'yes' if achieved or 'no' if not achieved, all cells had more than 5 counts and were analysed with Chi-square test of independence. Patient-reported reasons for cancellation of programme and patient or clinician reported side effects during the programme were also grouped to provide descriptive statistics and further narrative discussion.

Chapter 6. Results: Objective 1

6.1. Comparison of Hospital Stay Between the Three Groups

6.1.1. Three-Way Comparison of Overall Hospital length of Stay

Extended hospital stays and delayed discharges can result in reduced bed flow and bed availability, which may impact negatively on surgery dates for patients awaiting surgery. Patients require a ward bed for admission for surgery and successful patient transfer to theatre would be dependent upon the confirmed availability of an appropriate postoperative bed. Interventions that can influence patient throughput and bed flow are of primary importance at an organisational, financial and patient level.

Hospital length of stay (mean ±SD) for standard care patients (8.27 days ±5.47) was similar to patients who underwent virtual rehabilitation (8.13 days ±6.45). Patients who underwent face-to-face rehabilitation had the longest mean overall hospital length of stay (9.75 days ±9.61) shown graphically in figure 6.1.1.a. There was no significant difference between the three groups for overall hospital length of stay ($f=2.181$, $p=0.114$) and therefore statistically, preoperative intervention delivered either face-to-face or virtually was not considered superior to standard care at influencing length of stay and relevant group statistics are shown in table 6.1.1.a. Despite the lack of statistical significance, mean differences showed face-to-face rehabilitation had a 1.62 day greater hospital length of stay than virtual rehabilitation and a 1.48 day greater stay than standard care. The virtual

rehabilitation group had the shortest mean length of stay but there was very little difference in means between this group and standard care at 0.14 days. A 2-day reduction in length of stay was anecdotally considered to be of clinical relevance according to Thoracic surgeon opinion within the NHS Trust. This was largely based on clinical judgement and understanding of operational management for patient throughput, however the mean differences between the three groups were all under the 2-days.

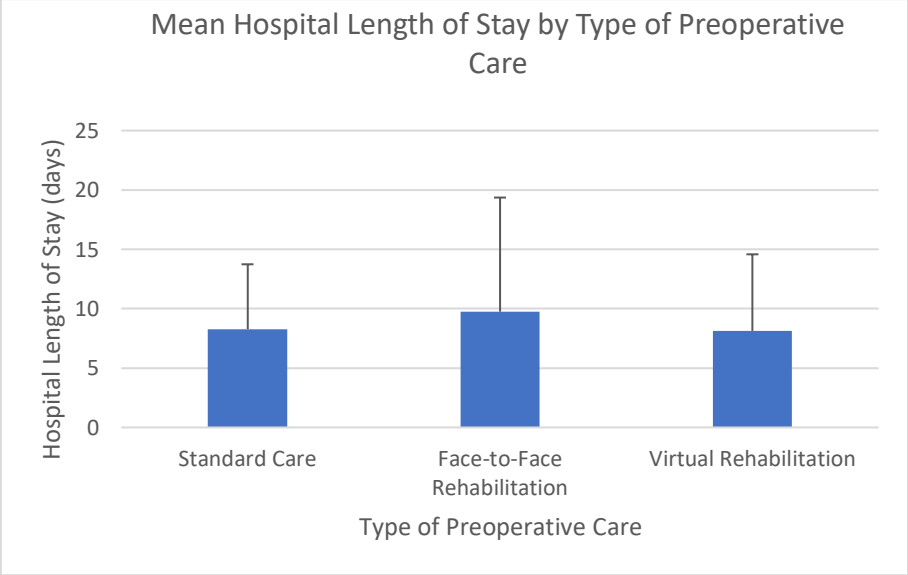

Figure 6.1.1.a. Bar Chart of Mean Hospital Length of Stay (in days) by Type of Preoperative Care

Table 6.1.1.a. Statistics for Hospital Length of Stay in the Three Groups

Variable		**Standard Care**	**Face-to-Face Rehabilitation**	**Virtual Rehabilitation**	**Significance ANOVA**
Hospital Length of Stay	*Mean (SD)*	8.27 (5.47)	9.75 (9.61)	8.13 (6.45)	*f=2.181 p=0.114 (NS)*
	min-max	2-43	2-63	1-35	
Totals	*n*	166	142	136	
NS - Non significance * significance					

All three groups had minimum values that were lower than the reported current National mean hospital length of stay of 6 days (NACAP, 2020). The virtual rehabilitation sample had the lowest minimum stay value of just 1 day whilst face-to-face rehabilitation and standard care samples both had 2 days as their lowest value. Clinically the shortest length of stays achieved across all groups would leave minimal room for improvement with intervention, since the surgical procedure itself would warrant at least an overnight hospital stay to monitor and establish medical stability. Conversely, the maximal values were substantial, the face-to-face rehabilitation had the largest maximal length of stay of 63 days, in comparison to maximal values for virtual rehabilitation and standard care at 35 and 43 days respectively and these are likely to be reflective of complicated postoperative recovery. The face-to-face rehabilitation group had both the highest maximum length of stay and the highest mean value in comparison to virtual rehabilitation with the lowest minimal and maximal values and lowest mean length of stay across all the groups. However, statistically neither intervention group differed significantly from standard care alone.

Overall hospital length of stay is a complex variable and longer lengths of stay may be due to a multitude of personal social circumstances and the availability of appropriate supportive networks upon hospital discharge. To negate the impact of these factors, the length of stay was determined by the date a patient was documented to be medically fit for discharge. This was determined by medical opinion and therefore added some subjectivity to this variable, particularly since this may be recorded by medical staff of varying levels of clinical experience.

6.1.2. Three-Way Comparison of Duration of High Dependency Level Care

Postoperative patients following lung resection via an open thoracotomy require a short stay on high dependency level care to monitor vital signs and assess stability for de-escalation to ward level. In uncomplicated cases the stay in high dependency care may be less than 24 hours. Patients may have extended periods in high dependency care where they have suffered postoperative complications that may include, but are not limited to, pulmonary complications. Higher dependency level care has associated higher costs due to the need for more intensive health professional input and the complexity of supportive equipment used within units. Since high dependency bed availability is at a premium in acute hospitals, it was reasoned that de-escalation to ward level care would occur based on patient condition irrespective of other organisational challenges and therefore this variable was included as the actual value as opposed to 'medical fitness for ward care.'

On initial inspection duration of high dependency care (mean ±SD) appeared comparable across the three groups. Standard care had the lowest mean stay in high dependency care (2.07 days ±2.45) with face-to-face rehabilitation (2.30 days ±4.09) and virtual rehabilitation (2.55 days ±4.50) both demonstrating similar durations, this is represented graphically in figure 6.1.2.a and referenced in table 6.1.2.a. There was no statistically significant difference between the groups ($f=0.579$, $p=0.561$) inferring that the preoperative intervention, performed either face-to-face or virtually did not influence duration of high dependency care.

Standard care had the lowest maximal stay in high dependency care at 17 days, whilst face-to-face rehabilitation and virtual rehabilitation groups had maximal stays of 43 days and 35 days respectively. Mean differences between the groups were less than 1 day, with face-to-face rehabilitation demonstrating a slightly longer duration of high dependency care than standard care of 0.23 days and virtual rehabilitation 0.48 days. These small mean differences are unlikely to impact clinically on patient throughput or bed availability for surgery.

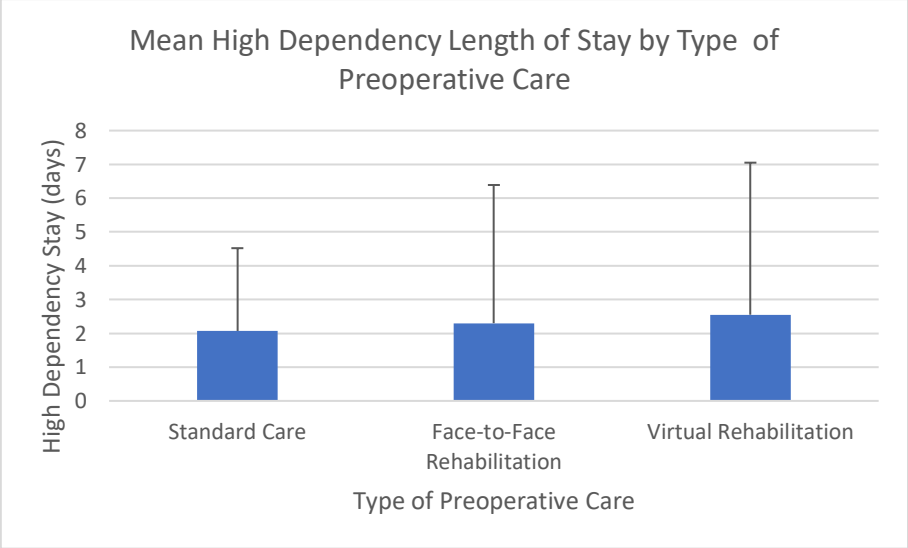

Figure 6.1.2.a. Bar Chart of Mean High Dependency Stay (in days) by Type of Preoperative Care

Table 6.1.2.a. Statistics for High Dependency Care in the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance ANOVA
High Dependency Care Stay	*Mean (SD)*	2.07 (2.45)	2.30 (4.09)	2.55 (4.50)	*f=0.579 p=0.561 (NS)*
	min-max	0-17	0-43	0-35	
Totals	*n*	166	142	136	
NS - Non significance * significance					

6.2. Comparison of Pulmonary Complications between the Three Groups

Postoperative complications are a potential cause of longer hospital stays or extended periods within higher dependency care. A stay free of postoperative complications would be desirable for both the patient and the NHS organisation. Postoperative complications of clinical severity classified by Clavien-Dindo require additional resources to diagnose and treat irrespective of location and level of care.

6.2.1. Three-Way Comparison of Severity of Postoperative Complications

Clavien-Dindo classification has five main grades, numbered 1 to 5, to stage complications in clinical practice. Patient who had an uncomplicated stay without notable deviation from postoperative recovery were given a score of 0 to enable complete data sets to be analysed for all groups.

The severity classification was low for all three groups and this is likely due to a large proportion of each sample not experiencing complications of a clinical severity to feature on the Clavien-Dindo system as shown in figure 6.2.1.a. Despite the low incidence overall, Kruskal-Wallis testing was statistically significant between the three groups for postoperative complication severity ($h=9.626$, $p=0.008$). Further analysis between groups provided statistical inference that the virtual rehabilitation classification was significantly lower than standard care ($h=9.435$, $p=0.002$). There was no significant difference between the values for face-to-face rehabilitation and virtual rehabilitation ($h=2.143$, $p=0.143$) or between face-to-face rehabilitation and standard care ($h=2.635$, $p=0.105$). This would suggest that virtual rehabilitation could be superior to standard care at reducing

the severity of postoperative complications as determined by the Clavien-Dindo classification system. However, it does not appear to differ significantly from face-to-face rehabilitation as referenced in table 6.2.1.a.

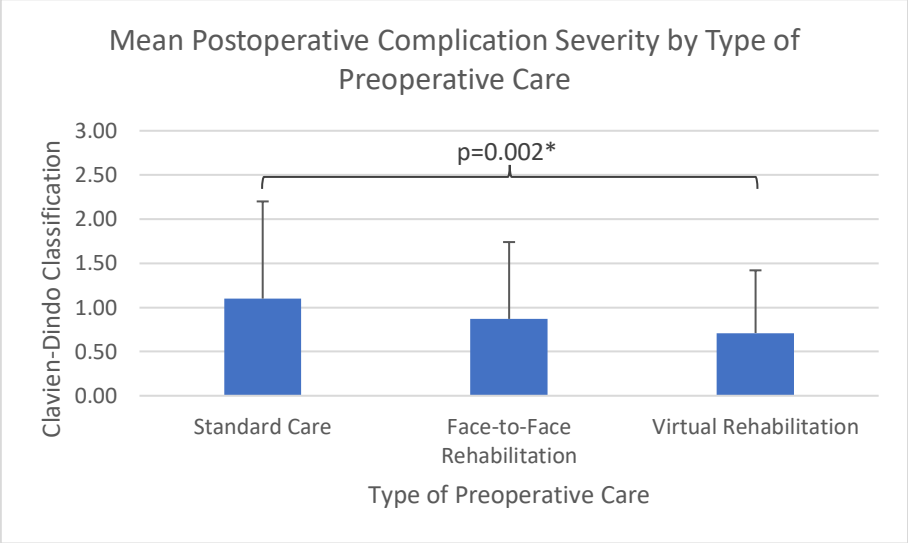

Figure 6.2.1.a. Bar Chart of Mean Severity Classification of Postoperative Complications by Type of Preoperative Care

Table 6.2.1.a. Statistics for Clavien-Dindo Classification in the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance Kruskal-Wallis	Post hoc Comparison
Clavien Dindo Classification	*0 (n)*	48.2% (80)	57.0% (81)	64.7% (88)	*h=9.626 p=0.008**	*SC & F2F p=0.105 (NS) SC & VR p=0.002* F2F & VR p=0.143 (NS)*
	1 (n)	18.7% (31)	16.2% (23)	18.4% (25)		
	2 (n)	18.7% (31)	18.3% (26)	8.1% (11)		
	3 (n)	4.8% (8)	0.0% (0)	1.5% (2)		
	4 (n)	9.0% (15)	7.7% (11)	5.1% (7)		
	5 (n)	0.6% (1)	0.7% (1)	2.2% (3)		
Totals	*n*	166	142	136		
NS - Non significance * significance						

Grade 1 on the classification is defined by any deviation from normal postoperative recovery that may be managed without surgical, endoscopic, or radiologic intervention. This management may require therapeutic regimes such as physiotherapy, electrolytes, and a small number of drug therapies such as analgesia

or anti-emetics. The raw data highlighted a large percentage of patients did not experience any clinically recognisable complications across all three groups and were therefore graded as 0. The virtual rehabilitation sample had the highest proportion of patients graded at 0 at 64.7%, face-to-face rehabilitation had 57.0% whilst standard care had the smallest proportion at 48.2%. A score of 0 did not classify no postoperative complications but suggested that if present did not require fundamental additions to therapeutic or medical management. It must be recognised that this does not mean that they are not of significance to the patient experiencing such complications despite a sub-clinical threshold.

6.2.2. Three-Way Comparison of Positive Radiological or Microbial Findings

Confirmed pneumonia or atelectasis on the radiology report of a postoperative chest x-ray was considered positive for the presence of a pulmonary complication. The virtual rehabilitation group had the lowest proportion of positive chest x-ray results at 20.6% compared to standard care at 30.1% and face-to-face rehabilitation with the highest proportion of positive findings at 33.8%. Virtual rehabilitation had statistically significantly lower positive chest x-rays than face-to-face rehabilitation (χ^2=6.017, p=0.013) whilst the comparison between virtual rehabilitation and standard care (χ^2=3.546, p=0.060) and between face-to-face rehabilitation and standard care (χ^2=0.478, p=0.489) were not significant, displayed graphically in figure 6.2.2.a with statistics referenced in table 6.2.2.a. The data extraction method did not enable differentiation between whether the positive radiological evidence

showed infiltrates suggestive of pneumonia or opacification suggestive of atelectasis.

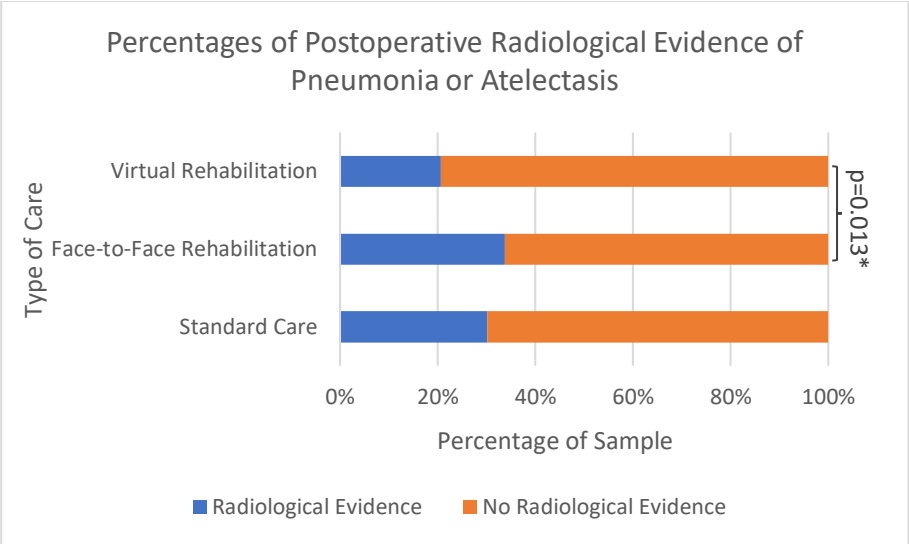

Figure 6.2.2.a. Proportion of Sample with Positive Findings Suggestive of Pulmonary Complications on Chest X-Rays by Preoperative Type of care

Presence and growth of bacteria through a positive sputum culture postoperatively was considered indicative of a bacterial chest infection. The virtual rehabilitation sample had the lowest proportion of positive sputum cultures at 11.8%, whilst face-to-face rehabilitation and standard care had higher proportions at 14.8% and 21.1% respectively and this is illustrated in figure 6.2.2.b. Virtual rehabilitation had a significantly lower proportion of positive sputum samples than standard care (χ^2=4.626, p=0.031). There was no difference between the incidence of positive sputum samples between intervention groups (χ^2=0.551, p=0.458) or between face-to-face rehabilitation and standard care (χ^2 = 2.039, p=0.153) suggesting that virtual rehabilitation may be superior to standard care for the incidence of bacterial respiratory infections, as shown in table 6.2.2.a.

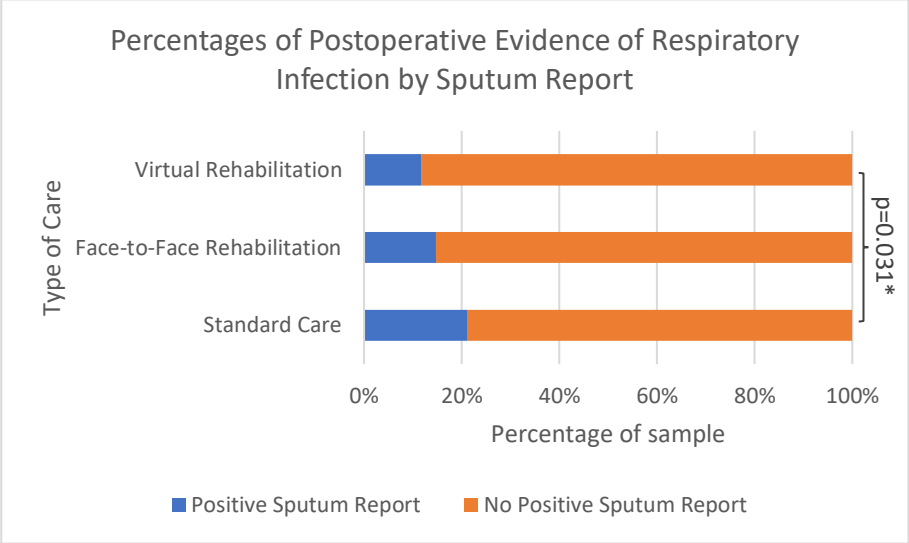

Figure 6.2.2.b. Proportion of Sample with Positive Findings on Sputum Microbiology by Preoperative Type of Care

Table 6.2.2.a. Statistics for Radiology and Sputum Microbiology in the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance χ2	Post hoc Comparison
Positive Chest X-Ray Findings	*Yes (n)*	30.1% (50)	33.8% (48)	20.6% (28)	*χ2=6.364 p=0.041**	*SC & F2F p=0.489 (NS) SC & VR p=0.060 (NS) F2F & VR p =0.013**
	No (n)	69.9% (116)	66.2% (94)	79.4% (108)		
Positive Sputum Sample	*Yes (n)*	21.1% (35)	14.8% (21)	11.8% (16)	*χ2=5.092 p=0.078 (NS)*	*SC & F2F p=0.153 (NS) SC & VR p=0.031* F2F & VR p =0.458 (NS)*
	No (n)	78.9% (131)	85.2% (121)	88.2% (120)		
Totals	*n*	166	142	136		
NS - Non significance * significance						

6.2.3. Three-Way Comparison of Antimicrobial Therapy and Oxygen Prescription

Therapeutic pharmacological management of a bacterial infection includes the prescription of antimicrobial therapy, typically antibiotics. The prescription of an oral or intravenous antibiotic during the patients' postoperative hospital admission was considered positive for a postoperative complication. The virtual rehabilitation

sample had the lowest proportion of patients with a documented antibiotic prescription at 16.2% whilst face-to-face rehabilitation and standard care both had greater and closely matched proportions at 23.9% and 23.5% respectively and this is shown graphically in figure 6.2.3.a. There was no statistically significant difference between frequencies of antibiotic prescription across the samples (χ^2=3.185, p=0.203). This suggests that preoperative intervention, delivered face-to-face or virtually does not reduce the frequency of antibiotic prescription in comparison to standard care alone with reference values in table 6.2.3.a. Antimicrobial therapy is not exclusively prescribed for bacterial respiratory infections and data collection did not discriminate between treatment for wider bacterial infections. Therefore, the lower proportion of antibiotic prescription evident with virtual rehabilitation may not necessarily be related to pulmonary complications.

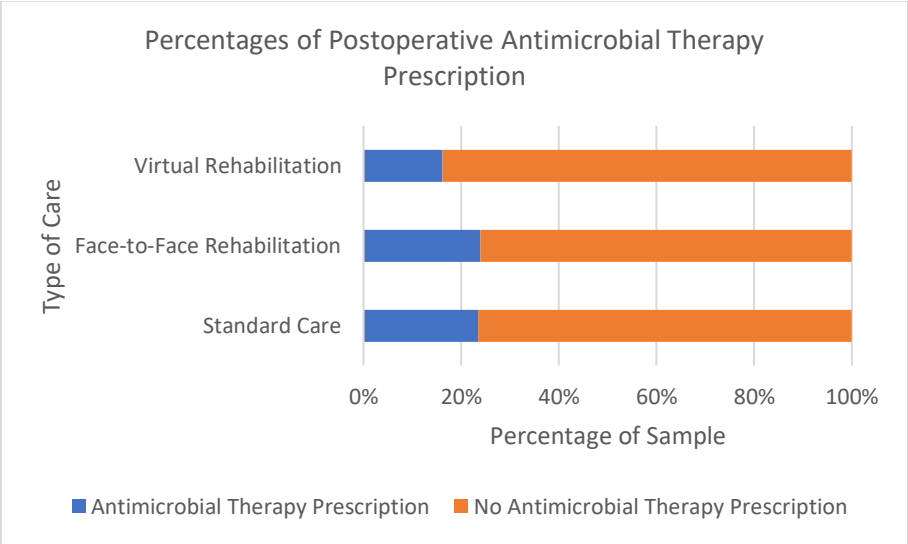

Figure 6.2.3.a. Proportion of Sample with Postoperative Antimicrobial Therapy Prescription by Preoperative Type of Care

The prescription of high-flow oxygen therapy would primarily relate to the therapeutic management of postoperative complications of a respiratory origin. Standard care had the lowest proportion of patients that required high-flow oxygen at 6.6%, this was in comparison to the intervention groups, where both face-to-face rehabilitation and virtual rehabilitation had closely matched proportions at 11.3% and 11.8% respectively. The apparent differences did not however achieve statistical significance (χ^2=2.854, p=0.240). This suggests that there is no significant difference between intervention or standard care for the need for high-flow oxygen delivered invasively or non-invasively as referenced in table 6.2.3.a. It is an interesting observation that standard care has the lowest proportion of patients treated with these devices postoperatively. The low proportion of high-flow oxygen prescription across the three samples is illustrated in figure 6.2.3.b.

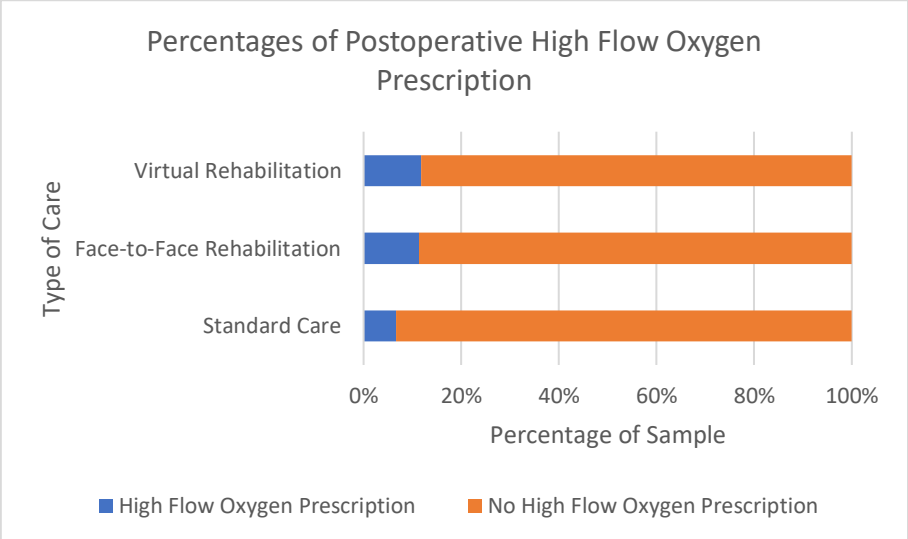

Figure 6.2.3.b. Proportion of Sample with Postoperative High Flow Oxygen Prescription by Preoperative Type of Care

Table 6.2.3.a. Statistics for Antimicrobial Prescription and Oxygen Therapy for the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance χ2	Post hoc Comparison
Antimicrobial Prescription	*Yes (n)*	23.5% (39)	23.9% (34)	16.2% (22)	*χ2=3.185 p=0.203 (NS)*	*SC & F2F p=0.926 (NS) SC & VR p=0.107 (NS) F2F & VR p =0.115 (NS)*
	No (n)	76.5% (127)	76.1% (108)	83.8% (114)		
Hi-Flow Oxygen Therapy	*Yes (n)*	6.6% (11)	11.3% (16)	11.8% (16)	*χ2=2.854 p=0.240 (NS)*	*SC & F2F p=0.151 NS) SC & VR p=0.119 (NS) F2F & VR p =0.897 (NS)*
	No (n)	93.4% (155)	88.7% (126)	88.2% (120)		
Totals	*n*	166	142	136		
NS - Non significance * Significance						

6.2.4. Three-Way Comparison of Tracheostomy Insertion

Tracheostomies are an artificial airway inserted for respiratory support or to facilitate weaning from mechanical ventilation. Mini tracheostomies may be inserted to access and clear secretions with a suction catheter when a patient is unable to expectorate independently. The face-to-face rehabilitation and standard care samples had the lowest and similar proportions requiring tracheostomy insertion at 3.5% and 3.6% respectively. The virtual rehabilitation sample had the highest proportion requiring this type of airway management postoperatively at 5.9%. These differences were not considered statistically significantly different (χ^2=1.232, p=0.540). This suggests that preoperative rehabilitation delivered face-to-face or virtually did not differ from standard care alone in the incidence of tracheostomy requirement postoperatively and the comparable frequencies are illustrated in figure 6.2.4.a and table 6.2.4.a.

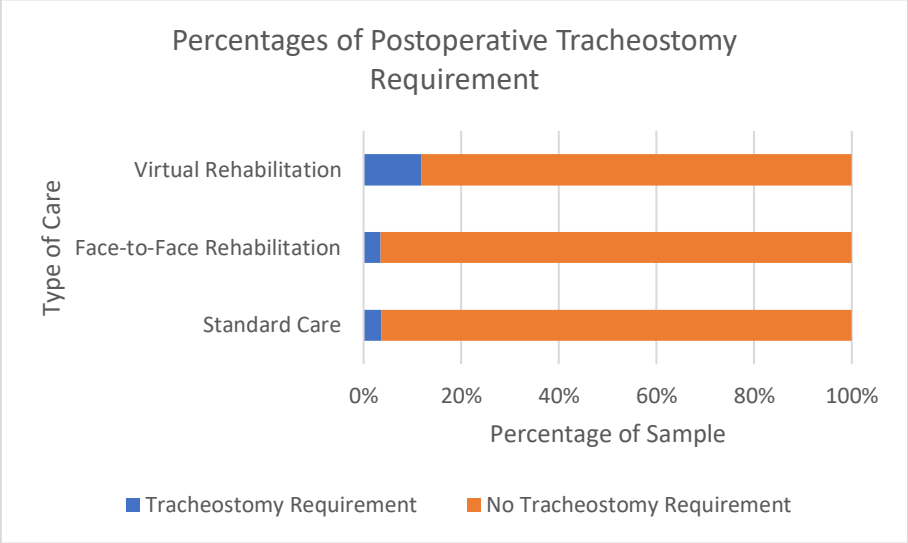

Figure 6.2.4.a. Proportion of Sample with Postoperative Tracheostomy Insertion by Preoperative Type of Care

Table 6.2.4.a. Statistics for Tracheostomy Insertion for the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance χ2	Post hoc Comparison
Tracheostomy Insertion	*Yes (n)*	3.6% (6)	3.5% (5)	5.9% (8)	*χ2=1.232 p=0.540 (NS)*	*SC & F2F p=0.965 (NS) SC & VR p=0.351 (NS) F2F & VR p =0.351 (NS)*
	No (n)	96.4% (160)	96.5% (137)	94.1% (128)		
Totals	*n*	166	142	136		
NS - Non significance * Significance						

It is worth noting that oxygen delivery devices and tracheostomy insertion are informed by Local Trust policies and pathways, established from relevant clinical guidelines. This type of clinical pathway can change over time with the emergence of new literature or when there is the need for an organisational shift in clinical management. The standard care sample was taken from patients receiving surgery between February 2018 to February 2019, it is possible that clinical practices and treatment pathways differed in recommendations for timing and type of oxygen administration and airway management in comparison to the intervention samples.

Furthermore, the SARS-CoV-2 pandemic resulted in a drastic organisational shift within the NHS. The employment of respiratory support and the need to allocate ventilation and respiratory resources differed during this clinical period and new clinical pathways were rapidly established with emergency guidance released for intensive care management and resource utilisation. These potential differences in practices over the study period should be acknowledged and results for this variable interpreted with caution.

6.2.5. Three-Way Comparison of Chest Drain Duration

Chest drains are inserted following lung resection to aid drainage of air and fluid accumulating perioperatively within the pleural space. Following the removal of cancerous tissue in lung resection the full expansion of remaining lung tissue is an important therapeutic outcome. Chest drains are removed when there is minimal leakage or drainage present, and a chest x-ray has confirmed adequate re-expansion of remaining lung tissue. A common pulmonary complication following lung resection is the persistent leakage of air resulting in prolonged chest drain requirement and subsequently an increased risk of infection and empyema; an infected pus forming within the thoracic cavity. Research has shown that persistent air leakage is one of the most important determinants for extended hospital length of stay in lung resection procedures (Varela et al., 2005; Brunelli et al., 2006; Huang et al., 2022). Therefore, the mean duration of chest drain insertion was an important outcome across the three samples. Early removal of chest drains has been considered as less than 48 hours in the literature (Xing et al., 2020) and

therefore chest drain insertion of greater than 2 days was considered an extended period in this study.

Duration of chest drain insertion (mean ±SD) was shortest in the virtual rehabilitation group (4.49 days ±5.43) and this was similar to standard care (4.63 days ±4.94). Face-to-face rehabilitation had the longest mean chest drain duration and widest standard deviation (5.70 days ±6.35). The mean difference in postoperative chest drain duration was 1.21 days greater for face-to-face rehabilitation when compared to virtual rehabilitation. A similar mean difference was evident between face-to-face rehabilitation and standard care at 1.07 days. Despite these differences, ANOVA was not statistically significant between the three groups ($f=2.025$, $p=0.133$) inferring that sample means were statistically comparable as referenced in table 6.2.5.a and illustrated in figure 6.2.5.a. A 1-day shorter chest drain insertion, as indicated in the mean differences, may be clinically significant to patients who may find the chest drains uncomfortable and restrictive. Removal of chest drains may also facilitate greater mobility and independence for patients whilst on the ward, enabling completion of self-care tasks unaided where any reduction in chest drain requirement is likely to be welcomed.

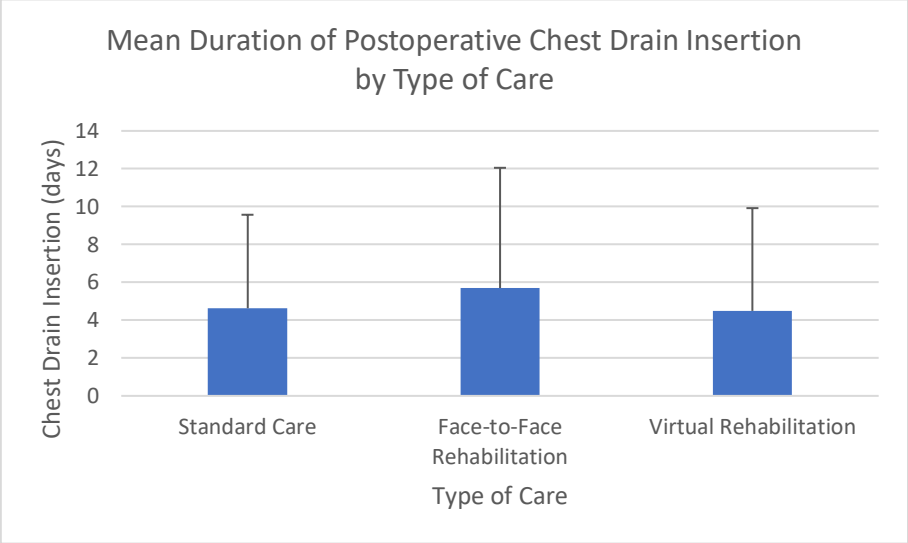

Figure 6.2.5.a. Bar Chart of Mean Postoperative Chest Drain Duration by Preoperative Type of Care

Table 6.2.5.a. Statistics for Chest Drain Duration in the Three Groups

Variable		**Standard Care**	**Face-to-Face Rehabilitation**	**Virtual Rehabilitation**	**Significance ANOVA**
Chest Drain Duration	*Mean (SD)*	4.63 (4.94)	5.70 (6.35)	4.49 (5.43)	*f= 2.025 p=0.133 (NS)*
	min-max	1-40	1-38	1-31	
Totals	*n*	166	142	136	
NS - Non significance * Significance					

All samples had a large range of values, with a minimum value of 1 day chest drain duration for all three samples, whilst maximum values for virtual rehabilitation, face-to-face rehabilitation and standard care were 31, 38 and 40 days respectively. Across all three samples more than half of the sample represented extended chest drain duration according to the 2 day time period outlined in the literature. This is likely due to the focus on high-risk patients in this study and therefore most likely to have delayed restoration in respiratory status postoperatively. Virtual rehabilitation had the largest proportion of patients with a chest drain duration of

2 days or less at 49.26% in comparison to face-to-face rehabilitation at 37.32% and standard care at 40.36% but this was not of statistical significance (χ^2=4.398, p=0.111).

Chest drain protocols can be individualised to local NHS Trusts and driven by individual surgeon preference. Data on the number and type of drains and duration of suction application were not collated within this study. Clinically, a greater number of chest drains may lead to better drainage of both air and fluid but can result in greater discomfort for the patient due to inflammation and trauma at the point of insertion. Chest drains may also be connected to suction, facilitating the removal of air and re-expansion of underlying lung tissue, this can limit a patients' postoperative mobility to the surrounding bed space area. Chest drain protocols regarding time, type and application can alter with time and the three samples span across three years, with the standard care sample at the earliest and virtual rehabilitation the latest end of the spectrum. Whilst NHS protocols largely reflect recommended clinical guidelines, there are no current specific guidelines regarding chest drains in postoperative lung resection care and therefore protocols can change depending upon surgeon preference, equipment advancement and changes within NHS Trust procedural updates. It is not clear whether there was any significant chest drain protocol changes within the study period but there had been changes within surgical workforce personnel that may impact upon findings, therefore any statistics should be viewed with caution.

6.3. Comparison of Hospital Readmissions during 12 Month Follow up

The hospital was a specialist centre for lung cancer surgery and accepted referrals from a large geographical area, including some referrals that would be classified as 'out of area' and therefore admissions following discharge are likely to have occurred at the patient locality and this information was inaccessible to the researcher, significantly affecting reliability of readmissions statistics. Furthermore, the cause for known hospital admissions was not recorded and therefore may have been unrelated to lung cancer diagnosis or postoperative recovery. Therefore, analysis was restricted to descriptive narrative as statistical testing would be misleading and fundamentally inaccurate.

No hospital admissions were reported in 84.9% of the standard care group, 83.8% of the virtual rehabilitation group and 78.9% of the face-to-face rehabilitation group. This was also reflected in low readmission mean and standard deviation values across all three groups (mean ±SD); Standard care (0.17 ±0.44), face-to-face rehabilitation (0.27 ±0.57) and virtual rehabilitation (0.28 ±0.76). Given the small number of hospital readmissions, the cumulative amount of time patients spent in hospital in days was also comparably small, with mean values for all three groups below 2 days. Mean cumulative hospital stay (mean ±SD) was similar across all three groups; Face-to-face rehabilitation (1.85 days ±6.14), virtual rehabilitation group (1.35 days ±4.81) and standard care (1.20 days ±5.58). Standard care had the greatest range of cumulative days in hospital, ranging 0-53 days, followed by face

to-face rehabilitation 0-46 days and virtual rehabilitation had the lowest range 0-35 days.

Surgeon follow-up consultations were performed within 3 months of discharge for lung resection and documented ongoing symptoms. A good recovery was documented in 78.3% of follow-up letters in patients who had received standard care, 73.9% or patients who had received preoperative face-to-face rehabilitation and 73.5% of patients who had received preoperative virtual rehabilitation. Patients with documented evidence of ongoing symptoms reflected a breadth of issues experienced by patients in the 3 months post-surgery.

Ongoing shortness of breath was the most frequently reported symptom in the standard care group (n=13) and the second most frequently reported symptom in virtual rehabilitation (n=10) and face-to-face rehabilitation (n=6). Persistent thoracic pain was the most frequently reported symptom in the intervention groups, virtual rehabilitation (n=11) and face-to-face rehabilitation (n=15). Pain was the second most frequent complaint in the standard care group (n=9). Other reported symptoms were weight loss associated with poor appetite; standard care (n=8), face-to-face rehabilitation (n=3) and virtual rehabilitation (n=2). Ongoing wound issues, related to healing, infection or numbness was reported in virtual rehabilitation (n=9), standard care (n=4) and face-to-face rehabilitation (n=1). Reduced mobility that had not returned to preoperative levels was also reported in face-to-face rehabilitation (n=6), standard care (n=4) and virtual rehabilitation (n=2). Arrythmias, renal complications, cognitive impairment, fatigue, nausea and

dizziness were also reported to a lesser extent. In-hospital deaths following lung resection occurred in standard care (n=4), face-to-face rehabilitation (n=3) and virtual rehabilitation (n=6).

Chapter 7. Results: Objective 2

7.1. Comparison of Survival Rates Between the Three Groups

7.1.1. Three-Way Comparison of 6 and 12-Month Postoperative Survival

Surgical resection is currently the primary curative intervention for lung cancer and determining whether preoperative intervention could influence postoperative recovery beyond the immediate short term hospital stay was considered a worthwhile outcome. Survival in days, up to 12-month follow-up (mean ±SD) were similar for standard care (332.42 days ±86.21), virtual rehabilitation (334.92 days ±87.53) and face-to-face rehabilitation (339.12 days ±80.76) with reference values in table 7.1.1.a. ANOVA did not reveal any significant difference in mean survival for standard care, face-to-face rehabilitation and virtual rehabilitation (f=0.241, p=0.786). Large standard deviations and wide ranges within survival data were evident across all three groups, survival in standard care ranged from 6 to 365 days, face-to-face rehabilitation ranged from 5 to 365 days and virtual rehabilitation from 10 to 365 days. All three groups had individuals within the sample who died during their hospital stay following surgery. This variation is reflective of the complex nature of survival that may be difficult to predict. Despite the lack of statistical significance it could be argued that any small increase in survival time could be of great significance to an individual and their loved ones. The highest mean survival in the face-to-face rehabilitation group was a 4.2 day mean difference in comparison to virtual rehabilitation and a 6.7 day mean difference to standard care. Standard care had the lowest mean survival in comparison to both intervention

groups. It is difficult to determine the individual worth of these mean differences clinically, but the potential significance any additional time may provide cannot be underestimated. Statistically, it cannot be inferred that preoperative intervention of either face-to-face or virtual delivery can significantly influence 12-month survival based on the follow-up data available.

Table 7.1.1.a. Statistics for Survival at 12 Months in days for the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance ANOVA
Survival at 12 months (days)	*Mean (SD)*	332.42 (86.21)	339.12 (80.76)	334.92 (87.53)	*f= 0.241 p=0.786 (NS)*
	min-max	6-365	5-365	10-365	
Totals	*n*	166	142	136	
NS - Non significance * Significance					

At 6 months 91.0% of patients within the standard care group were alive. The intervention groups also shared similar survival data to standard care, with 90.8% of patients also alive at 6 months in the face-to-face rehabilitation group and 91.9% alive in the virtual rehabilitation group. These frequencies appeared similar on inspection, and this was confirmed statistically, with non-significance (χ^2=0.120, p=0.942). All groups demonstrated a decrease in survival at 12-months, with 83.1% of patients still alive at 12-month post operation in the standard care group. This was lower than one-year survival in both intervention groups with 89.4% of patients alive at one-year in the face-to-face group and 87.5% alive in the virtual rehabilitation group. Statistically, 12-month survival was also not significantly different between the groups (χ^2=2.775, p=0.250). In real terms this represents a loss of standard care (n=13), face-to-face rehabilitation (n=2) and virtual rehabilitation (n=6) between the period of 6 months to 12 months. Standard care

had the lowest survival rates at 12 months and the biggest loss of patients between 6 to 12 months in comparison to intervention groups. Statistics from the National Lung Cancer Audit currently show UK one-year survival rates at 88.7% for patients following lung resection (RCP, 2020). Only the face-to-face rehabilitation group reflected mean rates higher than the National picture in the United Kingdom. However, statistical significance was not achieved suggesting that preoperative face-to-face rehabilitation and virtual rehabilitation intervention survival rates did not differ to standard care at 6 or 12-months post-operation. Survival at 6 months and 12 months for the three groups is shown graphically in figure 7.1.1.a with reference statistics in table 7.1.1.b. Long term survival is a pertinent and patient-focussed outcome but there are many unforeseeable circumstances that may delay or hasten death in patient or non-patient populations. Any indications of causality are not captured within simple deceased statistics.

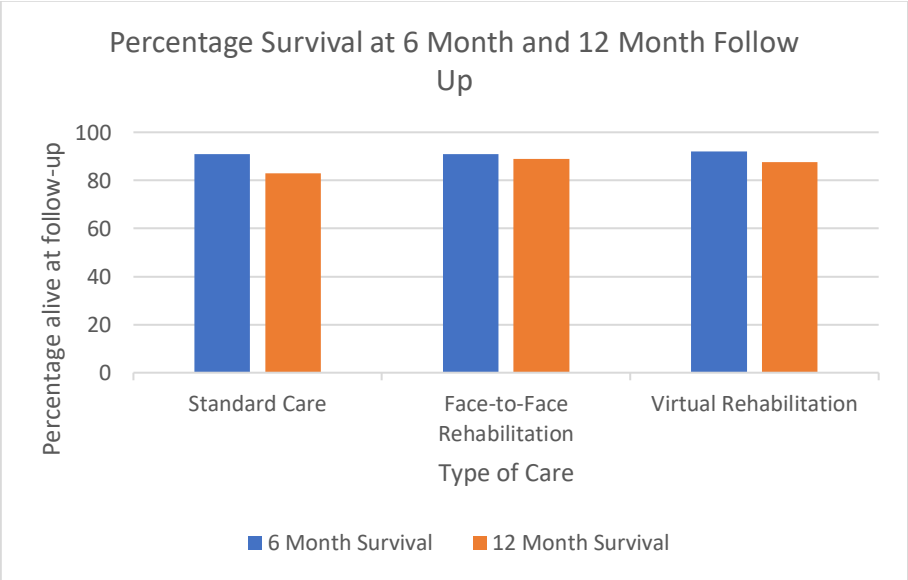

Figure 7.1.1.a. Proportion of Sample Survival at 6 month and 12 month Follow Up by Preoperative Type of Care

Table 7.1.1.b. Statistics for 6 and 12 Month Survival for the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance χ2	Post hoc Comparison
Survival at 6 months	*Yes (n)*	91.0% (151)	90.8% (129)	91.9% (125)	*χ2=0.120 p=0.942 (NS)*	*SC & F2F p=0.971 (NS) SC & VR p=0.770 (NS) F2F & VR p =0.752 (NS)*
	No (n)	9.0% (15)	9.2% (13)	8.1% (11)		
Survival at 12 months	*Yes (n)*	83.1% (138)	89.4% (127)	87.5% (119)	*χ2= 2.775 p=0.250 (NS)*	*SC & F2F p=0.112 (NS) SC & VR p=0.289 (NS) F2F & VR p =0.613 (NS)*
	No (n)	16.9% (28)	10.6% (15)	12.5% (17)		
Totals	*n*	166	142	136		
NS - Non significance * significance						

The National Lung Cancer Audit report identified 30-day survival at 98.1% following lung resection surgery in the United Kingdom (RCP, 2020). The sample data available in this data set was further inspected and identified that face-to-face rehabilitation had slightly favourable 30-day survival to the National picture at 98.6%. Largely comparable results were also evident with virtual rehabilitation having a 30-day survival at 96.3% and standard care 97.6% slightly under the National figures from the current audit report.

7.2. Survival Analysis of Collective Sample using Cox Regression Analysis

7.2.1. Factors Identifiable Preoperatively in Patient Presentation

Univariate cox regression showed no significant difference in preoperative rehabilitation strategies employed and 12-month mortality risk post lung resection HR 0.84 (p=0.269, 95% CI 0.61-1.15). Standard care in comparison to the preoperative rehabilitation interventions showed a non-significant increased risk of mortality; standard care in comparison to face-to-face rehabilitation HR 1.63

(p=0.129, 95% CI 0.87-3.04), standard care in comparison to virtual rehabilitation HR 1.36 (p=0.322, 95% CI 0.72-2.48). There was also no significant difference between the two rehabilitation strategies and survival at 12-months; Face-to-face rehabilitation in comparison to virtual rehabilitation HR 0.82 (p=0.609, 95% CI 0.42-1.67). The similarities in survival trajectories irrespective of type of preoperative preparation received are reflected in the Kaplan-Meier plot in figure 7.2.1.a and univariate cox regression statistics are shown in table 7.2.1.a.

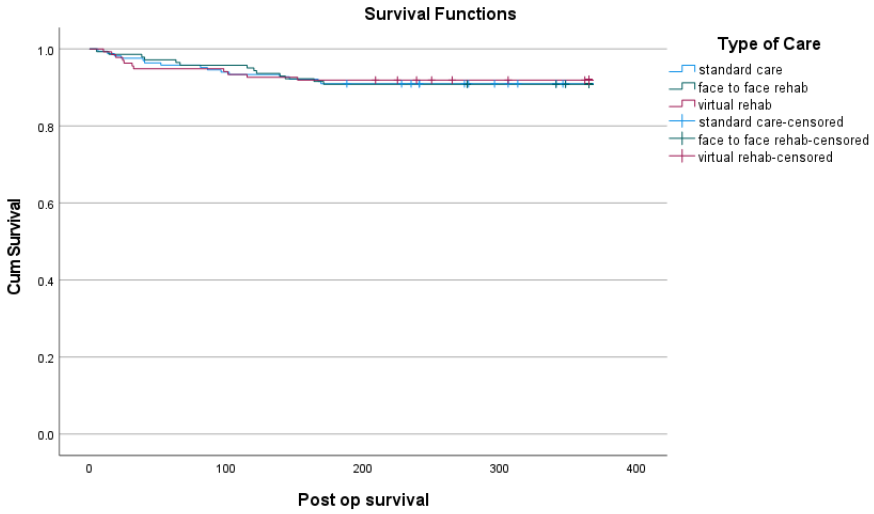

Figure 7.2.1.a. Kaplan-Meier Plot of Survival by Preoperative Type of Care

Despite the lack of statistical significance for preoperative rehabilitation strategies in comparison to standard care alone, preoperative physical activity status was associated with better survival at 12-months. Univariate cox regression showed that by unit increase in preoperative physical activity status the risk of mortality at 12-months post-surgery increased by 1.9 times HR 1.92 (p=0.001, 95% CI 1.33-2.77) suggesting mortality at 12-months following surgery is almost twice as likely for

individuals with limited mobility than for those individuals with higher levels of preoperative mobility as referenced in table 7.2.1.a. A physical activity status of 1 indicated good baseline activity, whilst a score of 2 and 3 indicated progressively lower physical activity. A classification of 1 had a 69% lower risk of mortality at 12 months in comparison to an activity status of 3 with HR 0.31 (p-0.001, 95% CI 0.12-0.60). Whilst an activity status of 2 had a 62% lower risk of mortality at 12 months than a physical activity status of 3 with a HR 0.38 (p=0.001, 95% CI 0.21-0.67). Only a physical activity status between 1 and 2 showed no statistical significance in 12-month mortality risk, HR 0.80 (p=0.506, 95% CI 0.41-1.56) The Kaplan-Meier plot for preoperative physical activity in figure 7.2.1.b shows the significantly poorer survival associated with a physical activity status classification of 3 in comparison to higher levels of physical activity status.

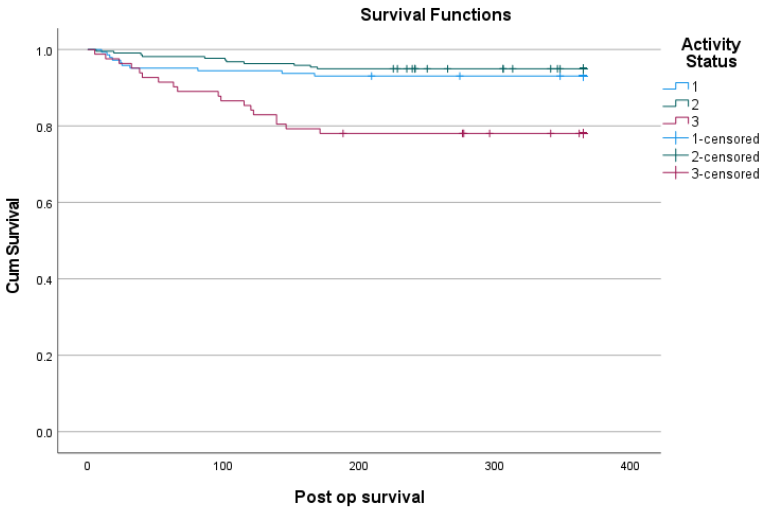

Figure 7.2.1.b. Kaplan-Meier Plot of Survival by Preoperative ECOG Activity Status

The preoperative assessment also included a past medical history review and univariate cox regression statistics related to the presence of medical conditions are shown in 7.2.1a. The presence of a renal condition had a statistically significant 2.1 increased likelihood of mortality at 12-months post-surgery, HR 2.13 (p=0.030, 95% CI 1.08-4.19) suggesting that individuals with a renal condition were twice as likely to die within 12-months following surgery than those individuals who did not. Similarly, a neurological condition also had a statistically significant 1.9 times greater chance of mortality postoperatively HR 1.92 (p=0.025, 95% CI 1.08-3.40) suggesting mortality at 12-months was almost twice as likely with a neurological condition. The presence of a musculoskeletal condition also had a statistically significant 1.8 times greater chance of mortality at 12-months post-surgery, HR 1.77 (p=0.027, 95% CI 1.07-2.94). The Kaplan-Meier plots demonstrating the poorer prognosis with a renal, neurological, and musculoskeletal conditions are shown in the Kaplan-Meier plots in figures 7.2.1.c, 7.2.1.d, 7.2.1.e respectively.

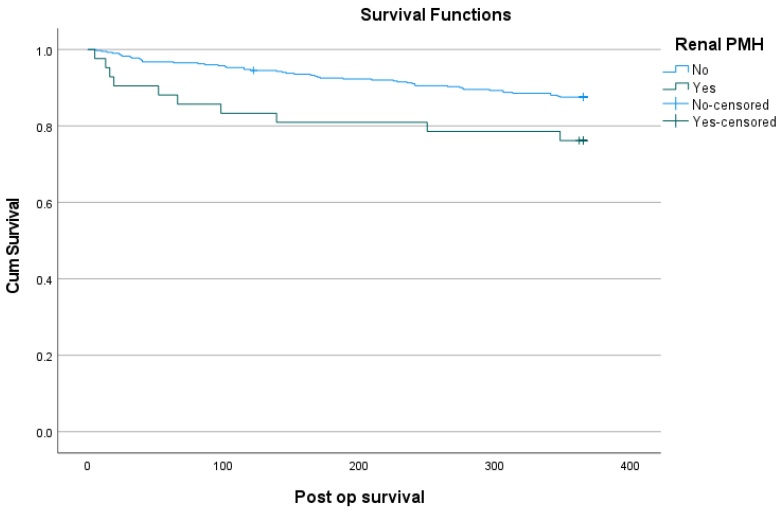

Figure 7.2.1.c. Kaplan-Meier Plot of Survival for Medical History of a Renal Condition

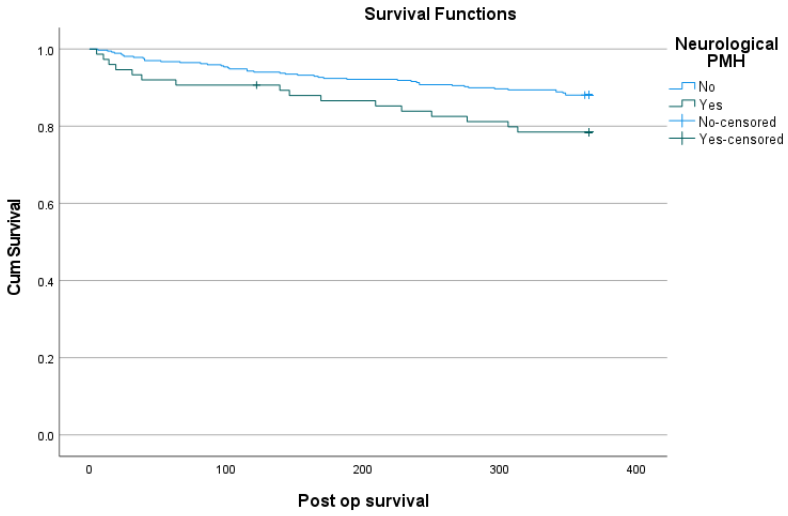

Figure 7.2.1.d. Kaplan-Meier Plot of Survival for Medical History of a Neurological Condition

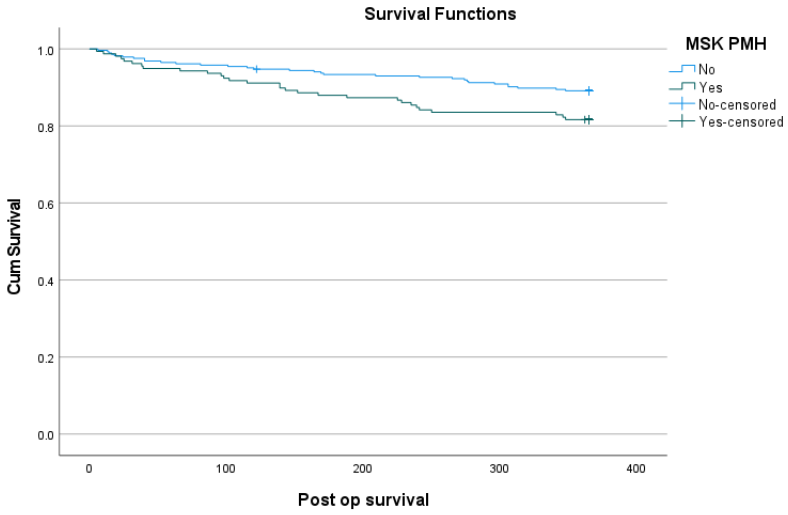

Figure 7.2.1.e. Kaplan-Meier Plot of Survival for Medical History of a Musculoskeletal Condition

A past medical history of a respiratory medical condition did not have a statistically significant increased risk of mortality postoperatively, HR 1.31 (p=0.297, 95% CI 0.79-2.17). A past medical history of a cardiac condition had no statistically

significant increased risk of 12-month mortality postoperatively, HR 0.97 (p=0.899, 95% CI 0.58-1.62). A past medical history of a gastric condition also had no statistically significant increased likelihood of mortality at 12 months postoperatively, HR 0.86 (p=0.613, 95% CI 0.49-1.53). The similarity in survival plots for those with and without a preoperative respiratory condition, cardiac condition and gastric condition is evident in the Kaplan-Meier plots available in Appendix 13.

Neither gender or smoking status significantly affected the risk of 12-month mortality following surgery in this study as referenced by statistics for these variables in table 7.2.1.a. Univariate cox regression showed that male gender did not statistically significantly increase the risk of 12-month post-surgical mortality, HR 1.10 (p=0.717, 95% CI 0.66-1.83). Current smoking status also did not show a statistically significantly increased risk of 12-month mortality following lung resection HR 0.98 (p=0.897, 95% CI 0.71-1.35). A preoperative non-smoker status appeared to halve the likelihood of 12-month mortality post-surgery in comparison to a current smoking status, although this did not achieve statistical significance HR 0.52 (p=0.090, 95% CI 0.25-1.11). A preoperative non-smoker status was also favourable to an ex-smoker status, to a lesser extent, with 15% fewer deaths at 12-months post-surgery, and this also did not achieve statistical significance HR 0.85 (p=0.69, 95% CI 0.40=1.84). A preoperative current smoking status had a non-significant 1.6 times increased likelihood of 12-month mortality in comparison to ex-smokers, HR 1.63 (p=0.081, 95% CI 0.94-2.83). Despite the lack of statistical inference with preoperative smoking status, a non-smoking status did appear

favourable towards 12-month survival and this trend is indicated in the Kaplan-Meier plot figure 7.2.1.f.

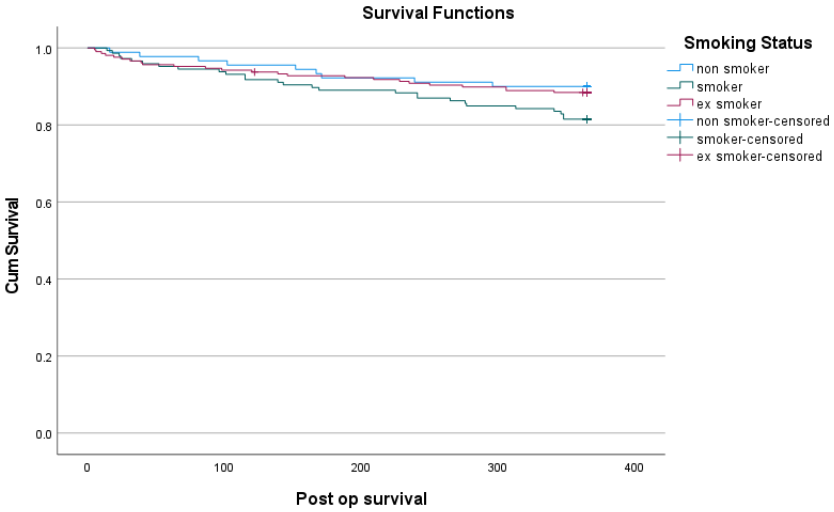

Figure 7.2.1.f. Kaplan-Meier Plot of Survival by Preoperative Smoking Status

Smoking status was recorded and analysed from preoperative assessment information only and an individuals' smoking status may have changed within the 12-month follow-up period and this change in status would not have been captured within this 12-month survival analysis. The period of enforced smoking cessation for the duration of the hospital admission and the success of surgical intervention may have acted as a catalyst and incentive for patients to continue with smoking cessation following hospital discharge. An updated smoking status within the post-discharge period would have increased the accuracy of survival analysis for this factor.

Table 7.2.1.a. Univariate Cox Regression Statistics for Factors Identifiable at Preoperative Presentation

Variable	Coefficient	Standard Error	Hazard Ratio (HR)	Significance	Confidence Interval
Preoperative Rehabilitation	-0.18	0.16	0.84	p=0.269 (NS)	0.61-1.15
Preoperative Physical Actvity Status	0.65	0.19	1.92	p=0.001*	1.33-2.77
Gender	0.94	0.26	1.10	p=0.717 (NS)	0.66-1.83
Renal Condition	0.75	0.35	2.13	p=0.030*	1.08-4.19
Neurological Condition	0.65	0.29	1.92	p=0.025*	1.08-3.40
Musculoskeletal Condition	0.57	0.26	1.77	p=0.027*	1.07-2.94
Respiratory Condition	0.27	0.26	1.31	p=0.297 (NS)	0.79-2.17
Cardiac Condition	-0.03	0.26	0.97	p=0.899 (NS)	0.58-1.62
Gastric Condition	-0.15	0.29	0.86	p=0.613 (NS)	0.49-1.53
Smoking Status	-0.02	0.17	0.98	p=0.897 (NS)	0.71-1.35
NS - Non significance * Significance					

7.2.2. Factors for Surgical Risk and Postoperative Status

Categorical variables for postoperative pulmonary complications were analysed with univariate cox regression. All individual factors associated with presence of postoperative complications showed some statistical significance for greater risk of 12-month mortality, with cox regression statistics for these variables shown in table 7.2.2.a at the end of this section. The greatest risk of mortality was associated with patients requiring a tracheostomy insertion and patients requiring high flow-

oxygen therapy during the acute postoperative period. Postoperative tracheostomy had a statistically significant greater likelihood of 12-month mortality HR 8.19 (p<0.001, 95% CI 4.25-15.77) indicating 8 times more individuals with a tracheostomy died within the follow-up period in comparison to those who did not require this form of invasive airway management, the significantly worse survival trend is shown in the Kaplan-Meier plot in figure 7.2.2.a.

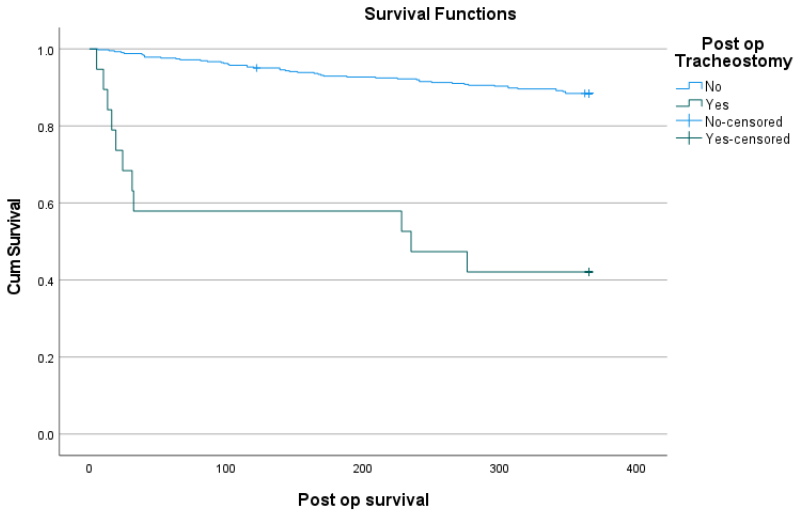

Figure 7.2.2.a. Kaplan-Meier Plot for Survival by Postoperative Tracheostomy Requirement

Almost 4 times more individuals who needed high-flow oxygen delivery through either invasive or non-invasive support in the postoperative period died within the 12-month follow-up period and this was considered statistically significant, HR 3.90 (p<0.001, 95% CI 2.17-7.00). The lower 12-month survival rates in the 12 months associated with greater oxygen and ventilation support during hospital admission is evident in the Kaplan-Meier plot in figure 7.2.2.b.

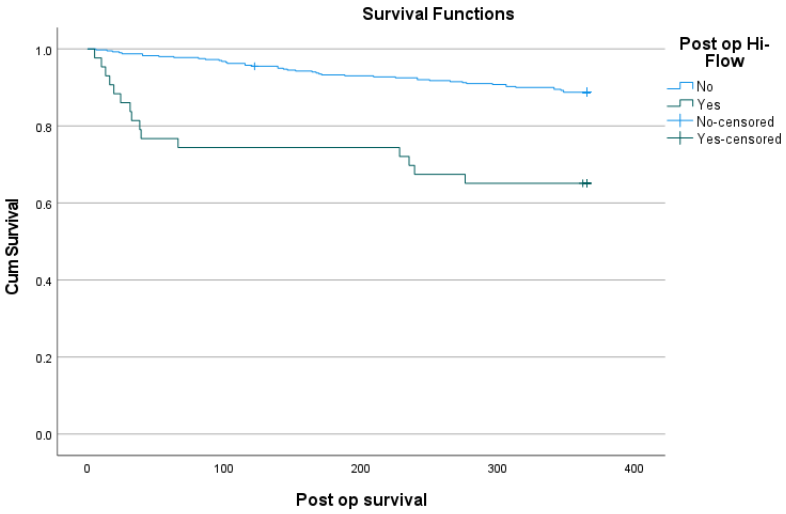

Figure 7.2.2.b. Kaplan-Meier Plot for Survival by Postoperative Oxygen Requirement

Postoperative antimicrobial therapy prescription had a statistically significant 2.3 times greater chance of 12-month mortality, HR 2.33 (p=0.002, 95% CI 1.38-3.94) indicating more than twice as many individuals who required antimicrobial therapy died in the 12-months following surgery. The poorer survival rates within the 12-month period following surgery associated with the need for antimicrobial therapy prescription during hospital admission is reflected in the Kaplan-Meir plot figure 7.2.2.c.

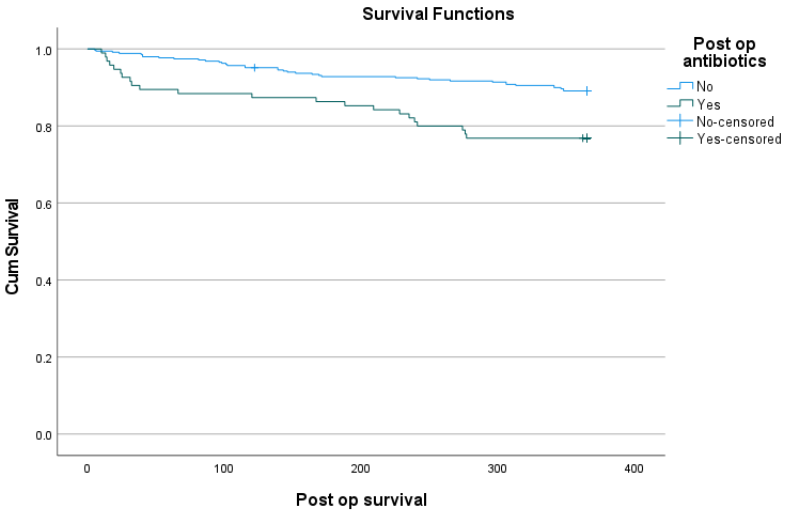

Figure 7.2.2.c. Kaplan-Meier Plot for Survival by Antimicrobial Therapy Requirement

The treatments required to manage postoperative pulmonary complications were all associated with significantly increased likelihood of 12-month mortality. Similarly, the investigations required to diagnose pulmonary complications also reflected an increased risk of mortality. More than twice as many individuals who had positive radiological evidence of pneumonia or atelectasis died within the 12-month follow-up period than those who did not have these findings. Radiological evidence of pneumonia or atelectasis postoperatively had a statistically significant 2.6 times greater chance of 12-month mortality, HR 2.62 ($p<0.001$, 95% CI 1.58-4.35) and the poorer survival is shown in the Kaplan-Meier plot in figure 7.2.2.d. A postoperative positive sputum culture also has a statistically significant 2.4 greater chance of mortality, HR 2.44 ($p=0.002$, 95% CI 1.41-4.25) with more than twice as many individuals dying in the 12-month follow up period where a positive sputum sample had been reported and this is shown in figure 7.2.2.e.

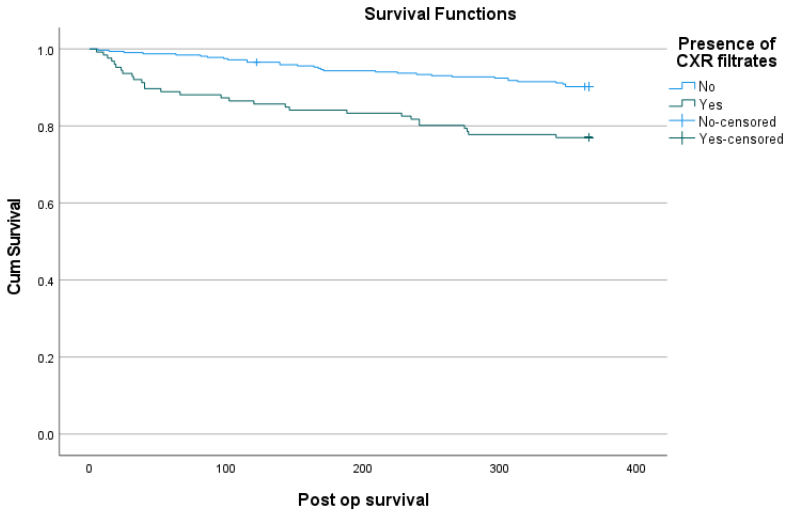

Figure 7.2.2.d. Kaplan-Meier Plot for Survival by Positive Postoperative Radiological Findings

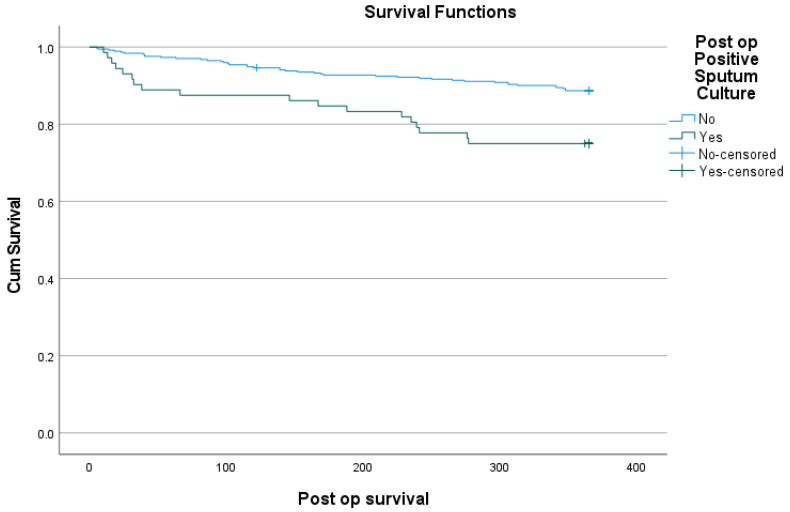

Figure 7.2.2.e. Kaplan-Meier Plot for Survival by Positive Postoperative Sputum Culture

The existing literature suggested that the extent of surgical resection was also associated with poorer outcomes post-surgery, with lobectomies associated with better survival than surgeries requiring removal of a higher proportion of lung tissue such as pneumonectomy (Myrdal et al., 2001; Strand et al., 2006; Roth et al.,

2008). In this study the type of surgical resection did not statistically significantly increase the likelihood of mortality within 12-months post-surgery, HR 1.23 (p=0.106, 95% CI 0.96-1.59). However, pneumonectomy, the surgical procedure requiring the greatest proportion of lung tissue removal was largely unrepresented in the study sample and the existing literature analysed substantially larger samples and incorporated 30-day mortality and up to five-year follow-up. The current literature has also identified that increased preoperative anaesthetic and surgical risk, as measured using the Thoracoscore classification, was associated with greater mortality post lung resection. The ASA classification was not used as a comparison in the existing literature, however the higher ASA classification that was used in this study did not statistically significantly increase the likelihood of mortality at 12 months post-surgery, HR 1.31 (p=0.311, 95% CI 0.78-2.19). The category associated with the greatest anaesthetic risk with a high ASA classification of 5 was under-represented within the total sample to draw accurate conclusions. Univariate cox regression statistics for type of lung resection and ASA classification are shown in 7.2.2.a and their Kaplan-Meier plots are available in appendix 11 for completeness of reporting, despite the lack of significance.

Table 7.2.2.a. Univariate Cox Regression Statistics for Factors related to Surgical Risk and Postoperative Status

Variable	Coefficient	Standard Error	Hazard Ratio (HR)	Significance	Confidence Interval
Tracheostomy Requirement	2.10	0.34	8.19	p<0.001*	4.25-15.77
Hi-Flow Oxygen Therapy	1.36	0.30	3.90	p<0.001*	2.17-7.00
Antimicrobial Therapy	0.85	0.27	2.33	p=0.002*	1.38-3.94
Positive Chest Xray Findings	0.96	0.26	2.62	p<0.001*	1.58-4.35
Postive Sputum Culture	0.89	0.28	2.44	p=0.002*	1.41-4.25
Type of Lung Resection	0.21	0.13	1.23	p=0.106 (NS)	0.96-1.59
ASA Classification	0.27	0.26	1.31	p=0.311 (NS)	0.78-2.19
NS - Non significance * Significance					

7.2.3. Factors Identifiable within the 12-Month Follow up Period

Post lung resection some patients require adjuvant therapy such as radiotherapy or chemotherapy that may impact upon recovery and survival rates. The study period also included the global SARS-CoV-2 pandemic prior to vaccination discovery and dissemination. This provided a further opportunity to explore the potential mortality impact of SARS-CoV-2 in the follow-up period. Almost 7 times more individuals who had a positive SARS-CoV-2 test in the immediate postoperative period or during the 12-month follow up died in comparison to those without a confirmed positive test. A confirmed diagnosis of SARS-CoV-2 in the 12-month postoperative period had a statistically significant 6.9 times increased risk of

mortality in the 12 months following surgery, HR 6.89 (p<0.001, 95% CI 2.96 -16.07) and the significantly worse survival associated with SARS-CoV-2 is shown in figure 7.2.3.a with the univariate cox regression statistics for this variable included in table 7.2.3.a.

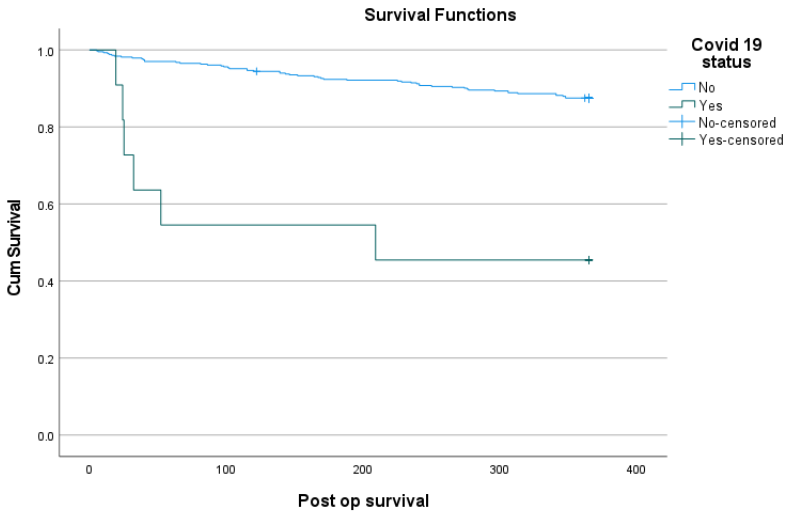

Figure 7.2.3.a. Kaplan-Meier Plot for Survival by SARS-CoV-2 Status

The need for adjuvant therapy through either radiotherapy or chemotherapy was not statistically significantly associated with poorer survival outcomes. Almost twice as many individuals who received radiotherapy died in the 12-month follow up period, however the requirement of radiotherapy within the 12-month postoperative period was not of statistical significance for 12-month mortality risk HR 1.86 (p=0.151, 95% CI 0.80-4.32). The requirement of chemotherapy in the 12-month follow-up period also did not significantly increase the likelihood of 12-month mortality following surgery, HR 1.14 (p=0.713, 95% CI 0.56-2.32). The cox regression statistics related to adjuvant therapy are shown in table 7.2.3.a and

Kaplan-Meir plots illustrating similar survival trajectories for those who did or did not receive adjuvant therapy are included in Appendix 14.

Table 7.2.3.a. Univariate Cox Regression Statistics for SARS-CoV-2 and adjuvant Therapy in 12-Months Post Surgery

Variable	Coefficient	Standard Error	Hazard Ratio (HR)	Significance	Confidence Interval
Positive SARS-CoV-2	1.93	0.43	6.89	p<0.001*	2.96-16.07
Radiotherapy	0.62	0.43	1.86	p=0.151 (NS)	0.80-4.32
Chemotherapy	0.13	0.36	1.14	p=0.713 (NS)	0.56-2.32
NS - Non significance * Significance					

7.3. Multivariate Cox Regression with Factors of Univariate Significance

Univariate cox regression suggested that the preoperative identifiable factors of poor baseline physical activity status and a past medical history of a renal, neurological or musculoskeletal condition statistically significantly increased the chance of dying within 12 months following surgical intervention for lung cancer. These preoperative factors achieving statistical significance at univariate analysis were first considered in multivariate analysis and showed that only activity status remained statistically significant for poorer survival at 12 months following surgery, HR 1.68 (p=0.009, 95% CI 1.14-2.47). Factors that were significant in univariate analysis that related to postoperative status were then included in multivariate analysis. This included the presence of all postoperative complications, whereby

only the need for a tracheostomy during the postoperative admission remained statistically significant on multivariate analysis, HR 4.04 (p=0.015, 95% CI 1.31-12.46).

The final multivariate analysis added a positive SARS-CoV-2 test alongside the need for a postoperative tracheostomy and poor preoperative activity status and the three variables remained significant. The multivariate regression showed a positive SARS-CoV-2 test HR 5.16 (p<0.001, 95% CI 2.17-12.28), the requirement of a postoperative tracheostomy HR 6.15 (p<0.001, 95% CI 3.11-12.17) and poor preoperative baseline activity HR 1.58 (p=0.016, 95% CI 1.09-2.29) were all significantly associated with 12-month mortality. This suggests that these factors are independently predictive of poor survival following lung resection surgery and these are shown in table.

Table 7.2.3.a. Multivariate Cox Regression Significant Statistics

Variable	Coefficient	Standard Error	Hazard Ratio (HR)	Significance	Confidence Interval
Preoperative Physical Activity Status	0.46	0.19	1.58	p=0.016*	1.09-2.29
Tracheostomy Requirement	1.82	0.35	6.15	p<0.001*	3.11-12.17
Positive SARS-CoV-2	1.64	0.44	5.16	p<0.001*	2.17-12.28
NS - Non significance * Significance					

Based on the findings of this study, those individuals with a tracheostomy insertion during hospital admission, a positive SARS-CoV-2 infection within the 12-month postoperative period and lower baseline activity status according to the ECOG classification 3 prior to surgery, are independently predictive of poorer survival in

the 12-month post-surgical period. This model may help to identify the most vulnerable and highest risk patients who may benefit from effective management strategies to modify the associated risk. The need for a tracheostomy following surgical intervention may be due to postoperative ventilatory compromise associated with respiratory muscle weakness and additional respiratory loading but may also be representative of perioperative complications requiring airway management and artificial ventilation. The infection risk associated with SARS-CoV-2 infection may not be an immediately modifiable risk factor although optimising immune status with the optimisation of health status is likely to be advantageous and suggests that postoperative strategies may be warranted in this patient group. The improvement of baseline activity at preoperative assessment may be a modifiable risk factor that can influence the postoperative course and patient survival. The results of survival analysis in this study suggest patients in the higher classifications indicative of poorer performance have the most to gain. A one-unit improvement in the ECOG status, from 3 to 2, could have significant benefits in survival. In real terms this would mean improving a patient activity status from limited self-care and confined to a bed or chair for more than 50% of waking hours to becoming independent in self-care and active for more than 50% of waking hours. Therefore, targeted preoperative strategies to promote daily activity and reduce overall sedentary time may prove effective.

Chapter 8. Results: Objective 3

8.1. The Effect of Two Modes of Rehabilitation on Pulmonary Function

Lung resection can cause a reduction in lung function and an increased loading of respiratory muscles in the immediate postoperative period. Increasing lung function prior to surgical resection could theoretically improve a patients' respiratory function to ensure that this acute reduction remains above a critical threshold that may lead to postoperative pulmonary complications. A specific threshold that would be protective against pulmonary complications has not been established within the current evidence base. In the absence of an evidence-based threshold any increase in pulmonary spirometry from pre to post intervention, was considered potentially worthwhile to optimise a patients' respiratory status to better withstand the immediate effects of surgery.

8.1.1. Comparison of Pre and Post Intervention FEV1 and % Predicted FEV1

Absolute pulmonary function measures were considered to three decimal points and predicted percentages to two decimal points to be sufficiently sensitive to differences in pre and post intervention values that may be of clinical significance. FEV1 (mean ±SD) in the face-to-face rehabilitation group showed a small increase from pre intervention to post intervention. Preoperative pre intervention FEV1 (2.002 litres ±0.837) in comparison to post intervention FEV1 (2.066 litres ±0.815), reflects a mean difference of 0.064 litres in this group. The difference between absolute pre and post intervention FEV1 was statistically significantly different

(t=3.904, p<0.001, 95% CI 0.032-0.096) inferring an increased FEV1 with face-to-face rehabilitation. It is difficult to establish whether this represents a clinically significant difference given the relatively small mean difference between pre and post intervention. FEV1 in the virtual rehabilitation group also showed an increase from pre intervention to post intervention. Preoperative pre intervention FEV1 (2.114 litres ±0.802) compared to mean post intervention FEV1 (2.139 litres ±0.801). The mean difference reflects an increase from pre intervention to post intervention of 0.025 litres. There was no statistically significant difference between pre and post intervention within the virtual rehabilitation group (t=1.891, p=0.064, 95% CI -0.002 + 0.051). Therefore, it cannot be statistically inferred that virtual rehabilitation can significantly increase FEV1. The comparison of pre and post intervention FEV1 means for both face-to-face and virtual rehabilitation are shown in figure 8.1.1.a with their respective statistics included in table 8.1.2.a.

The percentage predicted FEV1 considers the absolute value against predicted values for age, gender, height, and ethnicity. The percentage predicted FEV1 is often of greater clinical use than absolute values to establish respiratory defect at less than 80% predicted. In the face-to face rehabilitation group percentage predicted FEV1 values are below the 80% threshold for both pre and post intervention means.

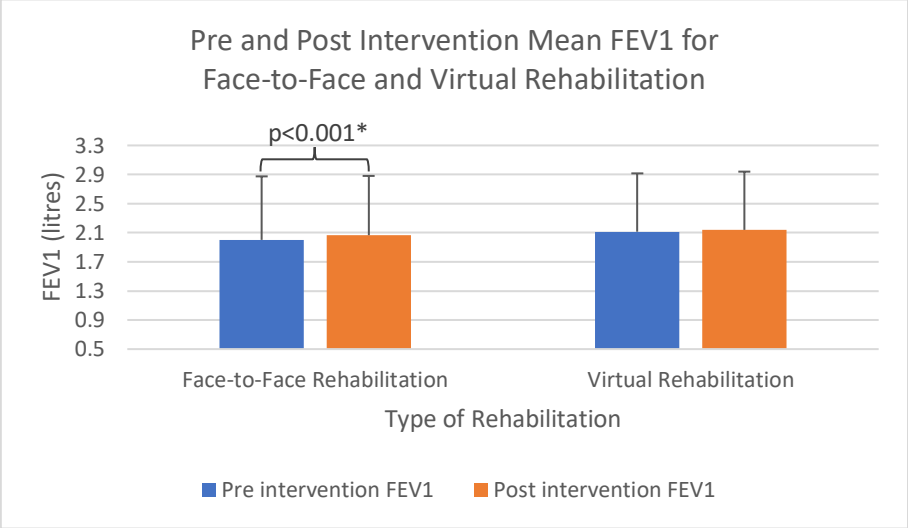

Figure 8.1.1.a. Pre and post intervention Mean FEV1with Face-to-Face Rehabilitation and Virtual Rehabilitation

The face-to-face rehabilitation group had a mean preoperative preintervention percentage predicted FEV1 (77.00% ±22.540) and a mean post intervention percentage (79.79% ±21.336). Standard deviations were large in both pre and post intervention samples. The mean values reflected a mean difference from pre to post intervention of 2.79% with face-to-face rehabilitation. The difference in pre and post intervention percentage predicted FEV1 was statistically significantly different (t=4.634, p<0.001, 95% CI 1.599-3.978), inferring increased percentage predicted FEV1 with face-to-face rehabilitation, although clinical significance of the difference cannot be inferred. The virtual rehabilitation group had pre and post intervention mean percentage predicted FEV1 values above the 80% threshold, suggesting higher respiratory function prior to intervention in comparison to face-to-face rehabilitation. The virtual rehabilitation group had a preoperative pre intervention mean percentage predicted FEV1 (86.26% ±22.002) and an increased

post intervention (87.51% ±22.560). There were large standard deviations in both pre and post intervention samples for virtual rehabilitation. The mean difference between pre and post intervention percentage predicted FEV1 reflected an increase of 1.25%. Statistical analysis did not infer a statistically significant difference between pre and post intervention values (t=1.614, p=0.112, 95% CI -0.303 + 2.793) and therefore it cannot be inferred statistically that virtual rehabilitation increased percentage predicted FEV1. A comparison of pre and post intervention percentage predicted FEV1 means with face-to-face rehabilitation and virtual rehabilitation is referenced in table 8.1.2.a and illustrated figure 8.1.1.b.

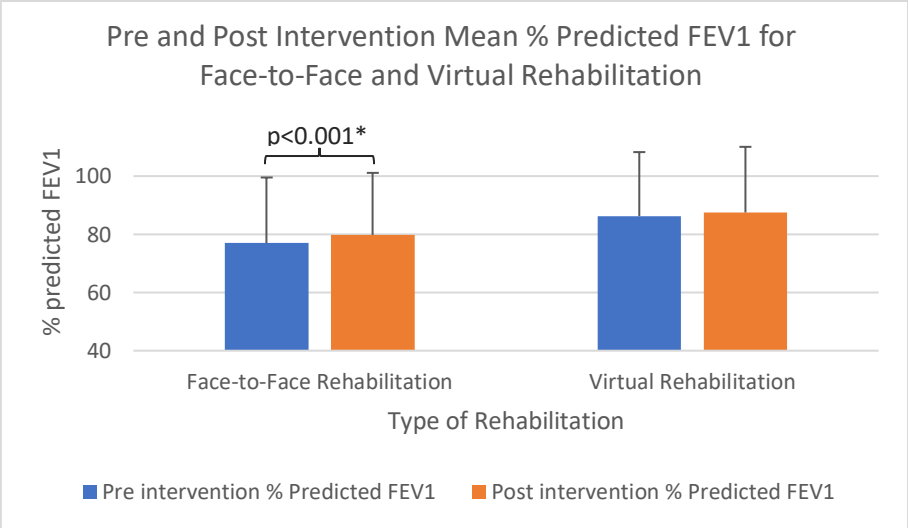

Figure 8.1.1.b. Pre and Post Intervention Mean % Predicted FEV1 with Face-to-Face Rehabilitation and Virtual Rehabilitation

Both intervention groups showed a mean increase in FEV1 and percentage predicted FEV1 scores reflecting some improvement with rehabilitation. Face-to-face rehabilitation achieved statistical significance with both absolute FEV1 and

percentage predicted FEV1 whilst differences in these measures were not statistically significantly different with virtual rehabilitation. The mean post intervention percentage predicted FEV1 remained below the 80% threshold indicative of respiratory defects. This may explain the lack of statistical significance in postoperative pulmonary complications in face-to-face rehabilitation in comparison to standard care. In contrast, the higher mean pre and post intervention percentage predicted FEV1 may have been protective in the virtual rehabilitation intervention group and explain the statistically significant difference in the severity of postoperative complications in comparison to standard care, despite the lack of significance between pre and post intervention FEV1 with virtual rehabilitation intervention.

8.1.2. Comparison of Pre and Post Intervention FVC and % Predicted FVC

Mean absolute values of FVC increased from pre to post intervention in the face-to-face rehabilitation group. The mean preoperative pre intervention FVC (3.159 litres ±1.010) increased to a mean post intervention FVC (3.242 litres ±1.016) representing a mean difference of 0.083 litres. The difference in pre and post intervention FVC was statistically significantly different ($t=4.303$, $p<0.001$, 95% CI 0.045-0.121). This infers a statistically significant increase in FVC with face-to-face rehabilitation. The clinical significance of this increase cannot be inferred although the mean difference was evidently small. Large changes in FVC are unlikely to be physiologically or anatomically feasible and therefore small changes may be of significance. Mean absolute FVC values also increased from pre and post

intervention in the virtual rehabilitation group. The preoperative and pre intervention mean FVC (3.090 litres ±1.062) in comparison to a post intervention mean (3.094 litres ±1.056). This represents a mean difference of 0.004 litres in the virtual rehabilitation group. The difference in pre and post intervention values was not statistically significantly different (t=0.092, p=0.927, 95% CI -0.083 + 0.091). Therefore, pre and post intervention FVC were not statistically significantly different with virtual rehabilitation intervention. A comparison of pre and post intervention mean FVC values for face-to-face rehabilitation and virtual rehabilitation samples is referenced in table 8.1.2.a and illustrated in figure 8.1.2.a.

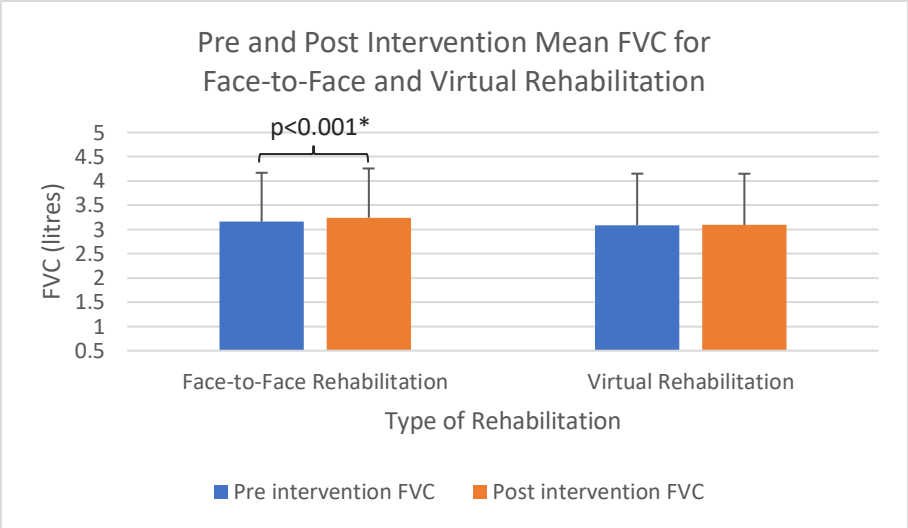

Figure 8.1.2.a. Pre and Post Intervention Mean FVC with Face-to-Face Rehabilitation and Virtual Rehabilitation

Percentage predicted FVC is a useful clinical measure and considers the absolute value in the context of predicted values based on age, gender, height and ethnicity. The mean percentage predicted FVC values increased from pre intervention to post

intervention in the face-to-face rehabilitation sample. The preoperative and pre intervention mean percentage predicted FVC (97.72% ±22.07) increased to a post intervention percentage predicted FVC (99.45% ±22.68). The mean difference from pre to post intervention was 1.73% in the face-to-face rehabilitation group. There was no statistically significant difference between pre and post intervention percentage predicted FVC (t=1.959, p=0.052, 95% CI -0.016 + 3.481) and therefore it cannot be inferred that there is a significant difference in percentage predicted FVC with face-to-face rehabilitation. It is worth noting that the p value of 0.052 is very close to significance at $p<0.05$ however the null hypothesis cannot be rejected. The mean percentage predicted FVC values also increased from pre to post intervention in the virtual rehabilitation group. The mean percentage predicted FVC (98.00% ±17.59) increased to a mean post intervention percentage predicted FVC (100.74% ±19.51). This represents a mean difference between pre and post intervention of 2.74%. The difference between pre and post intervention percentage predicted FVC was statistically significantly different (t=2.383, p=0.021 95% CI 0.331-3.858) inferring an increased percentage predicted FVC post intervention with virtual rehabilitation. The clinical significance of the degree of increase in percentage predicted FVC cannot be established and standard deviations in both pre and post intervention samples are large although comparable to each other. A comparison of pre and post intervention mean percentage predicted FVC values for face-to-face rehabilitation and virtual rehabilitation are included in table 8.1.2.a and shown graphically in figure 8.1.2.b.

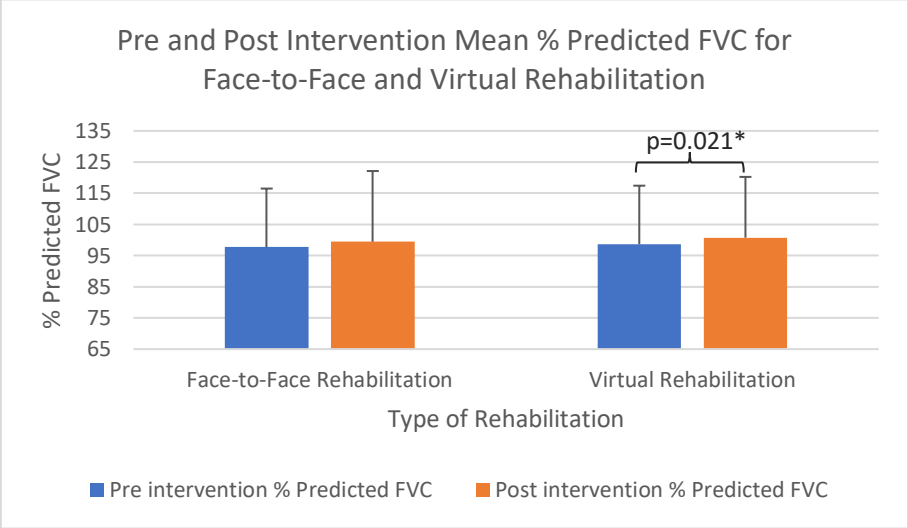

Figure 8.1.2.b. Pre and Post Intervention Mean % Predicted FVC with Face-to-Face Rehabilitation and Virtual Rehabilitation

It is conflicting that absolute FVC values achieved statistical significance with face-to-face rehabilitation but percentage predictive values for FVC did not achieve significance. Whilst absolute FVC values did not achieve statistical significance with virtual rehabilitation but percentage predicted FVC values did. Whether differences in absolute values or percentage predicted have greater clinical significance is not known, it appears that both interventions increase some element of FVC. Both pre and post intervention mean values for percentage predicted FVC were greater than the 80% threshold that would be indicative of a restrictive respiratory defect. Since poor FVC is a recognised independent risk factor for developing postoperative pulmonary complications these high pre and post intervention mean FVC values in both intervention samples may explain the overall low mean severity in postoperative complications in all groups.

Table 8.1.2.a. Statistics for Pre and Post Intervention FEV1 and FVC Measures

Variable	Type of Intervention	Pre Intervention Mean (SD)	Post Intervention Mean (SD)	Mean Difference	Significance
FEV1	*Face-to-Face Rehabilitation*	2.002 (0.837)	2.066 (0.815)	0.064	t= 3.904 p<0.001*
	Virtual Rehabilitation	2.114 (0.802)	2.139 (0.801)	0.025	t= 1.891 p=0.064 (NS)
% Predicted FEV1	*Face-to-Face Rehabilitation*	77.00(22.54)	79.79 (21.34)	2.79	t= 4.634 p<0.001*
	Virtual Rehabilitation	86.26 (22.00)	87.51 (22.56)	1.25	t= 1.614 p=0.112 (NS)
FVC	*Face-to-Face Rehabilitation*	3.159 (1.010)	3.242 (1.016)	0.083	t= 4.303 p<0.001*
	Virtual Rehabilitation	3.090 (1.062)	3.084 (1.056)	0.004	t= 0.092 p=0.927 (NS)
% Predicted FVC	*Face-to-Face Rehabilitation*	97.72 (18.79)	99.45 (22.68)	1.73	t= 1.959 p=0.052 (NS)
	Virtual Rehabilitation	98.00 (17.59)	11.74 (19.51)	2.74	t= 2.383 p=0.021*
NS - Non significance * Significance					

8.1.3. Comparison of Pre and Post Intervention piMAX

PiMAX (mean ±SD) is a measure of the negative pressure generated by an individual on maximum inspiration. The mean piMAX increased from pre intervention to post intervention in the face-to-face rehabilitation group, with a mean preoperative and pre intervention piMAX (81.505cmH_20 ±17.677) in comparison to a mean post intervention piMAX (82.649cmH_20 ±17.632). This represents a mean difference from pre to post intervention of 1.144cmH_20. The difference in pre and post intervention piMAX was considered of statistical significance in the face-to-face rehabilitation group (t=3.858, p<0.001 95% CI 0.558-1.730). The mean piMAX also increased from pre intervention to post intervention in the virtual rehabilitation group, with a preoperative pre intervention mean piMAX (80.276cmH_20 ±17.917) in comparison to a post intervention mean piMAX (81.588cmH_20 ±17.931). The mean difference in pre and post intervention in the virtual rehabilitation group was an increase of 1.312cmH_20 which is slightly larger than the mean difference with

face-to-face rehabilitation. The difference in pre and post intervention values for the virtual rehabilitation sample was also statistically significant (t=3.343, p=0.001 95% CI 0.535-2.089). This provides statistical inference that pre and post intervention values are statistically different with both face-to-face rehabilitation and virtual rehabilitation and these statistics are referenced in table 8.1.3.a. This represents a statistically significant increase in piMAX with either intervention and this comparison is shown in figure 8.1.3.a. A comparison of the mean difference in improvement between interventions further inferred that virtual rehabilitation demonstrated a significant improvement in piMAX in comparison to face-to-face rehabilitation (t=14.619, p=0.043, 95% CI 0.161-2.295). Clinical significance of the mean differences in piMAX cannot be inferred and threshold piMAX levels that may predispose or protect against postoperative pulmonary complications in lung resection have not been established within existing research or clinical guidance. Theoretically an increase in piMAX would indicate an increase in inspiratory muscle strength that could be advantageous to overcome the increased respiratory effort required from additional respiratory loading and altered ribcage biomechanics in the immediate acute postoperative period with lung resection. The similarity in baseline piMAX and increases post intervention with either face-to-face rehabilitation or virtual rehabilitation is of clinical interest when considered in context of timescales from referral to operation, where mean timescales were significantly longer in the face-to-face rehabilitation sample than virtual rehabilitation.

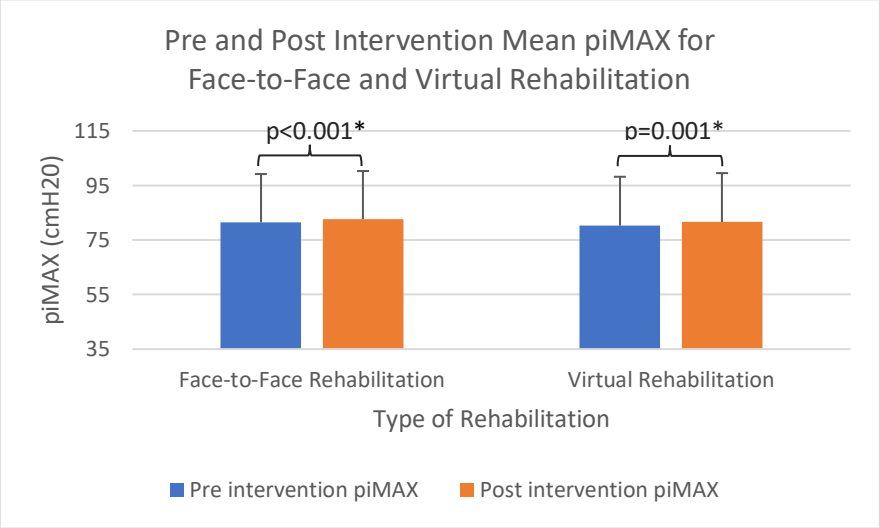

Figure 8.1.3.a.Pre and Post Intervention Mean piMAX with Face-to-Face Rehabilitation and Virtual Rehabilitation

Table 8.1.3.a. Statistics for Pre and Post Intervention piMAX Measures

Variable	Type of Intervention	Pre Intervention Mean (SD)	Post Intervention Mean (SD)	Mean Difference	Significance
piMAX cmH20	*Face-to-Face Rehabilitation*	81.505 (17.677)	82.649 (17.632)	1.144	t= 3.858 p<0.001*
	Virtual Rehabilitation	80.276 (17.917)	81.588 (17.913)	1.312	t= 3.343 p=0.001*
NS - Non significance * Significance					

8.2. The Effect of Two Modes of Rehabilitation on HRQOL

HRQOL EORTC-Q1Q-C30 scores were transformed as a percentage using a statistical package embedded into the Cardiac Rehabilitation departmental database. Pre and post intervention EORTC-QLQ-C30 questionnaires were completed by 52.8% of the face-to-face rehabilitation group (n=75) and 45.6% of the virtual rehabilitation group (n=62). Patient reported reasons for non-completion of questionnaires were not ascertained or recorded by rehabilitation staff.

There was a large range of EORTC HRQOL scores in both intervention groups. The face-to-face rehabilitation group had pre intervention scores ranging from 48 to 93 and post intervention scores ranging from 48 to 95 suggesting a wide spectrum in perceived quality of life within the sample. In the face-to-face rehabilitation group the EORTC HRQOL scores (mean ±SD) increased from pre intervention (70.75% ±9.680) to post intervention (72.08% ±9.803). The mean difference in pre and post intervention HRQOL EORTC scores was 1.33%. The difference in HRQOL scores with face-to-face rehabilitation was statistically significant (t=2.991, p=0.004, 95% CI 0.445-2.221).

The virtual rehabilitation sample also had a large range of EORTC HRQOL scores ranging from 56 to 91 at preintervention and 56 to 90 at post intervention. This suggested a slightly higher HRQOL baseline than the face-to-face rehabilitation group and this was evident with higher mean preoperative pre intervention scores for virtual rehabilitation (72.89% ±7.733) that also increased post intervention (73.50 ±7.388). The mean difference in pre and post intervention EORTC HRQOL scores was 0.61%. There was no statistical significance between pre and post intervention HRQOL scores (t=1.070, p=0.289, 95% CI -0.532 + 1.758) with virtual rehabilitation. Comparison in pre and post intervention mean HRQOL scores for both face-to-face and virtual rehabilitation is illustrated in figure 8.2.a and statistics referenced in table 8.2.a.

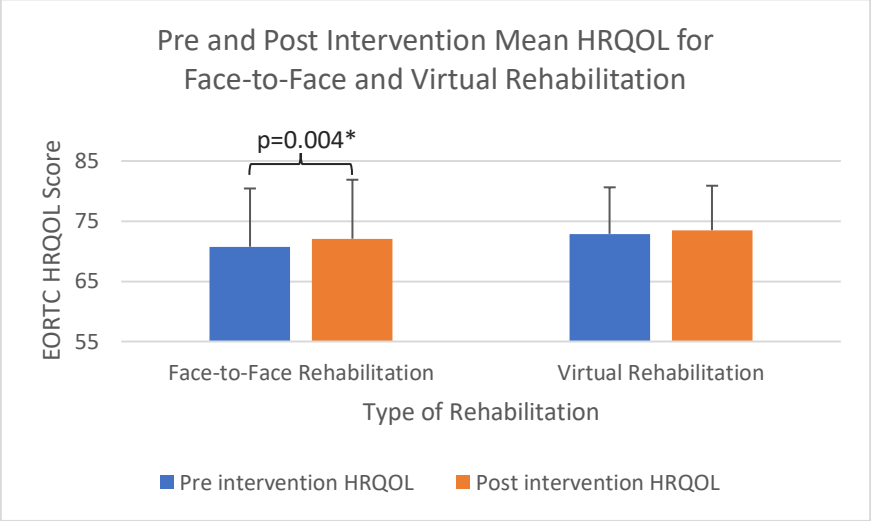

Figure 8.2.a. Pre and Post Intervention Mean HRQOL with Face-to-Face Rehabilitation and Virtual Rehabilitation

Table 8.2.a. Statistics for Pre and Post Intervention HRQOL Percentage Scores

Variable	Type of Intervention	Pre Intervention Mean (SD)	Post Intervention Mean (SD)	Mean Difference	Significance
HRQOL EORTC	*Face-to-Face Rehabilitation*	70.75 (9.68)	72.08 (9.80)	1.33	t= 2.991 p<0.004*
	Virtual Rehabilitation	72.89 (7.73)	73.50 (7.39)	0.61	t= 1.070 p=0.289 (NS)
NS - Non significance * Significance					

The EORTC-QLQ-C30 is a comprehensive questionnaire including a range of symptoms that would not necessarily be influenced by a short-term exercise-based rehabilitation strategy and this is reflected in the small mean differences between pre and post intervention groups for both face-to-face and virtual rehabilitation groups. Despite the statistically significant increase from pre to post intervention EORTC HRQOL scores in the face-to-face rehabilitation sample the mean difference was a minimal 1.33% and it is unclear whether this rise would result in a meaningful or significant change in HRQOL for the patient. The cumulative scores used in this analysis and reported within the Cardiac Rehabilitation database prevented further

statistical analysis to review individual aspects of the EORTC-QLQ-C30 that may have revealed whether increases from pre to post intervention scoring were centred on a particular aspect or dispersed across different sections of the scoring system.

Chapter 9. Results: Objective 4

9.1. Feasibility of Preoperative Service Delivery with Two Modes of Rehabilitation

Practicalities associated with service provision and delivery, including waiting times and targets were an important pragmatic aspect of this study, given the narrow timeframe available to optimise patient status prior to surgery. Safe and effective exercise prescription is also underpinned by the appropriate application of frequency, intensity, duration and mode of exercise delivery alongside a recognition of anticipated or accepted side effects (Ligouri, 2021). HIIT is a relatively new concept in preoperative lung cancer and therefore exploration of significant adverse events and patient reported side effects and clinician reported events was an important aspect of the analysis. Patients would only perform exercise at higher intensities if they felt able and a clinician deemed it safe and appropriate to prescribe.

9.1.1. Three-way Comparison of Waiting Times from Referral to Surgery between the Three Groups

The waiting times for surgery between the three groups were statistically significantly different ($f=7.848$, $p<0.001$). The length of time from referral to receiving surgical treatment (mean ±SD) for face-to-face rehabilitation (23.48 days ±11.39) was significantly longer than standard care (18.45 days ±19.92) ($p<0.001$, 95% CI 2.07-7.98) and statistically significantly longer than virtual rehabilitation (19.92 days ±12.12) ($p=0.033$, 95% CI 0.23-6.89). Mean values between standard

care and virtual rehabilitation did not differ significantly from each other (p=0.508, 95% CI -1.64-4.58). The mean values of referral to treatment times for the three groups are referenced in table 9.1.1.a and represented graphically in figure 9.1.1.a. This suggests that patients waited longer for curative surgical intervention when referred into face-to-face rehabilitation than if referred into the equivalent virtual rehabilitation programme with a mean difference of 3.56 days or if receiving standard care a mean difference of 5.03 days. An average extended 4 to 5 days wait for surgery is likely to be of clinical importance since surgical resection should take place within 28 days of diagnosis (NICE, 2019). The average waiting times for standard care and both intervention groups fell within the 28-day guidance. It is unclear within the literature whether those patients having surgery closer to the limit of the 28 days have significantly worse outcomes than those who underwent surgery at the lower end of that time frame. Although there was no statistical correlation with waiting times and length of stay in this study (r=-0.011, p=0.820).

There was large variation in the waiting times with an extensive spread between minimum and maximum values for all three groups with standard care ranging between 3-69 days, face-to-face rehabilitation 4-71 days and virtual rehabilitation 2-79 days. The 28-day target for surgery was exceeded by 17% of patients who received standard care, 18% of patients who received virtual rehabilitation and 31% of patients who received face-to-face rehabilitation. Close to a third of patients exceeding recommended timeframes in the face-to-face rehabilitation group is of clinical note but the data in this study cannot indicate a causative relationship between intervention and extended wait for surgery.

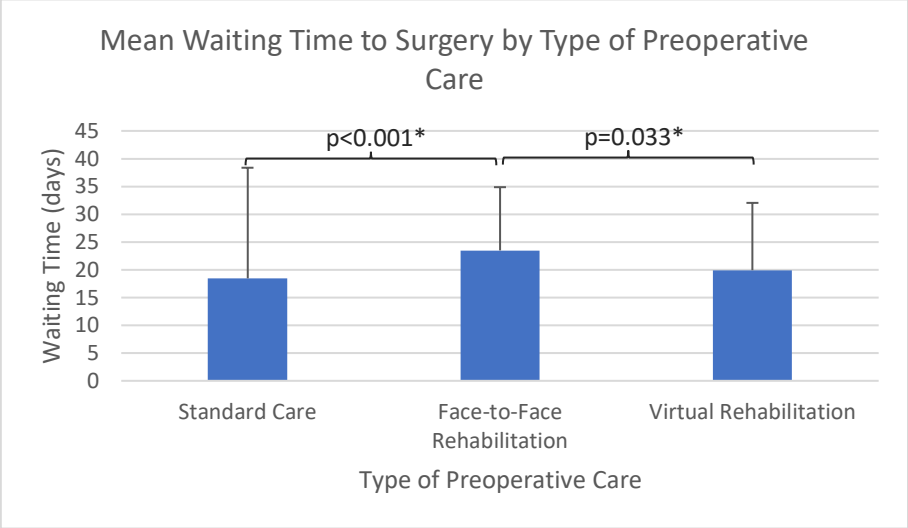

Figure 9.1.1.a. Mean Waiting Time to Surgery by Preoperative Type of Care

Table 9.1.1.a. Statistics for Referral to Surgery Times in the Three Groups

Variable		Standard Care	Face-to-Face Rehabilitation	Virtual Rehabilitation	Significance ANOVA	Post hoc Comparison Games-Howell
Referral to Treatment Time	*Mean (SD)*	18.45 (19.92)	23.48 (11.39)	19.92 (12.12)	*f= 7.848 p<0.001**	*SC & F2F p=0.001** *SC & VR p=0.508 (NS)* *F2F & VR p=0.003**
	min-max	3-69	4-71	2-79		
Totals	*n*	166	142	136		
NS - Non significance * Significance						

There are many factors that may delay surgery, including theatre space, hospital bed availability, patient preference and a host of other unforeseeable circumstances and therefore longer timescales from listing for surgery and receiving an operation may not directly relate to any intervention should this be identified. It was still considered an important analysis to include for consideration in service delivery as whilst direct inference may not be drawn from any statistical significance given the complexity of this variable, any suggestion of a delay to surgery may be of great clinical significance within this patient population.

9.1.2. Adverse Events and Side Effects with HIIT Exercise

No patients receiving face-to-face rehabilitation or virtual rehabilitation experienced any serious adverse events for the duration of their programme. Specifically, no patients who reached the set HIIT parameter 80% HRR or RPE 15-18 experienced any serious adverse events within their exercise session. 7 patients who received face-to-face rehabilitation reported experiencing 'light-headedness' and 1 patient experienced chest pain that was assessed to be of benign musculoskeletal origin. In all cases these symptoms were reported as mild, and they were of short duration that resolved on cessation of the specific exercise. None of the cases required medical escalation beyond the assessment and reassurance of the physiotherapist or exercise physiologist. These patients continued their exercise session with a modification or alternative exercise and were able to travel home on completion of the session. None of the patients who had reported side effects cancelled their exercise sessions and all subsequently completed the programme. No patients reported experiencing any symptoms during the delivery of the virtual rehabilitation exercise sessions. The monitoring of exercise intensity and the patient response to exercise was fundamentally different for virtual delivery in comparison to face-to-face sessions delivered in person and this may account for the difference in reporting and documentation of events. The virtual platform was new for both staff and patients and therefore technical issues and unfamiliarity with the systems could also have been a contributing factor in communication.

9.1.3. Patient Uptake and Adherence Between Two Modes of Rehabilitation

100% of patients accepted referral and attended the initial clinic appointment with both modes of rehabilitation delivery. The majority of patients received their initial clinic assessment within 3 days of referral, face-to-face rehabilitation (97%) and virtual rehabilitation (100%), by utilising an opportunistic approach to short notice 'unable to attend' appointments and the adoption of ad-hoc remote clinics within the programme.

All patients attended at least 1 exercise session in the face-to-face rehabilitation programme. 1 patient in the virtual rehabilitation programme did not attend any sessions due to acceptance of an earlier operation date. The physiotherapist advised patients at the initial clinic to attend the exercise sessions twice weekly, as recommended in current guidance for Cardiac Rehabilitation programme delivery (BACPR, 2017). In the face-to-face rehabilitation programme 66.9% of patients attended twice weekly sessions and 33.1% attended once weekly sessions. In the virtual rehabilitation programme 64.7% attended twice weekly sessions, 28.7% attended once weekly and 5.9% of patients attended three times a week due to the flexibility offered with remote delivery.

The number of sessions attended by patients (mean ±SD) were also consistent across the two intervention groups, face-to-face rehabilitation (4.06 days ±2.48) and virtual rehabilitation (4.02 days ±2.67). The maximum number of sessions attended by a patient in the face-to-face rehabilitation group was 14 in comparison to 12 sessions in the virtual rehabilitation programme. Patients attended sessions

until their operation date and therefore differences are likely due to the longer waiting times from diagnosis to surgery identified in section 9.1.1.

The service was implemented with the intention to deliver a minimum of twice weekly sessions for two weeks therefore attendance of at least 4 exercise sessions was considered an acceptable number of exercise sessions achieved. The 28-day window identified in NICE guidance would enable 8 sessions to be delivered over 4 weeks. The proportion of patients who achieved more than or equal to 2, 4, 6, 8, 10, 12 and 14 sessions are reported for face-to-face rehabilitation and virtual rehabilitation in table 9.1.3.a and illustrated graphically in figure 9.1.3.a. The majority of patients did receive at least two sessions with either face-to-face rehabilitation and virtual rehabilitation at 88.7% and 79.4% respectively. 50.7% of patients in face-to-face rehabilitation completed at least 4 exercise sessions prior to their operation, whilst a slightly higher percentage achieved this in the virtual rehabilitation group at 54.4%. Almost half of the patients referred into the programme did not receive the intended minimally acceptable number of sessions with either form of intervention. Only 9.2% of patients in the face-to-face rehabilitation group and 10.3% in the virtual rehabilitation group completed at least 8 sessions prior to their operation. These proportions in both intervention groups are likely to have limited the physiological benefits that could realistically occur within these timeframes. This is unlikely due to inefficiencies in rehabilitation processes, due to short turnaround times from referral to delivery, and this does raise concerns for the feasibility of exercise-focussed preoperative programmes in lung cancer.

Table 9.1.3.a. Number of Sessions Attended by Proportion of Rehabilitation Samples

Number of Sessions Attended	Total Number of Patients (% of sample)	
	Face-to-Face Rehabilitation	*Virtual Rehabilitation*
<2	142 (100)	136 (100)
≥2	126 (88.7)	108 (79.4)
≥4	72 (50.7)	74 (54.4)
≥6	37 (26.1)	34 (25.0)
≥8	13 (9.2)	14 (10.3)
≥10	3 (2.1)	6 (4.4)
≥12	2 (1.4)	4 (2.9)
≥14	1 (0.7)	0 (0)

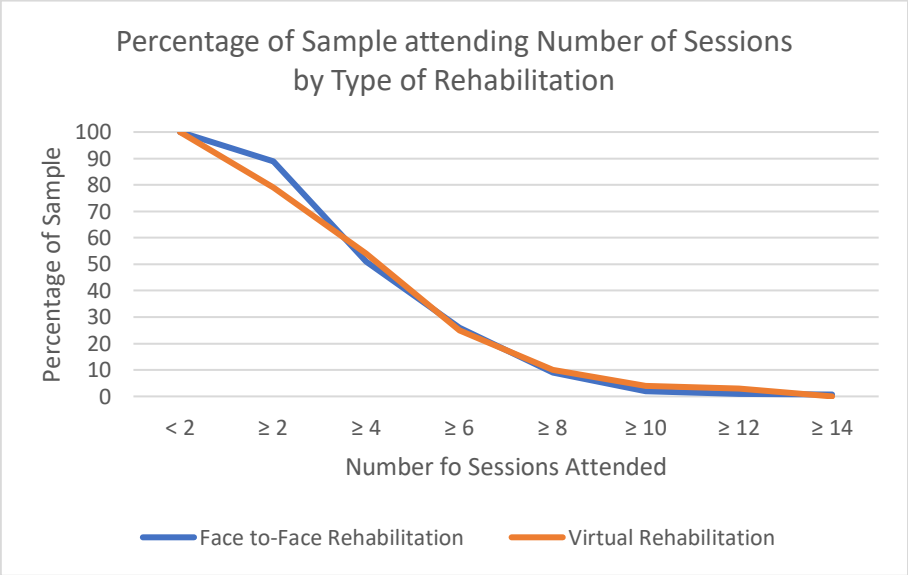

Figure 9.1.3.a. Number of Sessions Attended by Type of Rehabilitation shown as a Proportion of the Samples

9.1.4. Programme Completion with Two Modes of Rehabilitation

National Audit data consistently report completion rates at 50% for Cardiac and Pulmonary Rehabilitation programmes in the United Kingdom (NACAP, 2020; NACR 2020). The proportion of patients with lung cancer completing preoperative rehabilitation within the Cardiac Rehabilitation programme was well above this percentage, irrespective of whether it was delivered face-to-face or virtually. 73.2%

of patients completed the face-to-face rehabilitation programme (n=104) and 76.5% of patients completed the virtual rehabilitation programme (n=104).

Patient-reported reasons for cancellation were similar for both intervention groups and shown in figure 9.1.4.a. The most frequent reason cited for cancellation was the availability of an earlier operation date and this accounted for 73.7% of cancellations in face-to-face rehabilitation and 93.8% in virtual rehabilitation. New acute illness of cold, flu or gastro-intestinal symptoms accounted for 10.5% of face-to-face rehabilitation and 3.1% of virtual rehabilitation cancellations. Less frequent reasons for cancellation were delayed referral into the programme and prior travel and holiday arrangements. Travel and holiday commitments were not cited in the virtual rehabilitation group, likely due to the UK Government travel restrictions in place during the SARS-CoV-2 pandemic.

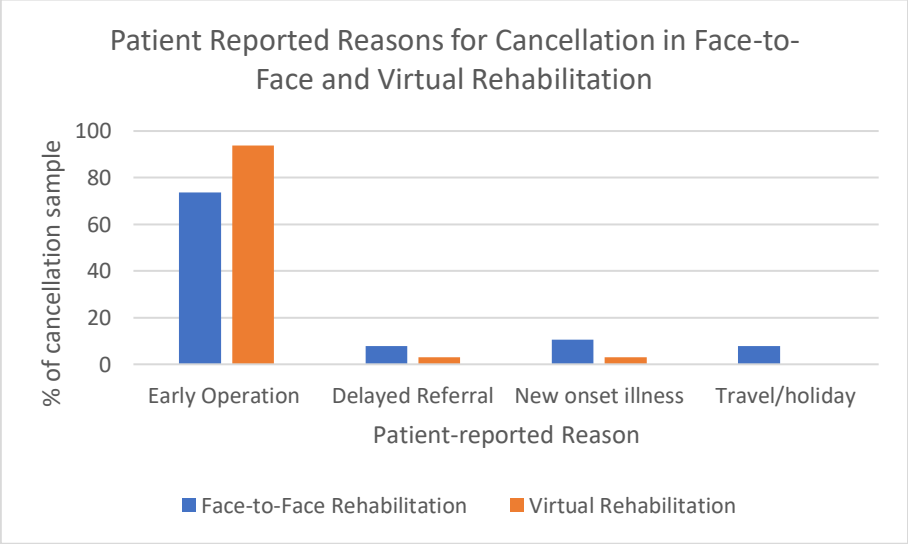

Figure 9.1.4.a. Patient Reported Reasons for Programme Cancellation for Face-to-Face Rehabilitation and Virtual Rehabilitation

9.1.5. Patient Attainment of HIIT with Two Modes of Rehabilitation

HIIT attainment was achieved by a similar proportion of patients in both face-to-face and virtual rehabilitation at 57.0% and 56.6% respectively. This corresponds to almost half of patients unable to achieve target parameters with face-to-face rehabilitation (43.0%) and virtual rehabilitation (43.4%). Interestingly, there was a higher proportion of cancellations within the group who did not achieve HIIT parameters within both intervention groups. In the group where HIIT had not been achieved 42% of patients cancelled in face-to-face rehabilitation and 33.9% in virtual rehabilitation. This is in comparison to 15% and 15.6% of patients cancelling in the groups where HIIT had been attained within face-to-face and virtual rehabilitation programmes respectively.

Total number of sessions completed (mean ±SD) by patients who achieved HIIT in face-to-face rehabilitation (4.5 ±2.46) and virtual rehabilitation (4.4 ±2.70) were also comparable. There was further consistency where HIIT had not been achieved in face-to-face rehabilitation (3.5 ±2.26) and virtual rehabilitation (3.5 ±2.6). This is an interesting observation given the similarity in proportions of patients able to achieve HIIT and the respective cancellation rates for both modes of delivery.

Patient-reported reasons for cancellation did not include non-attainment or difficulty with HIIT. Since the largest proportion of cancellations occurred due to early operation date availability the lack of attainment of HIIT may have been the result of reduced opportunity for exercise progression with fewer sessions and less patient familiarity with the programme. Cancellations were reported directly to

Rehabilitation staff and this may have impacted reasons given, whereby operation date, travel, or acute illness may have been perceived as acceptable responses as opposed to programme delivery and exercise prescription. Baseline characteristics of patients who were able to achieve HIIT and the feasibility of preoperative face-to-face rehabilitation with data from this study has been published within the Journal of Cancer Rehabilitation (Appendix 15).

Chapter 10. Discussion

10.1. Objective 1 Postoperative Recovery with Preoperative Rehabilitation

10.1.1. Preoperative Rehabilitation Influence on Hospital Length of Stay

Preoperative therapy of HIIT and IMT delivered either face-to-face or virtually did not influence postoperative hospital length of stay in comparison to standard care in this study. Preoperative face-to-face rehabilitation had the longest hospital length of stay at 9.75 days in comparison to virtual rehabilitation and standard care at 8.13 and 8.27 days, respectively. Hospital length of stay has been the primary outcome in a large number of trials and systematic reviews investigating preoperative rehabilitation in patients with operable lung cancer. This is perhaps unsurprising since the duration of hospital stay would be of importance to both patients, caregivers, healthcare personnel directly responsible for patient care and hospital management responsible for activity at organisational level. Non significance in hospital stay in this study is conflicting with the current literature on preoperative rehabilitation strategies that consistently identify significant reductions in overall hospital length of stay with exercise-based preoperative rehabilitation strategies with or without breathing exercises and respiratory muscle training. A large systematic review with meta-analysis by Sebio-Garcia et al. (2016) found the greatest improvement in hospital length of stay, with a shorter hospital stay by 4.83 days (95% CI, 3.76 – 5.9 days) with preoperative rehabilitation including any combination of endurance, resistance, flexibility and breathing exercises. Whilst the findings of this review are notable, clinical inference towards the most

effective strategy is limited with the inclusion of such extensive and varied exercise prescription. Similarly, a systematic review and meta-analysis by Cavalheri and Granger (2017) also found a reduction in hospital length of stay with preoperative intervention incorporating aerobic, resistance exercise and inspiratory muscle training, with a 4.24 day shorter hospital stay (95% CI, 3.06-5.43) with preoperative intervention in comparison to standard care. These findings are also supported by a number of systematic reviews that have shown significantly lower hospital length of stay with preoperative rehabilitation for patients with lung cancer including a 3.63 days shorter stay (95% CI, 2.29-4.96) with preoperative rehabilitation at low to moderate intensity exercise and breathing exercises including inspiratory muscle training (Vacchi et al., 2022) and a more modest but also significant reduction of 2.86 days with preoperative rehabilitation including low to high intensity exercise (Steffens et al., 2018). These reviews vary significantly in the preoperative rehabilitation strategy employed, with great disparity in exercise prescription of included studies, limiting the determination of the most effective strategy to utilise in clinical practice. Despite the reviews largely including randomised controlled trials within meta-analysis, the individual study quality has widely been graded poor based on methodological design. Studies included within the existing reviews also reflect a wide range of thoracic surgical procedures within the permitted inclusion criteria, inclusive of video-assisted keyhole surgery that would carry significant less risk and shorter hospital stays than open thoracotomy procedures. This study limited preoperative rehabilitation to preoperative high intensity exercise prescription and limited inclusion criteria to patients undergoing open thoracotomy

procedures for lung resection and considered high-risk for surgical complications based on their preoperative status at clinical assessment. A systematic review and meta-analysis by Li et al. (2019) identified that significant improvements in hospital length of stay with preoperative rehabilitation of 4.23 days (95% CI 2.32-6.14) were applicable to patients who did not present with COPD, whilst improvements were no longer significant for those patients within the sample with a confirmed diagnosis and history of COPD. COPD would potentially highlight a patient at higher risk of complications postoperatively and, depending upon disease severity, formed part of the inclusion criteria and may help to explain the lack of statistical significance for overall duration of hospital stay in this study. Hospital stay was also the recorded date a patient was deemed medically fit for discharge and it is unclear whether existing literature reviews used this approach or calculated the absolute duration of admission. Discharge from hospital can be affected and delayed by a range of social and personal circumstances that can result in unnecessary longer hospital stays. Clinically patients at higher surgical risk due to the complexity of preoperative health status may also be those with complex discharge needs that may result in a delayed discharge. This study aimed to control for this aspect and may also explain the non-significant difference in hospital stay with preoperative rehabilitation in comparison to standard care and the contradictory findings with some of the current evidence. According to National audit data for surgical outcomes in lung cancer, the median hospital length of stay with surgical lung resection is currently 6 days (RCP, 2019). All three groups analysed within this study had mean hospital length of stays greater than 8 days and this may also indicate

differences in patient complexity and postoperative management in the locality compared to the National picture. The NHS Trust used in this study serves a geographical area with high levels of deprivation that can directly relate to poorer health status, which may also contribute to longer hospital stays associated with surgical lung resection.

10.1.2. Preoperative Rehabilitation Influence on High Dependency Care

This study also included the length of time patients spent within high dependency level care during the hospital stay. High dependency level care is both labour and resource intensive and early bed availability in these areas also directly impacts on timely patient throughput and waiting times for surgery. Therefore, a positive influence on duration of high dependency care was included as a primary outcome, despite receiving less attention within current existing literature. This study indicated that preoperative face-to-face rehabilitation and virtual rehabilitation did not influence duration of high dependency care postoperatively in comparison to standard care alone. All three groups were very similar in the duration of high dependency level care with standard care at a mean length of stay of 2.1 days. Whilst face-to-face and virtual rehabilitation had mean length of stays at 2.3 days and 2.6 days. This similarity may indicate that movement from high dependency level areas post-surgery is predominantly protocol driven and may also reflect ward bed availability for safe stepdown alongside a stable patient clinical status. A randomised clinical trial by Licker et al. (2016) investigated short term preoperative HIIT in patients awaiting lung surgery and found a significant reduction in the time

spent in a post-anaesthesia care unit with rehabilitation at a median of 17 hours in comparison to a median 25 hours stay with standard care. The trial was conducted in Switzerland, and it is unclear whether post-anaesthesia care would equate to high dependency level care in the United Kingdom, although it does indicate some positive influence on early postoperative management. The mean duration for all three groups in this study were substantially greater than the median time scales highlighted in the trial by Licker at al. (2016) and this is likely due to the smaller trial sample sizes with 74 patients receiving intervention, the shorter prospective trial period and the inclusion of patients of lower surgical risk including video-assisted thoracic procedures. Rigorous study methodology would need to be considered in future studies to determine the effectiveness of preoperative interventions on postoperative high dependency care given the numerous confounding variables that may influence bed flow through hospital levels of care. The SARS-CoV-2 pandemic is likely to have introduced significant bias within this study, particularly relating to the virtual rehabilitation group whereby hospitals within the United Kingdom were under extreme pressures for critical care level bed availability and hospital procedures and protocols underwent rapid changes in an acute response to this unprecedented need and therefore results need to be viewed with caution.

10.1.3. Preoperative Rehabilitation Influence on Postoperative Complications

Systematic reviews evaluating preoperative rehabilitation strategies in patients awaiting surgical lung resection have predominantly focussed upon moderate intensity aerobic exercise used in combination with IMT or chest physiotherapy.

Specific exercise prescription regarding mode, frequency and delivery are often poorly defined within the selected studies and there is significant heterogeneity present in study populations and methodological approaches across the reviews (Sebio-Garcia et al., 2016; Pouwels et al., 2015; Steffens et al., 2018; Cavalheri and Granger, 2017; Sanchez-Lorente et al., 2018; Rosero et al., 2019; Li et al., 2019; Mans et al., 2015). Despite the limitations and disparity in approaches, the current evidence-base from systematic reviews with meta-analysis, has been largely supportive of preoperative exercise-based rehabilitation strategies in patients with lung cancer to reduce the risk of developing postoperative complications. Systematic reviews have repeatedly indicated that a combination of preoperative aerobic exercise and IMT may halve the risk of developing postoperative pulmonary complications, with some of the most promising result emerging from work by Cavalheri and Granger (2017) who identified a significant risk reduction (RR 0.33, 017-0.61). Similar positive results have also been established in the reviews by Mans et al. (2015) (RR 0.48, 0.26-0.89), Sebio-Garcia et al. (2016) (RR 0.45, 0.28-0.74), Steffens et al. (2018) (0.52, 0.36-0.74), Rosero et al. (2019) (RR 0.50, 0.39-0.69) and Li et al. (2019) (OR 0.44, 0.27-0.61). The consistency of these findings is particularly encouraging to support preoperative rehabilitation strategies in this patient population. It was therefore disappointing that this study did not establish convincing findings related to reduced incidence of postoperative pulmonary complications with preoperative intervention. There was no significant difference with preoperative rehabilitation delivered face-to-face or virtually in comparison to standard care for antimicrobial therapy prescription, high-flow oxygen delivery

through non-invasive or invasive devices or tracheostomy requirement post-operatively. There was however, significantly lower radiological incidence of postoperative pulmonary complications, as reported on postoperative chest x-rays with preoperative virtual rehabilitation in comparison to face-to-face rehabilitation or standard care and significantly lower positive sputum cultures reported with virtual rehabilitation in comparison to standard care. Positive radiological reporting of infiltrates or opacification suggestive of pneumonic changes or atelectasis were considered in this study. Analysis of specific investigations and treatments associated with postoperative pulmonary complications was considered a more comprehensive analysis for the purposes of this study, to help determine where preoperative strategies may demonstrate effectiveness. Similarly, a recent systematic review by Vacchi et al. (2022) found less convincing findings with preoperative IMT prior to surgical lung resection with a comprehensive breakdown of postoperative management and found no significant difference in the development of pneumonia (RR 0.56, 0.29-1.10), atelectasis (RR 0.81, 0.24-2.69) and need for mechanical ventilation beyond 48 hours (RR 0.43, 0.12-1.58). Preoperative intervention specifically incorporating HIIT for patients awaiting lung resection has also indicated a positive influence on postoperative pulmonary complications, a randomised controlled trial by Licker et al. (2006) found a significant risk reduction with this intervention for developing postoperative pulmonary complications (RR 0.54, 0.33-0.88). The intervention had no significant impact upon broader postoperative complications relating to cardiac or general surgical complications (RR 0.72, 0.55-1.05). Large systematic reviews focussing

upon specific frequency, mode and intensity of exercise prescription are currently lacking in the literature regarding preoperative rehabilitation strategies in lung cancer and whilst a range of exercise-based approaches appear favourable to influence some aspect of postoperative pulmonary complications, reviews that utilise large randomised controlled trials with specific and clearly defined exercise prescription would facilitate the comparative effectiveness across preoperative exercise-based strategies.

This study inferred that preoperative HIIT combined with IMT, delivered virtually, may reduce the severity of postoperative complications measured by the Clavien-Dindo classification. Virtual rehabilitation had a significantly higher proportion of patients with a lower severity classification than standard care alone. Work by Mak et al. (2016) on behalf of the international Consortium for Health Outcomes Measurement has defined a standard data set for research undertaken in patients with a diagnosis for lung cancer. The standard set for lung cancer outlines complications associated with treatment are likely to contribute significantly to patient treatment preference and, where surgical intervention is an option, any associated complications should be measured by the validated Clavien-Dindo classification tool. The trial by Licker et al. (2016) classified complications using a modification of the Thoracic Morbidity and Mortality classification (Seely et al., 2010) and reported complications assessed as grade 2 or higher and found no significance between patients with lung cancer receiving preoperative HIIT intervention in comparison to standard care. In the trial by Licker et al. (2016) at least one postoperative complication at grade 2 or higher occurred in 35.5% of the

intervention group and 50.6% of the standard care group, whilst this did not reach statistical significance in severity the overall incidence of complications was observed to be higher with standard care. Classification of postoperative complications and full reporting of all severity grades is currently under-researched and largely unreported within the existing literature. Standardisation of reporting postoperative complications within the literature will provide clarity for the comparison of effectiveness of interventions and facilitate the pooling of trial data in meta-analysis and this approach to reporting of complications should be a priority for future research in this field.

The reduction in the clinical severity of postoperative complications with virtual rehabilitation, is undoubtedly a welcome finding within this study. However, it must be viewed cautiously and in relation to the possible effect of changes in postoperative practice undertaken during the SARS-CoV-2 pandemic. Hospital protocols and resource provision underwent significant reform during this period and may have resulted in substantial changes to aftercare post-surgery specifically affecting the virtual rehabilitation group, that may have been a contributing factor to changes in classification grading. Virtual rehabilitation is a relatively new phenomenon in traditional outpatient Cardiac Rehabilitation programmes and was predominantly employed as a direct response to maintain service delivery during the SARS-CoV-2 pandemic whereby high-risk groups were shielding and remote outpatient healthcare delivery was preferred. Prior to admission for thoracic surgery, it became standard practice during the pandemic for patients to undergo testing for SARS-CoV-2 and to shield prior to admission, this would also limit

transmission and contamination risk of a wide range of pathogens associated with acute respiratory illness and shielding may also have offered additional protection in the development of postoperative pulmonary complications. The pandemic response and Government guidance to shield and undertake additional infection control procedures within the home and healthcare settings would not have applied to the pre-pandemic face-to-face rehabilitation group and standard care group and this may also have been a factor in the positive findings in lower postoperative complication severity and reduced incidence in radiological evidence of respiratory complications and positive sputum cultures found with virtual rehabilitation in this study.

10.2. Objective 2: Postoperative Survival

10.2.1. Preoperative Rehabilitation Influence on One-Year Survival

Preoperative rehabilitation combining HIIT and IMT delivered either face-to-face or virtually, did not appear to influence survival at either 6 months or 12 months following surgery in comparison to standard care alone in this study. In the standard set for lung cancer, mortality data has been highlighted as an important outcome for inclusion within any research including patients with lung cancer irrespective of the intended intervention (Mak et al., 2016). In this study short term preoperative rehabilitation of a few weeks duration and delivered on either face-to-face or virtual platforms did not appear to influence acute postoperative outcomes related to hospital length of stay and duration of high dependency care,

and so it is perhaps unsurprising that it also was shown to be ineffective at reducing longer term survival. The percentage survival at 12 months post-surgery across all three groups were broadly consistent with the survival data reported within the National Audit outcomes that currently reports 12-month survival at 88.7% with surgical intervention (RCP, 2019). Similarly, in this study survival at 12 months following surgery stood at 89% in the face-to-face rehabilitation group, 88% in the virtual rehabilitation group and 83% where standard care had been delivered. The comparable 12-month survival data to National statistics is particularly impressive, given that this study limited inclusion to those patients who underwent procedures through an open thoracotomy and were deemed high risk of complications based on complex preoperative health status that could adversely affect overall survival in both the short and long term. The National data report does not stratify for surgical risk and therefore the National reported survival will also have included patients who had undergone less invasive procedures and with a health status that would equate to substantially lower surgical risk. Whilst some studies investigating preoperative HIIT in patients awaiting surgical lung resection have included 30-day post-surgical short-term mortality (Licker et al., 2006), longer term survival statistics have rarely been considered. Where 12-month follow-up has been included in trial design outcomes have predominantly related to HRQOL and maintenance of physiological physical capacity and lung function (Sommer et al., 2018; Karenovics et al., 2017). The study by Karenovics et al. (2017) did include survival data at one-year and 93% of patients who had received preoperative HIIT rehabilitation were alive at 12 months in comparison to 91% who had received

standard care. Despite a slightly more favourable survival proportion in the rehabilitation group, the difference was not considered significant. The study by Karenovics et al. (2017) demonstrated higher overall one-year survival and this is conflicting to findings in this study and likely reflects differences in the inclusion criteria which included both open procedures and lower risk video-assisted thoracic surgeries within the trial.

Data collected within this study provided a further opportunity to explore possible predictive factors associated with mortality at 12-months following lung resection in high-risk patients across the combined data set. Preoperative rehabilitation intervention was insignificant as a predictor for 12-month survival and did not differ significantly from standard care alone, suggesting that undergoing preoperative rehabilitation would not be associated with increased survival in the longer term. No studies to date investigating preoperative rehabilitation consisting of combined HIIT and IMT, delivered face-to-face or virtually, have incorporated survival analysis and therefore this provides a realistic evaluation of the potentially limited value of such strategies in longer term survival. A positive SARS-CoV-2 test in the 12-month period following surgery, the need for a tracheostomy insertion during the hospital admission and lower levels of preoperative baseline physical activity as measured by the ECOG performance status, were predictive of increased mortality at one-year. In this study, gender was not prognostic of increased mortality risk and this differs to current literature that has associated male gender with worse survival (Myrdal et al., 2001; Strand et al. 2006) These were retrospective multicentre studies, reviewing large data sets from the early 1990's. The largest of the studies

by Strand et al. (2006) included 3211 records and five-year follow-up and this, alongside changes to surgical practice in the twenty-first century may account for different findings. Additionally, Strand et al. (2006) found increased age, large tumour size and pneumonectomy resection prognostic of poor survival rates. Similarly, Roth et al. (2008) in a smaller retrospective cohort study of 148 patients also found advanced age, poor lung function, advanced cancer stage and pneumonectomy resection predictive factors of worse outcomes at 30-day and five-year follow-up. This study considered different categorical variables to those included by Roth et al. (2008) and these may have clinical relevance by their non-significance for increased mortality risk. Non-significant factors such as presence of cardiac and respiratory conditions, type of resection, ASA classification and the need for postoperative adjuvant therapy were notable in their non significance in this study, although higher risk classifications were sparsely represented in the total sample and larger samples with greater representation across all categories would be required to draw accurate clinical conclusions.

10.3. Objective 3: Effectiveness of Preoperative Rehabilitation

10.3.1. Pulmonary Function as Outcome Measures for Preoperative Rehabilitation

This study inferred that HIIT combined with IMT, performed over a short preoperative period, improved pulmonary function in patients awaiting surgical resection for lung cancer. This is comparable to evidence from large systematic reviews investigating exercise-based preoperative rehabilitation strategies, with or

without inspiratory muscle training, in lung cancer populations. A meta-analysis by Sebio-Garcia et al. (2016) concluded that pulmonary function was significantly enhanced with preoperative exercise-based intervention for patients with lung cancer, achieving a standardised mean difference in FVC of 0.38 (95% CI, 1.14-0.63) and a standardised mean difference in FEV1 of 0.27 (95% CI 0.11-0.42). The improvements in preoperative lung function identified within this evaluation are modest by comparison with face-to-face rehabilitation achieving a significant mean difference of 0.064 litres in FEV1 and 0.083 litres in FVC. Virtual rehabilitation demonstrated minimal improvements following intervention that did not reach statistical significance, with a mean difference in FEV1 of 0.025 litres and FVC 0.004 litres. Cavalheri and Granger (2017) also concluded that preoperative rehabilitation could increase pulmonary function in a meta-analysis demonstrating a mean difference in percentage predicted FVC of 2.97% (95% CI, 1.78-4.16) with exercise-based intervention. Similarly in this study, virtual rehabilitation significantly improved percentage predicted FVC with a mean difference of 2.74% whilst face-to-face rehabilitation showed a smaller and non-significant increase with a mean difference of 1.73% with intervention. Contrary to these findings and meta-analysis by Sebio-Garcia et al. (2016), Cavalheri and Granger (2017) found no statistical difference in FEV1 pulmonary function measures with preoperative intervention. Percentage predicted FEV1 increased with preoperative intervention in this study, achieving a significant mean increase of 2.79% with face-to-face rehabilitation. Virtual rehabilitation achieved more modest increases in FEV1 that were not considered statistically significant. The meta-analysis in both systematic reviews

included preoperative lung cancer patients undergoing comparable surgical interventions to this study although the reviews also included patients at significantly lower surgical risk. Similarly, to this study, Cavalheri and Granger (2017) also included IMT within the exercise-based strategy, whilst Sebio-Garcia et al. (2016) included generic and ill-defined preoperative breathing exercises within the included studies. Both these reviews also included exercise-based prescription at a wide range of intensities, including low to moderate intensity exercise, whilst this study focussed on high intensity exercise combined with IMT in patients deemed at high surgical risk for the development of pulmonary complications.

The more conservative differences in pulmonary function in this study are likely due to smaller sample sizes and higher surgical risk classification for patients in comparison to the larger meta-analysis conducted within the systematic reviews. Due to the changes in clinical practice in response to the SARS-CoV-2 pandemic the routine use of pulmonary spirometry was contraindicated to minimise potential viral transmission and contamination through high-risk aerosol-generating procedures during 2020-2021 and this greatly affected data availability and data collection for virtual rehabilitation. Pulmonary function data was only available for 53 patients within the virtual rehabilitation sample and 142 patients within the face-to-face rehabilitation in this study in comparison to the larger cumulative samples within the systematic reviews. These reviews also included randomised controlled trials and a wide range of exercise modalities within their accepted study selection. Sebio-Garcia et al. (2016) included moderate intensity aerobic exercise alongside resistance, flexibility and non-specific breathing exercises whilst

Cavalheri and Granger (2017) included low to moderate intensity exercise and IMT strategies. Preoperative rehabilitation strategies conducted virtually did not feature within the included study selection for any subsequent meta-analysis conducted within the systematic reviews and therefore this study provides useful data on the effectiveness of this mode of delivery for preoperative rehabilitation strategies to enhance preoperative lung function. Comprehensive pulmonary function has been infrequently utilised as an outcome measure within existing systematic reviews and meta-analysis in preoperative rehabilitation for lung cancer and whilst the aforementioned reviews included the dynamic spirometry FEV1 and FVC measurements, inspiratory muscle pressures such as piMAX were omitted. PiMAX is considered an important measure clinically to establish maximum inspiratory muscle pressures and indicate the strength of respiratory muscles. FEV1 and FVC are essentially expiratory manoeuvres and therefore piMAX may be a more appropriate measure to establish improvement in inspiratory muscle strength. PiMAX has been commonly employed as an effective outcome measure for individuals with neuromuscular diseases associated with respiratory muscle weakness, but it has received less attention as an outcome measure for lung cancer. However, the size and location of the carcinoma may result in a restrictive deficit, impacting lung volumes achieved on inspiration. Furthermore, this patient population can be frail and elderly with a multi-morbid frailty status. The debilitating symptoms commonly associated with the condition include weight loss, fatigue and dyspnoea on minimal exertion which may lead to physical inactivity and global muscular weakness, inclusive of respiratory musculature. PiMAX significantly

increased with either face-to-face rehabilitation or virtual rehabilitation, with a mean difference of 1.14cmH20 and 1.31cmH20 respectively in this study. This measurement is the only outcome related to pulmonary function that achieved statistically significant improvement with both modes of preoperative rehabilitation delivery, suggesting that this may be a specific and sensitive measure to use for establishing physiological pulmonary effects with preoperative rehabilitation intervention in lung cancer in comparison to FEV1 and FVC. FEV1 and FVC and their respective percentage predicted measures are likely to have been used within existing literature since core guidelines reference these values to determine operability and risk, piMAX parameters are not currently cited within the existing guidelines for lung cancer or ASA classification and this may be due to the unfamiliarity with this relatively new measure in pulmonary function. A systematic review and meta-analysis by Neves et al. (2014) identified a significant improvement in piMAX with IMT in COPD patients, whereby piMAX increased by 27.98cmH20 (95% CI, 20.10-35.85). Whilst this review did not consider a preoperative patient population it does highlight patients with respiratory deficit can elicit improvements in inspiratory muscle strength with this form of training as measured by piMAX. Lung cancer patients may have pre-existing chronic respiratory conditions, such as COPD, since they share a common aetiology in extensive smoking histories. The improvements in piMAX were far higher in the review by Neve et al. (2014) in comparison to this study and this is potentially due to the overall poorer health status in cancer populations and the shorter training period available for treatment in the preoperative period. Inspiratory muscle

training was undertaken for a duration of up to 40 weeks within the included studies in the meta-analysis by Neves et al. (2014) and therefore significantly higher training effects could have been achieved.

A larger number of well controlled clinical trials utilising pulmonary function as a measure to establish the effectiveness or preoperative rehabilitation, and specifically an increase in the use of piMAX as a measure, will help to determine the comparability or superiority of this measure regarding sensitivity and specificity for physiological changes in lung function with preoperative rehabilitation intervention. Whilst generic pulmonary function parameters are reported within existing guidelines to consider for operability and surgical risk, the specific pulmonary function parameters that are associated with an increased risk of specific postoperative pulmonary complications in patients undergoing surgical resection for lung cancer have not been established. The identification of specific thresholds, that may be protective of developing postoperative complications would be of substantial clinical significance.

10.3.2. Exercise Capacity as an Outcome Measure for Preoperative Rehabilitation

Despite not being an outcome measure in this study, six-minute walking distance (6MWD) has been used within existing literature in lung cancer to determine whether exercise-based preoperative strategies influence physical capacity. Cavalheri and Granger (2017) found a significant mean improvement in 6MWD of 18.23 metres (95% CI, 8.50-27.96) with preoperative rehabilitation including IMT and aerobic exercise at low to moderate intensity. Recently a systematic review

and meta-analysis by Vacchi et al. (2022) specifically evaluated preoperative IMT for patients undergoing lung resection and found a significant improvement in functional capacity as measured by 6MWD of 28.93 metres (95% CI 0.28-57.58). 6MWD is a pragmatic and functional test employed in clinical practice used to estimate exercise capacity. $V0_2$ max is considered a gold standard in exercise testing to provide accurate inference to exercise capacity (Ligouri, 2021). This test has not been used as a routine outcome measure in current systematic reviews for preoperative rehabilitation with lung cancer patients whereby the focus has centred on hospital length of stay, postoperative pulmonary complications and changes in pulmonary function. Small randomised controlled trials investigating the effectiveness of HIIT in preoperative rehabilitation for lung cancer have included $V0_2$ peak, an estimation of $V0_2$ max, and shown significant improvements with preoperative HIIT intervention. Randomised controlled trials by Stefanelli et al. (2013) and Licker et al. (2017) both found a mean $V0_2$ peak improvement of 2.9ml/kg/min with short term HIIT rehabilitation in patients awaiting surgical lung resection. The trial by Licker et al. (2017) also included the functional 6MWD as an outcome measure and found a mean improvement of 66 metres with HIIT intervention. Similarly, a randomised controlled trial by Vagvolgyi et al. (2018) found a mean improvement of 63 metres with preoperative HIIT rehabilitation for patients with lung cancer. These trials also identified that measures of physical or exercise capacity, 6MWD and $V0_2$ peak, declined in the standard care control groups during the preoperative period. Therefore, preoperative rehabilitation may help to protect against functional decline that may have deleterious consequences

in the postoperative period. This study did not include a specific outcome measure for physical or exercise capacity and this omission is a significant limitation. This was largely due to the existing service constraints which did not include formal exercise testing and the methodological approach resulting in retrospective collection of existing data. The inclusion of exercise testing with patients pre and post intervention would be a substantial service improvement and provide useful data to understand and determine the effectiveness of preoperative rehabilitation strategies.

Clinically, the measurement of V0$_2$ max requires referral to and measurement within a laboratory-controlled environment by exercise physiologists with specialist clinical training. Often lung cancer patients requiring surgical resection do not warrant vigorous cardiopulmonary exercise testing to determine V0$_2$ max that can be resource intensive, may elicit unpleasant symptoms and potentially delay surgery. Therefore, this data was unavailable for this study, as it has not formed part of routine practice within this specialty. Despite this, relevant guidelines do provide useful parameters for V0$_2$ max and predictive surgical mortality risk for lung cancer surgery, whereby a V0$_2$ max of greater than 20ml/kg/min would be considered a low mortality risk and a V0$_2$ max less than 10ml/kg/min would be considered a high mortality risk that may contraindicate surgery as an appropriate intervention (Salati and Brunelli, 2016). Whilst determining V0$_2$ max through cardiopulmonary exercise testing for all patients requiring surgical lung resection may not be a pragmatic or feasible option in practice, the inclusion of this measure may be valuable in future research as an explanatory measure. Furthermore, V0$_2$

max can be effectively estimated with field based functional exercise tests that could prove of greater use in subsequent clinical practice. Whilst mortality risk associated with V02 max has been determined in current literature and included within relevant guidelines, the threshold for risk associated with specific postoperative pulmonary complications has not been established. Determination of the minimal threshold of V02 max or V02 peak that may be protective against postoperative complications could help to guide clinical decision-making and help to determine ultimate effectiveness of preoperative rehabilitation strategies in this patient population. This theoretical threshold may also help to explain the current disparity in current evidence related to the effectiveness of preoperative rehabilitation strategies towards the clinical outcome measures; postoperative complications and hospital length of stay.

10.3.3. HRQOL as an Outcome Measure for Preoperative Rehabilitation

Health-related quality of life (HRQOL) is an important outcome as a reflection towards how patients experience and live with a cancer diagnosis, the burden of symptoms and the effects of any treatments that may have an enhancing or deleterious effect upon quality of life. The standard set for lung cancer also references the importance of including HRQOL as a patient-reported outcome measure, given that lung cancer can be associated with burdensome symptoms and treatments are often linked to significant toxicity (Mak at al., 2016). Work by Mak at al. (2016) recommended the inclusion of HRQOL in research involving patients with lung cancer and cited the use of the European Organisation for the Research

and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30). This questionnaire also contains a lung cancer specific module QLQ-LC13. Despite the recognition of HRQOL as an important outcome in oncology research and more specifically lung cancer research, it has rarely been included as an outcome measure within current trials investigating exercise-based preoperative rehabilitation strategies for this patient population. A systematic review for preoperative IMT prior to surgical lung resection by Vacchi et al. (2022) reported no significant difference in HRQOL with the intervention. However, the review was unable to pool data for statistical analysis due to the substantial heterogeneity in scales and reporting. Trials specifically investigating HIIT as a preoperative rehabilitation strategy in patient with lung cancer have also found conflicting results in HRQOL measures. A randomised controlled trial by Karenovics et al. (2017) investigated preoperative HIIT and included one-year post-surgical follow-up and concluded that the intervention did not appear to be associated with better functional outcomes in comparison to standard care. This trial used the generic MRC dyspnoea score and Zubrod physical performance scores for analysis. Stefanelli et al. (2013) found equivalent results in a randomised controlled trial investigating preoperative HIIT in lung cancer and found that dyspnoea scores were unchanged with preoperative intervention, as measured by the modified BORG scale. Neither of these studies utilised the questionnaire recommended in the standard set for lung cancer. A feasibility trial by Sommer et al. (2018) identified more favourable results for HRQOL with preoperative and postoperative exercise-based intervention in patients with operable lung cancer. This study used a range

of generic and lung cancer specific questionnaires to assess HRQOL, including the EORTC-QLQ, the Short Form-36, the Functional Assessment of Cancer Therapy-Lung and the Hospital Anxiety and Depression Scale. Sommer et al. (2018) found that exercise-based rehabilitation significantly improved global quality of life, mental health and emotional wellbeing from diagnosis and at one year follow-up post-surgical lung resection. This was a feasibility study with a small sample of 40 patients and without a comparative control, it did however include lung cancer specific quality of life measures and these factors may account for the conflicting results across studies. The study by Sommer et al. (2018) also predominantly related to HIIT performed in the postoperative period since the preoperative intervention was deemed to be non-feasible due to the limited time available for intervention and the number of diagnostic procedures patients required within the preoperative period.

Similar to the existing literature, this evaluation also produced mixed results related to HRQOL measured with the EORTC-QLQ questionnaire, with face-to-face rehabilitation demonstrating a significant improvement in HRQOL whilst virtual rehabilitation showed a modest and non-significant difference. Face-to-face rehabilitation may have enabled patients to benefit from increased social interaction in the group format whilst patients who completed virtual rehabilitation remotely may not have experienced and benefited from this interaction. The questionnaires were also completed in person within the clinical environment by patients receiving face-to-face rehabilitation whilst the virtual rehabilitation completed these online and this may have introduced a potential source of bias.

The SARS-CoV-2 pandemic has also had a profound impact upon population health and wellbeing and the need for National and Local Lockdowns, the shielding of vulnerable groups such as those with a cancer diagnosis, coupled with the closure of public and community services may also have contributed to the lack of a significant difference in HRQOL with preoperative virtual rehabilitation intervention. Significant positive effects on depression scores and quality of life, measured with the Short Form-36, have been identified in reviews evaluating the effectiveness of virtual telerehabilitation models in coronary heart disease patients inclusive of heart failure populations in Cardiac Rehabilitation Services (Cavalheiro et al., 2021; Ramachandran et al., 2022). Virtual modes of rehabilitation delivery have received increased attention as a response to the pandemic and it is likely that an increased volume of research will emerge in the future to determine the effectiveness of these approaches in comparison to traditional face-to-face models of care. It will be paramount to establish appropriate outcome measures and ensure that effect on HRQOL is adequately measured within these trials to allow informed decisions for future clinical practice.

10.4. Objective 4: Feasibility of Preoperative Rehabilitation in Lung Cancer

10.4.1. Preoperative Rehabilitation Influence on Waiting Times for Surgery

Patients receiving face-to-face preoperative rehabilitation experienced significantly longer waiting times from referral to surgery in comparison to virtual rehabilitation and standard care. Causation by the delivery of face-to-face intervention was not

established within this study, however this mode of delivery was observed to have a mean wait of 23.48 days in comparison to shorter mean waiting times of 19.92 days with virtual rehabilitation 18.45 days with standard care although a longer waiting time to surgery did not correlate with a longer length of hospital stay within this study. The standard set for lung cancer highlighted the importance of identifying any potential delays in recognised curative treatments for lung cancer that may occur from possible interventions (Mak et al., 2016). Surgical lung resection has been established as an effective treatment option for operable lung cancer with curative intent and therefore it was important to consider the potential impact of delayed time to surgery with preoperative rehabilitation strategies. Whilst the additional wait time from rehabilitation referral date to operation date in the face-to-face rehabilitation group did not appear to be detrimental in worsening patient outcomes it also did not demonstrate an advantageous effect in the primary postoperative outcomes in this study, namely hospital length of stay, development of postoperative complications and 12-month post-surgery survival.

National lung cancer guidance recommends that surgical lung resection should be undertaken within 28 days of diagnosis once eligibility for surgery has been determined (NICE, 2019). The mean waiting times across the three groups in this study fell within this recommended timescale which may account for minimal adverse impact and non-statistical significance evident in many postoperative outcomes. Randomised controlled trials investigating HIIT as a preoperative rehabilitation strategy have also included the impact of intervention on surgical timescales and found no significant difference in time to surgery with enrolment

onto preoperative intervention. Licker et al. (2016) reported a median duration of 26 days to surgery in the rehabilitation group in comparison to a median of 25 days in standard care. This may indicate that the significantly longer timescales apparent in the face-to-face rehabilitation group may be due to differences in Hospital processes and potentially patient demand, since each of the study samples reflected a different year over a three-year period in this study. The National Lung Cancer Audit has reported an increase in 1000 lung resections undertaken per year over the last 3 years (RCP, 2019). The incline in resections may have resulted in an increase in waiting times for surgery between standard care and face-to-face rehabilitation. This demand may have reduced during the pandemic, whereby surgeons reconsidered eligibility criteria for surgical intervention based on risk of non-operation and potential exposure to viral transmission. Clinically it was observed that fewer elective surgical procedures were undertaken during peaks in the pandemic, this may have resulted in shorter wait times for operation in the virtual rehabilitation group in comparison to the face-to-face rehabilitation group. Complete National audit data reporting on lung resection has not yet been published to confirm any potential influence of volume and demand during this period.

Theoretically, differences in wait times for surgery between intervention groups in this study could also indicate Thoracic surgeons awareness of the timescales required for visible face-to-face programmes and compensated for these accordingly with intended surgical dates. The remote nature of virtual service delivery during the SARS-CoV-2 pandemic may also have meant the surgeons were

less aware of this service and did not factor this into decision-making. Furthermore, due to changes in operational procedures during the SARS-CoV-2 pandemic surgeons from all specialties may have experienced less autonomy and flexibility in theatre availability to select operation dates. An interesting survey by Shukla et al. (2020) investigated Cardiothoracic surgeon perceptions of preoperative rehabilitation and reported that 91% of respondents would be willing to delay surgery to optimise patients through preoperative rehabilitation. Despite the perceived benefit identified in this study 60% of surgeons were not aware of rehabilitation referral pathways for programmes despite confirmed availability of resources in the locality. Finally, 92% of surgeons responding to the survey also believed that further research into preoperative rehabilitation was needed (Shukla et al., 2020). The perceptions and attitudes of Thoracic surgeons have rarely been investigated and reported upon and this survey was undertaken in New Zealand, but it does reflect the positivity towards preoperative rehabilitation that has also been experienced clinically by the researcher at the local NHS Trust.

10.4.2. Adherence with Rehabilitation Delivered through a Cardiac Rehabilitation Service

Preoperative rehabilitation delivered face-to-face or virtually achieved 100% uptake in this study. This corresponds to the early patient and public involvement focus group that indicated there would be a patient desire to be prepared for surgery, with a receptiveness toward preoperative lifestyle intervention and guidance in this patient group. Twice weekly supervised sessions had been the

intention at service planning and implementation, however since this evaluation reflected real-world practice the need for flexibility was apparent. Virtual rehabilitation was able to accommodate three times a week supervised exercise on individual patient request and this reflects the greater flexibility afforded by remote delivery unhampered by venue booking, hire costs and staffing ratios required in face-to-face rehabilitation delivery. Adherence to the programme was also comparable across both face-to-face and virtual delivery with patient programme completion at 73.2% and 76.5% respectively. These percentages are lower than the participant adherence shown in recent trials of preoperative HIIT in lung cancer patients where adherence has been reported at 87% (Licker er al., 2016; Karenovics et al., 2017; Bhatia and Kayser, 2019). Theoretically, differences in adherence identified in this evaluation in comparison to trial data may reflect the reality of service level data collection as opposed to that where patients have accepted enrolment for research purposes. Trial patients may be directly invested in the research findings and may be more inclined to complete the programme in a different way to patients who have given their permission for data to be used for service evaluation but would not consider themselves research participants. There may also have been additional incentives within the clinical trials to encourage high rates of adherence to limit the potential impact of attrition on research findings. The proportion of patients completing preoperative rehabilitation, delivered face-to-face or virtually in this evaluation is favourable in comparison to current National audit data reporting current levels of uptake and adherence at 50% for registered Cardiac and Pulmonary Rehabilitation programmes within the United Kingdom

(NACAP, 2020; NACR 2020). It is also reassuring that reasons for cancellation were widely practical as opposed to symptom driven, with the highest proportion of patients cancelling due to the availability of an earlier operation date for both face-to-face and virtual rehabilitation. Similarly, Licker et al. (2017) reported earlier operation dates as a reason for drop out. It is worth considering that cancellations were self-reported and non-anonymised, it is possible therefore that the reasons highlighted in this evaluation reflect clinically and socially acceptable explanations for drop-out. There may be unexplored patient experiences that could hold further and greater relevance that would be worthy of further qualitative exploration.

10.4.3. HIIT as a Feasible Treatment Strategy for Patients with Lung Cancer

No serious adverse events were reported with preoperative rehabilitation delivered either face-to-face or virtually in this evaluation. Additionally, there were no patient or clinician reported side effects documented in the virtual rehabilitation programme. Eight patients receiving face-to-face rehabilitation reported mild short-lasting side effects associated with light-headedness and musculoskeletal related chest pain during the programme. This is consistent with current trials on HIIT as a preoperative rehabilitation strategy in lung cancer, with no serious adverse events reported across these trials (Licker et al., 2017; Stefanelli et al., 2013; Karenovics et al., 2017; Sommer et al., 2018; Bhatia and Kayser, 2019). This suggests that HIIT exercise could be a safe intervention for consideration as a rehabilitation approach in this patient population. The body of evidence supporting HIIT has largely been undertaken on healthy populations with prior experience of

exercise (MacInnis et al., 2017; Blue et al., 2018; Fransson et al., 2018; Hostrup et al., 2019). Similarly, to the findings of this study, emerging evidence has also indicted that HIIT can be prescribed safely in patient populations. Systematic reviews evaluating HIIT in coronary heart disease (Gomes-Neto et al., 2017; Hannan et al., 2018; Wewege et al., 2018), heart failure (Aruaujo et al., 2019; Gomes-Neto et al., 2018) and diabetes (da Silva et al., 2019; Lora-Pozo et al., 2019) have also indicated safety and efficacy with HIIT intervention. Wewege et al. (2018) reported a single significant cardiovascular event, two minor cardiovascular events and three patient reported complaints of musculoskeletal origin following HIIT intervention. It is worth noting that two non-cardiovascular events were also reported with moderate intensity exercise in the review. A review by Hannan et al. (2018) also reported a greater number of reported side effects with moderate intensity exercise than with HIIT, with nine and five events reported respectively. The absence of serious adverse events across the intervention groups and minimal patient reported side-effects in this study indicates that the programme was implemented safely irrespective of intensity achieved and mode of delivery.

The proportion of patients achieving HIIT was comparable between face-to-face rehabilitation and virtual rehabilitation modes of delivery at 57% and 56.6% respectively. Whilst this represents the larger proportion of the intervention samples, this also reflects that almost half of the patients were unable to attain HIIT level exercise throughout the preoperative rehabilitation programme. Parameters for HIIT intervention are poorly defined within the research for lung cancer populations and more broadly in exercise literature, leading to substantial disparity

with HIIT prescription within current literature. This evaluation considered HIIT attainment to equate to 80% HRR. It may have been more appropriate to consider an acceptable range for the percentage of HRR that would encompass the essence of vigorous or high intensity training, given that intensities can be experienced differently by individual patients. Whilst the rating of perceived exertion by the validated Borg scale was included to monitor patient response and facilitate safe exercise progression, the RPE alone did not categorise the patient as attaining HIIT level exercise. Dyspnoea and fatigue are common and debilitating symptoms reported in lung cancer (Cancer Research UK, 2022) and it is therefore feasible that this patient group would reach higher perceptions of exertional effort subjectively before physiological heart rate parameters were reached. The deciding factor for HIIT attainment was based on an absolute heat rate target and the high and narrow margins associated with this may explain the high percentages of patients not achieving HIIT in this study compared to trials undertaken in lung cancer populations (Stefanelli et al., 2013; Licker et al., 2017; Karenovics et al., 2017; Bhatia and Kayser, 2019). The collection of data to determine absolute percentage maximum heart rate attained during the evaluation would also have indicated the overall proximity to the HIIT target and this may have provided additional value for future clinical practice and clinical reasoning, whilst also establishing clearer parameters to define HIIT for this patient population. The emergence of HIIT for patient populations is still an unfamiliar intervention in some areas of current clinical practice, and it is unclear whether the limitation in HIIT attainment evident in some patients within this evaluation was determined by physiological limitations,

perceived ability, underlying patient and clinician preconceptions or clinical knowledge. Exercise prescription and monitoring in this study was determined by heart rate parameters and monitored by patient ratings of perceived exertion and specific exercise testing may have provided greater assistance and reassurance in exercise prescription. It has been observed clinically that patients with chronic conditions, unfamiliar with exercise environments, may be commenced on lower levels of exercise initially to foster confidence and engagement and this may also have attributed to the clinical practice in this evaluation. Further work investigating the attributes associated with early HIIT prescription and attainment in patient populations may also help to guide clinical-reasoning and establish a patient profile where HIIT can be safely prescribed in preoperative lung cancer populations. This study suggests that HIIT can be implemented safely, where appropriate, for this patient population but that it will not be an appropriate preoperative intervention for all patients with a diagnosis of operable lung cancer. It should be considered in accordance with patient health profile and following thorough clinical assessment. The intricacies of determining the appropriateness of early HIIT at an individual patient level is embroiled in the subtleties of clinical experience, judgement and knowledge and whilst a blanket approach to exercise-prescription in patient population should never be the aim of exercise-based research or practice, the more intervention options available to clinicians in clinical practice, the greater the ability to tailor programmes to individual needs. Ultimately HIIT appears to be a feasible option as a preoperative rehabilitation strategy in selected patients with a

lung cancer diagnosis, however a larger body of evidence is needed to understand the response to this mode of exercise and prescribe effectively.

Chapter 11. Conclusions

11.1. Preoperative Rehabilitation in Lung Cancer Results Summary

Preoperative rehabilitation intervention delivered either face-to-face or virtually improved pulmonary function but did not reduce hospital length of stay or duration of high dependency level care in comparison to standard care. The preoperative face-to-face rehabilitation group had the highest overall hospital length of stay at 9.75 days. Preoperative virtual rehabilitation did appear to positively influence postoperative complications with a reduction in the clinical severity of postoperative complications as graded by the Clavien-Dindo classification and this equated to a 0.39 lower mean severity grading in comparison to standard care. Virtual rehabilitation had a significantly lower proportion of patients with positive radiological evidence diagnostic of either atelectasis or pneumonia in comparison to face-to-face rehabilitation and standard care and lower proportion of positive sputum samples in comparison to standard care. However, the incidence of other key markers relating to the investigation and management of postoperative complications did not substantially differ between either intervention groups or standard care. Virtual rehabilitation and face-to-face preoperative rehabilitation were not superior to standard care in terms of requirement of antimicrobial therapy, the prescription of high flow oxygen therapy and the incidence of postoperative tracheostomy insertion. The preoperative intervention groups did not significantly improve 6 month or 12-month survival in comparison to standard care. Although the face-to-face rehabilitation group did appear to have a higher

percentage of patients alive at the 12-month post-surgery mark with a survival percentage at 89%. The number of hospital readmissions or cumulative hospital stay duration throughout that 12-month post-surgery period did not significantly differ between intervention groups or standard care alone. This indicated that virtual rehabilitation may be slightly superior to face-to-face rehabilitation in reducing the clinical severity of postoperative complications and potentially reducing the incidence of atelectasis and pneumonia as confirmed radiologically.

Both virtual rehabilitation and face-to-face rehabilitation improved individual aspects of pulmonary function as assessed through pre and post intervention spirometry. Mean inspiratory pressures improved significantly with both face-to-face and virtual forms of preoperative rehabilitation. Face-to-face rehabilitation demonstrated a mean difference with intervention at 1.144cmH_20 and virtual rehabilitation a mean difference of 1.312cmH_20 with intervention, with virtual rehabilitation demonstrating a statistically significant improvement in piMAX over face-to-face rehabilitation. Face-to-face rehabilitation significantly improved FEV1 and correspondingly percentage predicted FEV1 and FVC measures following intervention. Whilst virtual preoperative rehabilitation significantly improved percentage predicted FVC with intervention. This suggests that preoperative rehabilitation, delivered either face-to-face or virtually can positively influence pulmonary function although face-to-face delivery may be slightly superior in achieving a range of measures. Face-to-face preoperative rehabilitation also significantly improved health-related quality of life assessed by the EORTC-QLQ-C30 and whilst some improvement was also evident with virtual rehabilitation, this was

not significant. Whilst preoperative rehabilitation through face-to-face delivery appears superior for optimising a patients lung function and HRQOL prior to surgery, this does not appear to translate into important gains with hospital length of stay or the development of postoperative complications. Preoperative rehabilitation delivered virtually shows some evidence of reduced severity and incidence of pulmonary complications despite more modest improvements in pulmonary function and HRQOL with intervention, indicating that additional and unresearched factors are also likely to have influenced these findings and may also play an important preoperative role in optimising preparation for surgery.

11.2. Final Conclusions and Recommendations for Practice

Designated outpatient preoperative rehabilitation programmes are currently not routine practice within the United Kingdom, despite systematic reviews in the area indicating that these programmes can positively influence the incidence of postoperative complications and impact hospital length of stay. Results of this study suggest that outpatient Cardiac Rehabilitation programmes provide a viable opportunity to accept referrals for lung cancer patients preoperatively to optimise health prior to surgery. The Cardiac Rehabilitation exercise and education-based programme provides a suitable lifestyle modification model that would provide prompt access to services for patients with lung cancer, whilst utilising the expansion of an existing Rehabilitation service is likely to be the most cost-effective option, with efficient use of existing resources in comparison to commissioning for

the implementation of a new service in practice. Realistically the procurement of commissioned funds for a new service would require convincing evidence of cost-benefit effectiveness.

Preoperative rehabilitation consisting of combination therapy HIIT and IMT delivered in the short term can improve pulmonary lung function in preparation for surgical resection for lung cancer and may positively influence health-related quality of life. It is less clear whether this combined therapy delivered through a Cardiac Rehabilitation programme can produce tangible benefits in hospital length of stay and the incidence of postoperative pulmonary complications. Face-to-face rehabilitation and virtual rehabilitation models appear to demonstrate marginal healthcare service benefits, with early indications that virtual rehabilitation may perform better than face-to-face programmes in reducing severity of postoperative complications. Face-to-face and virtual platforms for rehabilitation require further investigation to fully understand the comparable effectiveness of these platforms and this should include economic investigation of cost-benefit analysis to consider recommendations for implementing preoperative rehabilitation services in lung cancer.

Chapter 12. Final Reflections

This study set out to determine and evaluate the effectiveness of preoperative rehabilitation intervention to optimise lung function and physical status to reduce postoperative pulmonary complications and hospital length of stay. Whilst the study indicated that the preoperative rehabilitation strategy of combined HITT and IMT could improve pulmonary lung function when measured by piMAX, FEV1 and FVC and their percentage predicted values these improvements did not convincingly transfer into beneficial improvements in length of stay or reduction in postoperative pulmonary complications. The inclusion of the separate virtual rehabilitation sample in addition to face-to-face rehabilitation was intended to provide a unique analysis that was opportunistic following significant changes in service delivery as a direct response to the SARS-CoV-2 pandemic. In reality the inclusion of the virtual rehabilitation group for analysis posed several challenges since the changes employed across healthcare in response to the pandemic resulted in numerous potential confounding variables that may have biased results for this sample. In particular the rapid changes to policies and procedures employed to patient admission, elective surgery, postoperative resource utilisation, the suspension of hospital visiting by loved ones, differences in postoperative discharge advice and the impact of National measures including shielding advice and National and Local Lockdowns could have significantly altered postoperative course and recovery in patients throughout the pandemic period limiting comparison between standard care and face-to-face preoperative rehabilitation.

The retrospective study approach set out to achieve a large data set, since current work in the field had focussed predominantly on prospective feasibility studies or randomised trials with small samples. It was theorised that the larger sample size afforded from retrospective data collection added statistical power to the data analysis. Whilst this approach undoubtedly allowed for a large sample size, despite the limited resources available to the researcher, it also limited the extent and depth of rich data. This retrospective approach meant that some outcome measures that could have provided additional understanding were not available to the researcher for collection. Most notably this included the omission of relevant exercise testing pre and post intervention using either laboratory or field-based exercise tests and the poor response rate to health-related quality of life questionnaires reducing the data set available for analysis.

The expansion of the existing Cardiac Rehabilitation programme to provide a referral pathway for high-risk preoperative lung cancer patients was initially implemented as a short-term service improvement that would be piloted and evaluated for efficacy to determine ongoing and sustained service delivery. This study indicates that the programme may be beneficial at improving some aspects of pulmonary function but did not ultimately prove beneficial for hospital length of stay, postoperative recovery and longer-term survival. These were primary outcome measures for this study and fundamental to determining the success of the programme for lung cancer patients. This raises both moral and ethical considerations for ongoing use of the service for patients with lung cancer. The study has not comprehensively proven or established that the preoperative

rehabilitation strategy can convincingly influence the primary aims and objectives of the study and therefore may not be considered an effective solution warranting further resources or commissioning. The continued provision and use of limited healthcare resources, the promotion of referral of lung cancer patients into a service that requires commitment to attend and adherence to an exercise programme that may not significantly improve postoperative outcomes could be considered morally unjustifiable. Improvements were identified in pulmonary function and to a lesser extent HRQOL with the rehabilitation programme, however these were secondary outcome measures for the purposes of this study. This does indicate that the programme may be of some value and produce benefits that were not directly related to the in-hospital recovery following surgery or longer-term survival. The beneficial effects of the preoperative rehabilitation programme and outcome measures that may show significance could be in areas that were not considered or analysed within this study due to confinements in the data collected and potential preconceptions by the researcher. In particular, HRQOL was primarily objectified in measurement and patient experience was not considered beyond patient reported side effects and reasons for cancellation in the programme. The inclusion of qualitative study could have provided extensive value to comprehensively understand patient experience beyond objective efficacy.

The decision to withdraw a potentially valuable service for patients is a dilemma, especially when the apparent ineffectiveness of treatment may be based on inadequate outcome measures that provide an incomplete picture of the potentially value an intervention may offer for the population under study.

Conversely, continuing to deliver a service that may be futile in changing the course of recovery for patients undergoing surgery is needlessly wasteful of resources. The labour and financial resources may be better redeployed to explore different interventions that may prove more beneficial to patient outcomes and healthcare service delivery in the future. Decision-making regarding service investment requires careful consideration of the cost of delivery, outcomes and associated quality of service provision. Effectiveness of interventions must be viewed with objectivity and impartiality to provide balanced recommendations for future practice, this is challenging as a researcher when personally invested in the sustainability of service delivery. The impartiality has resulted in conflicting feelings for the researcher, given that they held the role or Service Lead for the Cardiac Rehabilitation programme and are responsible for service direction and development. Undoubtedly the researchers' own personal preferences will have resulted in a degree of bias, however conscious or unconscious, that may have impacted the interpretation findings and conclusions within the evaluation.

Healthcare delivery is a public-facing service and therefore providing objectivity without subjective reasoning and understanding would be impractical and improbable in practice. It must also be considered that successfully leading service development and achieving service expansion and reform requires passion, energy and a willingness to trial relatively unknown interventions for a sufficient period of time to discover potential worth. As a researcher the mixed results obtained in this study were disappointing, as a Service Lead with a passion to improve the quality of care for patients with lung cancer the results alone do not infer ineffectiveness

of treatment or futility in service provision but a further opportunity to determine where the real benefits of rehabilitation interventions may be realised. Adaptability, commitment, resilience and a certain degree of optimism are hallmarks to success in healthcare roles. The opportunity to undertake research and complete a Professional Doctorate has also confirmed that these are the hallmarks needed for this level of academic study and research activity.

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Appendix 1 Research Ethics, NHS Approval and Registration

NHS
University Hospitals of North Midlands
NHS Trust

STATUS:	Approved ☒ Not Approved ☐

Service Evaluation Screener

Proposed study/evaluation/audit name:	The effectiveness of short-term rehabilitation programme of preoperative high intensity exercise and inspiratory muscle training to improve post-operative recovery in lung cancer patients undergoing surgical lung resection
Proposed Go live date:	NA retrospective approval
Requester name, department and job title:	Mrs Sonya Lockett, Cardiorespiratory Lecturer Keele University. (at the time of evaluation Service Lead for UHNM Cardiac Rehabilitation Service)
Requester email:	s.j.lockett@keele.ac.uk
Clinical Lead Name, job title and email:	Sonya Lockett, Service Lead for UHNM Cardiac Rehabilitation s.j.lockett@keele.ac.uk (The evaluation reviewed and approved by Mr Matthew Warrilow, Directorate manager Cardiology UHNM NHS Trust).

Project Description – A summary of the project and the aims	
1.1	To determine whether an existing outpatient Cardiac Rehabilitation programme may prove an effective referral pathway for lung cancer patients awaiting surgical resection within the Cardiothoracic Speciality to optimize preoperative preparation and positively influence postoperative outcomes. The aim of this study was to evaluate the feasibility of preoperative rehabilitation delivery based on patient uptake, completion rates and ability to achieve intended exercise prescription parameters within a Cardiac Rehabilitation programme. To determine whether there was an improvement in preoperative pulmonary function and postoperative recovery in relation to postoperative pulmonary complications, length of stay and survival with preoperative rehabilitation.

What are the benefits for UHNM? Will the results be shared with UHNM to improve patient care?	
1.2	The evaluation may identify an appropriate pathway for patients with operable lung cancer to optimize patients who may be at high risk of developing postoperative complications with associated longer complicated hospital stays and significant resource costs. Cardiac rehabilitation may be a viable pathway to implement preoperative rehabilitation for patients and a summary of significant findings will be

	shared with the UHNM Cardiac Rehabilitation and Cardiology Directorate, for consideration, on completion of the project.

Will Personal identifiable information be accessed?	
1.3	☒Yes ☐No

Will any external parties have access to Personal Identifiable Information?	
1.4	No external parties will have access to personal identifiable information.

Please provide details of the data collection method, this must include the systems being accessed, the data set required and by whom	
1.5	The researcher (Service Lead for UHNM Cardiac Rehabilitation) will be the sole person accessing, inputting and analyzing the data. The relevant data sets will be inputted into an MS excel spreadsheet on the researchers' personal laptop. The data will be anonymized at the point of entry onto the spreadsheet using coding and only the researcher will have access to the laptop which is stored securely in a locked cabinet. During data entry the researcher will hold an identifiable list of codes and therefore data will be pseudo-anonymized at the point of entry. This will be destroyed by the researcher after data entry has been checked for accuracy on initial inputting. The UHNM Cardiac Rehabilitation database will be accessed to ascertain uptake, adherence, completion status and the paper notes will be reviewed to determine whether exercise parameters were met. UHNM IPortal will be accessed to determine dates of surgery and date of discharge to determine length of stay and survival status. Medisec discharge letter will be reviewed to identify the type of lung resection and postoperative recovery (antibiotic prescription, tracheostomy and ventialtory requirements, positive radiological evidence). Databases and notes will be accessed within the UHNM Cardiac Rehabilitation Office and at no point will notes be removed from the Cardiac Rehabilitaiton Office.

Will the data set be fully anonymous prior to any publication?	
1.6	☒Yes ☐No

Where will the data be stored during and after the study/evaluation/audit?	
1.7	During the evaluation all research data will be stored electronically on Excel and exported onto SPSS on the researchers' personal laptop, this is password protected,

	owned and used exclusively by the researcher. When not in use the laptop will be stored in a locked cabinet and the key is the responsibility of the researcher. The SPSS imported data will be deleted from the computer following data analysis and the non-identifiable and coded data on the MS Excel spreadsheet will be held securely on the researchers' laptop for 10 years in accordance with Staffordshire University research policy. Once this period has passed the computer will be wiped clean.

Approval

Clinical Lead Name:	Mrs Sonya Lockett
Clinical Lead Signature and Date:	23/04/24
DSP Approval Signature:	
Audit registered date:	23/04/24

Clinical Audit Registration Confirmation: ID CA18124

[You don't often get email from clinicalaudit@uhns.nhs.uk. Learn why this i=
s important at https://aka.ms/LearnAboutSenderIdentification]

Clinical Audit ID CA18124 has been added to the Clinical Audit register.

Working Title: A service evaluation of the feasibility and effectiveness of a Preoperative Rehabilitation programme for patients undergoing lung resection within an existing Cardiac Rehabilitation Service.

Trust: UHNM

Division: Network Services

Directorate: The Heart Centre

Standards Reference: Service evaluation

Project Lead: Mrs Sonya Lockett

Contact e-mail: s.j.lockett@keele.ac.uk

RESEARCH ETHICS
Proportionate Review Form

The Proportionate Review process may be used where the proposed research raises only minimal ethical risk. This research must: focus on minimally sensitive topics; entail minimal intrusion or disruption to others; and involve participants who would not be considered vulnerable in the context of the research.

PART A: TO BE COMPLETED BY RESEARCHER

Name of Researcher:	Mrs Sonya Lockett
School	Life Sciences and Education

Student/Course Details (If Applicable)			
Student ID Number:			11029228
Name of Supervisor(s)/Module Tutor:			Professor Roozbeh Naemi
PhD/MPhil project:	☒		
Taught Postgraduate Project/Assignment:	☐	Award Title:	
Undergraduate Project/Assignment:	☐	Module Title:	

Project Title:	The effectiveness of short-term rehabilitation programme of preoperative high intensity exercise and inspiratory muscle training to improve post-operative recovery in lung cancer patients undergoing surgical lung resection
Project Outline:	Context: Lung cancer is the third most common cancer in the UK and accounts for 13% of all new cancer cases. The incidence of lung cancer is highest in people aged between 85-89 and 44% of new lung cancer diagnosis are in people aged 75 and over. These patients can be frail, elderly and have extensive past medical histories. Removal of cancerous tissue through surgery is the only curative approach. Patients undergoing these procedures are at significant risk of developing post-operative pulmonary complications due to altered diaphragmatic biomechanics, increased respiratory loading and inspiratory muscle fatigue, which can then precipitate the onset of atelectasis (lung collapse) and sputum retention. Theoretical basis: Current evidence suggests that lung cancer patients who present with poor preoperative lung function experience more postoperative complications and a greater length of hospital stay. Improvements in a patient's preoperative lung function through a preoperative rehabilitation programme could have a significant impact on the development of pulmonary complications following thoracic surgery. Objectives: To identify whether a preoperative rehabilitation intervention of high intensity interval training (HIIT) and inspiratory muscle training (IMT), delivered face-to-face or virtually, can reduce the incidence of postoperative complications, improve patient recovery to reduce hospital length of stay and influence 12 month survival in operable adult lung cancer patients. A further

	objective is to determine patient adherence to these interventions and ability to reach target ranges required to achieve high intensity training. Establishing whether virtual modes can offer comparable outcomes to face-to-face delivery in patient engagement, safety and efficacy in this patient population willf help inform future practice.
Give a brief description of participants and procedure (methods, tests etc.)	Aims: To compare standard care for patients scheduled to undergo lung resection with standard care in conjunction with preoperative rehabilitation (a combined approach of twice weekly high-intensity interval training (HIIT) and daily inspiratory muscle training (IMT) guided by a trained respiratory physiotherapist for 2-3 weeks prior to surgery through face to face or virtual platforms. Study population: Adult patients requiring lung resection through a thoracotomy incision at the Univeristy Hospitals of North Midlands NHS Trust during February 2018 – March 2021. This data is collated as part of the researchers clinical role and the study focuses on analysing this anonymised data. Sample Size: A total of 450 participants that will be case matched to provide 150 participants in three respective groups; standard care, face to face intervention plus standard care and virtual intervention plus standard care. Preoperative Case Identification: Reduced preoperative lung function (identified through spirometry FEV1 less than 80% predicted), received lung resection through a thoracotomy incision and having capacity to consent and follow preoperative instructions Exclusion criteria: Presence of contraindications to HIIT or IMT (e.g. undrained pneumothorax, tracheal stenosis, cardiovascular instability), patients undergoing minor procedures through video-assisted methods or mini-thoracotomy, patient known to have performed HIIT or IMT prior to case identification. Consent: All outcome data is available for the researcher to review retrospectively. This can be achieved through reviewing Medisec Discharge letters, UHNM Rehabilitation databases and patient profiles and Key Performance Indicators. All patients attending the Rehabilitation programme consented to their data being used for research purposes and service evaluation and development and will be netered into data warehouse a data cleasning system. All patient information will be anonymized and confidential throughout. Design: The researcher will compare data from the Standard care control group (i.e case identification February 2018 – February 2019) to the IMT and HIIT Face-to-Face Intervention group (i.e case identification March 2019 – March 2020) and IMT and HIIT Virtual Intervention group (ie case identification April 2020 – April 2021) in a cross-matched retrospective study. Patients will be matched in case and control groups by the independent risk factors associated with postoperative complications in lung resection surgery age, presence of COPD, number of comorbidities, BMI, smoking status and type of surgical resection. Standard care (Data from February 2018-2019): Patients receiving standard

University Research Ethics Committee (February 2018)

	care attended a pre-assessment clinic with a cardiothoracic nurse and junior doctor answering questions on current lifestyle. They complete an anaesthetic checklist, receive an explanation of the planned surgery and complete preliminary consent forms. Throughout the process patients have access to a specialist lung cancer nurse for ongoing care and support Face to face Intervention plus standard care (Data from March 2019 – 2020): Patients attended an outpatient clinic with a physiotherapist where lung function tests were completed using a hand-held spirometer. Patients are given an inspiratory muscle trainer and the resistance of the valve was set at 60-70% of piMAX by the physiotherapist. Patients advised to use the inspiratory muscle trainer, twice a day for 15 minutes, every day until the day of their operation, independently at home. Patients attended a community gym, exercised under the direct supervision of a physiotherapist or exercise physiologist. Patients completed 10-minute warm up, 10-minute HIIT and 5-minute cool down. HIIT is achieved at 80-90% of Heart Rate Reserve (HRR) and a Rating of Perceived Exertion (RPE) of 15–18 (Borg Scale – patient gives a numeric description of their feelings/sensation during exercise). Patients completed exercise on static bikes, rowing machines, treadmills and with hand-held weights. They exercise at high intensity for 1 minute and recover for 30 seconds at a time. Patients were asked to stop the exercise if they exceed 90% heart rate maximum on their heart rate monitor or report an RPE greater than 18. Virtual Intervention plus standard care (March 2020-2021): Patients attended a virtual or telephone consultation with a physiotherapist and were posted an inspiratory muscle trainer and portable pulse oximeter. When piMAX was unable to be assessed directly pressure parameters were set based on patient reported feedback and their observed use of the device. Patients accessed education material through audio podcasts and recorded exercise sessions within an online patient library and participated in live virtual sessions guided by the physiotherapist and both the recorded and live sessions were comparable to the programme completed in the face-to-face intervention group. Portable pulse oximeters enabled patients to self-assess and report heart rate measures throughout the sessions. Primary outcome measures: Presence of postoperative pulmonary complications and hospital length of stay. Hospital length of stay will be determined by reviewing UHNM NHS Trust Medisec discharge letters, calculated from logged admission and discharge dates. Thoracic Surgeons at UHNM NHS Trust consider a reduction in overall length of hospital stay by 2 days to be a clinically significant impact of the intervention. Presence of postoperative pulmonary complications will be determined by a documented prescription of antibiotics, requirement for additional ventilatory support (mechanical ventilation, CPAP, BIPAP, High flow oxygen therapy), requirement for tracheostomy and re-admission into high-dependency care during the patients hospital stay on medical records and Medisec discharge letters. The Hospital system Iportal will be used to determine length of time from diagnosis to surgical treatment and to review 12 month survival and readmissions following surgical intervention. Degree of health will be evaluated by reviewing the EORTC QLQ-C30 questionnaires given to patients pre and post intervention and posted 6 months from surgery. Secondary outcome measures: Lung function Tests (FEV, CPF and piMAX) will

	be used as explanatory outcomes and will be measured at baseline at the first assessment clinic, 2 days prior to surgery and 2 days postoperatively. Tolerance of HIIT and IMT will be determined by review of qualitative patient and clinician-reported comments and patient attendance rates and adherence to the intervention programme. HRR and RPE records on patient profiles will be reviewed to identify whether patients were able to exercise within HIIT 80% Max HRR training zones and UHNM Rehabilitation databases will be utilised to identify uptake, completion and drop-out rates in this group against current UK National Rehabilitation guidelines.		
Expected Start Date:	April 2021	Expected End Date:	March 2022

Relevant professional body ethical guidelines should be consulted when completing this form.

Please seek guidance from the School Ethics Coordinator if you are uncertain about any ethical issues arising from this application.

There is an obligation on the researcher and supervisor (where applicable) to bring to the attention of the School Ethics Coordinator any issues with ethical implications not identified by this form.

Researcher Declaration

I consider that this project has no significant ethical implications requiring full ethical review	☒

I confirm that:		
1.	The research will **NOT** involve members of vulnerable groups. Vulnerable groups include but are not limited to: children and young people (under 18 years of age), those with a learning disability or cognitive impairment, patients, people in custody, people engaged in illegal activities (e.g. drug taking), or individuals in a dependent or unequal relationship.	☒
2.	The research will **NOT** involve sensitive topics. Sensitive topics include, but are not limited to: participants' sexual behaviour, their illegal or political behaviour, their experience of violence, their abuse or exploitation, their mental health, their gender or ethnic status. The research must not involve groups where permission of a gatekeeper is normally required for initial access to members, for example, ethnic or cultural groups, native peoples or indigenous communities.	☒
3.	The research will **NOT** deliberately mislead participants in any way.	☒
4.	The research will **NOT** involve access to records of personal or confidential information, including genetic or other biological information, concerning identifiable individuals.	☒
5.	The research will **NOT** induce psychological stress, anxiety or humiliation, cause more than minimal pain, or involve intrusive interventions. This includes, but is not limited to: the administration of drugs or other substances, vigorous physical exercise, or techniques such as hypnotherapy which may cause participants to reveal information which could cause concern, in the course of their everyday life.	☒
6.	The research **WILL** be conducted with participants' full and informed consent at the time the study is carried out: • The main procedure will be explained to participants in advance, so that they ☐	YES ☐

	are informed about what to expect. • Participants will be told their involvement in the research is voluntary. • Written consent will be obtained from participants. *(This is not required for self-completion questionnaires as submission of the completed questionnaire implies consent to participate)*. • Participants will be informed about how they may withdraw from the research at any time and for any reason. • For questionnaires and interviews: Participants will be given the option of omitting questions they do not want to answer. • Participants will be told that their data will be treated with full confidentiality and that, if published, every effort will be made to ensure it will not be identifiable as theirs. • Participants will be given the opportunity to be debriefed i.e. to find out more about the study and its results.	☐ ☐ ☐ ☐ ☐ ☐	N/A ☒
7.	A risk assessment has been completed for this research project		YES ☒ N/A ☐

If you are unable to confirm any of the above statements, please complete a **Full Ethical Review Form**. If the research will include participants that are **patients,** please complete the Independent Peer Review process.

8. Information and Data Please provide answers to the following questions regarding the handling and storage of information and data:
a) How will research data be stored (manually or electronically)? All research data will be stored electronically on Excel and SPSS spreadsheets on a private lap top password protected, owned and used exclusively by the researcher. When not in use the laptop will be stored in a locked cabinet within their home and the key is the responsibility of the researcher. The laptop will travel to the workplace for data collection and will be in the possession of the researcher at all times. Where review of paper records are required they will be accessed in the work place only and returned to a locked filing cabinet as per current stipulated storage requirements.
b) How is protection given to the participants (e.g. by being made anonymous through coding and with a participant identifier code being kept separately and securely)? All research data will be anonymised at the point entered electronically onto excel and SPSS by the researcher using coding and individual identifier codes. The researcher will maintain a record of unique identifier codes for reference and this will be stored securely in a locked filing cabinet in their home office. This is accessed solely by the researcher. No paper records will leave the workplace and will return to a secure filing cabinet within the workplace once relevant data has been anonymised and entered onto the researchers spreadsheets.
c) What assurance will be given to the participant about the confidentiality of this data and the security of its storage? Retrospective databases and records are being used for this study and will be stored and filed as per the current stipulated guidelines within the workplace to maintain existing confidentiality good practices. The databases require signed permission and access codes and systems require unique log in and password codes. The databases and records are stored within password protected systems and offices. The researcher has permission and access in their current work role. Patients provide consent prior to commencing in the rehabilitation programme and give their

written consent for data to be accessed for research, evaluation and audit purposes. However, all potential records will go through a data warehouse system to cleanse the data and identify any participants who have subsequently requested that their data is not used for these purposes.
d) Is assurance given to the participant that they cannot be identified from any publication or dissemination of the results of the project? Participants will be removed if they have made a request that their data is not used for any evaluation, audit or research in the time from enrolling into the programme and data inputting. The data warehouse system allows for up to date cleansing of this data to uphold new changes in participants wishes. The anonymising of data at entry onto the spreadsheets ensures that participant data is non-identifiable in publication or dissemination of findings and participants are made aware of this on entry to the programme. These practices are followed for existing pathways for reporting to National audits within the researchers field of practice.
e) Who will have access to this data, and for what purposes? All currently employed rehabilitation clinicians have access to the workplace systems and databases that hold the raw data for the purposes of their clinical work but only the researcher will have access to the researcher produced Excel and SPSS spreadsheets to create data sets on selected cases through their personal password secure laptop.
f) How will the data be stored, for how long, and how will it be discarded? As per government guidelines the raw data will be held on workplace secure databases and locked filing cabinets for 8 years. The data stored on the researchers personal laptop will be held for 10 years in accordance with Staffordshire University research policy. This will allow time for publication of research and assist answering queries following publication. Once this period has passed the paper records will be disposed through confidential waste within the workplace and the laptop files will be wiped clean.

Supporting Documentation

All key documents e.g. consent form, information sheet, questionnaire/interview schedule are appended to this application.	☒

Signature of Researcher:	S.J.Lockett	Date:	01/03/2021

NB: If the research departs from the protocol which provides the basis for this proportionate review, then further review will be required and the applicant and supervisor(s) should consider whether or not the proportionate review remains appropriate. If it is no longer appropriate a full ethical review form **MUST** be submitted for consideration by the School Ethics Coordinator .

Next Step:

STUDENTS: Please submit this form (and supporting documentation) for consideration by your Supervisor/ Module Tutor.

STAFF: Please submit this form to your Head of Department or a Senior Researcher in your School. Once they have reviewed the form, this should be forwarded to the Research Administrators in RIIS (ethics@staffs.ac.uk) who will arrange for it to be considered by an independent member of the School's College of Reviewers .

PART B: TO BE COMPLETED BY SUPERVISOR/MODULE TUTOR (If student) OR Head of Department/ Senior Researcher (if staff)

I consider that this project has no significant ethical implications requiring full ethical review by the Faculty Research Ethics Committee.	☒

I have checked and approved the key documents required for this proposal (e.g. consent form, information sheet, questionnaire, interview schedule).	☒

Signature of Supervisor/ Head of Department/ Senior Researcher:	R.Naemi	Date:	04.03.2021

Next Step: Please forward this form to the Research Administrators in RIIS (ethics@staffs.ac.uk) who will arrange for it to be considered by an independent member of the School's College of Ethical Reviewers , having no direct connection with the researcher or his/her programme of study.

PART C: TO BE COMPLETED BY A MEMBER OF THE SCHOOL'S COLLEGE OF ETHICAL REVIEWERS

This research proposal has been considered using agreed University Procedures and is now approved.	☐
Or	
This research proposal has not been approved due to the reasons given below.	☐
Recommendation (delete as appropriate): Approve/ Amendments required/ Reject	

Name of Reviewer:		Date:	
Signature:			

Signed (School Ethical Coordinator)		Date:	

Life Sciences and Education

ETHICAL APPROVAL FEEDBACK

Researcher name:	Sonya Lockett
Title of Study:	SU_20_123 The effectiveness of short-term rehabilitation programme of preoperative high intensity exercise and inspiratory muscle training to improve post-operative recovery in lung cancer patients undergoing surgical lung resection.
Status of approval:	Approved

Thank you for addressing the committee's comments. Your research proposal has now been approved by the Ethics Panel and you may commence the implementation phase of your study. You should note that any divergence from the approved procedures and research method will invalidate any insurance and liability cover from the University. You should, therefore, notify the Panel of any significant divergence from this approved proposal.

When your study is complete, please send the ethics committee an end of study report. A template can be found on the ethics BlackBoard site.

Signed: **Date: 24th May 2021**

Dr Edward Tolhurst
pp.Chair of the Life Sciences and Education Ethics Panel

Appendix 2 Example Exercise Profile

University Hospitals of North Midlands NHS
NHS Trust

DATE Fit and well?					
Resting HR					
Target HR 80% HRR					
Warm up Device Time/Speed					
Treadmill time/speed					
HR/RPE					
Cycle Time/watts					
HR/RPE					
Row Time/500 split					
HR/RPE					
Weight Upper limb					
Weight kg					
Sets/Reps					
Weight Upper limb					
Weight kg					
Sets/Reps					
Weight Lower Limb					
Weight kg					
Sets/Reps					
Weight Lower limb					
Weight kg					
Sets/Reps					
Cool Down					
Adverse events					

Appendix 3 Patient Information Sheet

University Hospitals of North Midlands NHS
NHS Trust

Optimisation of lung function through pre-operative rehabilitation and inspiratory muscle training to reduce post-operative pulmonary complications following lung resection surgery

Mrs Sonya Lockett: Cardiac Rehabilitation Department, Trent Building, University Hospital of North Midlands NHS Trust, Newcastle Road, Stoke-on-Trent, Staffordshire, ST4 6QG

Tel: 01782 674094 Email: Sonya.Meigh@uhnm.nhs.uk

PATIENT INFORMATION SHEET

Please take the time to read the following information carefully and decide whether or not you wish for your data to be used for service development and evaluation purposes. A member of the Rehabilitation Team will be available to go through this with you and answer any questions that you may have.

1. **What is the purpose of this study?**

This study aims to help lung cancer patients better prepare for an operation. It is hoped that by strengthening patient's respiratory muscles through exercise and inspiratory muscle training they will have a better recovery following their operation and spend less time in hospital.

2. **What device or procedure is being tested?**

The Team is evaluating preoperative rehabilitation and inspiratory muscle training. The preoperative rehabilitation will require patients to attend a community gym twice a week to complete ½ hour – ¾ hour of exercise guided by a physiotherapist or exercise physiologist. This exercise will include short bursts of high intensity exercise which is intended to make patients breathless for a short period of time. The inspiratory muscle trainer is a small hand-held device, where patients breathe in and out through a mouthpiece to open a valve and strengthen their respiratory muscles. Patients will be given this device at the start of the programme and the appropriate resistance for the valve will be set by a physiotherapist. Patients should use this trainer at home, twice a day for 15 minutes, or as instructed by the physiotherapist.

3. **Why have I been invited to take part?**

You have been chosen because you are over 65 years of age, have recently been given a diagnosis of lung cancer which is planned to be operated on in 2 -3 weeks. You will be one of several patients that we will ask to use your data to help us identify how we can better prepare lung cancer patients for their operation and improve their recovery following surgery.

4. **Do I have to take part?**

It is up to you to decide whether or not to take part in the programme and allow your data to be used for development and evaluation purposes. We will go through the information sheet with you. If you agree for your data to be used you will be asked to sign a consent form, but you are free to withdraw at any time without giving a reason. This will not affect your treatment or the standard of care you will receive.

5. **What will happen to me if I take part?**

Read through the information sheet and ask as many questions as you like of the Rehabilitation Team to ensure you understand your treatment. You will receive routine treatment with the addition of preoperative rehabilitation and inspiratory muscle training. You may also be asked to complete a number of questionnaires.

All patients will receive routine treatment that includes a consultation with a surgeon to discuss the operation and treatment options, a visit to a pre-operative clinic where a nurse and doctor will complete a preoperative

checklist and explain your hospital stay and access to a specialist lung cancer nurse to support you through your diagnosis and surgery. Surgery will usually be planned for 2 -3 weeks following the consultation with the surgeon. During this time you will take part in exercise classes and use the inspiratory muscle trainer at home.

6. Expenses and Payments

There are no additional payments related to this evaluation.

7. What are the possible risks and disadvantages of taking part?

You will be exercising twice a week for two weeks before your operation. This exercise is intended to make your short of breath for a short period of time and if you are not used to exercise you may find that you get some muscle aching for a few days.

8. What are the possible benefits of taking part?

You will be closely monitored and followed-up by a health professional throughout the time in the rehabilitation programme and your data will be reviewed 12 months after surgery. You will have some important lung function tests completed prior to your operation. By agreeing to take part, we are hoping to better understand how to prepare lung cancer patients for surgery and plan future care.

9. What happens when the research stops?

This study is expected to take place over 3 years. At the end of the study we plan to publish the findings in medical journals or present them at medical conferences. You will not be identifiable in any reports or publications resulting from this study. If the findings from the study result in a change of practice we will produce information leaflets and posters to help inform future patients and recommendations of change in practice may be made available nationally throughout the National Health Service and within the hospital.

10. What if there is a problem?

If you have a complaint about any aspect of this study or the staff involved and wish to complain formally, you can do this through the NHS complaints procedure at the University Hospital of North Midlands NHS Trust, (telephone: 01782 555481). Alternatively, you can contact Service Lead Sonya.Meigh@uhnm.nhs.uk

You can also find further information on ethics in research on the National Research Ethics Service website (www.nres.npsa.nhs.uk)

11. Will my taking part be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. A copy of your contact details and signed consent form will be held by the Rehabilitation Team but all other information will be given a unique study number to ensure anonymity. No electronic version of the consent form will be kept. All patient information stored is kept on a password protected computer database or in locked filing cabinets and will not be accessed by anyone outside of the researcher.

12. What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens the Service Lead will tell you and discuss whether you should continue with the programme. If you decide not to carry on, your Surgeon will make arrangements for your care to continue. If you do decide to continue in the study he may ask you to sign an agreement outlining the discussion.

13. What if I change my mind about taking part?

If you initially consent to your data being used and then change your mind during the treatment, you can continue to receive rehabilitation but your results will not be used for the evaluation. If you withdraw from the programme you will not be contacted by the Rehabilitation team further, or be required to complete additional questionnaires. However you will be asked if any data collected up to the point of withdrawal can be retained and used for evaluation.

14. Who is organising and funding the research?

The study is organised and sponsored by the University Hospital of North Midlands NHS Trust.

15. Who has reviewed this study?

The programme and the intended evaluation has been reviewed by your thoracic surgical team, the rehabilitation team and the NHS Cardiothoracic Directorate.

16. Further information

If you require more information about this study, please call on of the telephone numbers provided to speak to a member of the rehabilitation team

THANK YOU FOR READING

If you have any questions or would like more information please contact the research study team

Sonya Meigh (Advanced Physiotherapist) Email: Sonya.Meigh@uhns.nhs.uk Tel: 01782 674094
University Hospital of North Midlands NHS Trust, City General, Newcastle Road, Stoke-on-Trent, Staffordshire, ST4 6QG

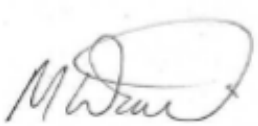
Appendix 4 Directorate Data Permission Letter

University Hospitals of North Midlands NHS
NHS Trust

To whom it may concern,

I hereby give my permission for Sonya Jayne Lockett to access the University Hospital of North Midland NHS Trust electronic systems and Departmental Databases for the purposes of her Doctoral Research investigating preoperative intervention on postoperative recovery following Thoracic Surgery. I understand that the use of NHS electronic resources will be required by her to obtain information relevant for the study and data entry and storage of this information will be anonymised, at the point of entry, and held confidentially. Access to UHNM NHS Trust electronic systems, including IPortal, Medisec and UHNM Cardiac Rehabilitation Admin and Clinical databases will take place on the Royal Stoke University Hospital site within the Cardiac Rehabilitation Department. Sonya has had prior training in using all of these systems and has existing and relevant access permissions, she is familiar with these systems and uses them regularly for her patient-caseload in her role as Service Lead and Advanced Physiotherapist in Cardiac Rehabilitation and therefore no additional training or approvals for access will be required in advance. The Cardiology Directorate and Heart Centre are fully supportive of this study.

Yours sincerely



Matthew Warrilow

Deputy Associate Director – Specialised Division
Directorate Manager, Heart Centre

Heart Centre
Ground Floor, Trent Building
Royal Stoke University Hospital & County Sites
University Hospitals of North Midlands NHS Trust
Newcastle Road, Stoke-on-Trent, Staffordshire, ST4 6QG

Appendix 5 NHS Quality Assurance Permission Letter

NHS
University Hospitals of North Midlands
NHS Trust

Royal Stoke University Hospital
Quality, Safety and Compliance Department
Newcastle Road
Stoke-on-Trent
Staffordshire
ST4 6QG
Tel: 01782 (6)76476
Email victoria.lewis@uhnm.nhs.uk

Dear Sir / Madame,

UHNM Cardiac Rehabilitation – Service Evaluation

I write regarding the above service evaluation project.

I can confirm that the Trust is happy for Sonya Lockett, Service Lead to undertake the project as stipulated in the project proposal form.

If you require any further information, then please do not hesitate to contact me.

Kind regards

VICTORIA LEWIS
Quality Assurance Manager

Appendix 6 EORTC QLQ-C30 Extract

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

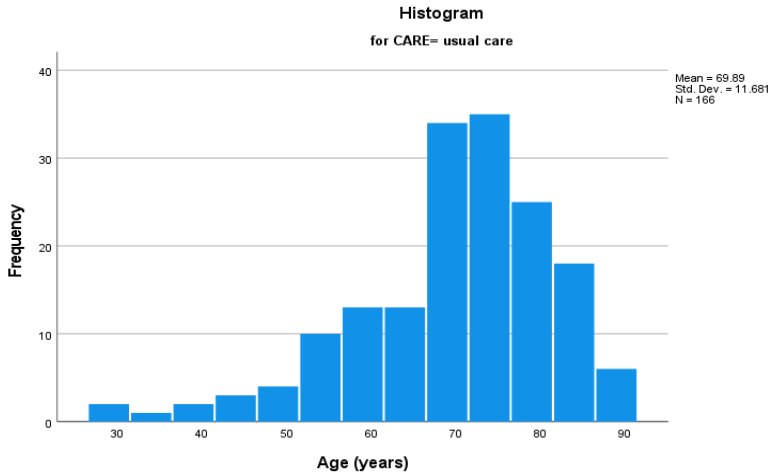
1	2	3	4	5	6	7
Very poor						Excellent

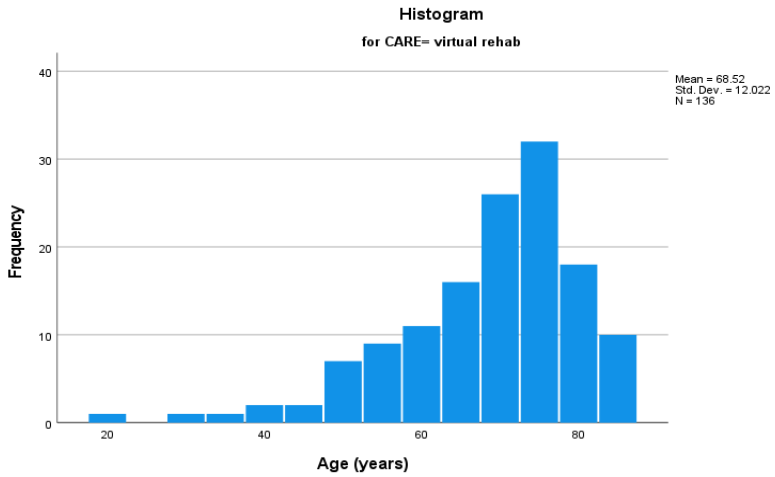
30. How would you rate your overall quality of life during the past week?

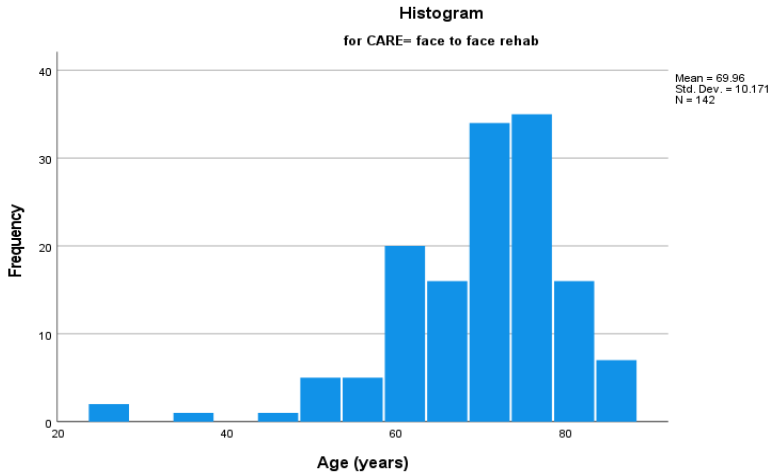
1	2	3	4	5	6	7
Very poor						Excellent

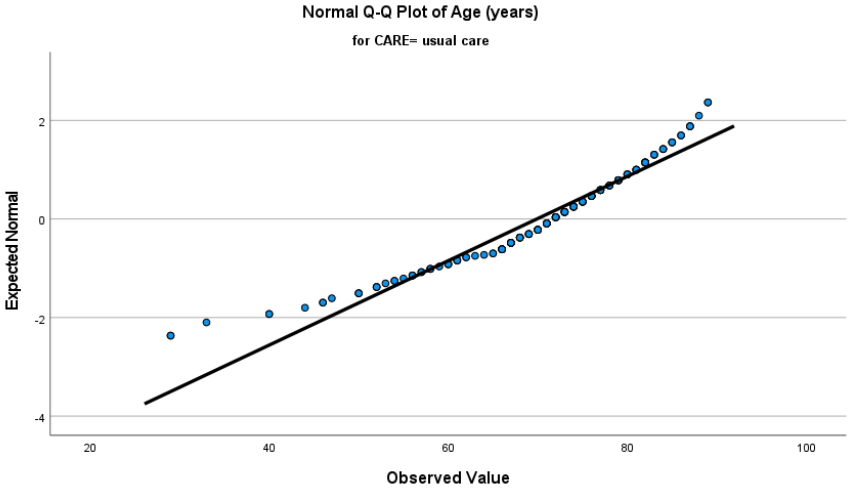
Appendix 7 Histograms and Q-Q plots for Baseline Characteristics

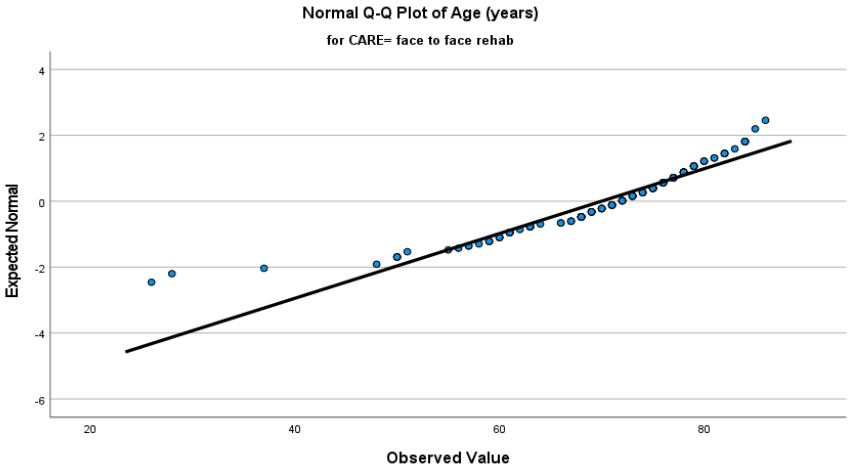
Age

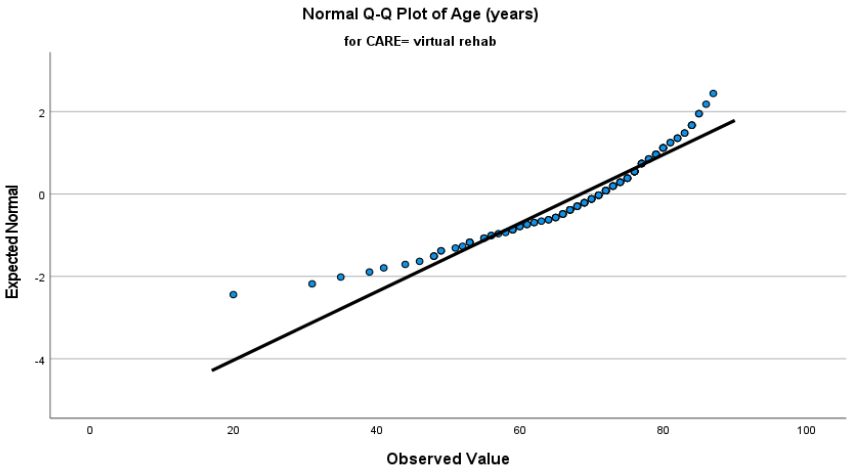




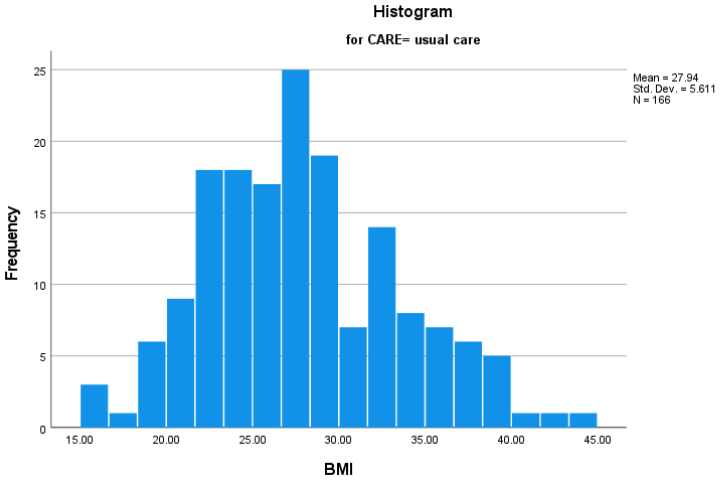


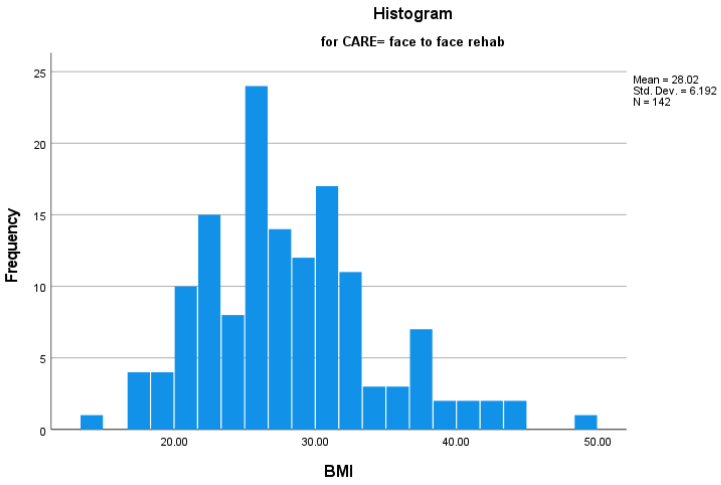

Normal Q-Q Plot of Age (years)
for CARE= usual care
Expected Normal
2
0
-2
-4
20
40
60
80
100
Observed Value

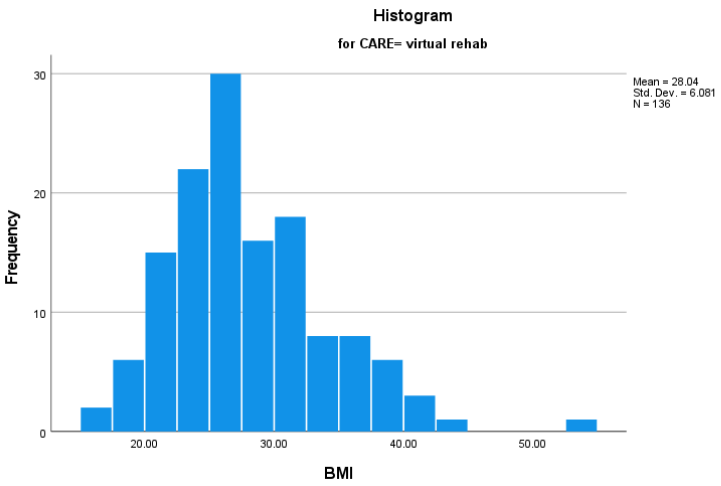

Normal Q-Q Plot of Age (years)
for CARE= face to face rehab
Expected Normal
4
2
0
-2
-4
-6
20
40
60
80
Observed Value

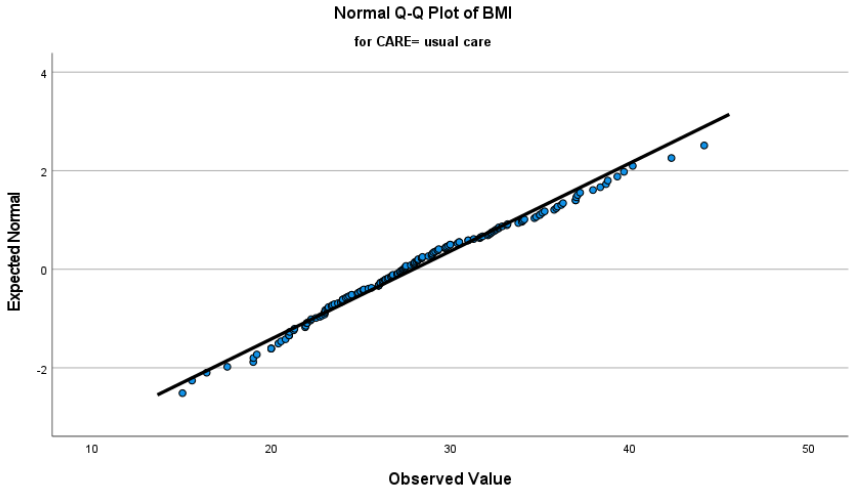

Normal Q-Q Plot of Age (years)
for CARE= virtual rehab
Expected Normal
2
0
-2
-4
0
20
40
60
80
100
Observed Value

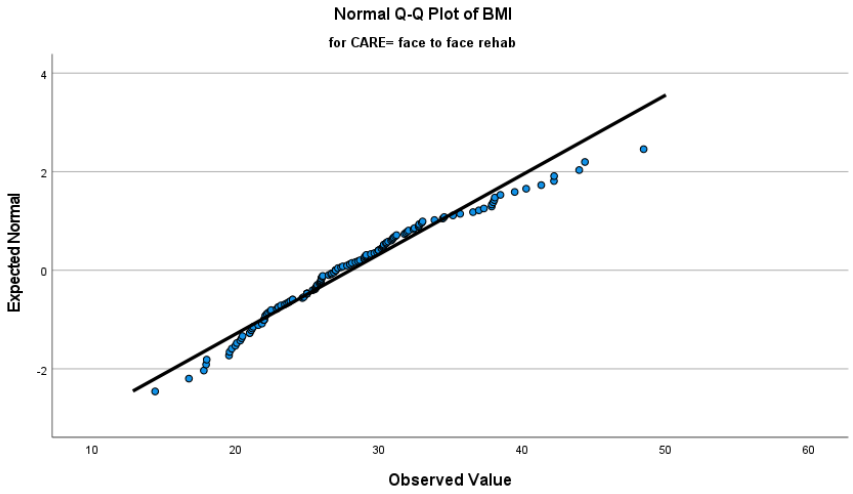
BMI

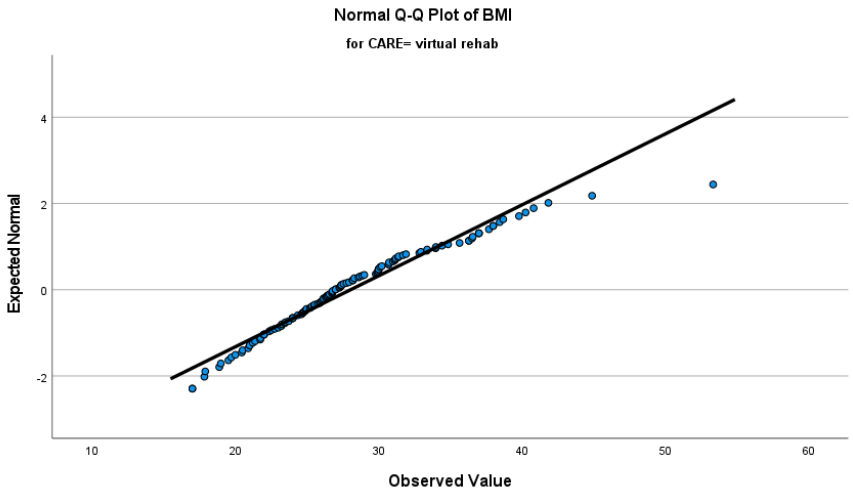

Histogram
for CARE= usual care
Mean = 27.94
Std. Dev. = 5.611
N = 166
Frequency
BMI


Histogram
for CARE= face to face rehab
Mean = 28.02
Std. Dev. = 6.192
N = 142
Frequency
BMI

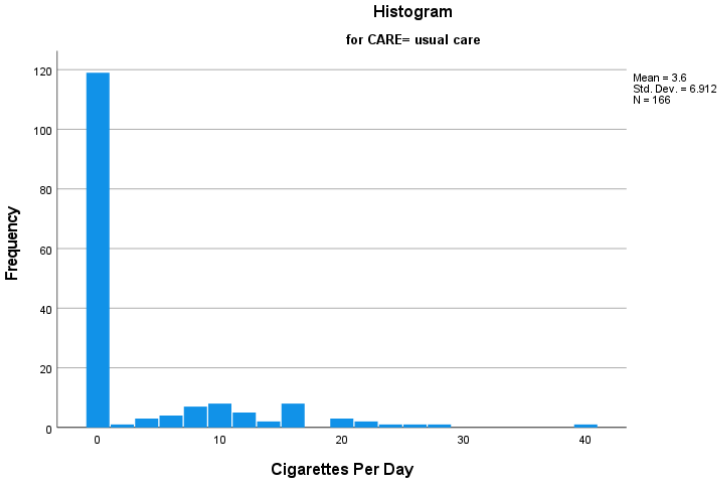

Histogram
for CARE= virtual rehab
Mean = 28.04
Std. Dev. = 6.081
N = 136
Frequency
BMI

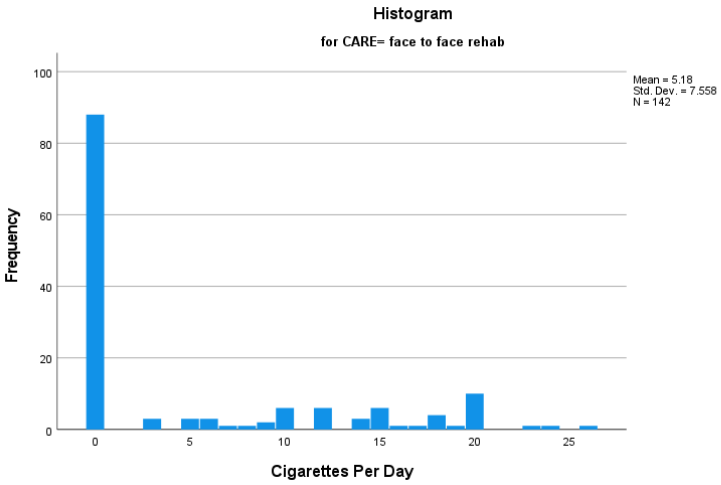

Normal Q-Q Plot of BMI
for CARE= usual care
Expected Normal
Observed Value
4
2
0
-2
10
20
30
40
50

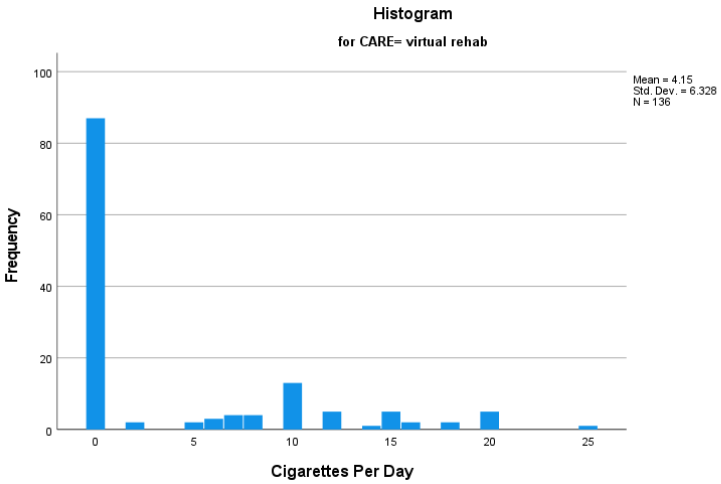

Normal Q-Q Plot of BMI
for CARE= face to face rehab
Expected Normal
Observed Value
4
2
0
-2
10
20
30
40
50
60

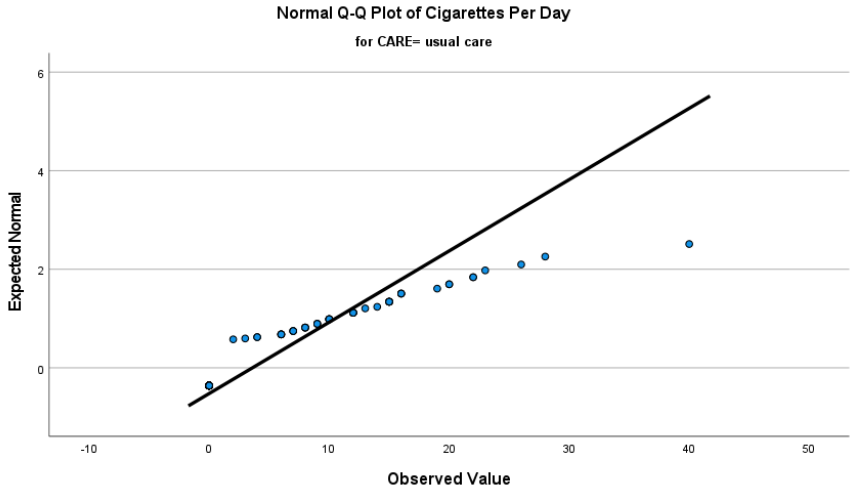

Normal Q-Q Plot of BMI
for CARE= virtual rehab
Expected Normal
Observed Value
4
2
0
-2
10
20
30
40
50
60

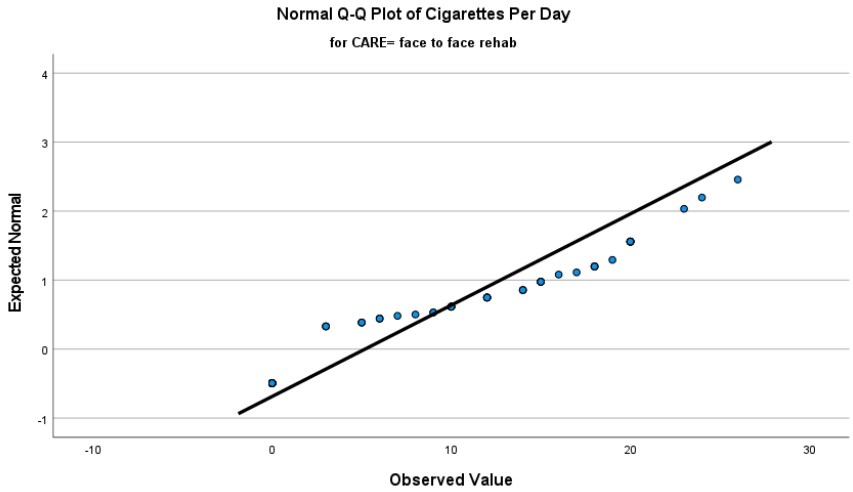
Cigarettes Per Day

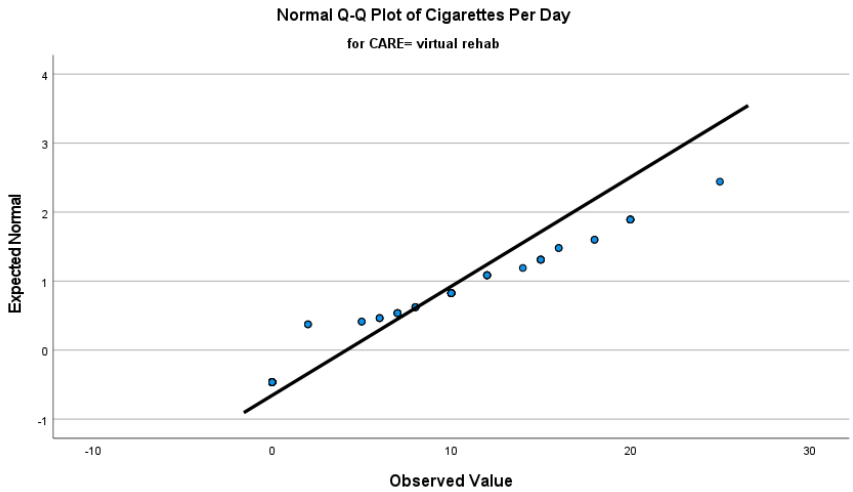




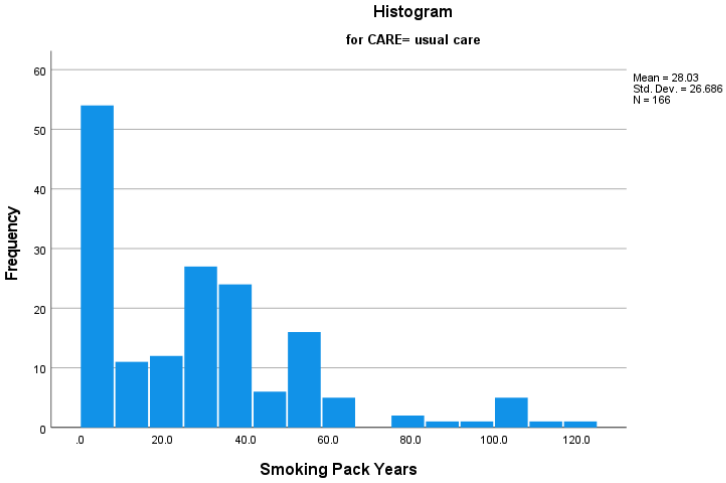


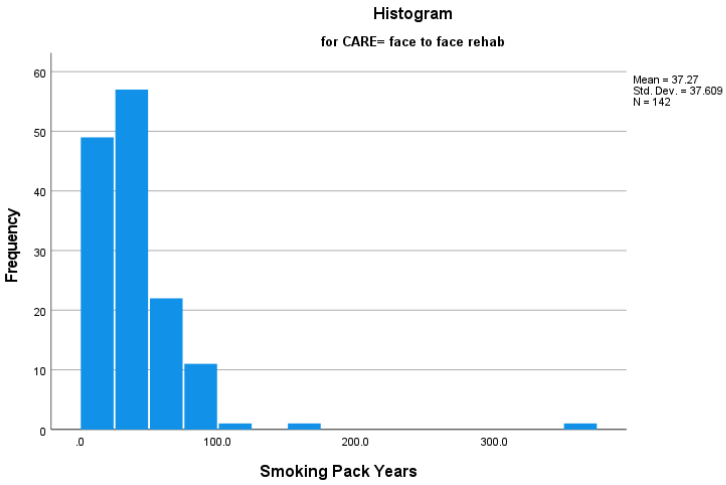

Normal Q-Q Plot of Cigarettes Per Day
for CARE= usual care
Expected Normal
Observed Value
6
4
2
0
-10
0
10
20
30
40
50

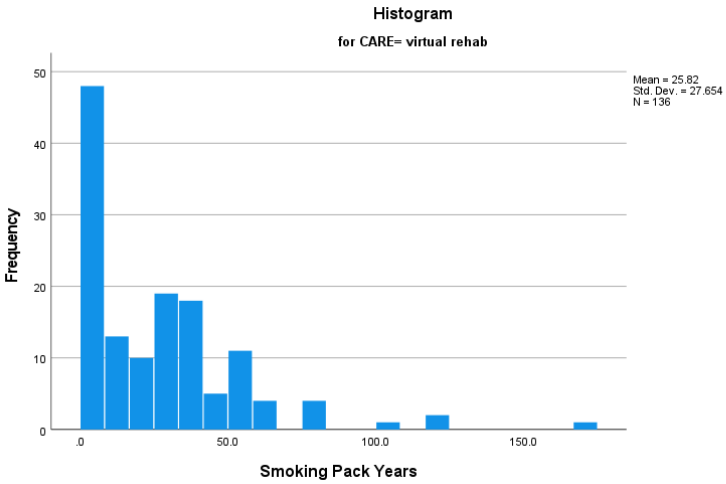

Normal Q-Q Plot of Cigarettes Per Day
for CARE= face to face rehab
Expected Normal
Observed Value
4
3
2
1
0
-1
-10
0
10
20
30

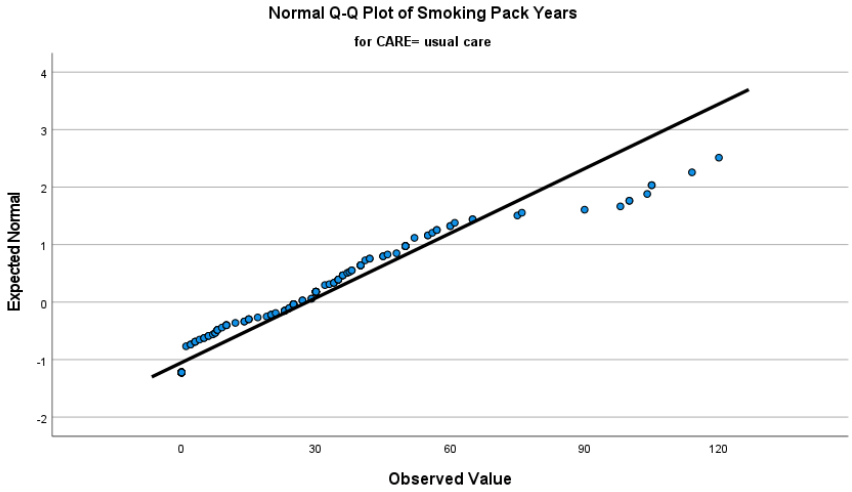

Normal Q-Q Plot of Cigarettes Per Day
for CARE= virtual rehab
Expected Normal
Observed Value
4
3
2
1
0
-1
-10
0
10
20
30

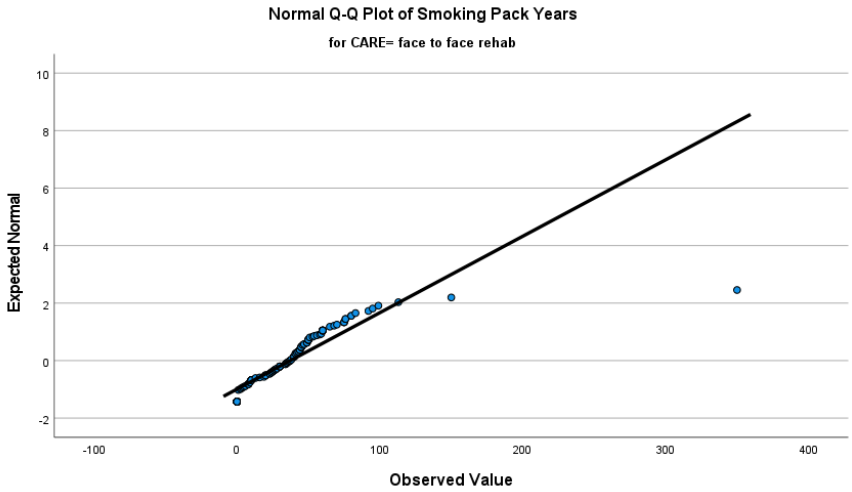
Smoking Pack Years

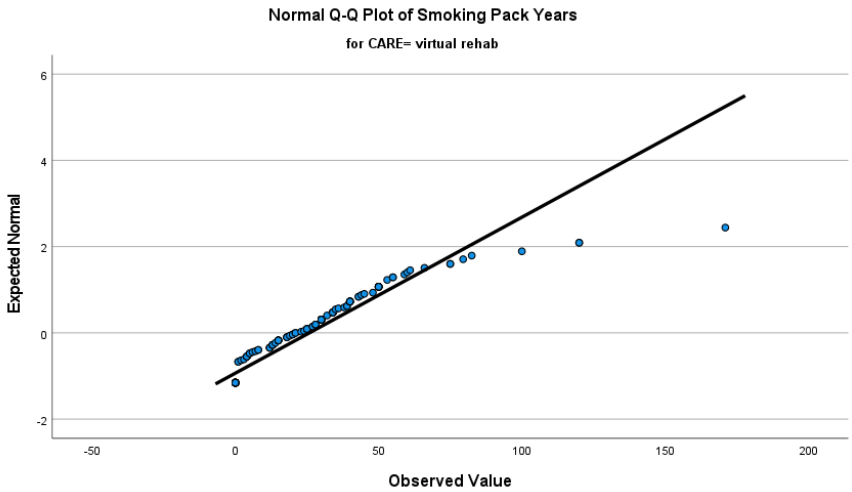




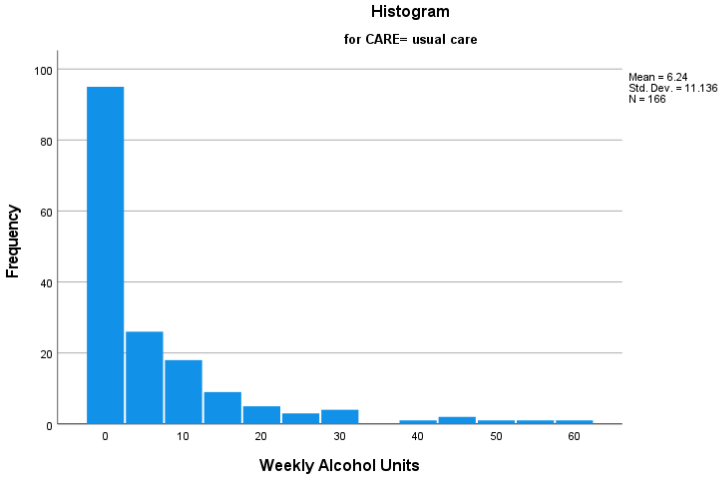


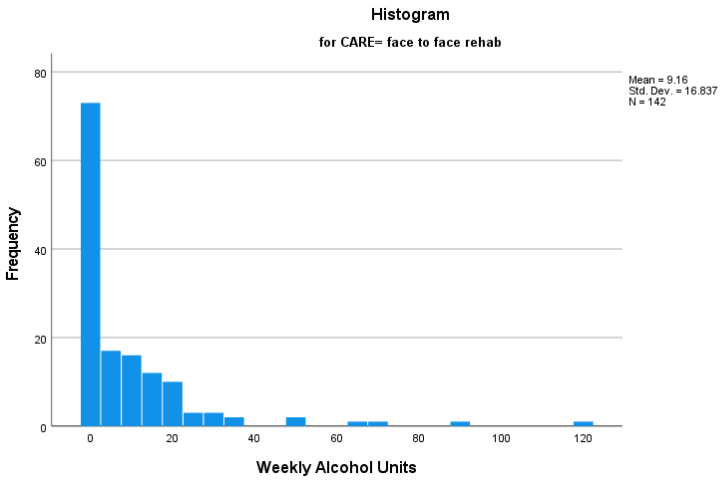

Normal Q-Q Plot of Smoking Pack Years
for CARE= usual care
Expected Normal
Observed Value
4
3
2
1
0
-1
-2
0
30
60
90
120

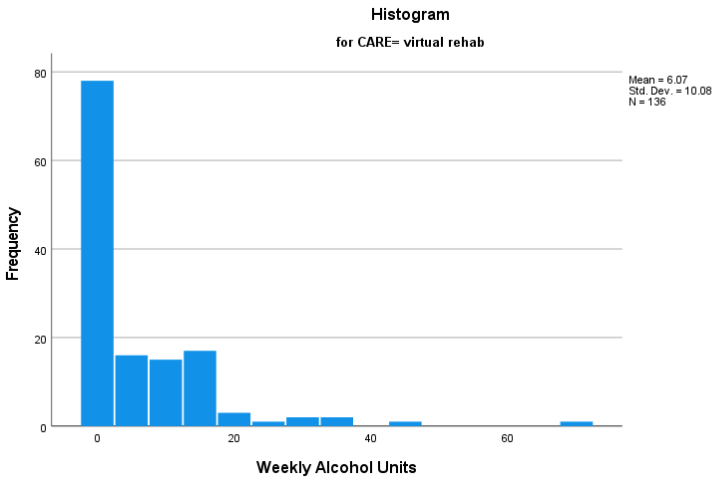

Normal Q-Q Plot of Smoking Pack Years
for CARE= face to face rehab
Expected Normal
Observed Value
10
8
6
4
2
0
-2
-100
0
100
200
300
400

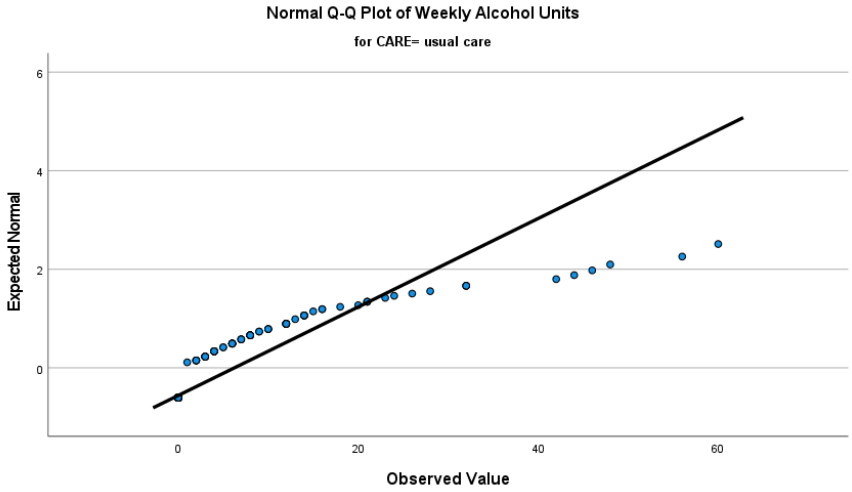

Normal Q-Q Plot of Smoking Pack Years
for CARE= virtual rehab
Expected Normal
Observed Value
6
4
2
0
-2
-50
0
50
100
150
200

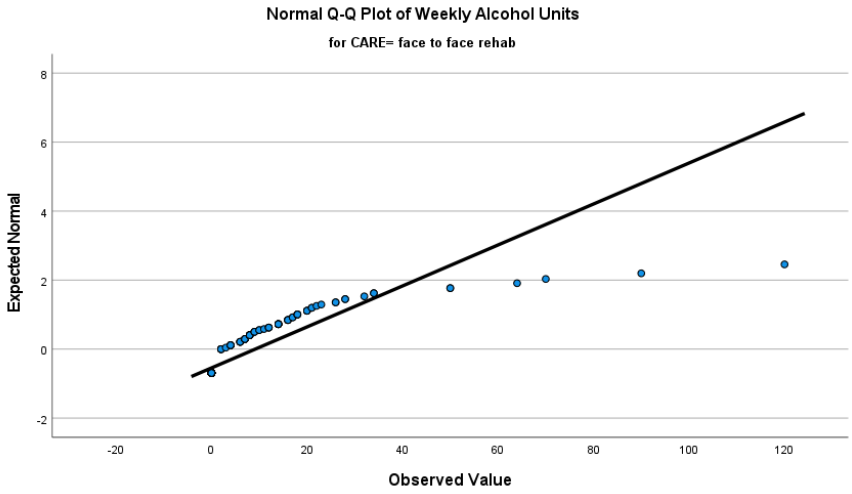
Alcohol Units Per Week

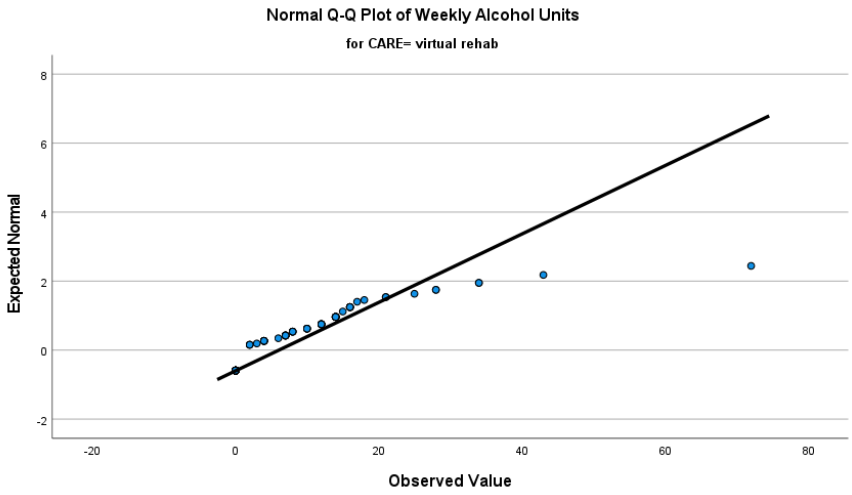




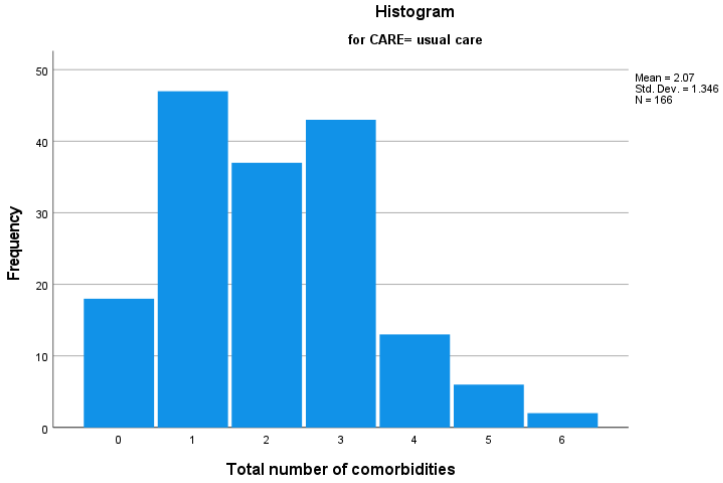


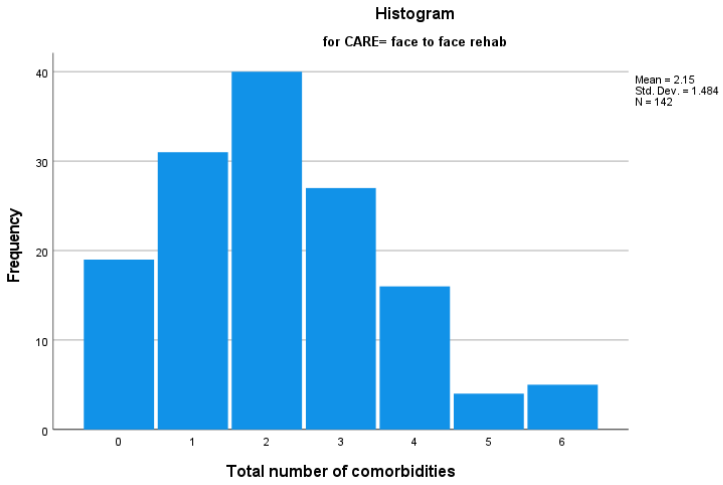

Normal Q-Q Plot of Weekly Alcohol Units
for CARE= usual care
Expected Normal
Observed Value
6
4
2
0
0
20
40
60

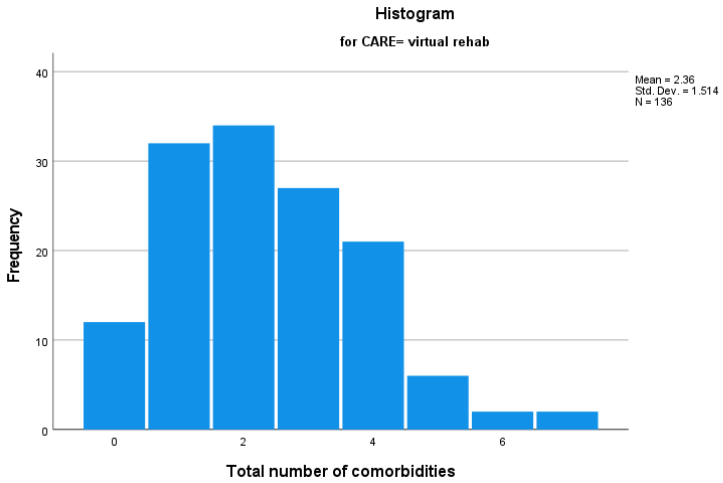

Normal Q-Q Plot of Weekly Alcohol Units
for CARE= face to face rehab
Expected Normal
Observed Value
8
6
4
2
0
-2
-20
0
20
40
60
80
100
120

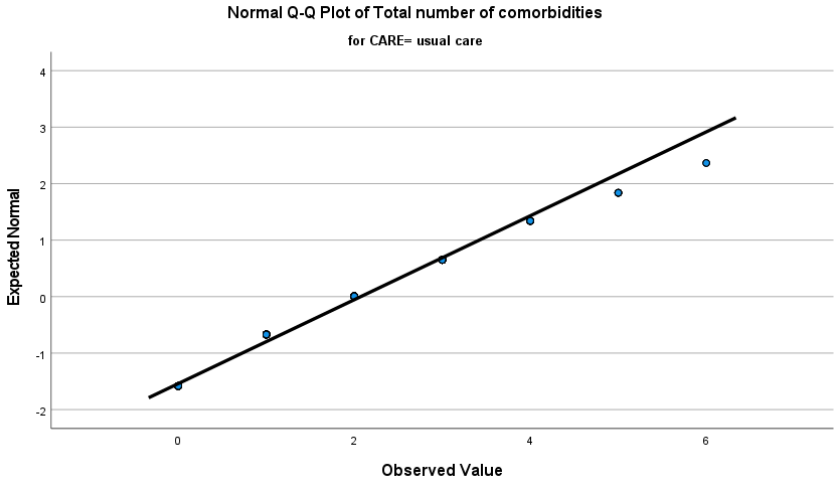

Normal Q-Q Plot of Weekly Alcohol Units
for CARE= virtual rehab
Expected Normal
Observed Value
8
6
4
2
0
-2
-20
0
20
40
60
80

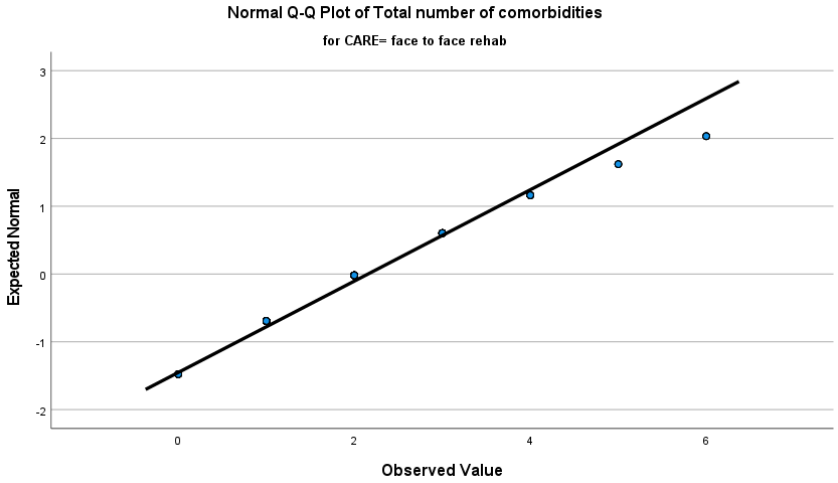
Number of Comorbidities

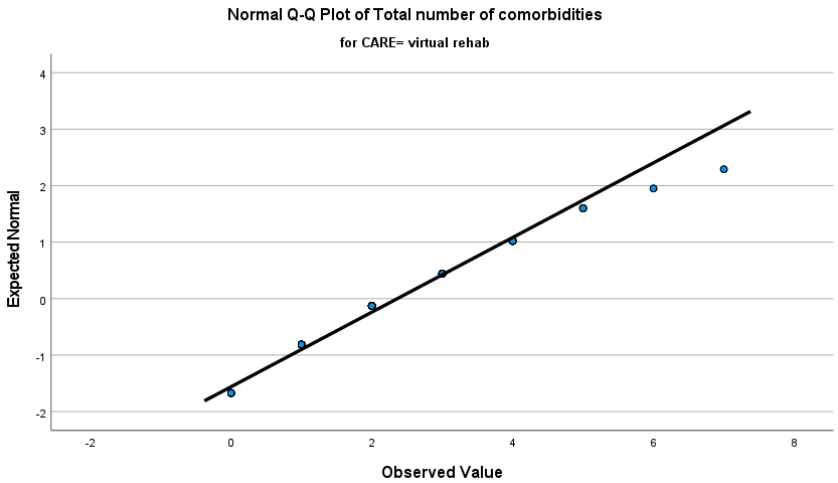






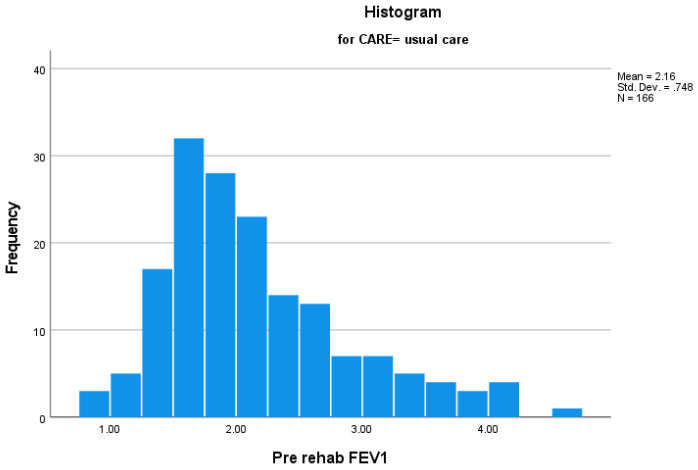

Normal Q-Q Plot of Total number of comorbidities
for CARE= usual care
Expected Normal
Observed Value
4
3
2
1
0
-1
-2
0
2
4
6

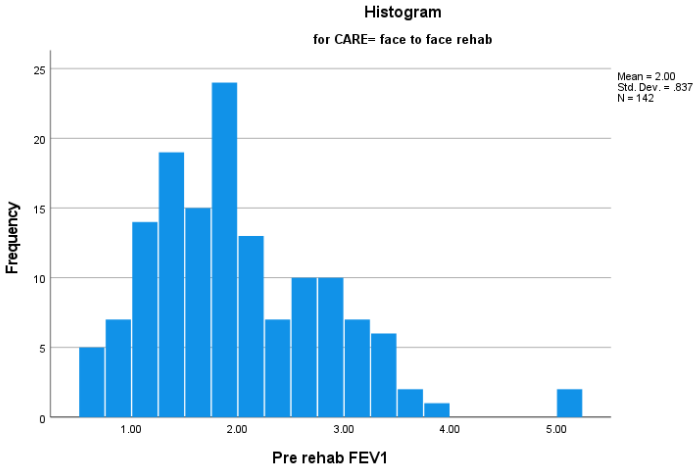

Normal Q-Q Plot of Total number of comorbidities
for CARE= face to face rehab
Expected Normal
Observed Value
3
2
1
0
-1
-2
0
2
4
6

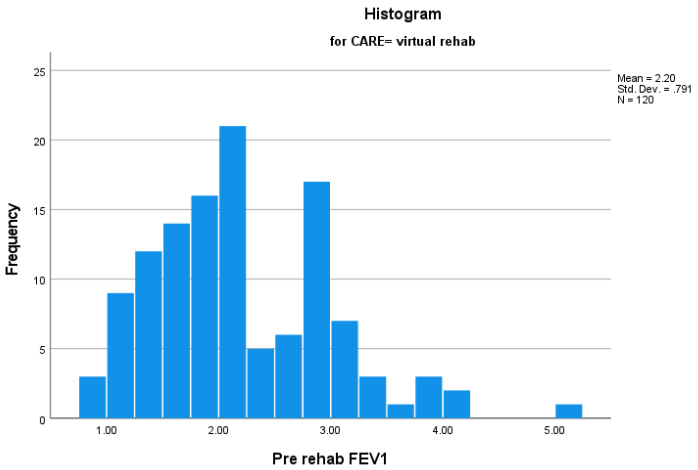

Normal Q-Q Plot of Total number of comorbidities
for CARE= virtual rehab
Expected Normal
Observed Value
4
3
2
1
0
-1
-2
-2
0
2
4
6
8

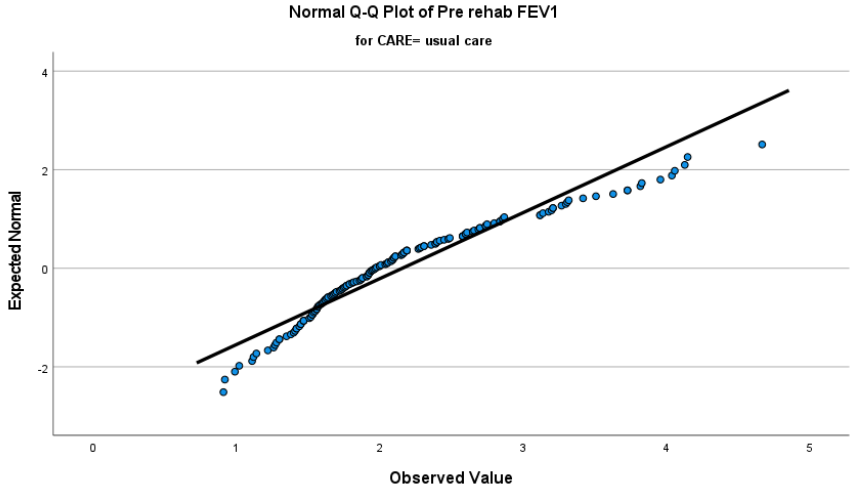
Appendix 8 Histograms and Q-Q plots for Preoperative Pulmonary Function

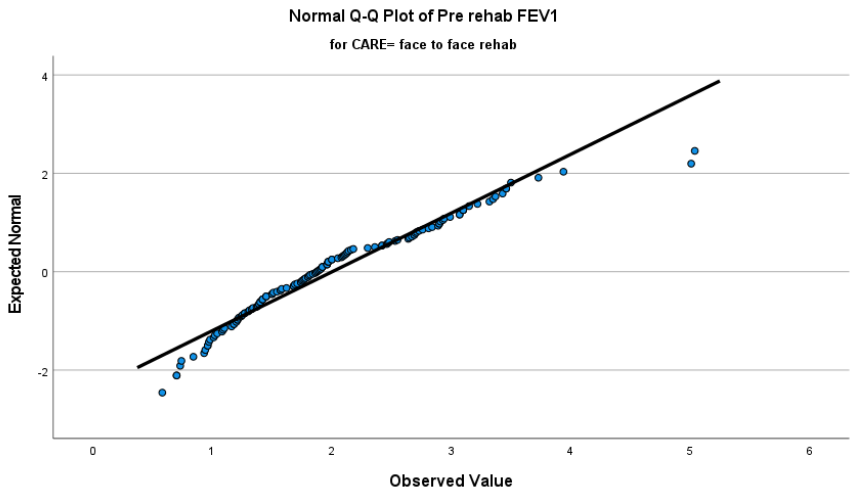
Preoperative FEV1

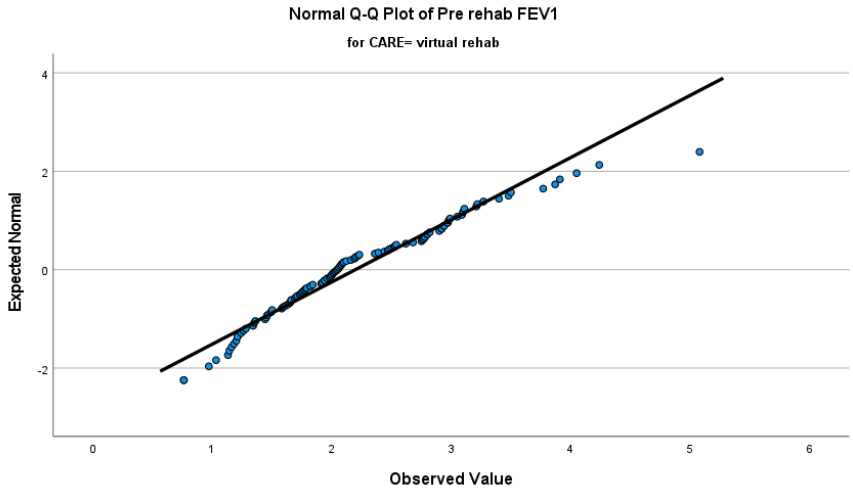




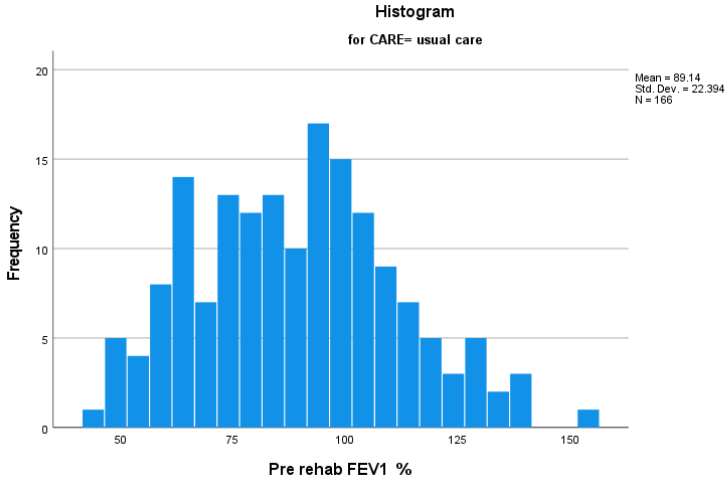


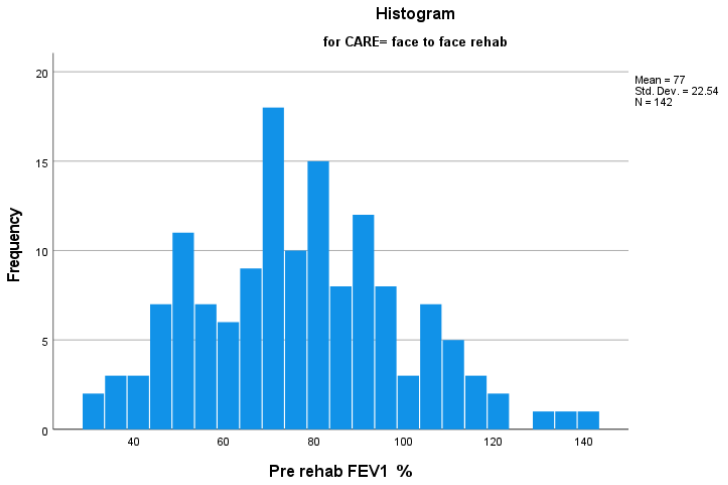

Normal Q-Q Plot of Pre rehab FEV1
for CARE= usual care
Expected Normal
Observed Value
4
2
0
-2
0
1
2
3
4
5

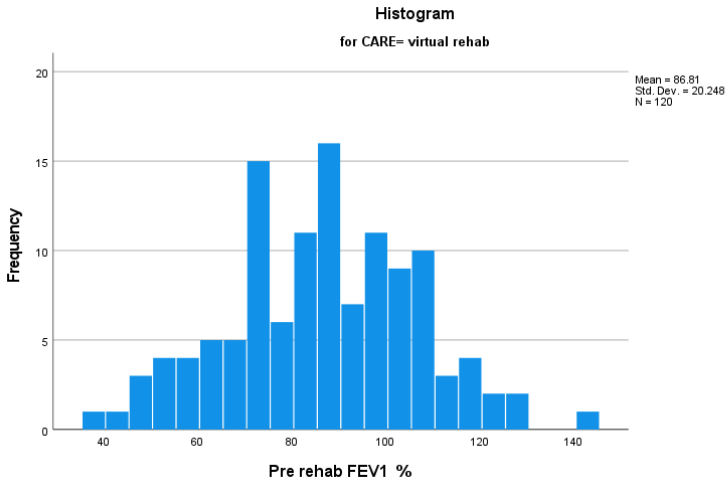

Normal Q-Q Plot of Pre rehab FEV1
for CARE= face to face rehab
Expected Normal
Observed Value
4
2
0
-2
0
1
2
3
4
5
6

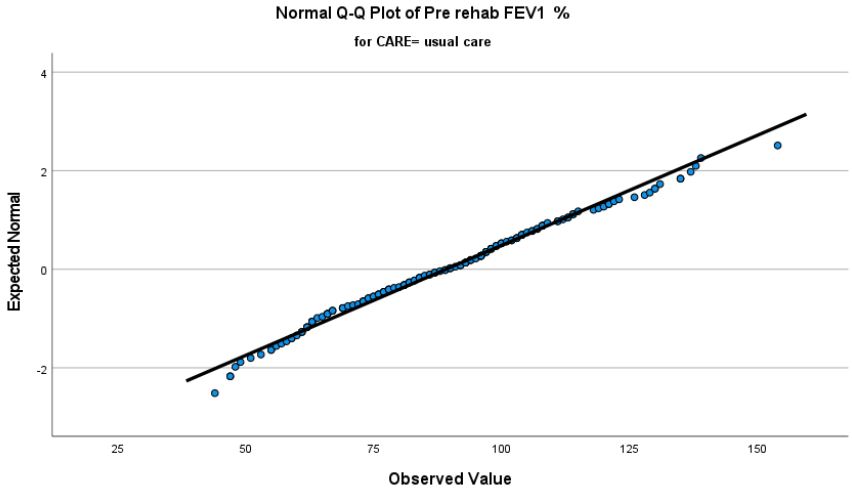

Normal Q-Q Plot of Pre rehab FEV1
for CARE= virtual rehab
Expected Normal
Observed Value
4
2
0
-2
0
1
2
3
4
5
6

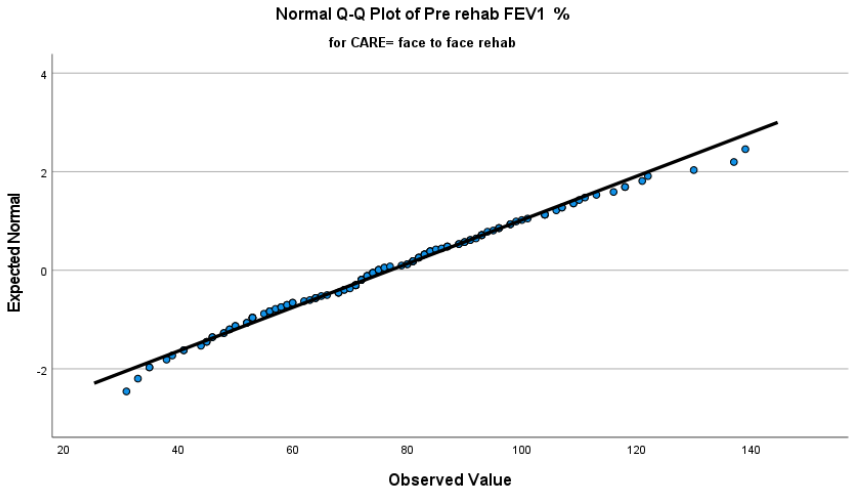
Preoperative Percentage Predicted FEV1

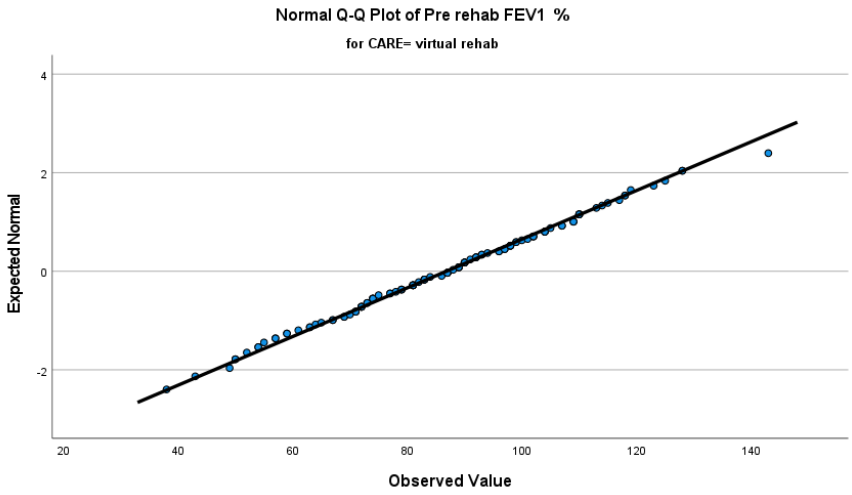




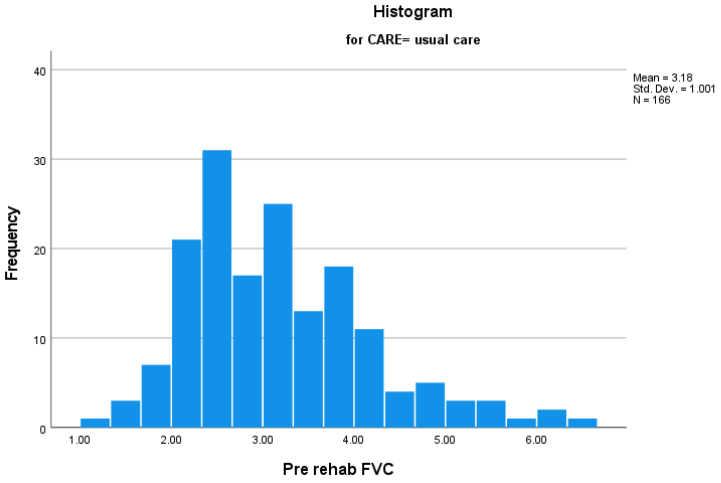


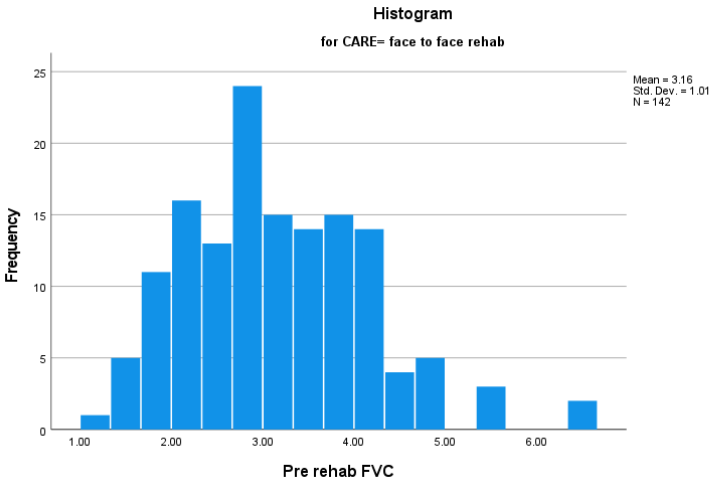

Normal Q-Q Plot of Pre rehab FEV1 %
for CARE= usual care
Expected Normal
Observed Value
4
2
0
-2
25
50
75
100
125
150

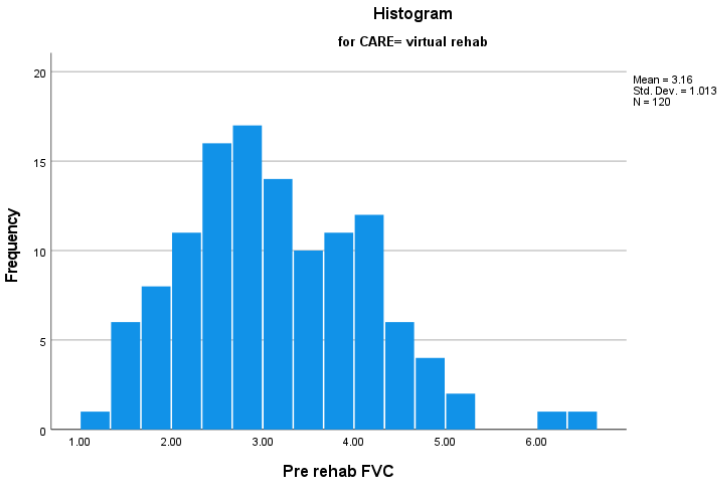

Normal Q-Q Plot of Pre rehab FEV1 %
for CARE= face to face rehab
Expected Normal
Observed Value
4
2
0
-2
20
40
60
80
100
120
140

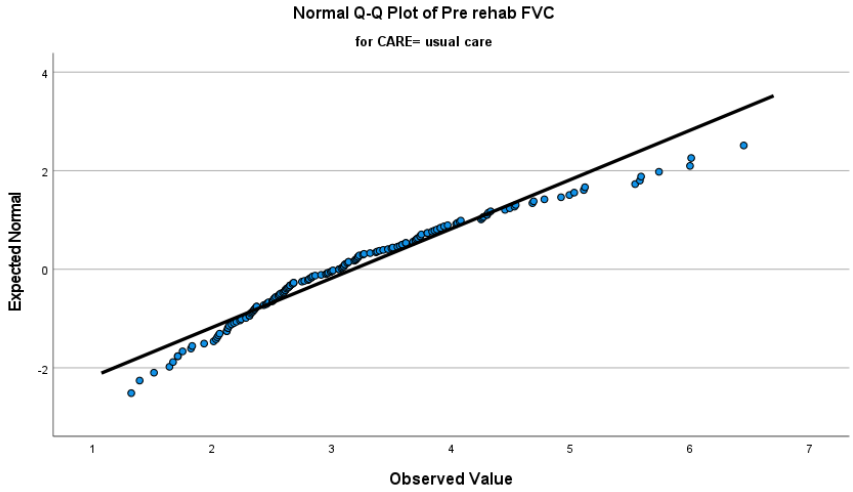

Normal Q-Q Plot of Pre rehab FEV1 %
for CARE= virtual rehab
Expected Normal
Observed Value
4
2
0
-2
20
40
60
80
100
120
140

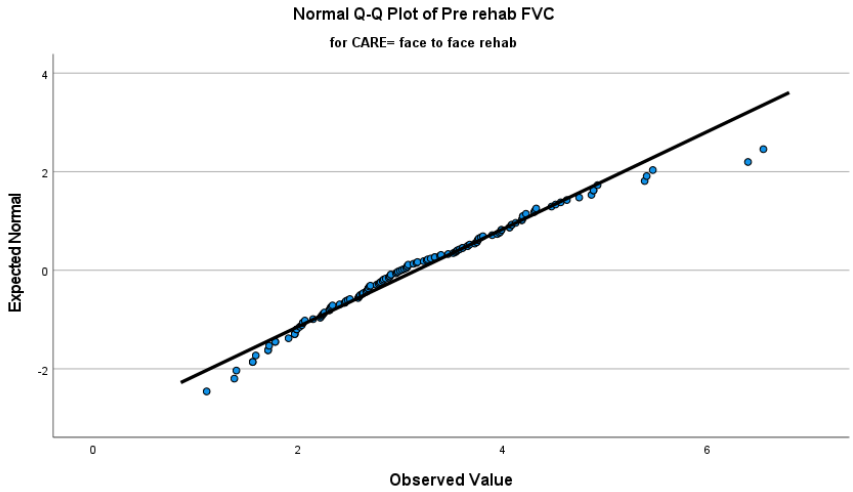
Preoperative FVC

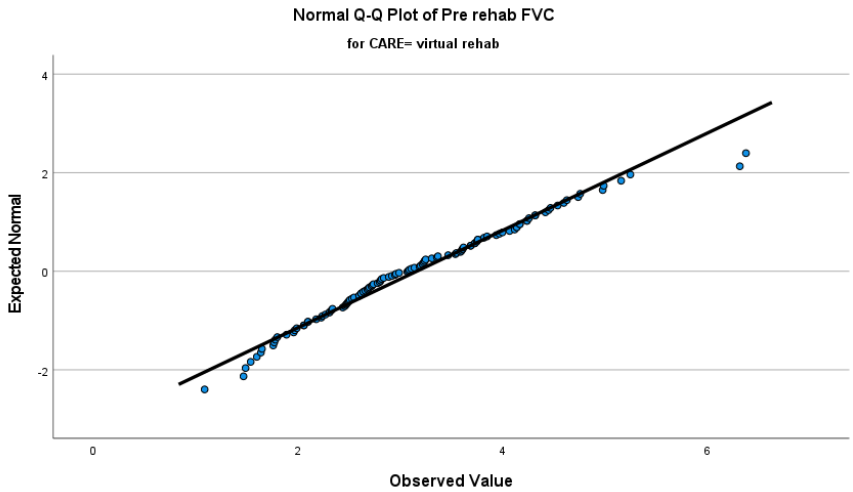




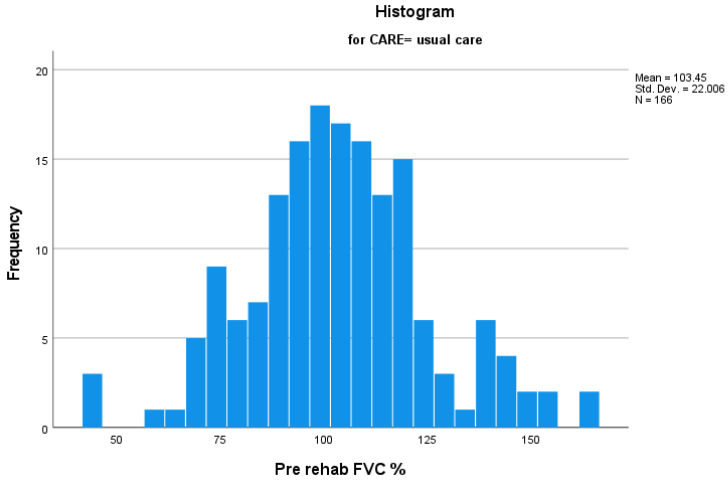


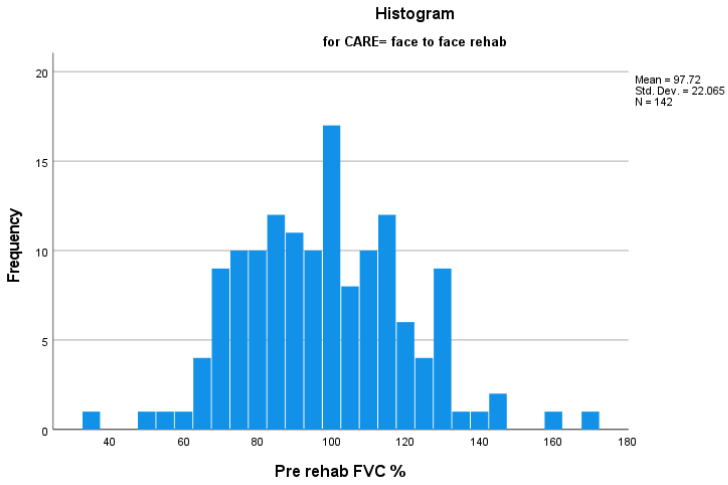

Normal Q-Q Plot of Pre rehab FVC
for CARE= usual care
Expected Normal
Observed Value
4
2
0
-2
1
2
3
4
5
6
7

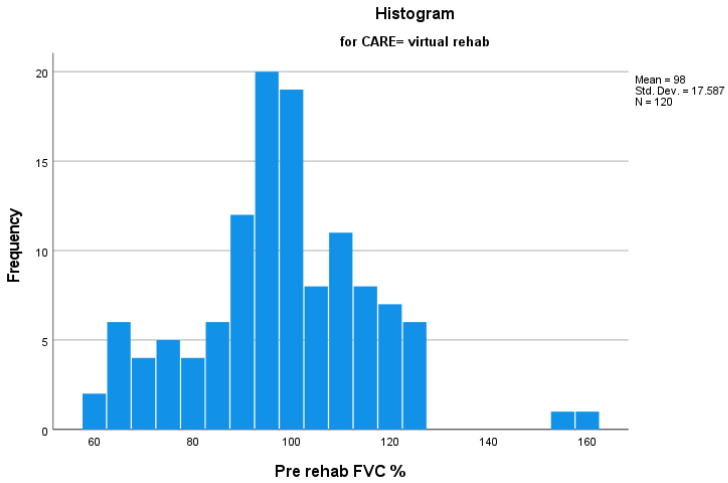

Normal Q-Q Plot of Pre rehab FVC
for CARE= face to face rehab
Expected Normal
Observed Value
4
2
0
-2
0
2
4
6

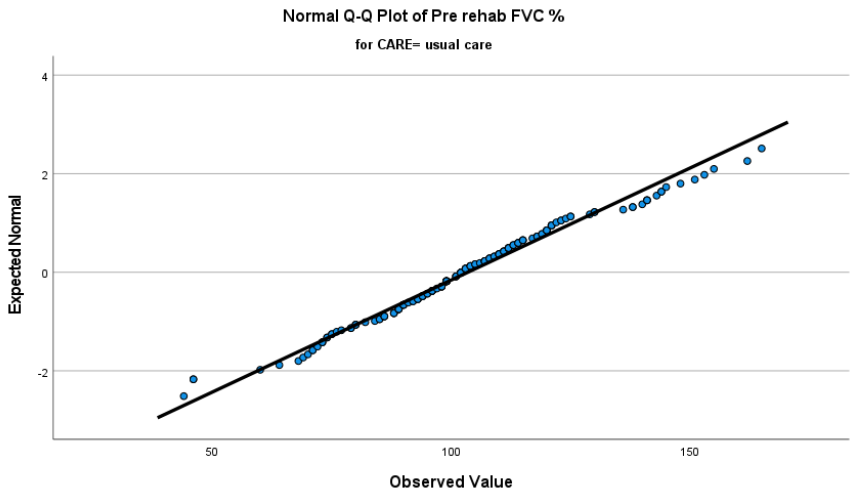

Normal Q-Q Plot of Pre rehab FVC
for CARE= virtual rehab
Expected Normal
Observed Value
4
2
0
-2
0
2
4
6

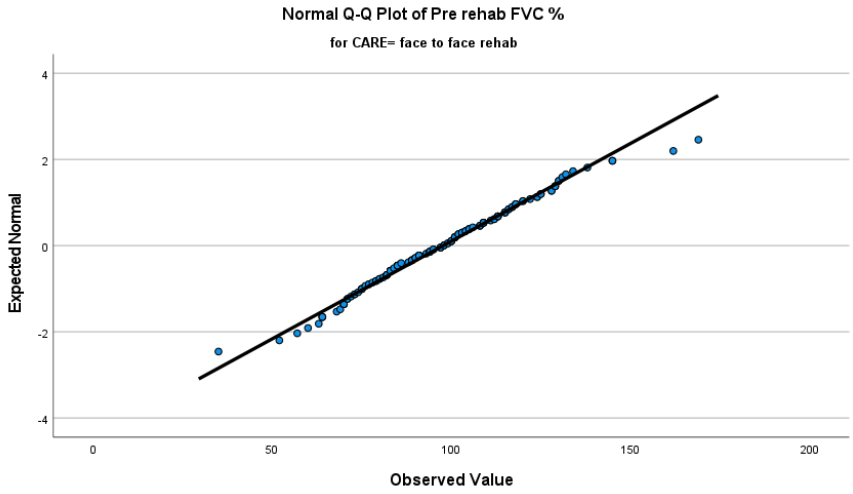
Preoperative Percentage predicted FVC

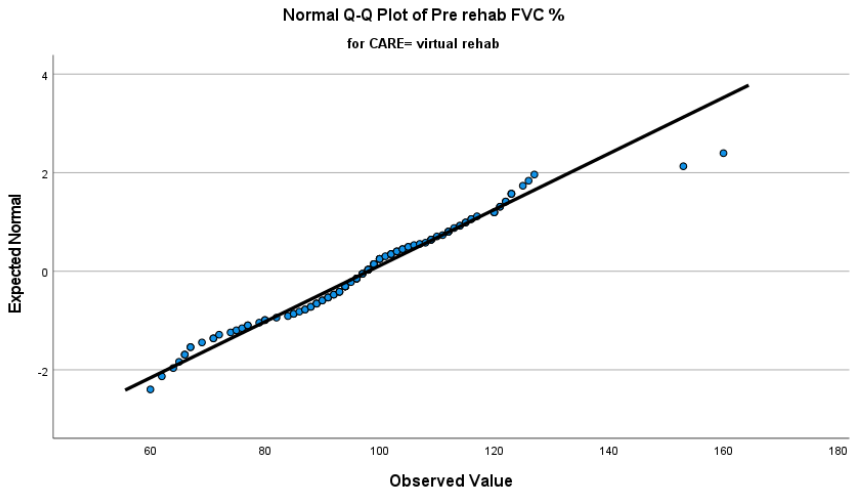




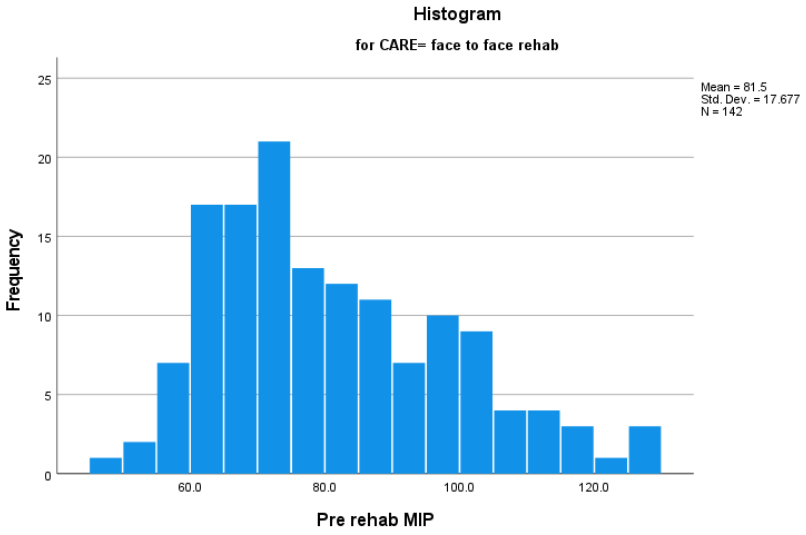


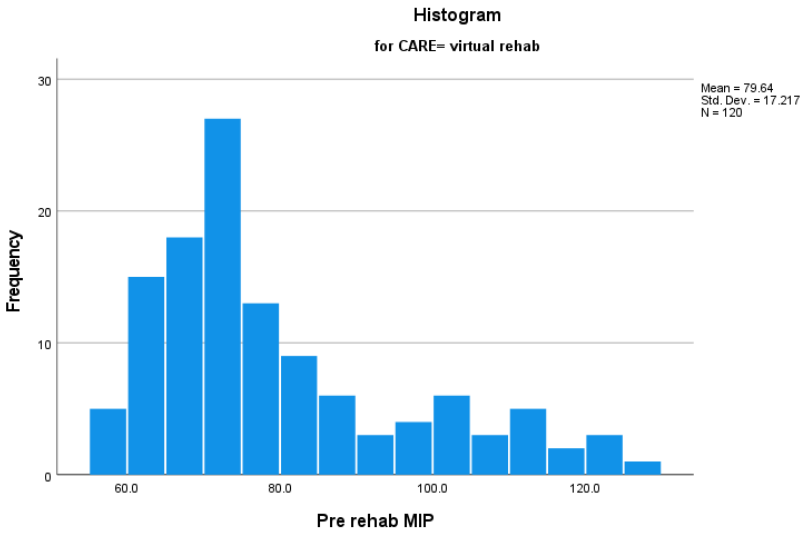

Normal Q-Q Plot of Pre rehab FVC %
for CARE= usual care
Expected Normal
Observed Value
4
2
0
-2
50
100
150

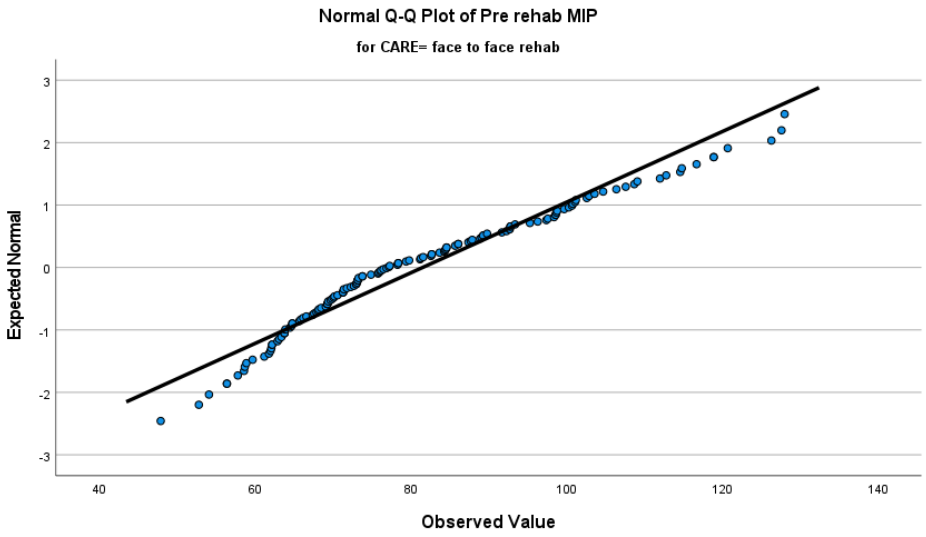

Normal Q-Q Plot of Pre rehab FVC %
for CARE= face to face rehab
Expected Normal
Observed Value
4
2
0
-2
-4
0
50
100
150
200

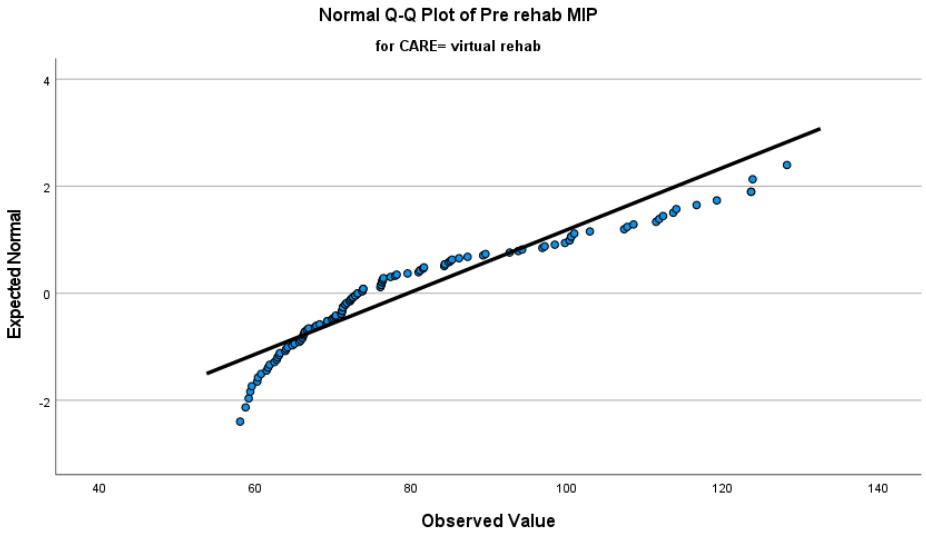

Normal Q-Q Plot of Pre rehab FVC %
for CARE= virtual rehab
Expected Normal
Observed Value
4
2
0
-2
60
80
100
120
140
160
180

Preoperative piMAX





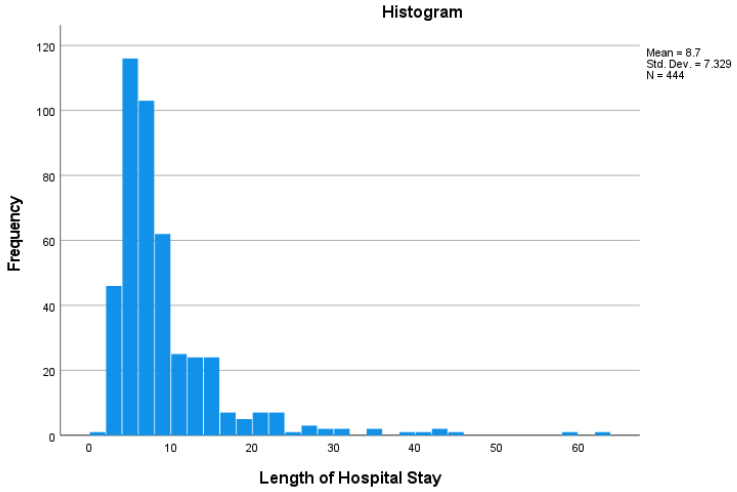

Normal Q-Q Plot of Pre rehab MIP
for CARE= face to face rehab
Expected Normal
Observed Value
3
2
1
0
-1
-2
-3
40
60
80
100
120
140


Normal Q-Q Plot of Pre rehab MIP
for CARE= virtual rehab
Expected Normal
Observed Value
4
2
0
-2
40
60
80
100
120
140

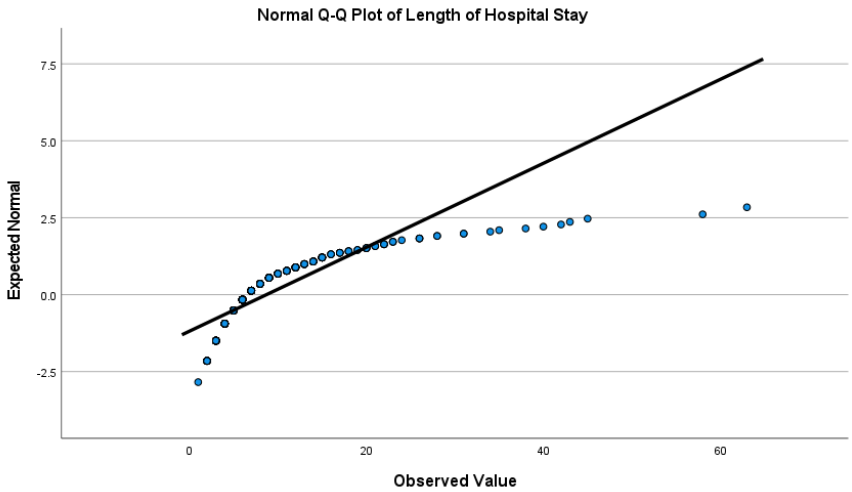
Appendix 9 Normality Data for Objective 1

Kolmogorov-Smirnov Test, Skewness and Kurtosis statistics for Hospital Length of Stay across the Three Groups and the Collective Total Sample

Variable	Intervention	K-S Statistic	Significance	Skewness Statistic (Standard Error)	Skewness Z-Score	Kurtosis Statistic (Standard Error)	Kurtosis Z-Score
Hospital Length of Stay	*Standard Care*	0.18	p<0.001	2.48 (0.19)	13.19	10.23 (0.38)	27.27
	Face-to-Face	0.27	p<0.001	3.30 (0.20)	16.26	12.60 (0.40)	31.19
	Virtual	0.23	p<0.001	2.11 (0.21)	10.05	4.73 (0.41)	11.44
	Total Sample	0.22	p<0.001	3.30 (0.12)	28.48	15.39 (0.23)	66.64



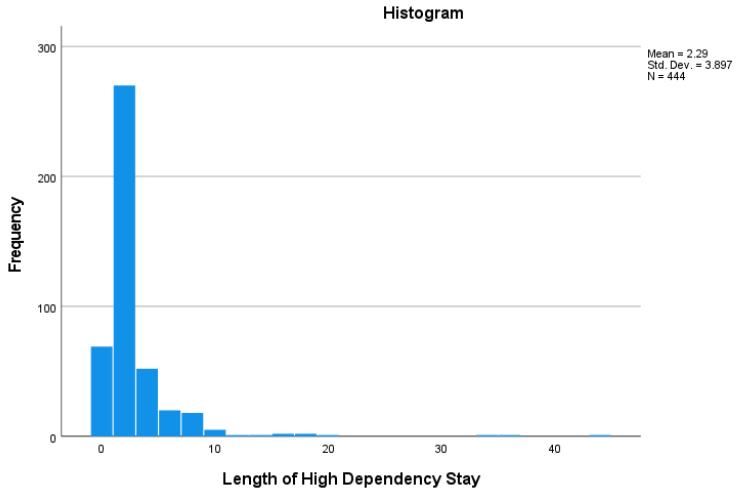
Histogram of Hospital Length of Stay for the Collective Sample



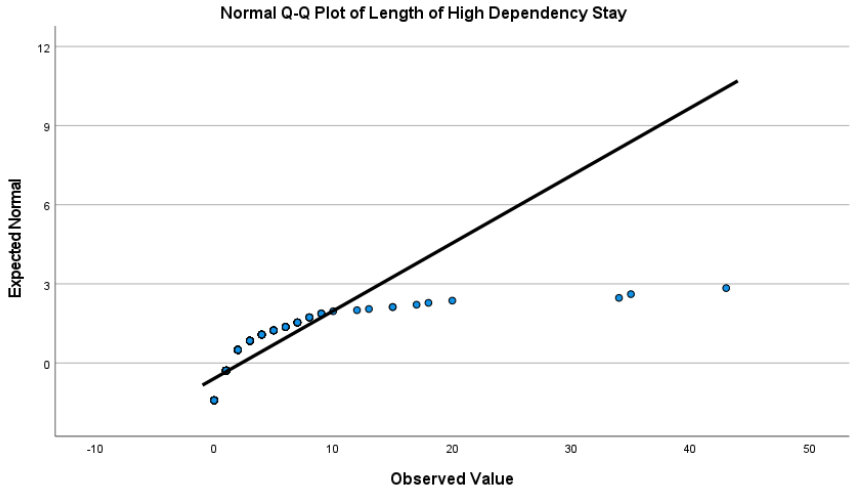
Q-Q plot of Hospital Length of Stay for the Collective Sample

Kolmogorov-Smirnov Test, Skewness and Kurtosis statistics for High Dependency Care Length of Stay across the Three Sample Groups and the Collective Total Sample

Variable	Intervention	K-S Statistic	Significance	Skewness Statistic (Standard Error)	Skewness Z-Score	Kurtosis Statistic (Standard Error)	Kurtosis Z-Score
High Dependency Care Length of Stay	*Standard Care*	0.30	p<0.001	2.68 (0.19)	14.26	9.75	26.01
	Face-to-Face	0.30	p<0.001	7.40 (0.20)	36.47	70.45	174.38
	Virtual	0.31	p<0.001	4.71 (0.21)	22.63	25.38	61.46
	Total Sample	0.29	p<0.001	6.01 (0.12)	51.78	48.68	210.75



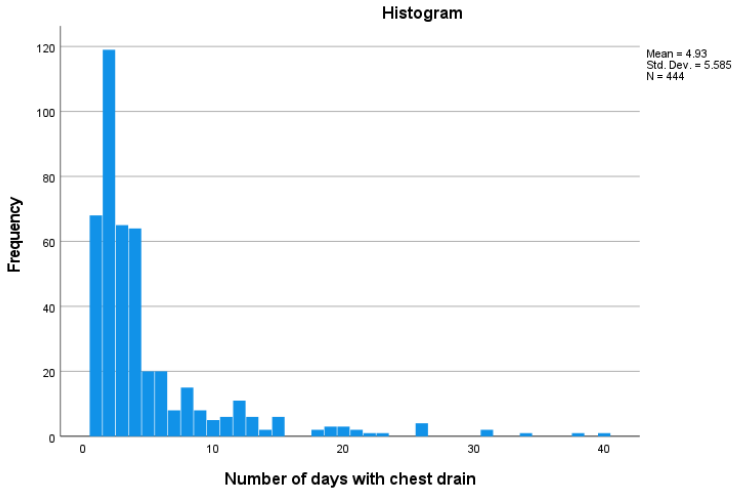
Histogram of High Dependency Length of Stay for the Collective Sample



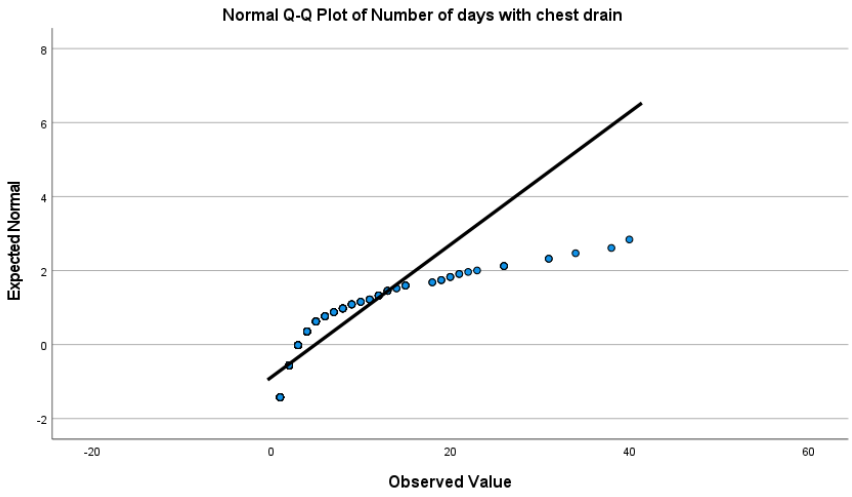
Q-Q plot of High Dependency Length of Stay for the Collective Sample

Kolmogorov-Smirnov Test, Skewness and Kurtosis statistics for Duration of Chest Drain Insertion variable across the Three Groups and the Collective Total Sample

Variable	Intervention	K-S Statistic	Significance	Skewness Statistic (Standard Error)	Skewness Z-Score	Kurtosis Statistic (Standard Error)	Kurtosis Z-Score
Chest Drain Insertion Duration	*Standard Care*	0.26	p<0.001	3.43 (0.19)	18.23	17.29 (0.38)	46.11
	Face-to-Face	0.27	p<0.001	2.73 (0.20)	13.42	8.85 (0.40)	21.91
	Virtual	0.29	p<0.001	2.84 (0.21)	13.67	8.33 (0.41)	20.18
	Total Sample	0.28	p<0.001	2.98 (0.12)	25.72	11.00 (0.23)	47.64



Histogram of Chest Drain Duration in Days for the Collective Sample

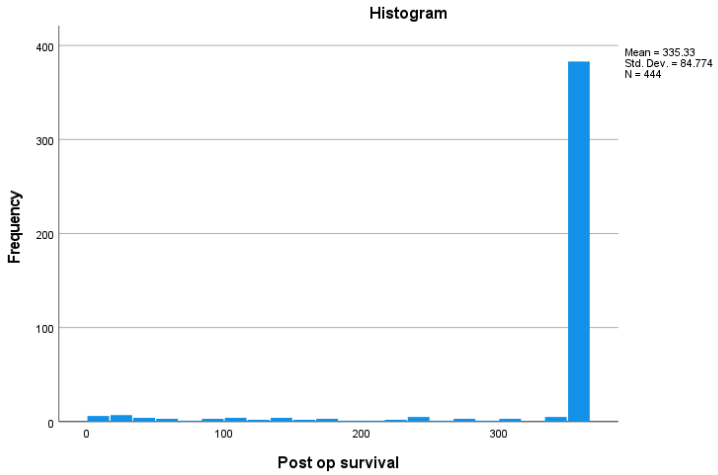


Q-Q plot of Chest Drain Duration in Days for the Collective Sample

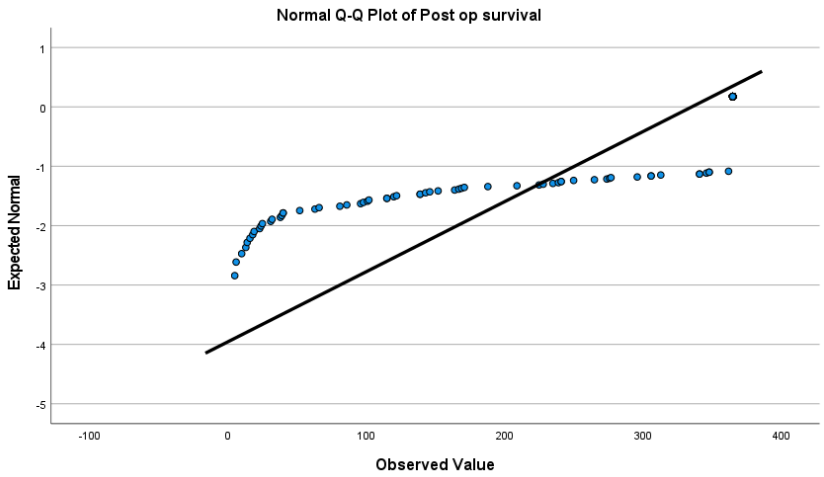
Appendix 10 Normality Data for Objective 2

Kolmogorov-Smirnov Test, Skewness and Kurtosis Statistics for the Postoperative Survival Days at One-Year Post-Surgery across the Three Groups and the Collective Total Sample

Variable	Intervention	K-S Statistic	Significance	Skewness Statistic (Standard Error)	Skewness Z-Score	Kurtosis Statistic (Standard Error)	Kurtosis Z-Score
Postoperative Survival Days at One-Year Follow-Up	*Standard Care*	0.48	p<0.001	-2.70 (0.19)	-14.34	6.08 (0.38)	16.20
	Face-to-Face	0.51	p<0.001	-3.04 (0.20)	-15.00	7.93 (0.40)	19.62
	Virtual	0.50	p<0.001	-2.90 (0.21)	-13.95	7.12 (0.41)	17.25
	Total Sample	0.50	p<0.001	-2.85 (0.12)	-24.53	6.78 (0.23)	29.34



Histogram of Postoperative Survival at One-Year in Days for the Collective Sample



Q-Q Plot for Postoperative Survival at One-year in Days for the Collective Sample

Appendix 11 Normality Data for Objective 3

Normality tests including Skewness and Kurtosis Statistics for Post Intervention Pulmonary Spirometry in Face-to-Face Rehabilitation and Virtual Rehabilitation Samples

Variable (post intervention)	Intervention	Normality Statistic	Significance	Skewness Statistic (Standard Error)	Skewness Z-Score	Kurtosis Statistic (Standard Error)	Kurtosis Z-Score
piMAX	*Face-to-Face*	0.11	p<0.001	0.63 (0.20)	3.11	-0.35 (0.40)	-0.87
	Virtual	0.19	p<0.001	0.99 (0.22)	4.56	-0.03 (0.43)	-0.08
FEV1	*Face-to-Face*	0.11	p=0.001	0.89 (0.20)	4.39	1.06 (0.40)	2.62
	Virtual	0.95	p=0.029	0.66 (0.33)	2.02	-0.18 (0.64)	-0.27
Percentage predicted FEV1	*Face-to-Face*	0.41	p=0.200	0.22 (0.20)	1.1	-0.19 (0.40)	-0.47
	Virtual	0.99	p=0.829	0.25 (0.33)	0.76	-0.33 (0.64)	0.51
FVC	*Face-to-Face*	0.08	p=0.016	0.59 (0.20)	2.89	0.29 (0.40)	0.71
	Virtual	0.98	p=0.395	0.48 (0.33)	1.48	0.48 (0.64)	0.74
Percentage predicted FVC	*Face-to-Face*	0.05	p=0.200	-0.01 (0.20)	0.06	-0.01 (0.40)	-0.03
	Virtual	0.97	p=0.128	0.17 (0.33)	0.53	0.56 (0.64)	0.87
		Blue text indicates a statistic is within statistical parameter for normal distribution					

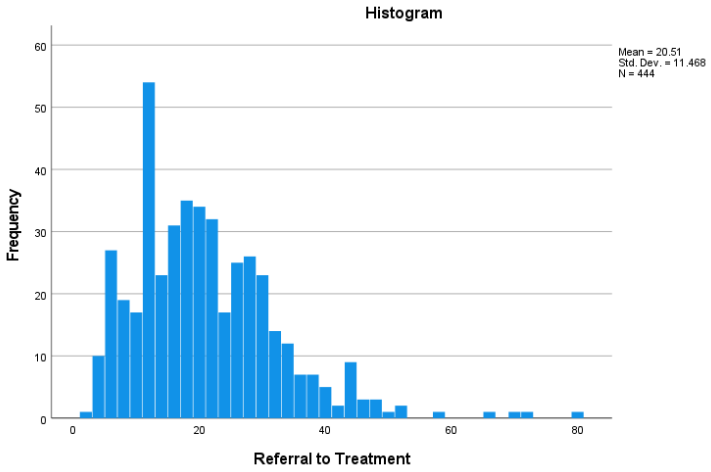
Shapiro-Wilk Test, Skewness and Kurtosis Statistics for Pre and Post Intervention HRQOL for Face-to-Face Rehabilitation and Virtual Rehabilitation Samples

Variable	Intervention	S-W Statistic	Significance	Skewness Statistic (Standard Error)	Skewness Z-Score	Kurtosis Statistic (Standard Error)	Kurtosis Z-Score
Pre Intervention HRQOL	*Face-to-Face*	0.95	p=0.003	0.56 (0.28)	2.01	-0.02 (0.55)	-0.03
	Virtual	0.99	p=0.667	0.20 (0.30)	0.66	-0.19 (0.60)	-0.31
Post Intervention HRQOL	*Face-to-Face*	0.97	p=0.117	0.17 (0.28)	0.61	-0.11 (0.55)	-0.20
	Virtual	0.97	p=0.073	-0.43 (0.30)	-1.42	-0.19 (0.60)	-0.31
		Blue text indicates a statistic is within statistical parameter for normal distribution					

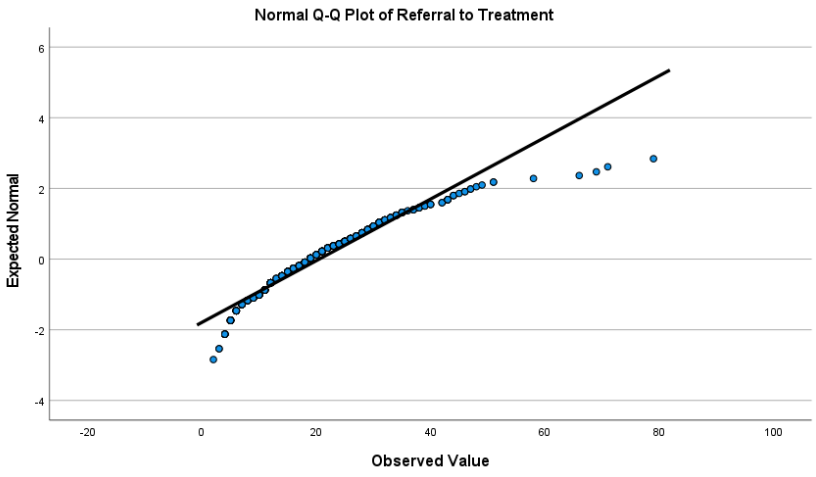
Appendix 12 Normality Data for Objective 4

Kolmogorov-Smirnov Test, Skewness and Kurtosis Statistics for Group Samples and Collective Total Sample

Variable	Intervention	K-S Statistic	Significance	Skewness Statistic (Standard Error)	Skewness Z-Score	Kurtosis Statistic (Standard Error)	Kurtosis Z-Score
Referral to Treatment Time	*Standard Care*	0.10	p<0.001	1.20 (0.19)	6.37	2.80 (0.38)	7.46
	Face-to-Face	0.10	p=0.001	1.01 (0.20)	4.97	2.15 (0.40)	5.33
	Virtual	0.11	p<0.001	1.52 (0.21)	7.28	3.95 (0.41)	9.56
	Total Sample	0.09	p<0.001	1.22 (0.12)	10.48	2.79 (0.23)	12.07

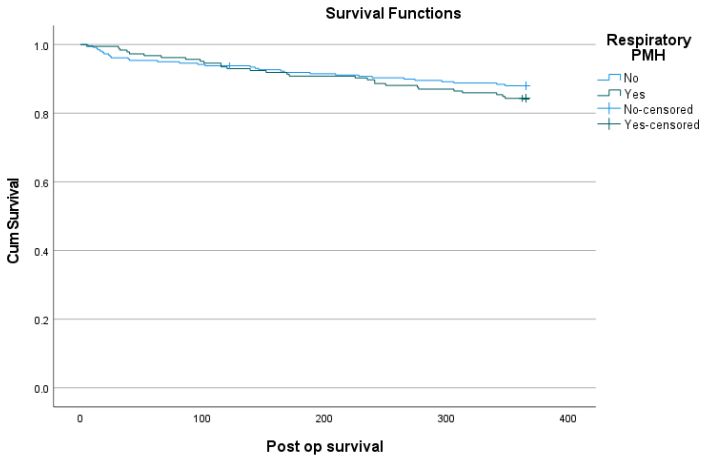


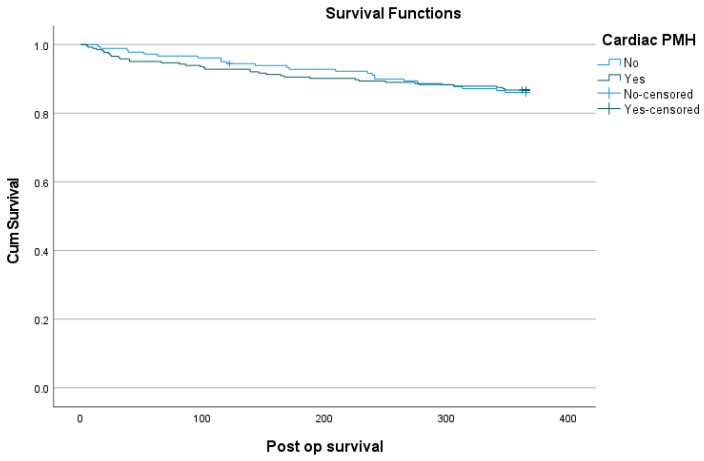
Histogram of Referral to Surgery Times for the Collective Sample

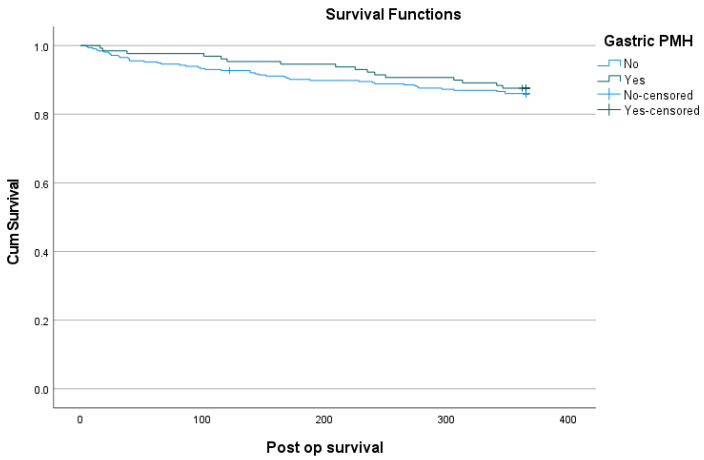


Q-Q Plot of Referral to Surgery Times for the Collective Sample

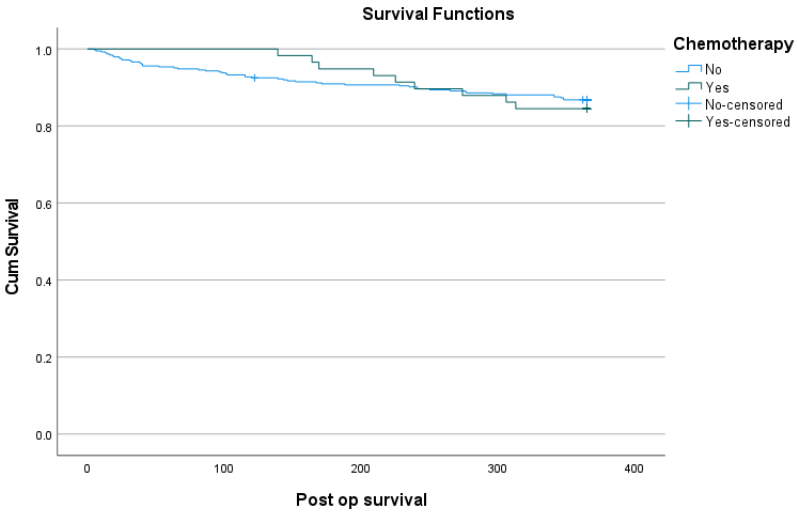
Appendix 13 Kaplan-Meier Plots (Conditions)

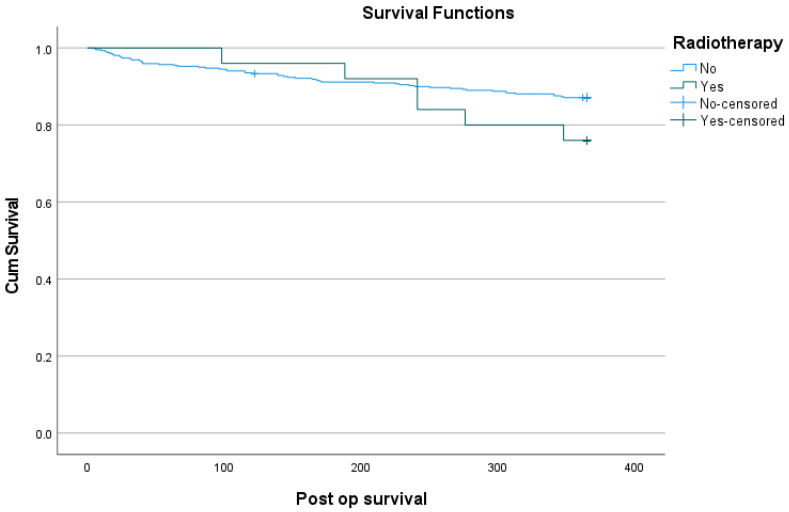






Appendix 14 Kaplan-Meier Plots (Adjuvant Therapy)





Appendix 15 Publication with a Subset of Objective 4 Data

JCR

THE FEASIBILITY OF PREOPERATIVE HIGH-INTENSITY EXERCISE FOR PATIENTS WITH OPERABLE LUNG CANCER: A SERVICE EVALUATION OF AN ESTABLISHED CARDIAC REHABILITATION PROGRAMME

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ABSTRACT

Background
Patients with operable lung cancer can be elderly, frail and multi-morbid with debilitating symptoms that can increase surgical risk and impair postoperative recovery. A short-term preoperative rehabilitation programme utilising the rapid physiological gains of high-intensity interval training could improve exercise capacity and optimise recovery if tolerated in this patient population.

Methods
A mixed-methods design was used to evaluate service delivery and review the feasibility of high-intensity interval training (HIIT) in patients with lung cancer awaiting surgical resection within an existing Cardiac Rehabilitation Service. A parameter of 80% heart rate reserve (HRR) was set to determine HIIT attainment.

Results
The service received 142 referrals for patients with lung cancer over a 12-month period. 100% of patients attended and initial appointment and 73% completed the Rehabilitation programme. 57% of patients achieved 80% HRR and no significant adverse events were reported. Younger age and higher baseline physical activity status were statistically significant for HIIT attainment. Gender, BMI, extent of planned surgical resection, and ASA classification did not appear to be significant in ability to achieve HIIT.

Conclusions
High uptake and completion rates can be achieved by offering patients with lung cancer access to a preoperative rehabilitation programme. HIIT can be safely considered as a preoperative exercise intervention although may not be achieved in all patient presentations, particularly elderly and those with lower baseline physical activity status. Clinical judgement should be applied in all circumstances.

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KEY WORDS

HIIT, LUNG CANCER, PREOPERATIVE REHABILITATION, CARDIAC REHABILITATION

INTRODUCTION

Patients diagnosed with lung cancer can suffer significant symptom burden impacting profoundly upon physical and mental health and overall quality and life. These symptoms can include, but are not limited to, pain, irritable cough, fatigue and restrictive breathlessness. According to UK Cancer Research the incidence of lung cancer is most common in older populations and 45% of new cases are diagnosed in those aged over 75 years old (1) therefore cases can often be complicated by a frail and multi-morbid status. Removal of cancerous lung tissue through surgical resection remains the most effective and curative treatment but also carries a significant risk of developing postoperative complications. Pulmonary complications are commonly estimated at 19 – 35% in this patient population, although have been reported as high as 60% in some cases (2-4) and are often related to regional lung collapse, sputum retention, ventilatory fatigue and respiratory failure postoperatively. The management of these complications can be both resource and labour intensive, including the provision of high concentration oxygen delivery, intravenous medications, mechanical ventilation and admission to high-dependency care with intensive staffing requirements and extended hospital stays. This can be distressing for patients and their carers and incur significant healthcare costs.

It is widely purported that preoperative rehabilitation prior to surgery can favourably influence the postoperative course and reduce hospital length of stay. Reviews suggest that preoperative exercise-based interventions can more than halve the risk of patients developing postoperative pulmonary complications following lung resection (5-7). Significant heterogeneity exists across reviews regarding patient presentation and exercise prescription including variations in mode, frequency and intensity, with many including low to moderate intensity exercise regimes across minor and major thoracic surgical procedures. Irrespective of these variations the current research is largely supportive of an exercise-based strategy for preoperative optimisation in lung cancer.

Prompt removal of cancerous tissue within 4 weeks is paramount in operable lung cancer management and therefore any preoperative intervention must be rapidly implemented and physiologically effective within short time constraints. High-intensity interval training (HIIT) has demonstrated significant potential for rehabilitation in patient populations. Physiological adaptations in capillary density, cellular oxidative capacity and mitochondrial activity have been observed within weeks of undertaking HIIT (8-11). Reviews evaluating HIIT in coronary heart disease (12–14), heart failure (15,16) and diabetic (17) populations have indicated HIIT is a safe and effective modality across high-risk multi-morbid patient groups. It is perhaps not surprising that short term preoperative HIIT is receiving increased attention in research to identify effective preoperative rehabilitation strategies in adult operable lung cancer patients, given the rapid physiological changes obtained and the limited preoperative period available in lung cancer management.

Exercise intensities at or greater than 80% of Heart Rate Reserve or Peak Work Rate have been used to determine HIIT in lung cancer (18). This exercise is characterized by short bursts of high energy work interspersed with regular intervals of lower intensity activity. A small number of randomised controlled trials have investigated preoperative HIIT in patients prior to surgical lung resection and these have reported improvements in exercise capacity with increases in six-minute walking distances and VO2 max following 2-3 weeks of this intervention (18-21). This intervention may also reduce the incidence of pulmonary complications following lung resection (18).

Preoperative HIIT has also averaged an impressive 90% adherence across the studies with no significant adverse events reported that could reasonably be attributed to HIIT intervention (18-21). Attrition across HIIT intervention groups was reportedly associated with poor motivation, unpleasant side effects from adjuvant chemotherapy treatments and non-intervention related hospitalisation (22). Whilst these results are encouraging, samples are small and patient presentations are restricted across studies, limiting clinical inference for the application of HIIT delivery into practice. A Cardiac Rehabilitation programme within a large teaching hospital extended referral criteria to include adult operable lung cancer patients awaiting lung resection to undertake a short-term HIIT intervention prior to surgery. The aim of this study was to review data from this programme after 12 months of delivery. The main objective of this study was to consider the feasibility and safety of HIIT as an optimising preoperative rehabilitation strategy to establish uptake and adherence patterns in clinical practice. The other objective of this study was to determine adverse events and intervention related side effects when HIIT is utilised in clinical practice across a range of operable lung cancer patient presentations.

METHODS

A mixed methods approach was utilised to evaluate service delivery and evaluate the feasibility of implementing HIIT training for lung cancer patients within an established rehabilitation service. The expansion of service delivery to include lung cancer was initially informed by patient and public involvement (PPI) focus group discussion with 8 local postoperative patients who had recovered from surgical lung resection performed within the NHS Trust in the last 12 months.
Subsequently the Cardiac Rehabilitation Service accepted preoperative lung cancer referrals made by surgeon request over a 12-month period. Eligible patients were subjectively identified by the surgeon based on perceived risk, including smokers or those with extensive smoking histories, poor baseline mobility, significant multi-morbid status or existing respiratory condition and sub-optimal pulmonary function tests. Referral was made by standard electronic hospital systems and supplemented by a direct email to a designated physiotherapist within the service following the surgeon review. This ensured that patients were fast-tracked into the programme, maximising the preoperative period available for rehabilitation. Clinics were either face-to-face or telephone clinics based upon patient preference and patient utilised short notice 'unable to attend' appointments or additional ad-hoc clinics booked by administration. 97% of patients received an appointment within 3 days of referral using this opportunistic approach. Patients completed an initial health and lifestyle assessment with a senior respiratory physiotherapist and were booked into an exercise programme at a community public gym contractually hired by the service.

The programme consisted of graded treadmill walking or walking with handheld weights, rowing and cycling via upright or recumbent bike. Heart rate and oxygen saturations were monitored using pulse oximetry and patients reported their rating of perceived exertion on the 6-20 Borg Scale. Patient to

staff supervision ratios were informed from existing rehabilitation guidelines for pulmonary conditions although it was noted that most patients required one to one supervision for the first two sessions and staffing levels were adjusted to reflect this. HRR was calculated using the Karvonen formula and the maximum % HRR reached and RPE were recorded at each session. HIIT was considered to have been reached when 80% HRR was achieved and recorded on at least one exercise station within the session. Patients could decide not to progress to these intensities at their own request or if restricted by the supervising clinician. Attendance and reasons for cancellation were logged on electronic clinic registers and baseline characteristics were recorded on a departmental database.

RESULTS

The PPI focus group were unanimous in their favourable support towards access for preoperative rehabilitation and felt they would have attended should this service have been available to them. They appeared motivated to optimize preparation for surgery and postoperative recovery but conceded they were apprehensive towards increasing physical activity levels independently. This was due to debilitating symptoms affecting their confidence to interpret safe levels of activity during the preoperative period. These symptoms predominantly related to pain, breathlessness and fatigue. A structured rehabilitation programme, where participation could be monitored and guided by health professionals was well-received by the group and they felt engagement would be possible despite these symptoms.

142 operable adult lung cancer patients were referred into the programme during the evaluation period. 100% of patients attended the initial assessment and were cleared by the physiotherapist to participate in HIIT, the baseline demographics of patients referred are shown in table 1.0. All patients attended at least one exercise session and 104 patients were able to complete the full rehabilitation programme as shown in figure 1.0. 38 patients (27%) dropped out of the programme prior to completion with patient-reported reasons for cancellation shown in figure 1.1. The frequent reason for cancellation was an earlier operation date becoming available within the early stages of the rehabilitation programme (74% n = 28), whilst less common cancellation reporting was due to existing holiday commitments (8% n = 3), delayed initial referral (8% n = 3) and patients reporting they had become unwell from a new onset illness (10% n=4) with cold, flu or gastro-related symptoms. Patients were advised at the initial clinic to attend supervised sessions twice weekly although they were not prevented from attending if they could only commit to once weekly with an additional home exercise session encouraged. Most patients opted for the preferred twice weekly sessions (67%, n = 95) in comparison to the once-a-week option (33%, n=47).
The HIIT target of 80% HRR on at least one station within

Table 1.0 Baseline characteristics of preoperative lung cancer referrals into Rehabilitation

Characteristics		Face to Face Rehabilitation
Gender	Male (n)	51% (73)
	Female (n)	49% (69)
Age	Mean (SD)	69.96 (10.17)
BMI	Mean (SD)	28.02 (6.19)
Total Number of Morbidities	Mean (SD)	2.15 (1.48)
Activity Status	1 (n)	29% (41)
	2 (n)	43% (61)
	3 (n)	28% (40)
ASA Classification	1 (n)	1% (2)
	2 (n)	17% (24)
	3 (n)	78% (111)
	4 (n)	4% (5)
Type of Surgery	Wedge Resection (n)	1% (2)
	Segmentectomy (n)	52% (74)
	Lobectomy (n)	47% (66)

Figure 1.0 Preoperative patients with lung cancer programme completion

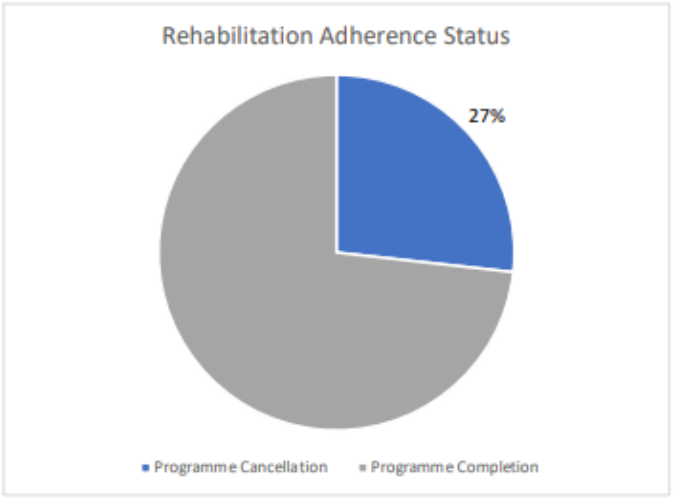
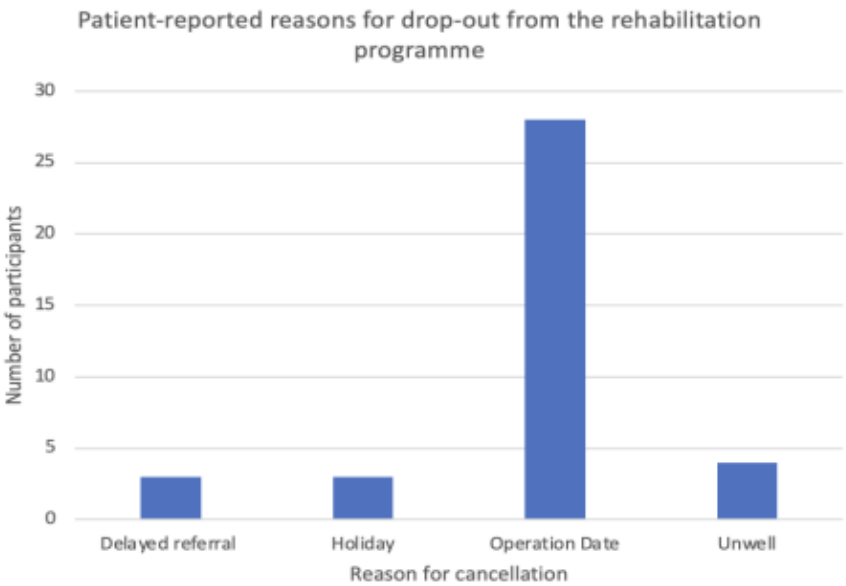


Figure 1.1 Preoperative lung cancer patient reasons for programme cancellation



a session was successfully reached by the larger proportion of patients (57%, n=81) in comparison to those who did not reach this target throughout the programme (43%, n=61). Interestingly, there was a higher proportion of cancellations within the group who did not achieve HIIT target parameters, where 42% patients cancelled in comparison to 15% in those achieving HIIT. This difference is also reflected in the mean total number of sessions completed, which was 4.5 sessions (SD 2.46) in those achieving HIIT and 3.5 sessions (SD 2.26) in those who did not. There were no significant adverse events reported by clinicians or patients throughout the evaluation period. Seven patients experienced 'light-headedness' and one patient experienced chest pain of musculoskeletal origin. These symptoms were reported as mild and of limited duration, resolving without medical escalation at the exercise setting.

Table 1.1 outlines the characteristics of patients who reached HIIT within the programme against those who did not. Patients achieving HIIT were younger, with a mean age of 67.12 (SD 11.27) in comparison to a mean age of 73.74 (SD 6.96) in those who did not, and this was statistically significant for HIIT attainment (t=4.304, p<0.01 95% CI 3.58-9.65). There was a higher proportion of males (54% n=44) compared to females (46%, n=37) in those where HIIT had been achieved and this gender ratio appeared reversed in those not achieving HIIT, with a higher proportion of females (52.5%, n=32) compared to males (47.5%, n=29) although this was not considered statistically significant (p=0.42).
A higher baseline activity status was statistically significant

Table 1.1 Comparison of baseline characteristics and achievement of HIIT during the programme

Characteristics		HIIT Achieved n=81	HIIT Not Achieved n=61
Gender	Male (n)	54% (44)	47.5% (29)
	Female (n)	46% (37)	52.5% (32)
Age	Mean (SD)	67.12 (11.27)	73.74 (6.96)
BMI	Mean (SD)	28.08 (6.27)	27.98 (6.17
Total Number of Morbidities	Mean (SD)	2.17 (1.59)	2.13 (1.35)
Activity Status	1 (n)	42% (34)	12% (7)
	2 (n)	38% (31)	49% (30)
	3 (n)	20% (16)	39% (24)
ASA Classification	1 (n)	2.5% (2)	0% (0)
	2 (n)	18.5% (15)	15% (9)
	3 (n)	76.5% (62)	80% (49)
	4 (n)	2.5% (2)	4% (3)
Type of Surgery	Wedge Resection (n)	1% (1)	1.5% (1)
	Segmentectomy (n)	53% (43)	51% (31)
	Lobectomy (n)	46% (37)	47.5% (29)

for HIIT achievement ($\chi 2$=16.92, p<0.01), whereby an activity status of 1 represents higher function and increasing numbers represent lower function. Patients achieving HIIT had a higher baseline activity status with 42% (n=34) in category 1, 38% (n=31) in category 2 and 20% (n=16) in category 3. This contrasts with those not achieving HIIT with 12% (n=7) of patients in category 1, 49% (n=30) in category 2 and 39% (n=24) in category 3. There is a similar pattern in ASA classification, where lower numerical values indicate a lower surgical risk. Both groups showed the highest proportion of patients in categories 2 and 3, but 2.5% of patients achieving HIIT had the lowest classification 1, in comparison to no patients in this classification where HIIT was not achieved, although ASA classification was not considered statistically significant (p=0.48).

The intended extent of surgical resection appeared consistent between the two groups (p=0.81) and the mean number of additional morbidities were comparable (p=0.87). Body mass index was also closely matched between groups, with

a mean of 28.08 (SD 6.27) where HIIT had been achieved, compared to 27.98 (SD 6.17) where it had not. Both groups represent an 'overweight' BMI classification, suggesting that additional weight is not a limiting factor to reaching HIIT targets (p=0.93).

DISCUSSION

Patient and public involvement indicated that a preoperative rehabilitation programme, including supervised exercise, would be well attended by operable lung cancer patients and the high uptake and completion rates in this service evaluation appear to confirm this. The adherence in this evaluation was slightly lower than the clinical trials achieving 90% but these studies were controlled, had smaller samples and limited patient risk profiles (18-22). HIIT also appears to be a safe exercise-based strategy to consider in lung cancer populations with no significant adverse events and this is comparable to the findings of large reviews in other high risk clinical populations (12-17) and smaller trials in lung cancer specific patient populations (18-21). A significant proportion did not achieve HIIT at any exercise station for the duration of the intervention. An inability to reach these targets seemed most likely in those who were older or with lower baseline physical activity. These factors may directly impact upon an individuals' ability to engage in early HIIT by influencing exercise capacity or clinicians and patients may hold preconceptions regarding exercise and advanced age and familiarity with exercise, affecting engagement with or prescription at higher intensity exercise. Evidence suggests that HIIT can be safely prescribed for those familiar with at least moderate levels of activity (23) and therefore these findings may reflect clinical judgements on safety in practice. Clinicians within the Cardiac Rehabilitation programme were experienced in HIIT prescription but were less familiar with lung cancer patients and possible responses to exercise, and this may have also contributed to the variable achievement of HIIT. Exercise prescription was determined and monitored by physiological heart rate monitoring and subjective ratings of perceived exertion. Prior exercise testing through sub-maximal tests, to obtain VO2 peak, may prove helpful in assisting clinicians in deciphering appropriate levels of exercise early with this relatively unfamiliar patient group. Clinical observation suggests that lower intensity exercise is often prescribed to those patients unfamiliar with exercise environments to first elicit confidence and engagement with the programme. The restricted preoperative timescales available in lung cancer management does not favour this approach, strategies to elicit early achievement and adherence with HIIT should be explored, whilst also ensuring patient and clinical safety. The decision in practice to prescribe HIIT for patient with lung cancer should be made after a through clinical assessment and appropriate supervision.

CONCLUSION

The evaluation suggests that a preoperative rehabilitation programme offered to patients with operable lung cancer can achieve high uptake and adherence. Effective and flexible referral strategies must be employed to optimise the preoperative period available for intervention. HIIT can be successfully implemented in this patient population, although this must be tailored to individual presentations to ensure safety and promote adherence. Patients who are younger with higher baseline physical activity may have greatest success to achieve HIIT within a 3-week programme. Gender, extent of surgical incision, smoking status, number of morbidities or BMI did not seem to influence ability to reach HIIT. It is unclear whether physiological capability, patient preference or clinician experience influenced attainment of HIIT, and this is worth future consideration and study.

Clinical Messages

Cardiac Rehabilitation programmes could offer a viable opportunity to extend referrals for lung cancer patients undergoing surgery within a Cardiothoracic Specialty.

High intensity interval training can be tolerated by some lung cancer patients and implemented safely in an appropriately supervised rehabilitation programme.

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Author contribution

SL and RN conceived and designed the manuscript. SL analyzed and interpreted the data results. SL and AP drafted the manuscript. SL, RN and AP edited and critical revised the manuscript. Statistical analysis was perfomed by SL and RN. SL, RN and AP supervised this study.
All authors read and approved the final manuscript.

Conflict of interest

The Authors have no conflicts of interest to report.

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