Improving Fitness and Quality of Life of Lymphoma Survivors Using Fitbit™ Monitors

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Chapter 4

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List of Abbreviations

FITT – Frequency, Intensity, Time, Type

MVPA – Moderate to Vigorous Physical Activity

PROMIS – Patient-Reported Outcomes Measurement Information System

BMI – Body Mass Index

FCRI – Fear of Cancer Recurrence Inventory

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Abstract

Lymphomas are among the most common cancers in Canada, with a relatively high survival rate due to treatment, specifically chemotherapy. However, chemotherapy can cause various side effects that can affect a patient's quality of life. These side effects, which include changes in body composition, reduced physical functioning, cancer-related fatigue, depression, anxiety, and insomnia, may be improved through physical activity. To date, no intervention aiming to increase physical activity using objective monitoring among individuals with lymphoma during the COVID-19 pandemic have been conducted, neglecting the potentially deleterious effects of quarantine and sedentary behavior in lymphoma patients. This is clinically meaningful, as improving adherence to physical activity is crucial in mitigating the severity of many chemotherapy-induced side effects.

The purpose of this study was to determine the implementation feasibility of our proof-of-concept study for future application in a randomized controlled trial. This included addressing retention rate, technical and safety issues that occurred throughout the intervention. Furthermore, this trial was designed to explore the preliminary effects of the *Lymfit* exercise intervention on participant adherence to physical activity, as well as on improvements in their overall health and well-being. We hypothesized that a Fitbit™ monitor would improve exercise adherence, as well as fitness and quality of life domains. We also examined improvements in side effects, barriers and facilitators to exercise and the sustainability of the program for the promotion of a healthy, active lifestyle.

This proof-of-concept study was designed as a single-armed trial with a pre- and post-test design in which 20 participants were prescribed a 12-week, personalized, remotely delivered, home-based exercise program. Fitbit™ monitors were given to participants to track their daily

activity pre-, during and post-exercise prescription. The Fitbit™ monitors also served the purpose of motivating participants to increase their physical activity levels by quantifying their efforts and motivating them to improve upon their Fitbit™ outcomes (i.e., activity levels). Fitbit™ data was collected via our *Lymfit* database and analyzed each week to assess participant changes in activity levels and exercise adherence. Participants were contacted bi-weekly to address the progress made and to adjust the program, where needed. Questionnaires were filled out at baseline and week 12 to explore changes in both health and well-being.

We found that activity levels and exercise adherence remained relatively stable and did not increase over 12 weeks. However, significant improvements were seen in several quality of life domains, including social participation, physical functioning, and sleep disturbance. The most frequently reported barriers were fatigue, lack of time, and lack of motivation. In contrast, the most frequently reported facilitators included wearing the Fitbit™, improved well-being and improved physical capacity.

The results indicate that the exercise program did not seemingly improve adherence and fitness outcomes, though it did improve health and well-being. Limiting factors, including limitations pertaining to the Fitbit™ monitor, participants baseline fitness characteristics, and COVID-19 may explain the lack of fitness improvements. More importantly, feasibility testing of the *Lymfit* intervention proved successful, with only a few minor technical issues reported. These technical issues included the inability of the Fitbits™ to track resistance training and a server issue that prevented a participant from receiving the quality of life questionnaire. Both issues were quickly resolved, and large-scale testing in a randomized controlled trial can now be conducted.

Résumé

Les lymphomes font partie des cancers les plus courants au Canada, avec un taux de survie relativement élevé grâce aux traitements, notamment la chimiothérapie. Cependant, la chimiothérapie peut causer divers effets secondaires qui peuvent affecter la qualité de vie du patient. Ces effets secondaires, qui comprennent les changements dans la composition corporelle, la réduction du fonctionnement physique, la fatigue liée au cancer, la dépression, l'anxiété et l'insomnie, peuvent être améliorés par l'activité physique. À ce jour, aucune intervention visant à augmenter l'activité physique à l'aide d'un suivi objectif chez les personnes atteintes de lymphome pendant la pandémie de COVID-19 n'a été menée, négligeant les effets potentiellement délétères de la quarantaine et de la sédentarité chez les patients atteints de lymphome. Ceci est important car l'amélioration de l'adhésion à l'activité physique est cruciale pour atténuer la gravité de nombreux effets secondaires induits par la chimiothérapie.

L'objectif de cette étude était de déterminer la faisabilité de la mise en œuvre de notre étude de preuve de concept pour une application future dans un essai contrôlé randomisé. Il s'agissait notamment de résoudre les problèmes de rétention, de technique et de sécurité qui se sont posés tout au long de l'intervention. En outre, cet essai a été conçu pour explorer les effets préliminaires de l'intervention d'exercice *Lymfit* sur l'adhésion des participants à l'activité physique, ainsi que sur les améliorations de leur santé et de leur bien-être en général. Nous avons émis l'hypothèse qu'un moniteur Fitbit™ améliorerait l'adhésion à l'exercice, ainsi que les domaines de la forme physique et de la qualité de vie. Nous avons également examiné les améliorations concernant les effets secondaires, les obstacles et les facilitateurs de l'exercice et la durabilité du programme pour la promotion d'un mode de vie sain et actif.

Cette étude de validation du concept a été conçue comme un essai à un seul bras avec un plan de pré-test et de post-test dans lequel 20 participants se sont vu prescrire un programme d'exercice à domicile personnalisé de 12 semaines. Des moniteurs Fitbit™ ont été remis aux participants pour suivre leur activité quotidienne avant, pendant et après la prescription d'exercices. Les moniteurs Fitbit™ avaient également pour but de motiver les participants à augmenter leur niveau d'activité physique en quantifiant leurs efforts et en les incitant à améliorer leurs résultats Fitbit™ (c'est-à-dire leurs données). Les données Fitbit™ ont été collectées via notre base de données *Lymfit* et analysées chaque semaine afin d'évaluer l'évolution des niveaux d'activité des participants et leur adhésion à l'exercice. Les participants ont été contactés toutes les deux semaines afin d'évaluer les progrès réalisés et d'adapter le programme, le cas échéant. Des questionnaires ont été remplis au début de l'étude et à la semaine 12 afin d'explorer les changements en matière de santé et de bien-être.

Nous avons constaté que les niveaux d'activité et l'adhésion à l'exercice sont restés relativement stables et n'ont pas augmenté sur 12 semaines. Cependant, des améliorations significatives ont été observées dans les domaines de la qualité de vie, notamment la participation sociale, la fonction physique et les troubles du sommeil. Les obstacles les plus fréquemment signalés étaient la fatigue, le manque de temps et le manque de motivation. En revanche, les principaux facilitateurs étaient le port du Fitbit™, l'amélioration du bien-être et de la capacité physique.

Les résultats indiquent que le programme d'exercices n'a apparemment pas amélioré l'adhésion et les résultats de la condition physique, bien qu'il ait amélioré la santé et le bien-être. Des facteurs limitatifs, notamment les limites du moniteur Fitbit™, les caractéristiques de base de la condition physique des participants et COVID-19, peuvent expliquer l'absence

d'amélioration de la condition physique. Plus important encore, les tests de faisabilité de l'intervention *Lymfit* se sont avérés concluants, seuls quelques problèmes techniques mineurs ayant été signalés. Ces problèmes techniques comprenaient l'incapacité des Fitbit™ à suivre l'entraînement en résistance et un problème de serveur qui a empêché un participant de recevoir le questionnaire sur la qualité de vie. Ces deux problèmes ont été rapidement résolus, et des tests à grande échelle dans le cadre d'un essai contrôlé randomisé peuvent maintenant être menés.

Preface and Contribution of Authors

Christopher Angelillo was the primary author with roles in data collection, analysis and interpretation, and thesis preparation.

Dr. Ross E. Andersen, Professor, Department of Kinesiology and Physical Education, McGill University, the candidate's supervisor, was actively involved in every step and decision made regarding the research study and the completion of this thesis. He also assisted in funding the study and purchasing the Fitbit™ monitors.

Dr. Nathalie Johnson conceived this study and assisted in participant recruitment. She also assisted in funding the study and purchasing the Fitbit™ monitors.

Wing Lam Tock assisted in designing the study, carrying out the study, and data collection.

Matthew Salaciak assisted in designing the study, data analysis, and ensuring the smooth operation of our Lymfit platform.

Dr. Christine Maheu was actively involved in designing the intervention and decisions made regarding the research study.

Dr. Ryan Reid assisted in data analysis and interpretation.

Chapter 1 – Introduction

1.1 Scope of the Problem

Lymphoma is currently the 5th most diagnosed cancer among adults in Canada and accounts for approximately 4% of all cancer diagnoses (Le et al., 2019). There are two main types of lymphoma, classified as Hodgkin's lymphoma and non-Hodgkin's lymphoma. Each have their own subtypes that vary in lethality and commonality. Non-Hodgkin's lymphomas make up most lymphoma cases, accounting for approximately 90% of all diagnoses (Le et al., 2019). In 2020, an estimated 10400 Canadians were diagnosed with non-Hodgkin's lymphoma, with an additional 1000 Canadians diagnosed with Hodgkin's lymphoma (Canadian Cancer Society, 2021). While the number of individuals diagnosed with lymphoma is high, there is also a relatively high survival rate among lymphoma patients. The survival rate of non-Hodgkin's lymphoma is approximately 65-70% 5 years after initial diagnosis (Boyle et al., 2017). The 5-year survival rate increases to approximately 85% among Hodgkin's lymphoma patients (Courneya et al., 2010). While these percentages may be encouraging, it does not necessarily indicate that the lives of lymphoma survivors will return to normal (i.e., pre-cancer diagnosis) once the cancer has subsided. These survival rates are often achieved through intensive treatment. These treatment methods include chemotherapy, radiation therapy, bone marrow transplant, immunotherapy, and many others (Canadian Cancer Society, 2021). Of those, chemotherapy is currently the most used and most effective treatment method for lymphoma (Canadian Cancer Society, 2021). While it may be very effective, chemotherapy can often trigger a variety of physical and psychological side effects that can linger post-treatment, often negatively affecting an individual's quality of life (Courneya et al., 2012). Common side effects that have been reported among lymphoma survivors include; changes in body composition,

reduced levels of physical functioning, cancer-related fatigue, depression, anxiety, and insomnia (Courneya et al., 2009; Aslam et al., 2014). In addition, cancer-related fatigue is the most prevalent side effect, affecting between 60-100% of all cancer patients (Vermaete et al., 2014). Cancer-related fatigue can also become an issue post-treatment, affecting approximately 30% of lymphoma survivors for years after treatment is completed (De Backer et al., 2007). This suggests that the side effects of lymphoma treatment can persist among many lymphoma survivors in both the short-term and long-term.

Recent literature has focused on possible remedies for the side effects associated with lymphoma treatment, most of which involve prescribed medications that are typically quite toxic and can cause side effects that may be worse than those of lymphoma treatment. These medications can include: antidepressants, sleep medications and many others. One natural remedy that has shown to have potential therapeutic benefits on the side effects of lymphoma treatment without the health risks associated with prescribed medication is regular physical activity. Studies have shown that a prescribed exercise program can be as effective as prescribed medication in mitigating the severity of nearly all side effects associated with lymphoma treatment. These side effects include significantly lower levels of cancer-related fatigue, improvements in physical functioning, lower levels of depression and anxiety, and an overall improved quality of life (Courneya et al., 2009).

Although research has shown the potential therapeutic benefits of adherence to physical activity for lymphoma survivors who have undergone or are undergoing treatment for lymphoma, it has yet to focus on increasing physical activity levels using objective monitoring (i.e., a wearable activity tracker) during the COVID-19 pandemic. This is neglecting the potentially deleterious effects of quarantine and sedentary behavior on lymphoma patients, which

is significant considering that improvements in adherence to physical activity is crucial in mitigating the severity of many chemotherapy-induced side effects.

Patients who do not fully adhere to the recommended exercise guidelines generally do not experience significant improvements in any of the side effects of lymphoma treatment. It is for this reason that tracking participants level of physical activity is crucial and must be done effectively. Attempting to track the physical activity levels of participants using objective monitoring devices (i.e., activity monitors) is an intriguing idea and has the potential to be a very effective method of measuring adherence to exercise. The use of activity monitors is common today and their popularity continues to rapidly grow among all age groups (Henriksen et al., 2021). However, their popularity in the general population has not yet led to their widespread use in clinical settings. Activity monitors have many potential benefits that activity tracking methods currently being used in clinical settings (such as patient diaries) do not. One such benefit is that they allow for an accurate, objective measure of time spent being physically active. Participants in previous exercise interventions have often overestimated their time spent in moderate to vigorous physical activity for a variety of reasons, including wanting to seem more physically active in the eyes of the investigators (Watkinson et al., 2010). This then causes an overestimation of overall adherence to the exercise program. With activity monitors, all data is measured quantitatively, theoretically eliminating the potential for overestimation or recall bias seen in previous studies that have tracked physical activity qualitatively. This study will implement activity monitors (specifically Fitbits^{TM}) to collect data on fitness and health outcomes such as steps taken, sedentary time, light active minutes, very active minutes, waking minutes and time spent asleep. They will also be implemented to increase motivation among participants. The use of activity monitors has been shown to increase motivation and improve

exercise habits through quantifying the user's efforts and motivating them to improve upon those numbers (Reid et al., 2017). This has been further investigated in an article by Beg et al. (2017). They revealed that exercise motivation was increased among breast cancer patients after being given an activity monitor. Improved self-monitoring and increased physical activity feedback were noted as being the two major catalysts in improving exercise motivation (Beg et al., 2017). Due to their motivational nature, activity monitors have been shown to be effective in exercise interventions. A systematic review conducted by Brickwood et al. (2019) determined that the use of activity monitors as the primary component or as a part of a broader exercise intervention has the potential to significantly increase participants physical activity levels including increased steps, increased MVPA, and increased energy expenditure (Brickwood et al., 2019). Therefore, it was expected that the Fitbit^{TM} monitors would improve motivation among our sample, thus leading to increased fitness and health outcomes.

1.2 Purpose

With this being a proof-of-concept trial, our primary purpose was to determine the feasibility of delivering an exercise intervention remotely using our *Lymfit* platform to capture data. This was determined through participant retention rates, technical issues on intervention delivery and data collection during the pandemic, as well as safety issues regarding the prescription of an unsupervised exercise intervention on a high-risk population.

The secondary purpose of this study was to determine the proportion of lymphoma survivors that adhered to the recommended exercise guidelines (using objective monitoring) and if a prescribed fitness program improved their health and well-being. The secondary purpose also included identifying the side effects of chemotherapy that may improve with adherence to the fitness program, barriers and facilitators that may affect a participant's adherence to the program

and determining the sustainability of the program for the long-term promotion of a healthy, active lifestyle.

1.3 Hypotheses

We hypothesized that feasibility testing of the exercise intervention would prove successful and would be ready for use in a randomized controlled trial. We also hypothesized that the use of an objective monitor (i.e., Fitbit™ monitor) would increase participant adherence to the prescribed exercise program by acting as a motivator in helping participants adhere to their respective exercise programs, as well as improve their overall fitness outcomes. Finally, we hypothesized that adherence to the prescribed exercise program would lead to improved health-related quality of life among participants.

1.4 Challenges Posed by COVID-19

The emergence and current presence of COVID-19 has presented certain challenges in organizing an exercise intervention with cancer patients. These challenges had to be addressed before the start of the trial. The first challenge involved the closures of fitness centers and gyms, forcing participants to exercise at home, thus minimizing the access to exercise equipment that they would normally have access to. This had a major impact in terms of how the personalized exercise programs were created as they had to be adapted for at-home exercise. To provide a well-rounded exercise prescription, the participants were each given a set of 5 different resistance bands that ranged from very light to very heavy. This allowed for more variety in the exercise programs. This also minimized the risk of COVID-19 infection as participants had the necessary equipment and did not have to attend a fitness center even after the restrictions on fitness centers were lifted.

Another challenge that COVID-19 had presented was the inability to meet with the participants in-person to conduct their baseline fitness assessments, as well as to prescribe and demonstrate the exercises that they will be doing throughout the intervention. It has forced the research team to conduct all assessments via online meetings using the Zoom™ platform, making it very difficult to fully encapsulate a participant's fitness capabilities and levels, as well as to prescribe their exercise program effectively. To bypass this inconvenience and get the most accurate measure of a participant's fitness level, a fitness questionnaire was created and was to be filled out by the participants during the first meeting. Existing fitness questionnaires did not inquire into all the necessary information required to assist the Kinesiologist in creating remotely delivered personalized home exercise programs. Therefore, the creation of a new fitness questionnaire was necessary for this study. The questionnaire is detailed and allowed for a thorough analysis of the individual's exercise history, current level of fitness, activities they do and do not enjoy, and current barriers to exercise. The questionnaire also asked participants which days, as well as what time(s) during the day the participants were available to exercise, which further assisted the Kinesiologist in creating a personalized home exercise program. To ensure that the participants clearly understood their exercise program, videos were used to demonstrate each exercise that comprised the exercise program. These videos came from multiple sources on Youtube™, which is an easily accessible and user-friendly platform.

Chapter 2 – Review of Literature

2.1 Introduction

Lymphoma is currently the 5th most diagnosed cancer among adults in Canada, with non-Hodgkin's lymphoma accounting for almost all lymphoma diagnoses (Le et al., 2019). Recent statistics have reported that in 2020, an estimated 10400 Canadians have been diagnosed with non-Hodgkin's lymphoma, with an additional 1000 Canadians diagnosed with Hodgkin's lymphoma (Canadian Cancer Society, 2021). These are significant numbers with major implications for the Canadian healthcare system. Those who are diagnosed with lymphoma often go through intensive treatment to improve their odds of survival from the disease. These treatment methods often include chemotherapy, radiation therapy, bone marrow transplant, immunotherapy, and many other treatments (Canadian Cancer Society, 2021). Of those, chemotherapy is currently the most effective and widely used method of treating lymphoma (Canadian Cancer Society, 2021). While it does seem to be the most efficacious treatment method for these patients, the side effects associated with chemotherapy can also significantly reduce the quality of life of lymphoma survivors post-treatment. The most common side effects include loss of muscle mass, increased adiposity, reduced levels of physical functioning, cancer-related fatigue, depression, anxiety, insomnia and reduced overall quality of life (Courneya et al., 2009; Aslam et al., 2014). Long-term side effects of chemotherapy including increased bodily pain, lingering negative effects on physical functioning and fatigue, decreased social functioning, heightened anxiety, and poorer general health have also been reported among cancer survivors 5-10 years post-treatment (Ganz et al., 2002). Of those, cancer-related fatigue seems to be the most prevalent side effect, which affects 60-100% of all cancer patients (Vermaete et al., 2014). Recent literature has focused on possible remedies for the side effects associated with

chemotherapy, most of which involve medications that are generally of high toxicity. These medications include: antidepressants, sleep medications and many others. One natural remedy that has shown to have potential therapeutic benefits on the side effects of chemotherapy without the health risks of prescribed medication is regular physical activity. A study conducted by Courneya et al. (2009) suggested that the intensity of the side effects associated with chemotherapy can be significantly reduced with physical activity, ultimately improving the quality of life of lymphoma survivors. Side effects such as cancer-related fatigue, depression and physical functioning were most notably affected. Although research has shown the potential therapeutic benefits of physical activity (specifically aerobic exercise) for lymphoma survivors who have undergone chemotherapy, it has yet to focus on increasing their physical activity levels using objective monitoring (i.e., a wearable activity tracker) during the COVID-19 pandemic, neglecting the potentially deleterious effects of quarantine and sedentary behavior in lymphoma patients. Currently, only 6.5% of lymphoma patients meet the recommended exercise guidelines during cancer treatment. This percentage increases slightly to only 21-29% post-treatment (Vermaete et al., 2014). These are exceptionally low percentages that must be increased for significant improvements to be seen in the overall quality of life of lymphoma patients and survivors. Therefore, this study will further enhance the current literature by providing healthcare professionals with a method of remotely motivating cancer patients and survivors to increase their physical activity levels at home, with minimal equipment. Furthermore, this study will further enrich the current literature's claims of reducing the severity of the symptoms of chemotherapy through physical activity, while demonstrating the importance of long-term adherence to physical activity.

The use of activity monitors has been shown to help individuals in adhering to the recommended exercise guidelines through quantifying their efforts and motivating them to continuously improve upon those numbers (Reid et al., 2017). This indicates that activity monitors can be used as a primary tool in improving overall adherence of lymphoma survivors and should be implemented in future exercise interventions. In addition, there continues to be an ongoing debate as to which exercise intervention strategies elicit the greatest benefits among lymphoma survivor's post-chemotherapy.

This literature review will examine recent statistics associated with lymphoma and its survival rate, the body's pathophysiological response to exercise with regards to physical and psychological side effects seen in lymphoma survivors, the ideal exercise guidelines for minimizing the side effects associated with chemotherapy, factors affecting short- and long-term adherence to an exercise program, and the effectiveness of activity monitors throughout an exercise intervention.

2.2 Population Statistics

Lymphomas are currently among the most prevalent cancer types in Canada. They account for approximately 4% of all cancers in both men and women and were estimated to have affected approximately 11400 Canadians in 2020 (Le et al., 2019; Canadian Cancer Society, 2021). Non-Hodgkin's lymphoma makes up most lymphoma cases, accounting for approximately 90% of all diagnoses (Le et al., 2019). While it is true that lymphomas are some of the most common cancers in Canada, there is also a relatively high survival rate among lymphoma patients. The survival rate of non-Hodgkin's lymphoma is approximately 65-70% 5 years after initial diagnosis (Boyle et al., 2017). This percentage increases to approximately 85% among patients diagnosed with Hodgkin's lymphoma (Courneya et al., 2010). While these

percentages may be encouraging, they do not necessarily indicate that the lives of lymphoma survivors will return to normal post-cancer. These survival rates are often achieved through intensive treatment, including chemotherapy, which triggers a variety of physical and psychological side effects that can linger post-treatment and significantly affect an individual's quality of life (Courneya et al., 2012). Therefore, while the main priority among oncologists is ensuring the survival of these individuals, it is also extremely important to monitor and implement strategies to reduce the side effects of chemotherapy to improve both the health and well-being of lymphoma survivors post-treatment.

2.3 Pathophysiology

2.3.1 Physical Side Effects

Many physical side effects are associated with chemotherapy and can significantly reduce a patient's physical capacity and decrease overall quality of life. The most common side effects include cancer-related fatigue, sleep disturbances and decreased physical functioning. This section will discuss these side effects in depth and investigate the effects of physical activity on each of these side effects.

2.3.1.1 Cancer-Related Fatigue. Cancer-related fatigue is one of the most common and debilitating side effects of chemotherapy, affecting most cancer patients and survivors and leaving them bedridden for significant portions of the day. Cancer-related fatigue can also be an issue post-treatment and affects approximately 30% of all cancer survivors, including lymphoma survivors, years after treatment has concluded (De Backer et al., 2007). Physical activity may be a possible solution to decreasing cancer-related fatigue among lymphoma survivors in both the short-term and the long-term.

Cancer-related fatigue is triggered by a physiological response that occurs in the body active and post-chemotherapy. Cancer-related fatigue in cancer patients often peaks immediately following chemotherapy (Vardy et al., 2016). To avoid fatigue, patients are often told by their healthcare professionals to rest and avoid physical activity. However, inactivity often results in cachexia, leading to a higher degree of fatigue after carrying out simple daily activities (Dimeo et al., 1998). This causes a paradox in which highly fatigued cancer patients are instructed to rest and avoid physical activity, though physical activity is needed to avoid muscle catabolism, thus decreasing levels of fatigue after carrying out daily activities. While there is logic in advising cancer patients to avoid strenuous activity, the evidence shows that inactivity significantly reduces the physical capacity of these patients (Adamsen et al., 2003).

A systematic review conducted by Liu, He and Feng (2019) investigated 6 randomized controlled trials that implemented exercise interventions in their treatment of lymphoma survivors. They noted that, overall, there were slight improvements in cancer-related fatigue post-treatment. They also stated that short-term exercise programs cannot significantly improve cancer-related fatigue and that long-term exercise interventions are needed if significant improvements are to be made. However, the authors of this meta-analysis seemed unfairly critical in their review of the 6 studies as they did not fully encapsulate the findings seen in the studies that were reviewed. While a long-term exercise intervention may have significantly greater effects on cancer-related fatigue post-treatment (although this has yet to be proven), short-term exercise interventions have also been shown to be effective (Courneya et al., 2009). A 12-week randomized controlled trial that investigated the effects of physical activity on physical functioning of lymphoma patients (termed the HELP trial) was conducted by Courneya et al. (2009). In this trial, patients were randomly assigned to an aerobic exercise intervention or usual

care group. It was found that the exercise group showed significantly lower levels of cancer-related fatigue after 6 months of follow-up. This was likely due to the higher levels of long-term adherence to exercise seen after the completion of the intervention, compared to the completion of usual care (Courneya et al., 2009). Nevertheless, it does show the effectiveness of a short-term exercise intervention on post-treatment cancer-related fatigue.

The exact physiological mechanism that leads to improvements in cancer-related fatigue during exercise active and post-treatment remains unknown. However, researchers have developed a variety of different hypotheses that may explain this phenomenon. One such hypothesis stems from the research conducted by O'Higgins et al. (2018), in which they hypothesized that cancer-related fatigue is linked to central and peripheral fatigue, which are affected by their own individual mechanisms. Central fatigue occurs due to the inability for the central nervous system to transmit neuronal impulses responsible for voluntary movement, affecting one's ability to complete physical and mental tasks. Peripheral fatigue likely occurs due to dysfunction of adenosine triphosphate (ATP) synthesis and is characterized by the muscle's inability to perform tasks in response to central stimulation (O'Higgins et al., 2018). There is currently no definitive explanation of the physiological improvements due to exercise on both central and peripheral fatigue, though it may be partially explained through improved neuronal impulse transmission and ATP synthesis. In a meta-analysis focusing on the effects of exercise on fatigue, Velthuis et al. (2010) hypothesized that physical capacity would be significantly reduced among cancer patients during treatment due to a lack of physical activity, as well as the medical intervention used to treat the patient. As physical capacity declines, normal physical activities begin to demand a higher percentage of physical capacity, causing premature fatigue. This hypothesis explains that exercise can increase physical capacity (thus reducing cancer-

related fatigue) by increasing cardiac output and capillarization, as well as increasing peripheral mitochondria.

It is very likely that neither of these hypotheses fully explains the physiological mechanism that causes cancer-related fatigue, as well as the improvements seen through exercise. It is most likely a combination of these (and other) physiological mechanisms that are responsible for the improvements in cancer-related fatigue seen during exercise interventions. Nevertheless, physical activity does seem to trigger a physiological response in lymphoma patients, causing improvements in cancer-related fatigue.

2.3.1.2 Quality of Sleep. Quality of sleep is another common issue often seen in lymphoma patients active and post-treatment. Low quality of sleep is often characterized by chronic fatigue, leg restlessness, use of sleeping pills and perhaps most notably, insomnia (Davidson et al., 2002). Approximately 30-50% of cancer patients (including patients suffering from lymphoma) will experience low quality of sleep, a much higher rate than that seen in the general population (12-25%) (Langford, Lee & Miasknowski, 2012). Insomnia, a well-known psychophysiological disorder, seems to be the most common sleep disturbance affecting the quality of sleep among cancer patients. Approximately 30-50% of cancer patients will develop insomnia (O'Donnell et al., 2004), which is unsurprisingly similar to the rate of cancer patients who experience low quality sleep. In most cancer patients, quality of sleep is often affected by other side effects of chemotherapy such as fatigue, depression, pain, and poor quality of life (Courneya et al., 2012).

Medications for individuals who experience sleep disturbances do exist and can work well, depending on the dosing strategy (Chung & Youn, 2017). However, most of these medications are often associated with additional side effects such as delirium, changes in appetite

(potentially causing eating disorders) and an increased risk of falling (Chung & Youn, 2017). In addition, sleeping medications are typically effective for acute sleep disturbances and are not recommended for those who have chronic sleep disturbances (Chung & Youn, 2017).

Exercise has been shown to have a significant positive impact on most treatment-related side effects that affect quality of sleep among lymphoma patients and survivors, without the potential side effects seen with prescribed medication. While there have been very few trials that have focused on the effects of aerobic or strength exercise on quality of sleep among lymphoma patients, there is preliminary evidence suggesting that aerobic exercise may improve quality of sleep among patients who suffer from sleep disturbances. This was first noticed by Courneya et al. (2012) in a randomized controlled trial with a particular focus on physical activity and its effects on quality of sleep among lymphoma survivors. Additional research is needed to confirm the findings seen in this trial, though there is compelling preliminary evidence for the use of exercise to treat sleep disturbances among these individuals.

While evidence on the effects of physical activity on quality of sleep is limited, evidence of the effects of yoga on quality of sleep among lymphoma patients is relatively plentiful. A randomized controlled trial on the effects of yoga on quality of sleep was conducted by Chen et al., (2009), in which lymphoma patients doing yoga were shown to be less prone to sleep disturbances, have improved duration of sleep, reported less use of sleep medication, and had a higher overall quality of sleep. These findings were further supported in other trials conducted with similar parameters, including one conducted by Manjunath and Tells (2005). It has been suggested that the mechanism by which yoga improves quality of sleep among lymphoma survivors largely involves its effects on cancer-related fatigue. Yoga seems to improve quality of sleep by promoting less daytime dysfunction, which is largely characterized by lower levels of

fatigue and napping throughout the day (Mustian, 2013). Therefore, an exercise intervention including a combination of both relaxation and physical exercise may be beneficial in improving quality of sleep among lymphoma survivors.

2.3.1.3 Physical Functioning. Physical functioning is defined as an individual's ability to perform basic daily activities and tasks (Garber et al., 2010). During treatment, lymphoma patients often experience a decrease in physical functioning due to intensive treatment methods (i.e., chemotherapy). This is known as physical deconditioning, which occurs in nearly all lymphoma patients (Courneya et al., 2009) and can persist for several years post-treatment. In fact, a study conducted by Stubblefield, Schmitz & Ness (2013) revealed that approximately 53% of adult cancer survivors will develop issues in physical functioning in the months and/or years post-cancer and treatment. These issues often include loss of muscle mass, decrements in bone health, and increased frailty (Stubblefield, Schmitz, & Ness, 2013). Regular physical activity has been shown to prevent physical deconditioning caused during the treatment process and lead to improvements in physical functioning. The HELP trial conducted by Courneya et al. (2009) investigated the effects of exercise on physical functioning, with results showing that patients in the aerobic exercise treatment group had improved physical functioning compared to the group receiving usual care. These improvements were seen in both patients receiving chemotherapy, as well as patients off treatment. The trial also suggested that VO_{2peak} is directly associated with improvements in physical functioning and that maximizing VO_{2peak} may significantly reduce the effects of physical deconditioning. These results are comparable to other exercise interventions conducted with lymphoma patients, as well as patients suffering from other types of cancer. In a randomized controlled trial consisting of fifty cancer survivors (including lymphoma survivors) Kneis et al. (2020) noted significantly greater improvements in

physical functioning in the exercise intervention group, compared to a control group. These results are unsurprising, considering what is known about the effects of exercise on physical functioning in the general population. Nevertheless, it is still very encouraging to see its significance among a population that suffers from major and unintentional physical deconditioning.

2.3.2 Psychological Side Effects

Exercise has also been known to have psychological benefits for many lymphoma survivors. During and post-treatment, lymphoma patients often exhibit many psychological side effects, including anxiety and depression. This may be due to the intense strain that the body goes through during the treatment process. Without proper treatment, these side effects can manifest in lymphoma survivors and cause significant declines in quality of life in both the short-term and long-term (Courneya et al., 2009). This section will investigate the benefits of an exercise intervention on these psychological issues and the mechanism that is responsible for these benefits.

2.3.2.1 Depression. Depression is one of the most prevalent and distressing psychological mood disorders caused by chemotherapy in lymphoma survivors. In fact, a study conducted by Hawkins et al. (2017) estimated that cancer survivors (including lymphoma) were twice as likely to be on antidepressant medication compared to the general population. With common side effects such as sexual dysfunction, weight gain and insomnia, antidepressant medication may be doing as much harm to cancer survivors as it does good (Khawam, Laurencic & Malone Jr., 2006). This may explain why potential natural remedies, such as physical activity, have been highly studied in clinical trials.

A systematic review conducted by Vermaete et al. (2013) indicated that lymphoma survivors who met the ACSM public health guidelines for physical activity reported lower levels of depression compared to those who did not meet these guidelines. These results are consistent in most of the general population, regardless of illness. Therefore, physical activity affects cancer survivors similarly to how it would affect the general population with regards to depression.

Further research is needed to validate the precise psychological mechanism that causes exercise to decrease depression, However, researchers suggest that physical activity releases endorphins, which significantly improves mood (Dinas et al., 2011). This is known as the "endorphin hypothesis". According to this hypothesis, endogenous opioid peptides are increased in the brain when exercising, which causes general euphoria and decreased levels of depression (Dinas et al., 2011). Other biologically active molecules that are known to affect mood and decrease depression, such as cytokines, adrenocorticotrophic hormone, and cortisol can also be increased by regular physical activity (Dimeo, 2001). While the degree to which depression is reduced after exercise remains unknown, there is sufficient evidence that shows that exercise can be a natural remedy for depression without the potential adverse side effects of antidepressant medication.

2.3.2.2 Anxiety. Like depression, anxiety is common among lymphoma patients and survivors. Both Hodgkin's lymphoma and non-Hodgkin's lymphoma survivors are extremely vulnerable to anxiety and tend to have higher levels of anxiety compared to other patients (Vargas-Roman et al., 2020). Long-term anxiety disorders are also common among cancer survivors. A systematic review conducted by Mitchell et al. (2013) revealed that cancer patients are at a significantly greater risk of developing anxiety disorders up to 10 years post-chemotherapy, compared to their healthy (i.e., cancer-free) counterparts. It has been reported that

the high rates of anxiety among lymphoma survivors may be partly due to fear of cancer recurrence (Vargas-Roman et al., 2020). Latella et al. (2020) conducted a descriptive study in which 136 lymphoma survivors responded to 1 item which asked them to rate how often they worry about the fear of cancer recurrence. Of the 136 lymphoma survivors, approximately 88% reported being fearful of cancer recurrence, even though the likelihood of cancer recurrence is quite uncommon (Latella et al., 2020; Ahmadzadeh et al., 2014).

Regular engagement in physical activity may alleviate the anxiety that lymphoma survivors report. Research has shown that physical activity done regularly can significantly reduce anxiety seen among lymphoma survivors. A meta-analysis on the effects of exercise on quality of life for cancer survivors was conducted by Mishra et al. (2012), which found that an exercise intervention can reduce anxiety among most types of cancer survivors, including lymphoma survivors, for up to 12 weeks post-intervention. The exact mechanism by which physical activity improves levels of anxiety among lymphoma survivors has yet to be proven. Although, it is likely that the "endorphin hypothesis" may play a role similar to the role it has in reducing depression. The degree to which anxiety is reduced in lymphoma survivors with regular participation in physical activity is also currently unknown. However, the evidence is clear that a well-created exercise intervention does reduce anxiety among lymphoma survivors.

2.3.3 Quality of Life

Many trials that have included an exercise intervention to treat lymphoma survivors have focused on its effects on overall quality of life, indicating that this is a significant issue and that there is a sense of urgency among the health community to improve these lives. Exercise has shown to have significant effects on quality of life of lymphoma survivors. Streckmann et al. (2014) conducted a randomized controlled trial with 61 lymphoma patients who were assigned to

either an exercise intervention or a control group. The exercise intervention consisted of both resistance and aerobic exercise. The researchers noticed significant improvements in quality of life within the exercise intervention group compared to the control group, regardless of the phase of therapy the patients were in at the time of the study. Similar results were shown by Courneya et al. (2009) in the HELP trial, where it was found that overall quality of life was significantly higher in the intervention group receiving aerobic exercise treatment when compared to the usual care treatment group. These results are consistent with findings involving other cancer patient populations as well. A study involving 57 cancer patients, including breast, ovarian, Hodgkin's lymphoma, non-Hodgkin's lymphoma, colorectal and testicular cancer indicated that strength exercise can significantly improve quality of life outcomes in all these cancer types. The results from these studies suggest that exercise significantly improves the quality of life of cancer survivors post-treatment.

The quality of life of lymphoma survivors is largely affected by a combination of all the physical and psychological side effects of chemotherapy that were discussed earlier in the "Pathophysiology" section, namely cancer-related fatigue, physical functioning, sleep quality, depression, and anxiety. However, quality of life may also be influenced by an interaction between social and motivational aspects of exercise. According to Courneya et al. (2003), improvements in quality of life that occur during exercise interventions can partially be explained by mastery achievements, positive feedback, and social interactions. With current research indicating that a post-treatment exercise intervention can lead to a reduction of the intensity of chemotherapy-related side effects, as well as an increase in these social and motivational variables, there is ample evidence that suggests that improvements in quality of life will usually follow suit.

2.4 Prescribing an Exercise Program

Prescribing an exercise program to a cancer patient can be challenging and requires an extensive review of a variety of fitness-related components. Physical activity may be done in many different forms, at different intensities and frequencies. Each type of physical activity has its own set of known fitness and health benefits (such as improved cardiovascular fitness, increase in muscle mass and bone strength, greater flexibility etc.). However, exercise interventions are only effective in reducing these side effects if they are prescribed properly, with the individual needs of each patient taken into consideration. This means that a proper balance of intensity, frequency and type of exercise needs to be tailored in any exercise intervention aimed at lymphoma survivors. This section will review the effectiveness of different exercise interventions to determine the ideal exercise program for lymphoma patients and survivors.

2.4.1 FITT Guidelines

Most exercise interventions that have been carried out in the past have used the FITT principle to create the exercise program that would eventually be prescribed to the participants. The FITT principle refers to exercise guidelines for a given population that considers the frequency, intensity, time, and type of physical activity to be done. It is generally used as a framework to prescribe an exercise program to the general public (i.e., healthy population) (Katsukawa, 2016). However, these guidelines have recently been adapted for cancer survivors due to recently published literature that has focused on enhancing the lives of cancer survivors. A recent study conducted by Campbell et al. (2019) recommended that cancer survivors should participate in physical activity at least 3 times per week at moderate to vigorous intensity, for 30 minutes each session, for at least 8-12 weeks, with aerobic exercise favored over strength training. Following these guidelines will improve many of the side effects cancer survivors face

post-treatment, including cancer-related fatigue, anxiety, depression, and overall quality of life. The HELP trial conducted by Courneya et al. (2009) represented these guidelines near perfectly. Their exercise intervention consisted of a 12-week aerobic exercise program done 3 times per week, at moderate to vigorous physical activity (MVPA). Similar parameters were used for a randomized controlled trial conducted by Oldervoll et al. (2011), consisting of patients with different types of cancers, though they incorporated components of strength and balance training into their exercise program as well.

While the frequency, intensity, and time aspects of the FITT guidelines for cancer patients seem to be somewhat consistent with most of the exercise interventions that have been completed, there seems to be some controversy concerning the type of exercise that should be implemented. Treating lymphoma survivors with exercise that is not aerobic based is a relatively new idea and must be further researched to fully understand what type of exercise program elicits the best response from lymphoma survivors.

2.4.1.1 Aerobic Exercise. Most trials that have been conducted with cancer survivors have used aerobic exercise as the primary method for exercise prescription, with encouraging results. A trial conducted by Courneya et al. (2009) indicated that, compared to usual care alone, aerobic exercise can significantly improve patient-rated outcomes including fatigue, physical functioning, depression, and overall quality of life. However, these results have been disputed by Liu et al. (2019), which stated that there were few significant benefits seen in this trial and suggested that short-term aerobic exercise interventions cannot significantly improve quality of life and cancer-related fatigue. They also stated that more attention should be paid to mind-body exercises such as Qigong, yoga, and Tai Chi. This conclusion was based on a trial conducted by Chuang et al. (2017), which indicated that a 21-day Qigong intervention can significantly

improve cancer-related fatigue, sleep quality and quality of life. However, compared to aerobic exercise programs, there have been very few trials that have implemented relaxation techniques within their exercise program.

2.4.1.2 Strength Training. To date, little has been done exploring the benefits of strength training for lymphoma survivors in exercise interventions. However, studies of the effects of strength training have been investigated among a variety of other cancer survivors. For instance, a study conducted by De Backer et al. (2007) investigated the effects of strength training on quality of life in a sample consisting of several types of cancer survivors, including Hodgkin's and non-Hodgkin's lymphoma survivors. This study showed preliminary evidence that strength training can significantly reduce fatigue and improve physical functioning, ultimately improving quality of life. A randomized controlled trial conducted by Segal et al. (2009) revealed similar results and concluded that, compared to aerobic exercise, resistance exercise produced greater long-term improvements in cancer-related fatigue among prostate cancer patients. While encouraging, the results from both trials cannot be concluded for lymphoma patients as the differences between cancer types on strength training outcomes were not investigated. Therefore, further research with lymphoma patients is needed to confirm the positive effects of strength training on these individuals.

2.4.1.3 Aerobic and Strength Training Combined. Research has yet to compare aerobic exercise interventions to strength training interventions. Therefore, deciding whether one intervention works better than the other in improving overall quality of life in lymphoma survivors is near impossible. However, one intervention design that may have significant benefits on the health and well-being of lymphoma survivors are interventions consisting of a combination of both aerobic and strength training. This type of exercise intervention is fairly

common among researchers using exercise to improve the lives of cancer patients. One such study that implemented this type of intervention was the trial conducted by Streckmann et al. (2014) in which participants in the intervention group were prescribed an exercise program consisting of aerobic, sensorimotor and strength training. Results indicated that a diversified exercise program can significantly improve the quality of life among lymphoma survivors primarily by decreasing the effects of therapy-induced peripheral neuropathy, which at substantial levels is often associated with impaired balance and a greater risk of falling. Similar results were seen in a randomized controlled trial conducted by Herrero et al. (2006), which suggested that 10 breast cancer patients who were assigned to the exercise intervention group reported greater muscle functioning, strength endurance and quality of life, compared to the group receiving standard care. These results indicate that overall physical functioning significantly improved in exercise interventions that combine both resistance training and aerobic exercise, perhaps more than in exercise interventions consisting of only one type of exercise.

After reviewing the literature, it appears as though, with proper administration, many types of exercise can be implemented in an exercise intervention to significantly improve the lives of lymphoma survivors. However, most interventions have focused on either aerobic or a combination of aerobic and strength training, strengthening the argument for the use of these exercise interventions.

It is important to note that the FITT guidelines mentioned should be implemented with caution. Each patient that participates in an exercise intervention has different needs and capabilities. Therefore, researchers must individualize the exercise program to fit their needs.

2.4.2 Cancer Stage

There is some debate with regards to the appropriate stage of cancer treatment that an exercise program should be prescribed. More specifically, the debate revolves around the effectiveness of an exercise program during treatment, in comparison to post-treatment. In a meta-analysis conducted by Hilfiker et al. (2018), they reported that, while aerobic and resistance training are both similarly effective in reducing cancer-related fatigue during and post-treatment, relaxation interventions seem to be most effective in reducing fatigue during treatment. The importance of relaxation seems to decrease significantly post-treatment. However, more research is needed to confirm these results as this was the only study that considered relaxation interventions in their methodology. The conclusion that aerobic and resistance exercise are both similarly effective in reducing cancer-related fatigue during and post-treatment was supported by Puetz & Herring (2012) in a meta-analysis comparing the effects of exercise on cancer patients during and post-cancer treatment. During treatment, exercise seems to mitigate cancer-related fatigue, whereas exercise also seems to reduce cancer-related fatigue post-treatment. It was thus concluded that exercise seems to have a palliative effect during treatment and a recuperative effect post-treatment in cancer patients. However, these results are generalized for all cancer patients and do not specify differences between cancer types in fatigue reduction. Furthermore, research has yet to investigate if the recommended exercise guidelines previously mentioned need to be adapted based on the stage of cancer treatment (i.e., active vs post-treatment). However, the preliminary evidence for the prescription of exercise during and post-treatment are promising.

2.4.3 Supervised and Unsupervised Exercise

There is ongoing research comparing center-based, supervised exercise programs to home-based, unsupervised exercise programs. Much of the research done on exercise and cancer survivors tends to favor the implementation of a supervised exercise program, largely due to higher levels of adherence compared to an unsupervised exercise program (Courneya et al., 2012). However, certain factors must be accounted for before making this conclusion. A study conducted by Ormel et al. (2018) noted that exercise programs done at an exercise center (supervised) may negatively influence adherence due to lengthy travel times. Therefore, adherence to a center-based supervised exercise program is only heightened if the exercise center is near the patient's home. Otherwise, adherence tends to favor unsupervised, home-based exercise programs (Ormel et al., 2018). In addition, the context in which the exercise program will be taking place must also be considered before designing an exercise program using a supervised approach. A great example of this is the current COVID-19 pandemic, which has forced many restrictions on teams running clinical trials for cancer survivors. With social distancing being enforced due to the infectious nature of the illness, it has been deemed unsafe for center-based, supervised exercise programs to be arranged. Therefore, this new reality has forced exercise programs to be done at home, which are largely unsupervised. That said, unsupervised exercise programs can benefit lymphoma survivors in a variety of ways. A follow-up study to the HELP trial was conducted by Courneya et al. (2015), which explained that unsupervised exercise programs are generally not encouraged except in cases in which the participants are unable or unwilling to attend the supervised exercise sessions. Therefore, for those who do not have the means of attending supervised exercise sessions or who feel uncomfortable in doing so can greatly benefit from an unsupervised, home-based exercise

program. In addition, a home-based, unsupervised exercise program allows cancer survivors to go at their own pace, which is the more favorable option for most lymphoma survivors. In fact, in a study examining the exercise preferences of lymphoma survivors, Vallance et al. (2006) surveyed 431 lymphoma survivors and noted that approximately 59% of them preferred an unsupervised exercise program in which they can exercise at their own pace. Finally, while adherence to an exercise program does tend to favor supervised exercise, there may be other methods to improve the level of adherence that is lost in an unsupervised exercise program, such as an activity monitor. Therefore, an unsupervised exercise intervention, when done and implemented correctly, can be just as effective as a supervised exercise intervention (Brocki et al., 2014).

2.5 Exercise Adherence

Adherence, defined in this context as a cancer patient's ability to meet the recommended exercise guidelines in both the short-term and long-term, has been proven to be the largest factor in determining long-term improvements in quality of life. Two different categories of adherence will be explored in this literature review: short-term and long-term adherence. Short-term adherence is defined as a cancer patient's ability to complete a prescribed exercise program throughout the entire intervention. Long-term adherence is defined as a patient's ability to adhere to the recommended exercise guidelines following their participation in an exercise intervention. Both short-term and long-term adherence are important in improving and maintaining a high quality of life. This section will examine the effectiveness of an exercise intervention on adherence and suggestions that can be implemented to increase both short- and long-term adherence.

2.5.1 Short-Term Exercise Adherence

Total completion of an exercise intervention is essential in ensuring lymphoma survivors fully benefit from the exercise program. This is also the most difficult task for researchers to accomplish. A systematic review conducted by Ormel et al. (2018) reported low adherence in studies that treated cancer patients using an exercise intervention. Approximately half of the patients that are enrolled in an exercise intervention complete the offered exercise program (Husebø et al., 2012). The reported low levels of adherence to exercise are likely due to a combination of different variables which Courneya et al. (2010) summarized as a complex interaction among demographic, medical, behavioural, and psychosocial variables. Medical variables, including intensity of cancer treatment and advanced disease stage are associated with lower adherence to the exercise intervention. Behavioural and psychosocial variables, including motivation, self-efficacy, fitness level, and family support are associated with adherence to exercise (Ormel et al., 2018). Increasing these behavioural and psychosocial variables should be considered when designing an exercise intervention.

2.5.2 Long-Term Exercise Adherence

One of the primary goals of any exercise program is to ensure that patients continue to exercise independently long after completing an exercise intervention. This is one of the most difficult components of an exercise intervention as it requires researchers to follow-up with the participants multiple times for several years post-intervention. Studies have shown that an exercise intervention is effective in increasing adherence to the recommended exercise guidelines post-intervention. Courneya et al. (2012) completed a follow-up study to their HELP trial where they prescribed an exercise program to lymphoma survivors. In their follow-up analysis, the researchers noted that approximately 55% of lymphoma survivors were meeting the

recommended exercise guidelines six months after their participation in the HELP trial, which is greater than the 28% participation rate that was seen at baseline. They explained that while this percentage is greater than the percentage of participants that were meeting the exercise guidelines at baseline, improvements need to be made to increase post-intervention adherence to exercise.

According to Courneya et al. (2012), 16 variables predicted adherence to exercise post-intervention. Of those 16 variables, the strongest predictor was receiving another exercise program post-intervention. Approximately 70% of participants who were prescribed an exercise program post-intervention adhered to the recommended exercise guidelines long-term. This percentage dropped to 36% for participants who were not provided with an exercise program. Another important predictor investigated in this study was perceived fatigue and physical functioning. According to Courneya et al. (2012), patients who perceived themselves as having higher physical functioning and lower fatigue post-intervention were more likely to continue exercising 6 months later. While unsurprising, it does reveal the importance of creating an exercise program that maximizes improvements in physical functioning and minimizes fatigue in lymphoma survivors. Other significant predictors of post-intervention exercise behaviour were level of physical activity at baseline, younger age, and type of lymphoma (i.e., non-Hodgkin's or Hodgkin's lymphoma). Patients previously diagnosed with Hodgkin's lymphoma are more likely to adhere to the recommended exercise guidelines post-intervention compared to patients diagnosed with non-Hodgkin's lymphoma. This may be partly due to age, considering Hodgkin's lymphoma patients are generally younger than non-Hodgkin's lymphoma patients, and younger age is positively related to higher levels of exercise adherence post-intervention (Courneya et al., 2012). These results have significant implications for future research regarding exercise and

lymphoma survivors. Future research needs to emphasize the importance of prescribing an exercise program that patients can follow once the intervention has been completed.

2.5.3 Activity Monitors

Many different methods have been discussed with regards to increasing adherence among cancer survivors. One recommendation suggested by Ormel et al. (2018) was to implement the use of objective monitoring devices in an exercise intervention such as a wearable activity monitor. To date, there have not been any trials completed that have provided lymphoma patients and survivors with activity monitors (such as a Fitbit™) to track their daily activity levels. A systematic review conducted by Maddocks et al. (2009) reported that most home-based exercise interventions have used a patient diary as the primary tool to assess adherence to a prescribed exercise program, whereas center-based exercise interventions used an attendance register to assess adherence. Having participants write their daily activity in a diary can be problematic as it can lead to recall bias and a significant overestimation of the amount of physical activity done on any given day (Moseley, 2006).

While there have not been any studies that have used activity trackers to track lymphoma patient's daily activity, it has been hypothesized that providing patients with activity trackers could improve adherence by maximizing patient participation in the exercise program, as well as increasing motivation for those who are unmotivated (Ormel et al., 2018). Fitbit™ is one of the most well-known activity trackers on the market and has been shown to be a valid and reliable measure of different exercise variables, while also being a low cost-effective alternative to many other activity monitors currently available such as ActiGraph GT3X+. A study conducted by Reid et al. (2017), compared Fitbit™ monitors to ActiGraph GT3X+, a gold standard in

measuring activity, with results indicating that Fitbit™ (particularly those worn on the wrist) were as accurate as ActiGraph GT3X+ in measuring steps taken, and nearly as accurate in measuring light intensity activity. Additionally, they showed that MVPA can be increased using a Fitbit™ monitor as a self-monitoring device. Therefore, there is potential for Fitbits™ to increase levels of physical activity among individuals who decide to wear one. Lesser-known activity trackers have also been tested for validity and reliability in measuring steps taken, with most of them proving to be similarly valid and reliable measures of steps taken and light-intensity activity (Kooiman et al., 2015; Gorzelitz et al., 2020). However, given its popularity, participants may respond more favorably if they are given a Fitbit™ monitor, as opposed to other lesser-known brands currently on the market.

Though most activity trackers (including Fitbit™) may not be accurate in measuring exact minutes spent in MVPA, they are accurate in measuring daily increases or decreases in those levels (Reid et al., 2017). This data can serve as a potential motivator for patients as they attempt to increase their level of activity each day. Therefore, it may be worthwhile to provide lymphoma survivors with an activity tracker to increase their adherence to a prescribed exercise program. This is especially true during the COVID-19 pandemic, where supervised exercise programs are not feasible, thus forcing participants to exercise at home, unsupervised.

There is also the potential for activity monitors to increase adherence to the exercise guidelines of cancer (lymphoma) patients long after the completion of an exercise intervention (i.e., long-term). A randomized controlled trial was conducted by Singh et al. (2020) in which half of the participants that had previously participated in the SAFE trial received Fitbit™ monitors to increase levels of physical activity post-intervention. They observed that patients who had received a Fitbit™ monitor reported higher levels of physical activity 12

weeks following the completion of the SAFE trial, compared to those who did not receive a Fitbit™ monitor. This trial was conducted with women who were diagnosed with breast cancer. Nevertheless, results are encouraging and shows the potential benefits of providing activity monitors to participants to increase long-term adherence to exercise.

2.6 Conclusion

This literature review examined the importance of exercise among lymphoma survivors. It showed that regular participation in physical activity can have major implications for the side effects seen in lymphoma survivors active and post-treatment. It also showed that the body's physiological response to exercise seems to explain the significant reduction among physical symptoms (i.e., fatigue, insomnia, and physical functioning), as well as psychological symptoms (i.e., anxiety and depression) that arise due to intensive treatment methods, such as chemotherapy. While aerobic exercise seems to be more effective than strength training in alleviating many of these side effects, more research is needed to definitively prove this. Additionally, further research on the effects of exercise interventions consisting of a combination of aerobic and strength training is needed. Adherence to exercise in both the short-term (during an exercise intervention) and long-term (post-exercise intervention) is relatively low among lymphoma survivors. While adherence rates to exercise post-intervention were higher than adherence rates at baseline, it is still very low considering the potential benefits of physical activity for lymphoma survivors. Demographic, medical, behavioural, and psychosocial variables likely play a role in the low adherence levels seen during and post-intervention among lymphoma survivors. Improved motivation, self-efficacy, fitness level, and family support all seem to be associated with higher levels of adherence to exercise. Therefore, improving those conditions may significantly improve adherence. In addition, prescribing an exercise program

following the conclusion of an exercise intervention seems to be the most effective method of improving long-term adherence to exercise. Finally, there is preliminary evidence on the use of activity monitors to significantly improve adherence to exercise in both the short-term and the long-term. Activity monitors also seem to be reliable measures of steps taken, as well as light intensity activities, allowing patients to self-supervise their exercise behaviours. This is particularly important due to the current nature of the COVID-19 pandemic, which essentially forces lymphoma survivors participating in exercise interventions to carry out the exercise program at home, unsupervised. Fitbits™ are currently the most popular and affordable activity monitors currently on the market, making them the prime candidate for use among lymphoma survivors. There have not been any trials done that have implemented an activity monitor in an exercise intervention among lymphoma survivors. However, the preliminary evidence of the effectiveness of activity monitors is sufficiently strong and warrants further investigation.

Given what is known with regards to exercise and its benefits, exercise can have significant clinical implications in the fields of hematology and oncology (Dittus et al., 2015). However, it is important to note that exercise can be harmful for certain lymphoma patients and survivors (Courneya & Friedenreich, 1999). Conditions such as cachexia, anemia, metastatic bone disease, thrombocytopenia and neutropenia are potential factors that may make it dangerous for these patients to partake in an exercise intervention (Courneya & Friedenreich, 1999). Future research must consider this, especially during times of COVID-19, where center-based, supervised exercise programs are not possible.

Chapter 3 - Methodology

This study was a 3-month proof-of-concept trial and is the pilot for a larger randomized controlled trial. Ethics approval was obtained by the McGill University Health Center Research Ethics Board (see Appendix A), and informed consent was obtained from the recruited participants.

3.1 Participants

Participants were recruited at the Jewish General Hospital located in downtown Montreal by their hematologists, including co-investigator of this study, Dr. Nathalie Johnson. To be eligible for this study, participants must have been diagnosed with non-Hodgkin's or Hodgkin's lymphoma and must have received chemotherapy at some point prior to their enrollment in the study. The date of their cancer diagnosis, as well as when they received chemotherapy, was not of concern for the proof-of-concept trial. However, the randomized controlled trial will require participants to have completed chemotherapy within the last 6 months from the start of the intervention. Participants must have also received approval from their hematologist as having no contra-indications to physical activity. Finally, participants must have had access to a cellular phone or another device that could download and install activity tracking applications.

Once recruited, participants were contacted by the research coordinator to collect informed consent via videoconferencing. Recruitment commenced June 2021 and ended November 2021.

3.2 Design and Procedures

The proof-of-concept trial followed a single-armed trial in which all participants were assigned to the exercise prescription group. The primary purpose of this trial was to determine the feasibility of the *Lymfit* intervention for future use in a randomized controlled trial. Feasibility was determined through monitoring participant retention rates, technical issues on intervention delivery and data collection during the pandemic, as well as safety issues within the exercise intervention. We wanted to know if we could deliver an exercise intervention remotely to this vulnerable population. This information will be used as pilot data as we seek funding for a larger trial in the future. The secondary purpose of exploring the preliminary effects of the intervention on exercise adherence and well-being was investigated using Fitbit™ monitors, and three self-reported health outcomes (i.e., quality of life, fear of cancer recurrence, and fear of COVID-19).

Each participant was prescribed a 12-week, home-based exercise program, which was constructed based on the recommendations from the FITT guidelines for cancer survivors. Field experts have unanimously agreed that it is recommended that these individuals perform exercise at a minimum of 3 times per week (Frequency), at moderate to vigorous intensity (Intensity), for 30 minutes each session, for at least 8-12 weeks (Time), while including a combination of cardiovascular and resistance training (Type) (Campbell et al., 2019). Prior to starting their exercise program, participants were asked to fill out four different questionnaires, including the PROMIS-29 questionnaire, which were also required to be filled out again upon completion of the intervention (see Appendix B). The PROMIS-29 questionnaire assessed participants' quality of life and included outcomes such as the ability to participate in social roles/activities (PROMIS 1), anxiety/fear (PROMIS 2), depression/sadness (PROMIS 3), fatigue (PROMIS 4), pain

interference (PROMIS 5), physical function (PROMIS 6), and sleep disturbance (PROMIS 7). Fear of COVID-19 and fear of cancer recurrence questionnaires were also filled out at baseline and again upon completion of the intervention. Participants were asked to fill out the COVID-19 questionnaire so that the investigators could measure if exercise improved stress and anxiety relating to COVID-19 from pre- to post-intervention, thus improving overall quality of life during a pandemic that is persisting for multiple years. This is especially important considering that cancer survivors perceive themselves as being at a higher risk of severe illness if infected with COVID-19, increasing their overall fear and anxiety compared to the general population (Cerda & García, 2022). Finally, participants were asked to fill out a fitness questionnaire at baseline, which assessed their current and prior level of fitness (i.e., prior to lymphoma diagnosis), physical activities that they do and do not enjoy (i.e., preferences of one type of exercise over another), days/times during the week that the participant would be available to exercise, and current barriers to exercise. This questionnaire was not used as a method of data collection, nor was it used in data analysis. Rather, it was used as a guide to tailor personalized workout programs that participants would be motivated to engage in and enjoy doing for the duration of the 12-week study.

After completing the baseline questionnaires, participants were sent a package that included a Fitbit™ monitor, a set of 5 resistance bands of varying resistance levels, and a measuring tape. The Fitbit™ monitor that they were given was either a Fitbit™ Inspire 2 or a Fitbit™ Charge 4. These Fitbit™ monitors are designed to be worn on the wrist and were used to gather objective data on a variety of fitness and wellness measures including steps taken, sedentary minutes, light activity minutes, very active minutes, calories burned, heart rate, waking minutes and total time spent sleeping. Participants were instructed to wear their Fitbit™ every

day for the duration of the study. Reminders were sent out to participants via email to place their Fitbit™ back on their wrist if they had taken it off for 24 hours. This was done to ensure that the most accurate reading of a participant's activity throughout each day was attained.

3.2.1 Rationale for Use of Fitbit

The decision to use wrist-worn activity monitors such as the Fitbit™ Inspire 2 and Fitbit™ Charge 4 in this trial was supported by a study that focused on validity and reliability of Fitbits™. The study, conducted by Reid et al. (2017), compared Fitbit™ monitors to an ActiGraph GT3X+, with results indicating that wrist-worn Fitbits™ were as accurate as ActiGraph in measuring steps taken. Additionally, these researchers showed that moderate to vigorous physical activity can be increased using a Fitbit™ monitor as a self-monitoring device. It was thus concluded that wrist-worn Fitbit™ monitors are valid and reliable devices for low intensity activities and steps taken, making them a feasible option for this study.

Funding for the Fitbit™ monitors was provided by Dr. Nathalie Johnson's funds raised during the 2018 and 2019 Ride to Conquer Cancer fundraiser, as well as funding from Dr. Ross Anderson.

3.2.2 Prescribing an Exercise Program

The prescribed exercise programs were created based on the needs and preferences of each participant, which were communicated to the investigators in the fitness questionnaire, as well as the FITT principles for cancer survivors. Therefore, each participant was given an exercise prescription that focused on exercises they enjoyed doing, while also ensuring that they were meeting the minimum exercise guidelines stated in the FITT principles (Campbell et al., 2019). The exercise programs consisted of both aerobic and resistance training at varying levels

of intensity and duration, depending on the participants current and changing fitness levels. These programs were constructed using videos found on Youtube™, which would demonstrate the exercises that the participants would be performing. Follow-up Zoom™ meetings with the participants were conducted every two weeks to discuss if adjustments to the workouts of their program needed to be made. These adjustments often included: increasing the difficulty of each workout, increasing the length of each workout and/or increasing the number of days per week that participants would be exercising. If participants were comfortable with their current exercise program, then no changes would be made. The inherent purpose of these meetings was to ensure that participants were constantly motivated and proceeded safely in adhering to their program. If certain exercises were unenjoyable for participants, or if the current exercises were becoming too easy, then they would be adapted to become more enjoyable and/or more challenging, which would theoretically increase their motivation to adhere to the daily workouts of the program. These follow-up meetings, coupled with the Fitbit™, maximized motivation and minimized the risk of physical inactivity.

3.3 Data Collection

Data collection was primarily done using an online database created specifically for this study. The database, currently known as *Lymfit*, is located at the Jewish General Hospital and is capable of securely storing most of the data from this study, including Fitbit™ data and questionnaire responses for each participant. Each Fitbit™ monitor had to be registered and connected to the server prior to providing the participants with them. Once connected, the *Lymfit* database was able to automatically collect data from the Fitbits™ (i.e., steps taken, sedentary minutes, light, moderate and vigorous physical activity, quality of sleep, heart rate, calories burned and sleep) daily and store it for future statistical analyses. The investigators had constant

access to the *Lymfit* database and were able to retrieve data at any time. The database was, and continues to be protected by a firewall to prevent anyone who is not a member of the research team from accessing the data without permission. This security system was implemented to protect patient confidentiality throughout the study. In addition, participant data was de-identified by assigning each patient's Fitbit™ device with a code name (e.g., Lymfit001) and an email (e.g., Lymfit001@ladydavis.ca), such that Fitbit™ had no access to personal patient data other than the date of birth, height, and weight.

Finally, participants were emailed a logbook questionnaire every two weeks, which asked them to record the number of days they spent in light, moderate and vigorous physical activity in the past two weeks, as well as any barriers and facilitators to exercise that hindered or helped their ability to adhere to their exercise program. This logbook would give the investigators a secondary method of monitoring participants physical activity levels in the case of a Fitbit™ malfunction, as well as informing the investigators of the most common barriers and facilitators that participants encountered throughout the intervention. This information was used as a component for the analysis of the secondary purposes of the study.

3.3.1 Questionnaire Outcome Measurements

3.3.1.1 Quality of Life (PROMIS-29). Items in PROMIS-29 use a 5-point Likert-type scale. The raw scores from each of the 7 domains (PROMIS 1-7) were uploaded to the HeathMeasures scoring service and converted into T-scores. For domains such as fatigue, anxiety/fear, pain interference, depression/sadness and sleep disturbance, a higher T-score represented worsening conditions. For domains such as the ability to participate in social roles/activities and physical functioning, a higher T-score represented improving conditions

(Cella et al., 2010). The reliability and construct validity of the PROMIS-29 v2.1 were supported in a previous study of cancer survivors (Kang et al., 2022).

3.3.1.2 Fear of Cancer Recurrence. Fear of Cancer Recurrence was assessed using the Fear of Cancer Recurrence Inventory (FCRI; Simard & Savard, 2009). The FCRI is a multidimensional, 42-item questionnaire measuring seven factors pertaining to fear of cancer recurrence: triggers, severity, psychological distress, coping strategies, functioning impairments, insight, and reassurance. Each item is rated on a five-point Likert scale ranging from 'not at all' or 'never' (0) to 'a great deal' or 'all the time' (4). A subscale score was calculated by summing the item scores of each factor subscale. The total score (ranges from 0 to 168) was then calculated based on the scores of each subscale. Considering that the question for item 13 ("I believe that I am cured, and the cancer will not come back") is addressed in the opposite direction of other questions, the response scale to item 13 was reversed before calculating the total score. Higher summary score of FCRI indicated higher levels of fear of cancer recurrence. In addition, the nine-item severity subscale of the FCRI (FCRI Severity) has an empirically validated cut-off score (≥ 13 points) for screening clinically significant levels of fear of cancer recurrence.

3.3.1.3 Fear of COVID-19. Fear related to the pandemic was assessed using the Fear of COVID scale (FCV-19S), a seven-item scale assessing the fear of COVID–19. The items are rated on a five-point Likert scale ranging from "strongly disagree" (1) to "strongly agree" (5) with total scores ranging from 7 to 35. Higher total scores represented higher levels of fear. The reliability and validity of the FCV19S have been established (Ahorsu et al., 2020).

3.4 Statistical Analyses

Analyses for the proof-of-concept trial was mostly descriptive as the sample size was not large enough for meaningful inferential analyses. However, significance testing was conducted between baseline and week-12 questionnaire scores to see if these scores significantly increased or decreased from pre- to post-intervention. All data from the proof-of-concept trial were analyzed using IBM SPSS Statistics version 26 and R version 4.2.0.

3.4.1 Demographic Characteristics

Descriptive statistics were collected and analyzed to provide a summary of basic demographic characteristics including age, sex, height, and weight. Fitness characteristics, such as body mass index (BMI) and waist circumference, were also collected and analyzed from each participant to broadly encapsulate the fitness level of each participant prior to commencing the intervention.

3.4.2 Fitbit Outcomes

The means of multiple Fitbit™ fitness and sleep outcomes including time spent being very active, time spent in light activity, time spent being sedentary, steps taken, waking minutes and total sleep time, were calculated weekly from baseline (1 week prior to the start of their exercise program) to week 12. First, the seven-day average for each Fitbit™ outcome was calculated for each participant individually, for 13 weeks (including baseline). Those scores were then used to calculate the weekly means of the entire sample. This allowed for a comparison of weeks 1-12 to baseline among those Fitbit™ outcomes, while also showing an increase or decrease in overall physical activity on a week-to-week basis. There were 2 conditions that the Fitbit™ data needed to meet to be eligible for this analysis. Firstly, for a week of Fitbit™

data to be eligible for analysis, participants must have had enough data for a minimum of 4 of the 7 days during that given week. This threshold was determined based on the guidelines established by Trost et al. (2005), which stated that between 3 and 5 days of objective monitoring is required to reliably estimate physical activity outcomes in adults. Therefore, if a participant did not wear their Fitbit™ for 4 or more days in any given week, the Fitbit™ data from that participant for that week would not be included in the calculations. Although the cutoff is 4 days, if the participant had enough data for 5, 6 or 7 days in a week, then those days would also be averaged and included in the analysis. Secondly, a day of data must have consisted of a minimum of 1000 steps to be eligible for the required 4 out of 7 days of data. If a participant did not have a minimum of 1000 steps on a given day, it was assumed that the participant did not wear the Fitbit™, thus that day would not count towards the required minimum of 4 of 7 days. The 1000-step threshold was determined by the investigators prior to commencing the intervention and was based on the guidelines established by Craig et al. (2010), which stated that values <1000 or >30000 daily steps can be considered cut points for identifying outliers. Therefore, any values that fall below 1000 steps or above 30000 steps were removed from analyses to clean the data (Craig et al., 2010). All Fitbit™ score means, except for steps taken, were calculated as time spent in minutes. To make it easier to compare the exercise habits of these participants to the recommended exercise guidelines, the Fitbit™ outcome "very active minutes" was referred to as time spent in moderate to vigorous physical activity (MVPA).

3.4.3 Questionnaire Outcomes

A Wilcoxon Signed-Rank Test was conducted to compare and determine if there was a statistically significant change among the scores in the PROMIS-29 health outcomes (PROMIS 1-7) from pre- to post-exercise prescription (baseline and week 12). Fear of cancer recurrence

and fear of COVID-19 questionnaire scores were analyzed using a Wilcoxon Signed-Rank Test as well to determine if there were any statistically significant changes from pre- to post-exercise prescription.

3.4.4 Patient-Reported Barriers/Facilitators to Exercise

Finally, participants responses to their barriers and facilitators to exercise were gathered and analyzed by examining the most frequent barriers and facilitators that participants reported. This allowed the investigators to understand the most common barriers and facilitators that lymphoma patients face, which, in turn, allowed for improvements to be made when creating/adjusting their respective exercise programs, thus improving the overall intervention.

Chapter 4 – Manuscript 1

A Proof-of-Concept Trial for Lymfit: A Personalized, Virtual Exercise Intervention to Improve Health Outcomes of Lymphoma Survivors During COVID-19

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Abstract

Background and Objective. Treatments for lymphoma can lead to reduced physical functioning, cancer-related fatigue, depression, anxiety, and insomnia. These side effects may negatively impact the cancer survivor's quality of life. Evidence has mounted in support of physical activity prescription as a highly therapeutic approach to mitigating the short- and long-term side effects of cancer treatments. Yet, cancer survivors' participation in physical activities remain suboptimal, which has been further exacerbated by the deleterious effects of isolation during the COVID-19 pandemic. The *Lymfit* intervention aims to offer motivational support, expert guidance, and personalized exercise prescription to optimize physical activity among lymphoma survivors. This proof-of-concept study explores implementation feasibility (retention, technical and safety issues), and the preliminary effects of *Lymfit* on various health outcomes. **Methods.** This was a single-armed trial with a pre- and post-test design. 20 lymphoma survivors were recruited to participate in the 12-week *Lymfit* intervention. Wearable activity trackers (Fitbit^{TM}) were given to participants as a motivational tool and for data collection purposes. Participants received a personalized exercise program and kept weekly contact with a Kinesiologist for 12 weeks. Physiologic metrics were collected by the Fitbit^{TM} monitors and were stored in the *Lymfit* database. Self-reported questionnaires measuring health outcomes were collected at baseline and at post-intervention. **Results.** Overall, 17 participants were included in the analysis process. The sample cohort consisted of 10 female (58.8%) and 7 male (41.2%) participants. The mean age of the cohort was 31.5 ± 7.3 years. 3 participants were excluded from the analyses due to non-compliance issues. 70% of participants successfully completed the intervention. No adverse effects were reported. Participants maintained adequate physical activity levels throughout the study. Significant changes in self-reported health outcomes at post-

intervention were observed. **Significance.** With access to resources and facilities being limited during the COVID-19 pandemic, the *Lymfit* intervention filled an immediate need to provide physical activity guidance to young adults who have survived lymphoma. Findings provide preliminary support that the remote implementation of the *Lymfit* intervention is feasible and demonstrated promising results in quality of life outcomes. A large-scale randomized controlled trial is warranted to further evaluate the effects of the *Lymfit* intervention on lymphoma patients.

Introduction

Lymphoma is the fifth most common cancer among adults in Canada. It is estimated that approximately 12,000 Canadians were diagnosed with lymphoma in 2021[1]. There are two main subtypes of lymphoma: Hodgkin's and non-Hodgkin's. Lymphoma is most commonly treated with multi-agent chemotherapy, radiation, and/or immunotherapy [2]. The more recent novel agents and cellular therapies [3] have markedly improved the cure and remission rates [4]. The development of treatment options has dramatically improved lymphoma patients' survival rates as well [5]. Despite being highly curable, treatment agents may trigger a variety of negative physical and psychological side effects that can linger post-treatment and significantly affect an individual's quality of life, post-treatment.

Treatment-induced toxicity in lymphoma survivors may cause a wide range of health issues [6]. For instance, radiation treatment to the neck, supraclavicular, and/or mediastinal region increases the risk of radiation-induced hypothyroidism and pulmonary toxicities [7]. Lymphoma survivors are also susceptible to cardiovascular complications owing to the exposure to anthracycline-based regimens and mediastinal/thoracic radiation therapy [8,9]. Specifically, the risks of developing post-treatment myocardial infarction, arrhythmias, and congestive heart failure among lymphoma survivors are significantly higher than among the general population [10,11]. Besides the treatment-induced long-term effects, cancer survivors encounter a variety of psychological and functional challenges upon the completion of traditional cancer treatment. These challenges include increased anxiety [12], fear of cancer recurrence [13], reduced levels of physical functioning [14], cancer-related fatigue [15] and decreased cognitive capability [14], all of which can lead to chronic fatigue and reduced quality of life [16,17].

While researchers have discovered a myriad of health-promoting interventions (e.g., dietary or nutritional modifications) that can benefit the health of cancer survivors, the positive effect of physical activity remains one of the most promising options, demonstrating the highest therapeutic value on improved psychological and physical health [18,19]. In lymphoma patients, moderate to vigorous physical activity (MVPA) pre- and post-treatment are positively associated with various cancer-related outcomes including improved survival[20,21], improved quality of life [22], improved sleep quality [23], higher physical functioning and lower fatigue [24-28].

Despite the overwhelming benefits of physical activity, creating and implementing lifestyle modifications remains tremendously challenging for cancer survivors [29]. The American College of Sports Medicine suggested that physical activity interventions designed for cancer survivors should follow the FITT principles [29]: a minimum of 3 times per week (**F**requency); at a moderate to vigorous level (**I**ntensity); for 30 minutes each session, for at least 8 to 12 weeks (**T**ime); with aerobic activity favored over resistance training (**T**ype). While the programs should be specific to cancer type, treatments, and/or outcomes, the FITT principles have been widely adopted in exercise interventions for cancer patients and survivors [30].

Although no physical activity intervention studies have been conducted among lymphoma patients in Canada, a structured and supervised exercise intervention was tested among lymphoma patients in Italy and yielded promising results [25]. This Italian in-person intervention was offered in a group format at the oncology institute's gym, where participants were engaged in 60-minute physical activity sessions twice a week, for eight weeks. The results of the study demonstrated significant improvements in physiological outcomes such as fatigue, body mass index (BMI), flexibility, balance, and functional mobility [25].

While the effectiveness of a structured and supervised exercise intervention to mitigate cancer-related side effects has been well established, the coronavirus disease (COVID-19) pandemic has greatly impacted the format, mode of delivery and implementation of physical activity interventions [31]. Since the beginning of 2020, public health safety measures were imposed by provincial governments in Canada to limit viral transmission. As a result, opportunities for regular physical activity at health and fitness centers were severely compromised. The home environment emerged as the only viable indoor opportunity for physical activity, which decreased many cancer survivors' motivation to engage in physical activity [32]. Accordingly, the American College of Sports Medicine had released a call to action at the beginning of the pandemic for researchers to develop novel and flexible approaches to physical activity that account for limitations imposed by the pandemic [33].

Physical activity format and modality preferred by cancer survivors during the pandemic include professional guidance, delivered using digital or remote platforms, and home-based programs that offer exercise choices [32]. As reported by lymphoma survivors, the most promising components for supporting physical activity maintenance include goal setting, accountability, and convenience [34]. In addition, remote interventions using technology such as wearable activity monitors and mobile phones are increasingly being used to incorporate evidence-based components while meeting the expressed desire for convenience and accountability among cancer survivors [35-37].

To date, no intervention aiming to increase physical activity in individuals with lymphoma during the COVID-19 pandemic have been conducted, neglecting the potentially deleterious effects of quarantine and sedentary behaviour in this population [38]. These findings underscore the urgent need to develop innovative and enjoyable home-based physical activity

interventions that promote social distancing, are cost-effective, and have a wide reach to help mitigate the compounding effects of the pandemic on physical inactivity among lymphoma survivors.

Considering this gap in the literature, the *Lymfit* intervention was established to remotely deliver professionally guided, tailored exercise programs, incorporating the use of Fitbit™ monitors, with the goal of improving physiologic and psychological health in lymphoma patients and survivors. This proof-of-concept trial aimed to explore the implementation feasibility of the intervention by assessing retention rate, technical and safety issues, and the preliminary effects of *Lymfit* on various health outcomes.

Methodology

Study Design

According to the Medical Research Council framework [39], the fundamental elements of health intervention development include: engagement with stakeholders (patient partnership), identification of uncertainties, and continuous refinement of intervention. Hence, the purpose of this proof-of-concept trial was to examine whether an intervention is suitable for further testing using a single-arm (single cohort), pre-post-test design. Specifically, this was aimed to evaluate the feasibility of the design of the 12-week *Lymfit* intervention (i.e., retention rates, technical issues on intervention delivery and data collection during the pandemic, and safety issues) and to explore the preliminary effects of the intervention on study outcomes, including fitness outcomes (i.e., light activity minutes, MVPA, sedentary time, sleep time, and step count) captured by Fitbit™ monitors, and three self-reported health outcomes (i.e., quality of life, fear of cancer recurrence, and fear of COVID-19). The study's protocol was approved by the Research Ethics Board at the Jewish General Hospital (Montreal, QC) in October 2019. All patients provided

written, informed consent. The reporting of intervention components and procedures is in accordance with the Template for Intervention Description and Replication (TIDieR) guidelines [40] (**Supplementary document A**).

Participants, Setting and Recruitment

This was a single-center study. All study participants were recruited at the Segal Centre, Jewish General Hospital located in downtown Montreal, Quebec. To have been eligible for this study, participants must have met the following inclusion criteria: (1) previously diagnosed with non-Hodgkin's or Hodgkin's lymphoma; (2) have completed chemotherapy; (3) have had the approval of their hematologist as having no contra-indications to exercise; and (4) had access to a smartphone or an electronic device (e.g., tablet) that allowed them to attend virtual meetings and to install the Fitbit™ application. The date of their cancer diagnosis and the duration of remission was not a criterion for enrollment in this proof-of-concept trial.

All participants were recruited by their hematologists. Once recruited, participants were contacted by the research coordinator to collect informed consent via videoconferencing. Recruitment commenced June 2021 and ended November 2021. Data collection ended in February 2022 when the last recruited participant completed the *Lymfit* intervention. At the time of data collection, Montreal was in the third wave of the COVID-19 pandemic. A vaccine passport mandate came into effect in September 2021 and a curfew was implemented at the end of December 2021 and lasted until mid-January 2022.

Study Procedures

After providing consent, the eligible participants completed a set of baseline questionnaires (i.e., demographic + self-reported questionnaires assessing fear of cancer recurrence, quality of life, and fear of COVID-19) electronically. All participants were registered

to the *Lymfit* platform and assigned a Fitbit™ monitor. Each Fitbit™ was mailed to the participant's home address along with a set of five resistance bands of varying resistance levels.

One important merit of Fitbit™ devices is that it allows for data transfer via Bluetooth technology to the Fitbit™ application program interface through Fitbit's™ smartphone application. The information technology team at the Lady David Institute of the Jewish General Hospital had developed the *Lymfit* platform on a password-protected secured server. This platform allowed the research team to document participants' information, and to capture and store participants' Fitbit™ metrics in a secured database via the Fitbit™ application program interface. This security system ensured full patient confidentiality throughout the study. In addition, participant data was de-identified by assigning each participant's Fitbit™ device with a code name (e.g., Lymfit001) and an email (e.g., lymfit001@ladydavis.ca), such that the Fitbit™ company had no access to personal identification data.

Once the Fitbit™ monitors and resistance bands were received by the participants, the research coordinator met with the participants via videoconferencing to guide the participants and connect their Fitbit™ to their smartphone application using the *Lymfit* study account assigned to them. During the same meeting, the study Kinesiologist administered a baseline fitness assessment (**Supplementary document B**), which allowed the Kinesiologist to design a personalized exercise program depending on a variety of self-reported fitness variables, including their current and prior level of fitness (i.e., prior to lymphoma diagnosis), physical activities that they do and do not enjoy (i.e., preferences of one type of exercise over another), and days/times during the week that the participant would be available to exercise. Answers collected in this fitness assessment were not included in the data analysis process. It was used solely for the creation of the personalized exercise programs. Thereafter, participants were

instructed to wear the device on the wrist of their non-dominant hand for 1 week (seven consecutive days; referred to as week 0) and to maintain their usual level of activity. The data collected in week 0 was considered participants' baseline activity levels. Considering the information collected in the baseline physical assessment and the objective baseline activity level obtained during week 0, the Kinesiologist designed a tailored exercise program for each participant. At the end of week 0, participants met with the Kinesiologist in another videoconferencing meeting to discuss the personalized exercise program. The exercise programs were designed based on the FITT principles suggested by the American College of Sports Medicine Cancer Survivorship exercise guidelines [29], as well as the participant's baseline physical assessment results.

Based on participants' baseline activity levels and exercise preferences, the Kinesiologist encouraged participants to gradually increase their minutes of MVPA. The exercise prescription consisted of both aerobic and resistance training at varying difficulty and duration (depending on the current fitness level of each participant), while meeting the minimum exercise guidelines suggested by the FITT principles. These programs were constructed using videos found on Youtube™, which would demonstrate the exercises that the participants would be performing. Most of the resistance training workouts implemented the resistance bands in some capacity. An example of an exercise program for one of the study participants is shown in **Supplementary document C**.

For inactive participants or participants who lacked the motivation to exercise, the initial goal was to increase steps taken. The Kinesiologist and participants explored opportunities during the meeting based on the progress in the past two weeks. As these small milestones were achieved, the goal changed to increase the intensity and duration of the activities. For

participants who were active at baseline, the exercise program was tailored accordingly. Participants who were successfully achieving 90 minutes of MVPA/week were encouraged to gradually increase their MVPA to 150 min/week to meet the Canadian general population guidelines [41].

During the 12-week *Lymfit* intervention, the study Kinesiologist followed up with each participant every two weeks to review their progress and to adjust the program where needed. These meetings were done to ensure that the participants were constantly motivated to adhere to their exercise program for the duration of the intervention. If a participant did not enjoy a particular workout, then the workout would be adjusted or changed completely to be more enjoyable, thus increasing motivation.

Post-intervention questionnaires assessing self-reported study outcomes administered at baseline were again collected at the end of the intervention. All participants kept the Fitbit™ as a nonmonetary incentive, regardless of whether or not they successfully completed the intervention. Over the course of the intervention, if a participant's Fitbit™ had not been synced to the smartphone application for more than 12 hours; taken off their wrist for more than 12 hours; had low battery level (below 20%), email reminders were sent out to the participants to ensure that the most accurate reading of a participant's activity throughout each day was attained.

Finally, participants were emailed a logbook questionnaire every two weeks, for the duration of the intervention. This questionnaire asked participants to record the number of days they spent in light, moderate and vigorous physical activity. This was done as a precaution in the event of a Fitbit™ malfunction. Furthermore, the logbook asked participants to record any barriers and facilitators they may have experienced in the past two weeks. Participants responses

to this were analyzed to provide a basic summary of the most common barriers and facilitators that lymphoma patients reported regarding physical activity. This may allow for improvements to be made regarding the exercise prescription in future exercise interventions.

Data Collection and Outcome Measurements

Demographic and Clinical Characteristics. Demographic variables including age, sex, body mass index (BMI), height, and weight were collected to broadly encapsulate the characteristics of each participant prior to commencing the intervention. The participant's primary diagnosis and the time since their last chemotherapy treatment were collected to represent their clinical characteristics. This information is displayed in Table 1.

Implementation Feasibility. This outcome was assessed by 1) **retention rate**, 2) **technical issues**, and 3) **safety** (i.e., adverse events). In bi-weekly meetings with the Kinesiologist, participants were instructed to report any adverse events during the intervention. Any technical and safety issues were documented in a study log by the study coordinator and the Kinesiologist.

Physiologic Metrics. Metrics including light activity (minutes/day), MVPA (minutes/day), sedentary time (hours/day), totals sleep time (hours/day), and steps taken (steps/day) were captured via the Fitbit™ monitors and stored on the *Lymfit* platform. Participants were instructed to sync their Fitbit™ to the smartphone application daily to allow the captured data to be transferred to the *Lymfit* platform.

Fitbits™ are a valid and reliable measure of different activity variables, while also being a cost-effective alternative compared to other research-grade activity monitors [42]. A study conducted by Reid and colleagues compared Fitbit™ monitors to an ActiGraph GT3X+

accelerometer, a gold standard in measuring activity in clinical trials, with results indicating that Fitbits™ (particularly those worn on the wrist) were as accurate as ActiGraph GT3X+ in measuring activities, particularly step counts and light activities [43]. It was thus concluded that wrist-worn Fitbit™ trackers are a valid and reliable device for low intensity activities and steps taken, making them a feasible option for this study.

Self-Reported Health Outcomes

Three self-reported study outcomes were collected using validated instruments at baseline and at week 12 (post-intervention).

Quality of Life was evaluated using the 29-item Patient-Reported Outcomes Measurement Information System® (PROMIS–29 Profile v2.1) obtained from the PROMIS Health Organization (https://www.promishealth.org). The PROMIS measure perceived health status along seven domains, with items answered on five-point Likert scales. There are four items on each of the following domains: ability to participate in social roles/activities (PROMIS 1), anxiety/fear (PROMIS 2), depression/sadness (PROMIS 3), fatigue (PROMIS 4), pain interference (PROMIS 5), physical function (PROMIS 6), and sleep disturbance (PROMIS 7). Domain scores were obtained by summing the item scores for each domain. Raw scores generated for each domain were transformed into a T–score using the scoring service from the Health Measures Assessment Center (https://www.assessmentcenter.net/ac_scoringservice) [44]. For negatively worded domains such as anxiety/fear, depression/sadness, fatigue, pain interference, and sleep disturbance, a higher T-score represented worsening conditions. For positively worded domains such as the ability to participate in social roles/activities and physical functioning, a higher T-score represented improving conditions [45]. The reliability and construct validity of the PROMIS-29 v2.1 were supported in a previous study of cancer survivors [46].

Fear of Cancer Recurrence was assessed using the Fear of Cancer Recurrence Inventory (FCRI) [47]. The FCRI is a multidimensional, 42-item questionnaire measuring seven factors pertaining to fear of cancer recurrence: triggers, severity, psychological distress, coping strategies, functioning impairments, insight, and reassurance. Each item was rated on a five-point Likert scale ranging from *'not at all' or 'never' (0*) to *'a great deal' or 'all the time' (4)*. A subscale score can be computed by summing the item scores of each factor subscale. The total score (ranging from 0 to 168) was then calculated based on the scores of each subscale. Considering that the question for item 13 ("I believe that I am cured and the cancer will not come back") is addressed in the opposite direction of other questions, the response scale to item 13 was reversed before calculating the total score. Higher FCRI summary scores indicated higher levels of fear of cancer recurrence. In addition, the nine-item severity subscale of the FCRI has an empirically validated cut-off score (≥ 13 points) for screening clinically significant levels of fear of cancer recurrence [48]. Psychometric properties of the English version FCRI including internal consistency and test–retest reliability have been confirmed in different cancer survivors [49].

Fear related to the pandemic was assessed using the Fear of COVID-19 scale (FCV-19S) [50], a seven-item inventory assessing the fear of COVID–19. The items are rated on a five-point Likert scale ranging from *"strongly disagree" (1)* to *"strongly agree" (5)* with total scores ranging from 7 to 35. Higher total scores represented higher levels of fear. The reliability and validity of the FCV-19S has been established [50].

Data Analysis

Descriptive statistics were used to provide a summary of basic demographic and physical characteristics of study participants. For the feasibility outcomes, retention rate was calculated as

a percentage of the total number of those who were initially enrolled, and any technical and safety issues were reported narratively.

Physiologic metrics were reported using descriptive statistics (i.e., frequency, percentage, mean, standard deviation). For all metrics captured by the Fitbit™ (i.e., light activity minutes, MVPA, sedentary time, sleep time, and steps taken), the daily averages were computed (i.e., the mean of a seven-day period from Monday to Sunday) from week 0 to week 12. This allowed the investigators to assess changes in Fitbit™ metrics on a week-to-week basis. To account for missing data, a day with a daily step count less than the predetermined cut-off of 1000 steps/day was excluded from the weekly average as it was assumed that the participant did not wear the Fitbit™ that day. The day was included in the seven-day average only if the participant had more than 1000 steps in the day. This cut-off was determined based on a previous study, which stated that values <1000 or >30000 daily steps should be considered outliers and may be removed from analyses to clean the data [51]. A cut-off point for four out of seven days was also required for that week to be considered a valid daily average [52]. If there were fewer than four valid days of data for that particular week, that week of data for that participant was omitted from the analysis. Although the cutoff is 4 days, if the participant had enough data for 5, 6 or 7 days in a week, then those days would also be included in the analysis. If a non-compliant participant had more than four invalid weeks out of the 12 weeks, they were considered a loss to follow-up.

For the three self-reported health outcomes, data was first screened for normality of distributions using the Shapiro-Wilk Test. Given the lack of normality, a nonparametric (one-sided) Wilcoxon Signed-Rank Test was conducted to compare and determine if there was a statistically significant within-group change among the scores in the three self-reported health

outcomes (i.e., PROMIS, FCRI, and Fear of COVID-19,) from pre- to post-intervention. The effect size estimate r for the non-parametric test was calculated by converting the z-score with the equation $r = z/N$ [53] and was interpreted using Cohen's guidelines for r of 0.1= small effect, 0.3 = medium effect, and 0.5 = large effect [54]. Data analysis was performed using R™ version 4.2.0 (R Core Team, Vienna, Austria) and α was set at 0.05.

Finally, barriers and facilitators reported in the logbook questionnaires were analyzed to determine the barriers and facilitators that were most frequently reported throughout the intervention. This was done by simply calculating the frequency at which each barrier and facilitator appeared in the logbook questionnaires. The three most frequently reported barriers and facilitators were noted in the results.

Results

Participant Characteristics

The baseline demographic characteristics of the participants are presented in Table 1. The mean age of this study cohort was 31.5 ± 7.3 years, 58.8% were female and 53% of the study participants' BMI were above 24.9. Regarding participant's clinical characteristics, 76.5% (n = 13) were diagnosed with Hodgkin's lymphoma and 76.5% (n = 13) had completed their treatment (i.e., chemotherapy) over one year ago.

Table 1. Baseline Demographic and Clinical Characteristics of Participants (N = 17)

Variables	**mean**	**sd**	**n**	**%**
Age (years)	31.5	7.3		
Height (cm)	170.4	9.8		
Weight (kg)	75.7	18.8		
BMI				
Healthy (18.5-24.9)			8	47.1
Overweight (25-29.9)			7	41.2
Obese (30+)			2	11.8
Sex				
Male			7	41.2
Female			10	58.8
Diagnosis				
HL			13	76.5
DLBCL			4	23.5
Time since chemotherapy completion				
> 1 year			13	76.5
< 6 months			4	23.5

Note: Sex, BMI, diagnosis and time since diagnosis are expressed as n (%); Age, Height, and Weight are expressed as Mean (SD).

Implementation Feasibility

Retention rate of this proof-of-concept trial was 70%. 20 participants were consented and enrolled in this trial. Of those, 14 participants completed the *Lymfit* intervention, including the post-intervention questionnaires. Two participants withdrew from the study at weeks 3 and 10. The reasons given by the participants for discontinuation from the study included a change in career path, personal issues leading to depression, and a self-belief that they would not be able to participate consistently for the duration of the study. One participant did not complete the post-intervention questionnaire and was considered a loss to follow-up. With the participant's permission, Fitbit™ data collected from these three subjects up to the time of the subject's withdrawal/end of intervention were retained and analyzed. Another three participants were non-compliant with the intervention, wearing the Fitbit™ less than four days per week, for over four weeks of the intervention. The partial data collected from the three participants were not included in our analyses. In terms of demographic and clinical characteristics, the three excluded

participants, which included two males and one female, completed chemotherapy over one year ago. The mean BMI of the three excluded participants was 27.1, which would categorize them as "overweight".

Overall, 17 participants' Fitbit™ data were included in the analysis. **Technical issues** were noted in this study. For instance, resistance training was not accurately tracked by the Fitbit™, which could lead to potentially inaccurate minutes spent in MVPA. In addition, a minor server issue prevented one of our participants from receiving the PROMIS-29 questionnaire post-intervention. This was immediately resolved by the *Lymfit* technical support staff. No **adverse events or other safety issues** were reported by the study participants, except for one participant reporting a mild skin irritation induced by a metal (nickel) piece attached to the Fitbit™ monitor.

Physiologic Metrics

Fitbit™ metrics including light activity, MVPA, sedentary time, total sleep time, and steps per day were recorded daily to determine the activity levels of this cohort at baseline (week 0). Mean light activity minutes at baseline was 217.9 ± 94.7 minutes per day. MVPA was 21.1 ± 14.2 minutes per day. It is important to note that at baseline, 76.5% (n = 13) of participants met the recommended weekly physical activity guidelines (i.e., 90 minutes of MVPA per week [29]). Interestingly, the mean sedentary minutes at baseline was 13.8 ± 2.7 hours, which far exceeded the daily recommended sedentary behaviour guidelines of less than 8 hours of sedentary time [41]. The mean sleep time (i.e., total time spent asleep) for this population was also lower than the recommended guidelines, with a baseline of 6.6 ± 1 hours, and only 35.29% (6) met the recommended sleep guidelines of seven to nine hours [41] at baseline. Finally, the mean daily steps taken at baseline was 8144 ± 3615.9 steps per day.

As shown in Figure 1, the mean light activity minutes increased from baseline to the approximate halfway mark of the study, then gradually declined until the end of the study. It ranged from a high of 242.1 ± 81.05 minutes at week four to a low of 208.5 ± 91.2 minutes at week seven. The daily average time spent in MVPA fluctuated from baseline throughout the 12 weeks post-exercise prescription, ranging from a high of 22 ± 16.4 minutes at week 5 to a low of 15.1 ± 13.3 minutes at week 7. Mean sedentary minutes fluctuated from the baseline, though each week during the exercise intervention reported lower mean sedentary minutes than baseline. It ranged from a high of 13.7 ± 3.4 hours at week 6 to a low of 13 ± 2.5 hours at week 4. Mean sleep time steadily increased from the baseline, ranging from a high of 7.1 ± 1.4 hours at week 12 and a low of 6.6 ± 1.2 hours at week 9. Finally, the mean steps per day fluctuated from the baseline as well, ranging from a high of 8755.3 ± 4250.4 at week 8 post-exercise prescription to a low of 6699.4 ± 2467.5 at week 10 (Fig 1).

Of the four participants (23.5%) who did not meet the recommended physical activity guidelines for cancer survivors at baseline, all four of them increased their daily average MVPA from baseline to week 12. At baseline, these four participants averaged a mean of 4.5 ± 5.7 minutes of MVPA. This increased to 10.2 ± 16 minutes at week 12. Similar improvements were made in mean sedentary time. At baseline, these participants averaged 13.4 hours of sedentary time, which decreased to 12.9 hours at week 12. Similarly, the mean light activity minutes increased from 178.2 minutes at baseline to 215.9 minutes at week 12. Finally, mean daily steps taken saw a sharp improvement in these four participants as well, which increased from 4312.3 steps at baseline to 5584.2 steps at week 12.

Self-Reported Health Outcomes

Wilcoxon Signed–Rank Tests were used to examine the pre- and post-intervention changes in self-reported health outcomes. The results including medians (Mdn), effect sizes

(ES), z-scores, and p-values are displayed in **Table 2** and **Fig 2**. Of the seven quality of life domains measured by PROMIS-29, analysis results revealed that three domains had a significant change in scores from pre- to post-intervention. **PROMIS 1** scores improved significantly from pre-intervention (Mdn = 48.15) to post intervention (Mdn = 54.95; Z = − 2.01, $p = 0.022$), signifying a significant overall improvement in their ability to participate in social activities. **PROMIS 6** scores increased marginally from pre-intervention (Mdn = 48.6) to post intervention (Mdn = 57.0; Z = − 1.69, $p = 0.045$), signifying a significant improvement in overall physical functioning. Finally, participants scored statistically significantly lower on **PROMIS 7** scores from pre-intervention (Mdn = 51.05) to post intervention (Mdn = 48.0; Z = 0.76, $p = 0.023$), signifying a decrease in sleep disturbances post-intervention.

Table 2. Self-Reported Health Outcomes Baseline and 12-Week Comparisons

Variables [a]	**Mdn** [b] **(baseline)**	**Mdn (12-week)**	**Effect size (interpretation)**		**Z score**	**p-value**
PROMIS 1	48.15	54.95	0.54	(large)	-2.01	0.022 *
PROMIS 2	48.30	56.00	0.17		-0.65	0.742
PROMIS 3	49.55	45.40	0.02		0.08	0.466
PROMIS 4	55.50	55.10	0.30		1.13	0.127
PROMIS 5	41.60	41.60	0.05		-0.18	0.572
PROMIS 6	48.60	57.00	0.45	(medium)	-1.69	0.045 *
PROMIS 7	51.05	48.00	0.53	(large)	2.00	0.023 *
FCRI	71.50	70.00	0.21		0.76	0.220
FCRI Severity	19.50	17.50	0.51	(large)	1.90	0.029 *
FCV-19S	14.00	12.00	0.31		1.16	0.122

[a] PROMIS 1 = ability to participate in social roles/activities; PROMIS 2 = anxiety/fear; PROMIS 3 = depression/sadness; PROMIS 4 = fatigue; PROMIS 5 = pain interference; PROMIS 6 = physical function; PROMIS 7 = sleep disturbance; FCRI = Fear of Cancer recurrence Inventory; FCV-19S = Fear of COVID Scale
[b] Mdn = Median
* $p < 0.05$

Results revealed that **FCRI Severity** significantly decreased from pre-intervention (Mdn = 19.5) to post-intervention (Mdn = 17.5; Z = 0.76, $p = 0.029$), indicating that participants had lowered fear of cancer recurrence immediately post-intervention. It is important to note that this

cohort of participants reported a clinical level of fear of cancer recurrence (≥ 13 points) both pre- and post-intervention. However, the total FCRI score had no significant changes from pre- to post-intervention ($p = 0.22$). Considering the relatively high FCRI severity scores pre- and post-intervention, it is possible that fear of cancer recurrence did act as a potential moderator during the exercise intervention, influencing the participants' adherence to their exercise prescription. However, this was beyond the scope of this investigation.

No significant differences were detected in mean scores for the other four quality of life domains of the PROMIS-29 questionnaire, which include PROMIS 2 ($p = 0.742$), PROMIS 3 ($p = 0.466$), PROMIS 4 ($p = 0.127$) and PROMIS 5 ($p = 0.572$), indicating that there were no significant reductions in anxiety/fear, depression/sadness, fatigue, or pain interference. Finally, results showed that while participant's reported FCV-19S scores decreased from baseline (Mdn = 14.00) to post-intervention (Mdn = 12.00), these changes were not significant ($Z = 1.16$, $p = .122$), indicating that there was also no significant reduction in the participant's fear of COVID-19 immediately post-intervention, as expected.

Barriers/Facilitators to Exercise

Participants reported a total of 98 reasons for missed exercise sessions, represented by 11 different barriers to physical activity. The three most frequently reported barriers from the logbook questionnaires were fatigue (n = 21), lack of time (n = 16), and lack of motivation (n = 14), in that order. Other barriers including work (n = 12), stress (n = 9), pain (n = 9), flu/COVID-19 (n = 6), school (n = 4), bad weather (n = 3), vacation (n = 2) and anxiety due to fear of cancer recurrence (n = 2) were also reported.

Conversely, participants reported 113 reasons for being motivated to exercise, represented by 11 different facilitators to physical activity. The three most frequently reported facilitators from the logbook questionnaires were wearing the Fitbit™ (n = 23), improved well-being (n = 21) and improved physical capacity (n = 17), in that order. Other facilitators including reduced stress (n = 12), motivation due to the workout program (n = 12), improved sleep (n = 9), a sense of accomplishment (n = 7), weight loss (n = 4), symptom alleviation (n = 4), goal achieving (n = 2), and training with a partner (n = 2) were also reported.

Discussion

The primary aim of this proof-of-concept trial was to determine the implementation feasibility of delivering a remote exercise intervention during the COVID-19 pandemic by assessing retention rate, as well as evaluating technical and safety issues. Determining the preliminary effects of the intervention on physiologic and health changes also contributed to the refinement of future trials.

The main finding of the present proof-of-concept trial was the successful implementation and delivery of the *Lymfit* exercise intervention among lymphoma survivors during the COVID-19 pandemic. The retention rate of this study was considered acceptable at 70% when compared to the 10–42% average attrition rate estimated for clinical trials of exercise interventions for cancer patients in the literature [55]. There were a few minor technical issues regarding the *Lymfit* platform. One such issue involved the inability to send the PROMIS-29 questionnaire to a participant due to a server issue. This was resolved by the *Lymfit* technical support staff immediately upon detection of the issue. This finding is consistent with previous literature that has also demonstrated the feasibility of delivering a home-based exercise intervention during the COVID-19 pandemic among high-risk individuals [56]. However, to our knowledge exercise

interventions have not been conducted through which fitness data was measured objectively among lymphoma survivors (i.e., from Fitbit™ metrics). This presented an additional challenge of ensuring that the technology used in this study (Fitbit™ and *Lymfit* platform) worked properly in unison and were feasible for use in a home-based exercise intervention. This proof-of-concept trial proved the capacity to which technology can be feasibly integrated into an exercise intervention to objectively measure and track participants' fitness and activity outcomes. This proof-of-concept trial confirmed that the *Lymfit* platform is ready to be implemented into a larger trial.

Overall quality of life also improved among the participants. The total sleep time among this cohort had shown an upward, albeit insignificant trend from baseline to week 12. Participants who were already meeting the seven to nine hours daily sleep guidelines for adults at baseline continued to meet the guidelines throughout the entire study. A gradual though insignificant increase was seen in those who averaged less than seven hours of sleep per day at baseline. As expected, the results in this study also showed a significant decrease in sleep disturbances post-intervention as reported by participants. This outcome was in accordance with the literature, which had reported on the association of physical activity with decreased sleep disturbances and improved sleep quality among cancer patients and survivors [57,58]. Among the three self-reported health outcomes, significant improvements were observed in some domains relating to quality of life, including the ability to participate in social roles, physical functioning, and sleep disturbance. This is consistent with previous literature, which has shown that performing physical activity post-treatment can significantly improve domains related to quality of life in cancer patients including physical functioning and social role satisfaction [59]. Improvements in sleep disturbances have also been reported in a previous trial involving cancer

patients, which concluded that patients who reported sleep disturbances due to chemotherapy were able to improve their quality of sleep for 3-6 months upon completion of an exercise intervention [60]. Although the severity of fear of cancer recurrence had decreased slightly immediately following the completion of the intervention, the severity levels both pre- and post-intervention were above the cut-off for clinical fear of cancer recurrence. This finding indicates that exercise alone may not be sufficient in diminishing the psychological effects of cancer and its treatments. Psycho-educational intervention provided at the end of treatment has shown promising results in mitigating the level of fear of cancer recurrence for cancer survivors [61]. Future studies can incorporate additional psycho-educational strategies to mitigate anxiety about the recurrence of cancer among lymphoma survivors. Finally, fear of COVID-19 did not significantly decrease from pre- to post-intervention. This finding was inconsistent with previous literature, which indicated that sedentary (non-athlete) participants had increased fear of COVID-19 compared to active participants (athletes) [62]. This result suggests that physical activity alone is not sufficient in reducing fear of COVID-19 among cancer patients and survivors. This is likely since those with chronic illness are significantly more fearful of COVID-19 due to the heightened threat of severe illness it poses to them [63]. More research is needed to determine possible solutions that may significantly decrease stress and anxiety relating to COVID-19 among lymphoma patients.

Surprisingly, Fitbit™ activity metrics, including light activity minutes, MVPA, sedentary time and steps taken, did not significantly improve upon completion of the exercise intervention. This contradicts previous research that have indicated that a home-based exercise intervention can significantly improve fitness outcomes, particularly MVPA, among a sedentary population [64]. However, the *Lymfit* study cohort were already moderately active at baseline. Most

of the study participants met the physical activity guidelines at baseline (week 0). The daily average MVPA of this sample at baseline exceeded the recommended physical activity guidelines for cancer patients of 90 minutes per week [29]. Similarly, the baseline daily step average of 8144, while not quite meeting the recommended guidelines of 10000 steps per day, was relatively high and placed this sample in the "somewhat active" category [65]. However, of the participants who did not meet the recommended physical activity guidelines at baseline (i.e., less than 90 minutes of MVPA at baseline), all of them were able to significantly improve their Fitbit™ fitness metrics, including increased weekly MVPA, increased steps taken and decreased sedentary time. This clearly indicates the benefits of a home-based exercise program on individuals who are considered sedentary. This is a positive development as the participants that will be recruited in the randomized controlled trial phase of this study are more likely to be less active or inactive at baseline due to more precise inclusion criteria as to the period that participants must have completed chemotherapy (within the last 6 month). Previous literature has indicated that breast cancer patients undergoing or have recently undergone chemotherapy are much less likely to meet the recommended exercise guidelines than those who have not undergone chemotherapy, or those who completed chemotherapy years ago [66]. It is noted that only 13% of breast cancer patients undergoing or have recently undergone chemotherapy will meet the recommended exercise guidelines [66]. Therefore, it is expected that the participants in the randomized controlled trial will be much more sedentary as most of them will be undergoing or have recently undergone chemotherapy. Though more importantly, the exercise intervention did also help those who were already adequately active pre-intervention in maintaining their levels of physical activity during the intervention throughout the COVID-19 pandemic, when sedentary behaviour increased dramatically among the general population [67].

Despite being moderately active, sedentary minutes among the study cohort at baseline was high and remained high throughout the intervention. This may be explained by the Fitbit™ monitor's inability to accurately record movements that do not sustain an elevated heart rate such as short-distance walking, which also overestimates sedentary time. In line with the literature, a recent study has reported that Fitbit™ monitors can overestimate sedentary time by an average of 37 minutes a day in adults of a healthy weight range, which is likely due to an inaccurate classification of some light activity as sedentary time [68]. The pandemic and the restrictions that followed may also explain this observation. This study was conducted at the height of the 3rd wave of the COVID-19 pandemic, where physical distancing, lockdowns and home quarantines were either mandated or strongly encouraged. These restrictions led to steep declines in physical activity and increases in sedentary time among adults in the general population [67]. Therefore, an intervention designed to reduce sedentary behaviours would likely have benefitted this cohort much more than one designed to increase physical activity. This type of intervention could involve assisting participants in setting goals designed to reduce sedentary behaviours (e.g., cannot surpass "x" number of hours of sedentary time per day), as well as discussing the risks of increased sedentary time with them.

The reported barriers to physical activity in this intervention were consistent with previous literature, which has indicated that fatigue, lack of time, pain, stress, work, and injury as some of the most common barriers to exercise among breast cancer patients [69]. The reported facilitators of physical activity in this intervention were also similar to previous reports, which noted that improved physical health, improved well-being, and gaining control over one's health were the three most frequently reported facilitators of physical activity [34] . Documenting the barriers and facilitators that influence motivation to physical activity is an essential step in

increasing physical activity levels among cancer (particularly lymphoma) patients and survivors. In addition to facing more barriers, cancer patients and survivors also tend to face barriers that are more severe than those that the general population tend to face, such as cancer-related fatigue, more severe anxiety, and increased discomfort due to chemotherapy [69]. Therefore, it is clear that cancer patients and survivors may benefit from tailored exercise prescriptions that minimize the negative influence of their exercise barriers, while maximizing the impact of their exercise facilitators.

This proof-of-concept trial should be interpreted within the context of important strengths. Firstly, this study was among the first to demonstrate that a remote exercise intervention can be implemented safely and effectively during the COVID-19 pandemic in a high-risk population. This intervention was able to improve quality of life outcomes during a period where quality of life amongst the general population was worsening, while maintaining physical distancing to prevent viral transmission. Given the remote design of this intervention, patients were not required to travel to a specific location for training and were allowed to train in the safety of their own homes. This was significant as avoiding public areas and risk of COVID-19 infection was the number one priority throughout the intervention. Secondly, this study was among the first to implement Fitbit™ monitors to track and collect physiologic metrics for analysis. To our knowledge, no study had previously implemented the use of activity monitors to track the physical activity levels of lymphoma patients post-chemotherapy throughout the COVID-19 pandemic. The implementation of such technology opens a variety of different ways that fitness data can be prescribed, interpreted, and analyzed. Further, Fitbits™ are cost-effective and can be easily adopted into clinical practices, thus benefiting all cancer survivors completing their treatments [36]. Lastly, *Lymfit* was uniquely positioned to provide a remotely

delivered physical activity intervention during the pandemic, which was in time to address the immediate needs of lymphoma survivors. There are growing concerns that the lockdown and social distancing restrictions imposed by the provincial governments have limited opportunities for people to be physically active [67]. Further, the general population increased their sedentary time and reduced their physical activity levels during quarantine, contributing to controversial psychological outcomes [70]. Cancer patients and survivors are disproportionally impacted by the pandemic [71,72]. With uncertainty regarding post-pandemic physical activity environments and behaviours, the *Lymfit* intervention may help foster clinically meaningful improvements in lymphoma survivors' MVPA and quality of life.

Several limitations within this study should also be noted. Firstly, the sample size of this proof-of-concept trial may have been too small to make inferences regarding quality of life and fitness metrics. However, due to the pilot nature of this trial, it was important to maintain a small-scale study cohort and not prolong the pilot phase of the study. Secondly, this proof-of-concept trial was a single-site study, meaning that participants were recruited solely from the Jewish General Hospital in Montreal. The COVID-19 pandemic and subsequent restrictions limited opportunities to expand the trial to multiple sites, thereby limiting the generalizability of the results. Furthermore, the single cohort pre-and post-test design impeded the ability to draw initial intervention effectiveness conclusions. This was inevitable and unavoidable in a proof-of-concept trial with a small participant pool. Thirdly, as a proof-of-concept trial, participants' baseline physical activity levels and their differences in exercise motivation were not considered to be an inclusion criterion for the intervention. Further, individuals who view physical activity as important are more likely to participate in interventions such as *Lymfit*. These preexisting differences among lymphoma survivors may have led to potential selection bias, which can be

confounders and may have potentially influenced the study observations. Future trials might benefit from certain screening procedures to select patients who are less active; engaged in more sedentary behaviours; or lack exercise motives to participate in the intervention. Finally, most of the study participant's time since treatment completion was over one year, which may have inadequately captured the effects of physical activity during the critical early survivorship period.

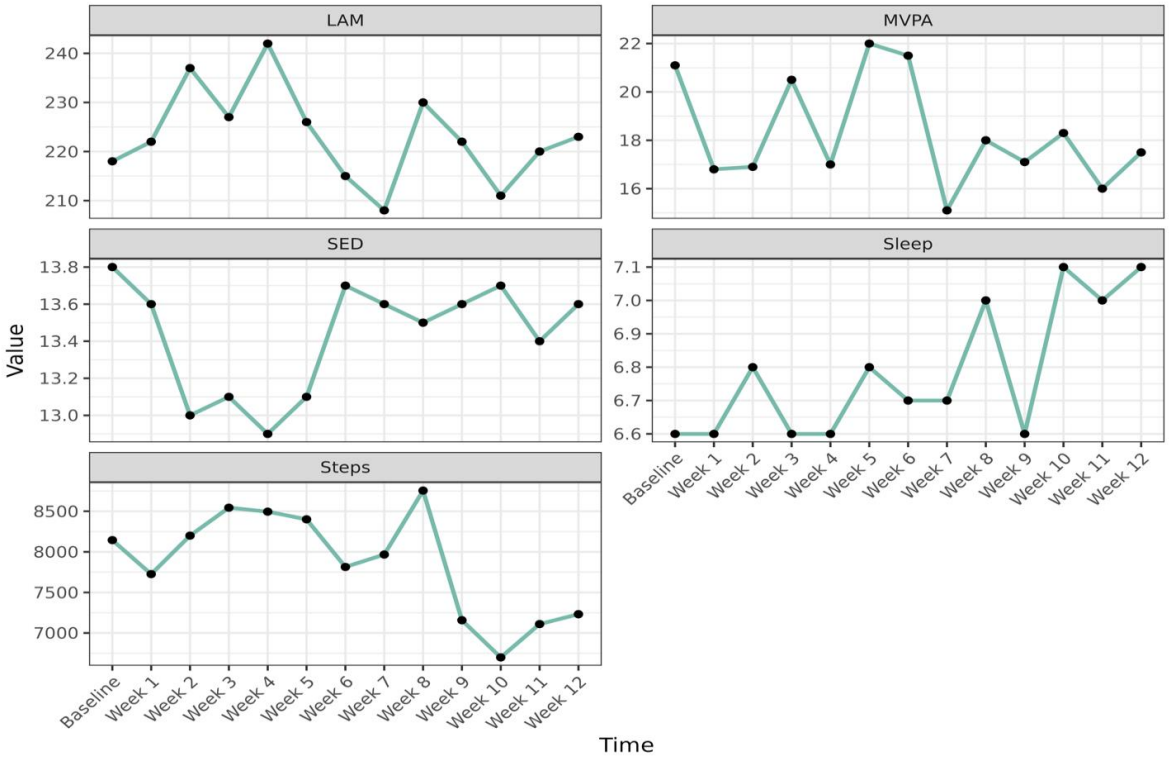
The results seen in this proof-of-concept trial can have major clinical implications, specifically that exercise can be remotely delivered and tracked, thereby improving the quality of life of cancer patients and survivors, during and post-treatment. It would provide healthcare professionals with a healthy alternative to mitigate the toxic effects of medication which may improve their patient's short- and long-term quality of life. Furthermore, it would provide healthcare professionals with a broader outreach and allow them to treat patients living long distances from treatment centers, or patients who want to avoid public spaces and potential exposure to COVID-19. Future trials should focus on lymphoma patients who are still undergoing treatment or immediately post-treatment to determine if a personalized exercise program is an effective intervention to improve quality of life and physical fitness in this population. In the future, exercise scientists should become key members of trans-disciplinary teams that care for lymphoma survivors.

Conclusion

This proof-of-concept trial established the practicality and feasibility of *Lymfit*, a virtual, personalized exercise intervention that is timely and valuable during the unprecedented

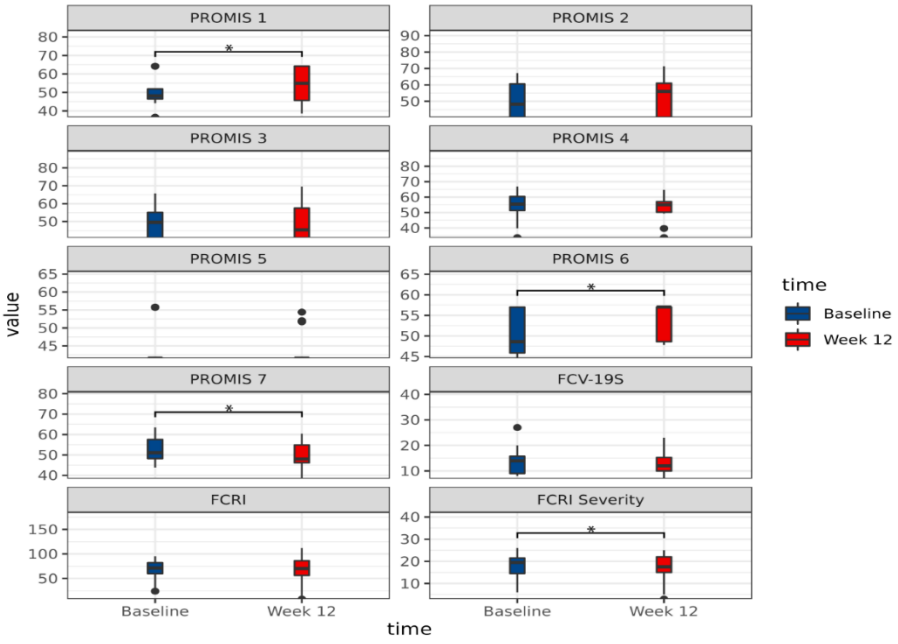
circumstances of the pandemic. Promising trends in physiological metrics and several self-report health outcomes have been noted in the study results, demonstrating the preliminary success of *Lymfit* to improve the health and well-being among lymphoma survivors. Barriers and facilitators to exercise among lymphoma survivors were also revealed, which demonstrated the influence they can have on adherence to physical activity. The scientific evidence is constantly consolidating the crucial and positive impacts of regular physical activity in reducing the fear of cancer recurrence and improving both short- and long-term side effects of chemotherapy among cancer survivors. Future research examining the *Lymfit* intervention on a larger scale with long-term follow-ups is warranted.

Fig 1. Changes from Baseline to 12 Weeks Across All Physiological Metrics.



*****Note: LAM = light activity minutes (mins/day); MVPA = Moderate to vigorous intensity physical activity (mins/day); SED = sedentary time (hours/day), Sleep = total sleep time (hours/day); Steps = steps taken (steps/day)

Fig 2. Comparisons Between Baseline and 12 Weeks Across All Self-Reported Health Outcomes



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Supplementary Documents

Supplementary document A.

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.		
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).		
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.		
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.		
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.		
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.		
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.		
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.		
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).		
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.		
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.		

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

Supplementary document B. Baseline Fitness Assessment

Fitness Questionnaire

Name:

Instructions: Please fill out this form as completely as possible.

Height: Weight: WC:

1. How often were you participating in physical activity prior to diagnosis?
   a. 4 to 5 times per week
   b. 2 to 3 times per week
   c. 1 to 2 times per week
   d. Not at all
2. Are you currently involved in regular exercise? Yes No
3. What sport or activity has worked for you in the past?
4. What type of exercise do you enjoy the most?
5. What type of exercise do you dislike and why?

Rate yourself on a scale of 1 (least fit) – 10 (most fit) for each fitness category

6. How good is your stamina?

   1 2 3 4 5 6 7 8 9 10

7. How strong do you think you are?

   1 2 3 4 5 6 7 8 9 10

8. How flexible do you think you are?

1 2 3 4 5 6 7 8 9 10

9. How coordinated do you think you are?

1 2 3 4 5 6 7 8 9 10

10. How much time are you willing to devote to an exercise program?

_____Min/Day ____Days/Week

11. Are there any barriers that may prevent you from exercising on any given day? (e.g., lack of time, family obligations, lack of motivation…)

12. What days and/or time (morning, afternoon or night) are you available to exercise throughout the week?

Supplementary document C. Weekly Exercise Prescription Sample

Time/ Period	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Morning	Resistance Training Workout video 1: Lower Body Using the red resistance band: 1. 1.5 squats: 30 seconds 3:20 2. 20-30 second rest 3. Off-set reverse lunge: 30 seconds each leg 3:17. 4. 20-30 second rest 5. Standing hip abductions: 30 seconds each leg 1:53 6. 20-30 second rest 7. Single leg Romanian deadlift: 30 seconds each leg 2:55. 8. 20-30 second rest	Cardiovascular Endurance See workout video 2	Resistance Training Workout video 3: Upper Body Using the yellow or red resistance band: 1. Banded shoulder press (right arm): 30-45 seconds 0:26 2. Rest 15 seconds 3. Banded shoulder press (left arm): 30-45 seconds 1:25 4. Rest 15 seconds 5. Pulse raises: 30-45 seconds 2:31 6. Rest 15 seconds 7. Triceps extension (right arm): 30-45 seconds 3:36 8. Rest 15 seconds 9. Triceps extension (left arm): 30-45 seconds 4:40 10. Repeat the circuit (1-9) once more. Rest 60-90 seconds	Cardiovascular Endurance See workout video 2	Resistance Training Workout video 4: Core Using the yellow or red resistance band: 1. Ab Bicycles: 30 seconds 0:55 2. Rest 15 seconds 3. Plank jacks: 30 seconds 1:44 4. Rest 15 seconds 5. Ab marches: 30 seconds 2:27 6. 15 second rest 7. Plank side crunches: 30 seconds 3:12 8. 15 second rest 9. Switch kicks: 30 seconds 3:58 10. 15 second rest	Rest	Rest

Chapter 5 – Summary, Conclusion, Recommendations and Practical Applications

5.1 Summary

The initial purpose of this proof-of-concept trial was to determine the feasibility of our *Lymfit* intervention and to determine if it was ready to be applied to a large-scale randomized controlled trial. This included addressing retention, technical and safety issues that occurred throughout the intervention. Once feasibility had been established, this study's secondary purpose was to then analyze initial participant adherence to the recommended exercise guidelines and examine if a personalized fitness program that followed the FITT guidelines for cancer patients could improve adherence, as well as health and well-being. This included identifying which (if any) chemotherapy-induced side effects can be improved with adherence to the fitness program, as well as identifying barriers and facilitators to exercise and determining the sustainability of the program for the long-term promotion of a healthy, active lifestyle.

20 participants were initially recruited for this 12-week, single-armed trial and registered into our *Lymfit* database. Each of them were given a Fitbit™ monitor to track their daily physical activity levels, as well as resistance bands to use as part of the exercise intervention. They were also each prescribed a workout program designed to increase their short-term and long-term exercise levels. These exercise programs were tailored based on the needs and preferences of each participant, while following the FITT guidelines for cancer survivors. Questionnaires, including the PROMIS-29, fear of cancer recurrence and fear of COVID-19, were also given to participants to see if improvements to their overall health and well-being would be seen upon completion of the intervention. Finally, logbooks were sent to the

participants every two weeks to report their barriers and facilitators to exercise. Due to COVID-19 and the restrictions that followed, the entire procedure of this trial was done remotely, with Zoom™ being the primary method of communication with participants.

Fitness outcomes, including MVPA, light activity, sedentary minutes, steps taken, total sleep time and waking minutes did not significantly improve from baseline to week 12, according to the data provided from the Fitbits™. However, significant improvements in these fitness outcomes were noticed when only considering the participants who did not meet the recommended exercise guidelines at baseline.

Based on questionnaire scores, improvements in quality of life from baseline to week 12 were seen in 3 domains: Ability to participate in social roles/activities, physical function, and sleep disturbance. Only slight, insignificant improvements were seen in the anxiety/fear, depression/sadness, fatigue, and pain interference domains. Fear of cancer recurrence reduced significantly as well over the course of this study, suggesting that increased physical activity may reduce fear and anxiety associated with cancer recurrence. Fear of COVID-19 scores saw only slight, insignificant improvements from pre- to post-intervention. This suggests that increasing physical activity alone did not necessarily decrease fear of COVID-19 early in the pandemic. However, further research regarding these health outcomes is needed to validate these claims.

5.2 Conclusion

A few conclusions can be made from the proof-of-concept trial. Firstly, this study showed the practicality and effectiveness of our remote *Lymfit* intervention, which is especially noteworthy given the COVID-19 pandemic and the limitations it has placed on this proof-of-concept trial. This means that we are now able to commence the randomized controlled trial with

the same (albeit slightly modified) *Lymfit* platform. Secondly, it is important to note that the results seen in the proof-of-concept trial are preliminary and should not be considered inferential. Meaningful inferential statistical analyses will occur during the randomized controlled trial, where many more participants will be recruited. However, based on the results of the proof-of-concept trial, as well as the specific inclusion criteria of the randomized controlled trial as to the time period that the participants must have completed chemotherapy, it certainly seems likely that adherence to an exercise program will lead to significant improvements in fitness scores of lymphoma survivors during the randomized controlled trial. Finally, quality of life, fear of cancer recurrence, and fear of COVID-19 scores were very encouraging in the proof-of-concept trial, clearly showing the potential for exercise to improve the health and well-being of lymphoma survivors. We are optimistic that the results of the randomized controlled trial will further prove the benefits of exercise on short- and long-term health-related quality of life.

5.3 Future Recommendations

Upon commencing the randomized controlled trial, there are a few adjustments that should be made to the intervention. Firstly, adjustments to the exercise prescriptions should be made based on the barriers and facilitators that were reported by the participants during the proof-of-concept trial. It is important to find ways to work around the barriers (i.e., fatigue, lack of time and lack of motivation), as well as ways to work with the facilitators (i.e., Fitbit™, improved well-being and improved physical capacity) to improve adherence to the intervention. Now that the most common barriers and facilitators among lymphoma survivors have been identified, we can now make the necessary adjustments prior to the start of the exercise intervention in the randomized controlled trial. Secondly, more emphasis should be placed on reducing the amount of time spent being sedentary. It is likely that participants in the randomized

controlled trial will be highly sedentary, as was seen in the proof-of-concept trial. Therefore, suggesting minor lifestyle changes and daily activities that can be done to reduce sitting time, coupled with a personalized workout program, may be even more beneficial to their overall health and well-being. Lastly, due to the limitations of Fitbit™ monitors with regards to tracking resistance training, having participants self-report the amount of time they spent doing resistance training per week into their Fitbit™ application will be essential in ensuring the most accurate reading of weekly MVPA.

5.4 Practical Applications

The results seen in this proof-of-concept trial may have significant clinical implications and may provide oncologists, as well as other healthcare professionals who work with cancer patients, more insight as to the short-term and long-term importance of physical activity for patients who are suffering from the side effects of chemotherapy. Physical activity has generally been discouraged for cancer patients who have recently completed or are completing chemotherapy due to the perception that it would increase fatigue. It is our hope that the results of this study, coupled with those from the randomized controlled trial, will prove that physical activity can have significant benefits for cancer patients post-treatment. Furthermore, it is our hope that this study could provide these healthcare professionals some insight as to how they can implement regular physical activity into their patients' lives without the need of sending them to a fitness center or hiring a personal trainer.

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Appendix A. Research Ethics Board Approval

Hôpital général juif
Jewish General Hospital

Quality Program
Programme de la qualité

Chantal Bellerose, Dt.P, B.Sc, M.Sc Admin Santé

Quality Program Coordinator
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October 18, 2019

Dr. Nathalie Johnson
Department of Medicine
Jewish General Hospital

Subject: "Lymfit Study to Improve fitness in Lymphoma Survivors"

Dear Dr. Johnson,

Thank you for submitting your Proposal entitled, "Lymfit Study to Improve fitness in Lymphoma Survivors".

Based on the information you have submitted to the Quality Program in October 2019, the above-mentioned project outlines the compliance to the conditions for confidentiality, denominalization of data, sampling, data access, collection and secure storage of data.

We wish you success in this quality assurance study.

Sincerely,

Chantal Bellerose, Dt.P, B.Sc, M.Sc Admin Santé
Adjointe à la DGA des programmes de soutien, évaluation et performance
& Directrice DQEPEA
Coordonnatrice de la qualité, de la gestion des risques, de l'agrément, de l'éthique clinique et de l'expérience usager

cc.: Dr. MacNamara
Dr. Trafiro
Dr. Eintracht
Dr. Bitzas

Appendix B. A Complete Set of Questionnaires Assessing the 3 study Outcomes

Quality of Life PROMIS-29 (29-items)

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Cognitive Function - Abilities **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PC6r	I have been able to concentrate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC27r	I have been able to remember to do things, like take medicine or buy something I needed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Pain Intensity **In the past 7 days…**					
Global07	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 **Worst pain imaginable**

Fear of Cancer Recurrence Questionnaire

Fear of Cancer Recurrence Inventory

Most people who have been diagnosed with cancer are worried, to varying degrees, that there might be a recurrence of the cancer. **By recurrence, we mean the possibility that the cancer could return or progress in the same place or in another part of the body.** This questionnaire aims to better understand the experience of worries about cancer recurrence. Please read each statement and indicate to what degree it applied to you **DURING THE PAST MONTH** by circling the appropriate number.

0 Never	1 Rarely	2 Sometimes	3 Most of the time	4 All the time

The following situations make me think about the possibility of cancer recurrence:

1.	Television shows or newspaper articles about cancer or illness	0	1	2	3	4
2.	An appointment with my doctor or other health professional	0	1	2	3	4
3.	Medical examinations (e.g. annual check-up, blood tests, X-rays)	0	1	2	3	4
4.	Conversations about cancer or illness in general	0	1	2	3	4
5.	Seeing or hearing about someone who is ill	0	1	2	3	4
6.	Going to a funeral or reading the obituary section of the paper	0	1	2	3	4
7.	When I feel unwell physically or when I am sick	0	1	2	3	4
8.	Generally, I avoid situations or things that make me think about the possibility of cancer recurrence	0	1	2	3	4

0 Not at all	1 A little	2 Somewhat	3 A lot	4 A great deal

9.	I am worried or anxious about the possibility of cancer recurrence	0	1	2	3	4
10.	I am afraid of cancer recurrence	0	1	2	3	4
11.	I believe it is normal to be worried or anxious about the possibility of cancer recurrence	0	1	2	3	4
12.	When I think about the possibility of cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family)	0	1	2	3	4
13.	I believe that I am cured and that the cancer will not come back	0	1	2	3	4

14. In your opinion, are you at risk of having a cancer recurrence?

0 Not at all at risk	1 A little at risk	2 Somewhat at risk	3 A lot at risk	4 A great deal at risk

15. How often do you think about the possibility of cancer recurrence?

0 Never	1 A few times a month	2 A few times a week	3 A few times a day	4 Several times a day

16. How much time per day do you spend thinking about the possibility of cancer recurrence?

0 I don't think about it	1 A few seconds	2 A few minutes	3 A few hours	4 Several hours

17. How long have you been thinking about the possibility of cancer recurrence?

0 I don't think about it	1 A few weeks	2 A few months	3 A few years	4 Several years

0 Not at all	1 A little	2 Somewhat	3 A lot	4 A great deal

When I think about the possibility of cancer recurrence, I feel:

18.	Worry, fear or anxiety	0	1	2	3	4
19.	Sadness, discouragement or disappointment	0	1	2	3	4
20.	Frustration, anger or outrage	0	1	2	3	4
21.	Helplessness or resignation	0	1	2	3	4

My thoughts or fears about the possibility of cancer recurrence disrupt:

22.	My social or leisure activities (e.g. outings, sports, travel)	0	1	2	3	4
23.	My work or everyday activities	0	1	2	3	4
24.	My relationships with my partner, my family, or those close to me	0	1	2	3	4
25.	My ability to make future plans or set life goals	0	1	2	3	4
26.	My state of mind or my mood	0	1	2	3	4
27.	My quality of life in general	0	1	2	3	4

0 Not at all	1 A little	2 Somewhat	3 A lot	4 A great deal

28.	I feel that I worry excessively about the possibility of cancer recurrence	0	1	2	3	4
29.	Other people think that I worry excessively about the possibility of cancer recurrence	0	1	2	3	4
30.	I think that I worry more about the possibility of cancer recurrence than other people who have been diagnosed with cancer	0	1	2	3	4

0 Never	1 Rarely	2 Sometimes	3 Most of the time	4 All the time

When I think about the possibility of cancer recurrence, I use the following strategies to reassure myself:

31.	I call my doctor or other health professional	0	1	2	3	4
32.	I go to the hospital or clinic for an examination	0	1	2	3	4
33.	I examine myself to see if I have any physical signs of cancer	0	1	2	3	4
34.	I try to distract myself (e.g. do various activities, watch television, read, work)	0	1	2	3	4
35.	I try not to think about it, to get the idea out of my mind	0	1	2	3	4
36.	I pray, meditate or do relaxation	0	1	2	3	4
37.	I try to convince myself that everything will be fine or I think positively	0	1	2	3	4
38.	I talk to someone about it	0	1	2	3	4
39.	I try to understand what is happening and deal with it	0	1	2	3	4
40.	I try to find a solution	0	1	2	3	4
41.	I try to replace this thought with a more pleasant one	0	1	2	3	4
42.	I tell myself "stop it"	0	1	2	3	4
	Do you feel reassured when you use these strategies?	0	1	2	3	4

Fear of COVID-19 Scale (FCV-19S; 7-items)

No.	Item	Strongly disagree	Disagree	Neural	Agree	Strongly agree
1	I am most afraid of coronavirus-19	1	2	3	4	5
2	It makes me uncomfortable to think about coronavirus-19	1	2	3	4	5
3	My hands become clammy when I think about coronavirus-19	1	2	3	4	5
4	I am afraid of losing my life because of coronavirus-19	1	2	3	4	5
5	When watching news and stories about coronavirus-19 on social media, I become nervous or anxious	1	2	3	4	5
6	I cannot sleep because I'm worrying about getting coronavirus-19	1	2	3	4	5
7	My heart races or palpitates when I think about getting coronavirus-19	1	2	3	4	5

Fitness Questionnaire

Name:

Instructions: Please fill out this form as completely as possible.

Height: Weight: WC:

13. How often were you participating in physical activity prior to diagnosis?
    e. 4 to 5 times per week
    f. 2 to 3 times per week
    g. 1 to 2 times per week
    h. Not at all
14. Are you currently involved in regular exercise? Yes No
15. What sport or activity has worked for you in the past?
16. What type of exercise do you enjoy the most?
17. What type of exercise do you dislike and why?

Rate yourself on a scale of 1 (least fit) – 10 (most fit) for each fitness category

18. How good is your stamina?

    1 2 3 4 5 6 7 8 9 10

19. How strong do you think you are?

    1 2 3 4 5 6 7 8 9 10

20. How flexible do you think you are?

    1 2 3 4 5 6 7 8 9 10

21. How coordinated do you think you are?

1 2 3 4 5 6 7 8 9 10

22. How much time are you willing to devote to an exercise program?
_____Min/Day ____Days/Week

23. Are there any barriers that may prevent you from exercising on any given day? (e.g., lack of time, family obligations, lack of motivation…)

24. What days and/or time (morning, afternoon or night) are you available to exercise throughout the week?