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An Exercise and Wellness Behavior Change Program for Solid Organ Transplant: A Clinical Research Protocol for the Transplant Wellness Program

Jenna A. P. Sim[1], Maneka A. Perinpanayagam[2], Vanessa Bahry[2], Kathryn Wytsma-Fisher[2], Kelly W. Burak[2,3], Debra L. Isaac[2,4], Stefan Mustata[2], and S. Nicole Culos-Reed[1,3,5]

Abstract

Background: Exercise prehabilitation is an evidence-based, safe, and effective method to increase quality of life, physical fitness and function, and post-surgical outcomes in solid organ transplant (SOT) patients. However, few prehabilitation programs for SOT patients exist in practice. Furthermore, there is a lack of multimodal prehabilitation programs that include behavior change support. To address this need, the Transplant Wellness Program (TWP) was designed.
Objectives: The objective of the TWP is to assess both the effectiveness and implementation of a comprehensive and multimodal exercise and wellness behavior change intervention for patients undergoing kidney or liver transplant.
Design: The TWP is a hybrid effectiveness-implementation trial consisting of exercise and wellness behavior change support.
Patients: Individuals who are in evaluation or listed for kidney or liver transplant in Southern Alberta, Canada.
Measurements: The primary outcomes of self-reported exercise and quality of life are assessed at intake, post-exercise intervention, 6 months post-intake, 12 weeks post-transplant, and annually for 5 years after program completion. Functional fitness measures will be assessed at intake, post-exercise intervention, 12 weeks post-transplant, 6 months post-intake, and 1-year post-intake. The reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework is used to determine the impact of TWP at the individual and health care system level.
Methods: Recruitment began in November 2023 and will continue until November 2028. Participants take part in a 12-week exercise intervention and are offered individualized and group behavior change support. Continued exercise support is offered through maintenance classes after the completion of the 12-week intervention.
Limitations: The design of the hybrid effectiveness-implementation trial with a single experimental group will not allow for comparisons to a control or usual care group, potentially impacting internal validity. Differences in number of participants between organ groups (kidney vs liver) and cohorts (pre-transplant vs post-transplant) will likely be uneven, requiring consideration when running and interpreting analyses.
Conclusions: The TWP aims to support patients throughout the transplant journey through a multimodal and comprehensive exercise and wellness behavior change program. Results from this study will determine the effectiveness of the program and inform future scale-up and sustainability.
Trial registry number: NCT06367244.

Résumé

Contexte: La préadaptation à l'exercice physique est une méthode sûre et efficace, fondée sur des données probantes, qui permet d'améliorer la qualité de vie, la condition physique fonctionnelle et les résultats post-chirurgicaux chez les patients transplantés d'organes solides (TOS). Cependant, en pratique, il existe peu de programmes de préadaptation pour les patients TOS. Il manque également de programmes multimodaux de préadaptation avec soutien au changement de comportement. Pour répondre à ce besoin, le Transplant Wellness Program (TWP), un programme de mieux-être en transplantation, a été conçu.
Objectif: L'objectif du TWP est d'évaluer la mise en œuvre et l'efficacité d'une intervention complète et multimodale visant à modifier les comportements en matière d'exercices et de bien-être des patients subissant une greffe de rein ou de foie.
Conception: Le TWP est un essai hybride d'efficacité et de mise en œuvre qui consiste à offrir du soutien au changement de comportement en matière d'exercices et de bien-être.

Sujets: Les personnes en évaluation ou inscrites pour une greffe de rein ou de foie dans le sud de l'Alberta (Canada).
Mesures: Les principaux critères d'évaluation de l'exercice physique et de la qualité de vie autodéclarée sont mesurés à l'adoption du programme, lors de l'intervention post-exercice, 6 mois après l'adoption, 12 semaines après la transplantation et annuellement pendant 5 ans après la fin du programme. La condition physique fonctionnelle est évaluée à l'adoption du programme, lors de l'intervention post-exercice, 12 semaines après la transplantation, puis 6 mois et 1 an après l'adoption. Le cadre RE-AIM (portée, efficacité, adoption, mise en œuvre et maintenance) est utilisé pour déterminer l'effet du TWP au niveau de l'individu et du système de santé.
Méthodologie: Le recrutement s'est amorcé en novembre 2023 et se poursuivra jusqu'en novembre 2028. Les participants prennent part à une intervention d'exercices physiques de 12 semaines et se voient offrir un soutien individualisé et de groupe pour favoriser le changement de comportement. Un soutien continu à l'exercice physique est offert sous forme de cours visant le maintien des habitudes après les 12 semaines de l'intervention.
Limites: La conception de cet essai hybride d'efficacité et de mise en œuvre réalisé auprès d'un seul groupe expérimental ne permettra pas de comparaisons avec un groupe témoin ou de soins habituels, ce qui pourrait affecter la validité interne. Les nombres de sujets dans les différents groupes selon l'organe transplanté (rein c. foie) et les cohortes (pré- c. post-transplantation) seront probablement inégaux; ceci devra être pris en compte lors de l'exécution et de l'interprétation des analyses.
Conclusion: L'objectif du TWP est de soutenir les patients tout au long du parcours de transplantation par le biais d'un programme complet et multimodal de changement de comportement en matière d'exercices et de bien-être. Les résultats permettront de déterminer l'efficacité du programme et d'orienter son expansion et sa pérennité.

Keywords
Solid organ transplant, exercise, behavior change, implementation, prehabilitation

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Introduction

In 2022, nearly 3000 Canadians received a solid organ transplant (SOT), with close to 4000 more on the waitlist.[1] The SOT is the complete or partial transplant of the kidney, liver, lung, heart, or pancreas and can be a lifesaving treatment for individuals with end-stage disease or organ failure.[2,3] Pre-SOT, many patients are frail and have reduced cardiorespiratory fitness.[4-7] Post-SOT, many recipients experience reduced aerobic and exercise capacity, muscle atrophy, and increased risk of secondary chronic disease.[8-10] As rates of chronic disease and SOT patients rise, combined with increased post-transplant survivorship,[11] there remains a need to better support SOT recipients pre-transplant to enhance surgical outcomes and quality of life (QOL) post-transplant.

Exercise is an evidence-based tool to support symptom management, functional, mental, and emotional well-being, and overall quality of life in those living with chronic diseases.[12-14] Exercise prehabilitation involves structured programming that aims to increase patient physical and mental capacity prior to surgery.[15] Exercise prehabilitation can reduce length of hospital stay, postsurgery complications, and postsurgery morbidity.[16-19] In kidney, liver, and heart transplant populations, pilot studies, randomized controlled studies, and systematic and scoping reviews have demonstrated the effectiveness and safety of exercise prehabilitation.[6,18-20] Although there has been less research in lung transplants, the literature points toward exercise being safe and effective for this population as well.[21-23] Furthermore, national SOT organizations have called for exercise to be incorporated into standard care for SOT patients. For example, in 2019, the Canadian Society of Transplantation issued a position statement recommending exercise as a safe and effective tool for SOT recipients pre-transplant and post-transplant.[8] Despite this call to action and accumulating evidence,[6,8,18-23] exercise is not included in the standard care pathway for SOT patients.[4,8] In addition, exclusively exercise-based interventions are not enough to result in long-term behavior change.[24,25] Rather, exercise interventions (EIs) that are delivered utilizing autonomy-supportive approaches, eg, using tenets from Motivational Interviewing,[26] recognize constructs beyond individual behavior control (eg, environmental factors, socioeconomic influences, social support), and target building self-efficacy and regulatory skills, can have a larger impact on long-term exercise behavior adherence.[27-30]

[1]Faculty of Kinesiology, University of Calgary, AB, Canada
[2]Department of Medicine, Cumming School of Medicine, University of Calgary, AB, Canada
[3]Department of Oncology, Cumming School of Medicine, University of Calgary, AB, Canada
[4]Southern Alberta Transplant Program, Alberta Health Services, Calgary, Canada
[5]Department of Psychosocial Resources, Tom Baker Cancer Centre, Alberta Health Services, Calgary, Canada

Corresponding Author:
S. Nicole Culos-Reed, Faculty of Kinesiology, University of Calgary, 2500 University Drive NW, Calgary, AB T2N 1N4, Canada.
Email: nculosre@ucalgary.ca

Table 1. Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Patient has not been cleared for participation by attending physician
Listed (active or temporarily inactive) or in evaluation for kidney or liver transplant	Unable to provide informed consent
Able to provide written informed consent and understand study information in English	Clinical condition that makes the intervention unsafe or infeasible (eg, unable to follow instruction due to refractory encephalopathy)
Approval to exercise from Canadian Society of Exercise Physiology Clinical Exercise Physiologist	Unsafe environment for virtual participation
Has access to an Internet connected device	Recent variceal bleeding in patients who cannot tolerate prophylaxis with non-selective beta blockers.

Beyond exercise, there is a lack of overall wellness behavior change support for SOT recipients. Many individuals experiencing end-stage disease or awaiting SOT report experiencing depression, anxiety, high symptom burden, and poor health-related quality of life.[31-35] Owing to the long wait time for transplant,[36,37] the pre-transplant period is an ideal opportunity to support overall patient wellness. Wellness is a multidimensional state of overall health and well-being.[38] Although exercise and physical activity are components of wellness, behaviors such as sleep, nutrition, and stress reduction are also important to overall health and well-being. Despite the importance of all wellness behaviors for improved quality of life in those living with chronic diseases, there remains a need for comprehensive wellness behavior change supports for individuals undergoing SOTs.

To address this gap, the Transplant Wellness Program (TWP), a hybrid effectiveness-implementation trial, was designed. Previous work by members of the research team on exercise prehabilitation for patients with end-stage kidney disease informed the development of the TWP.[39] The TWP is a multimodal supportive care program initially for kidney and liver transplant populations in Alberta, Canada, and in year 2 will begin delivery for lung transplant patients. The TWP will target lifestyle behavior change, with a specific focus on exercise, to enhance wellness of SOT patients. In addition, the TWP research team will work to build relationships with registered dieticians, social workers, and sleep services to incorporate additional resources that enhance well-being and quality of life of SOT patients. A central component of the TWP is the person-centered and autonomy-supportive approach, which aims to help build participant self-efficacy and build skills in the participants for long-term behavior change. The TWP aims to improve the outcomes of SOT patients across the transplant timeline (starting pre-transplant and continuing post-transplant), as well as reduce health service utilization. Our objectives are to evaluate the implementation and effectiveness of the TWP to better understand the components that contribute to implementation of a sustainable, effective wellness program for SOT patients.

Methods and Analysis

Design and Setting

A hybrid type 2 effectiveness-implementation study design[40] is being used to determine the effectiveness and implementation of the TWP intervention (NCT06367244). Hybrid effectiveness-implementation trials can be used to help reduce the knowledge-practice gap by simultaneously measuring outcomes related to an intervention's impact and implementation.[40] In the context of SOT, exercise has been well-established as an efficacious and safe method of prehabilitation and rehabilitation;[6,41-43] however, the effectiveness and implementation of multiphasic and multimodal programs with behavior change support are limited.[18] This study will use mixed methods to determine the effectiveness and implementation of the TWP. In addition, a patient advisory board (PAB) was formed in July 2023, to inform the development and implementation of the TWP. The PAB consists of transplant patients and a caregiver. Participants who are among the first to complete the intervention will be invited to join the PAB and help guide the continued implementation and adaptations to the TWP. Ethics approval was received from the University of Calgary Conjoint Health Research Ethics Board (REB23-0281).

Participants and Screening

Participant enrollment began in November 2023 and will continue until November 2028. Adults who are on the waitlist or are in evaluation for kidney or liver transplant in Alberta, Canada, can provide informed consent and understand study information in English, have approval to exercise from a Canadian Society of Exercise Physiology—Clinical Exercise Physiologist (CEP), and have an Internet connected device are eligible to participate (see Table 1 for inclusion and exclusion criteria).

Participants are referred to the TWP by their health care provider (HCP) through either written or verbal "consent to contact." The TWP project coordinator then contacts the potential participant to provide further information and

obtain consent. All study data and consent forms are collected via a secure web-based data collection software, Research Electronic Data Capture (REDCap). Within 48 hours of signing consent, the study CEP will call the participant to conduct screening and physical activity readiness via the PARQ+. If further medical clearance is needed, the participant's referring physician is contacted for clearance to exercise. Although the TWP was designed primarily as a prehabilitation program, due to the unpredictable nature of transplant surgeries, participants will be eligible to start the TWP post-transplant if they provide consent pre-transplant and have less than 12 weeks until their scheduled transplant. Once cleared, the participant is placed in either cohort 1 (>12 weeks from intake to transplant surgery) or cohort 2 (<12 weeks from intake to transplant surgery). Participants in cohort 1 will be scheduled into the EI, whereas those in cohort 2 are informed they will be contacted 12 weeks post-transplant to be scheduled into the program. It is expected that the majority of patients will be in cohort 1 of the TWP, as the average wait time for a liver or kidney transplant exceeds 1 year.[36,37] If a participant begins in cohort 1 and receives their transplant before completing 50% of the intervention, they will be invited to re-start the intervention as cohort 2 at 12 weeks post-transplant.

Exercise Intervention

The EI is delivered by a CEP with transplant-specific training, clinical experience with transplant populations, and behavior change training. The behavior change training consists of an online evidence-based health coaching course through Thrive Health Services,[44] plus additional hands-on training with a behavior change expert, and feedback from an expert via fidelity checks during the intervention. The EI is delivered within a positive motivational climate,[45] using tenets from health coaching[46] and Motivational Interviewing.[26] To facilitate building the positive motivational climate, the CEP engages with participants in a person-centered, autonomy-supportive approach. For example, the CEP will use open-ended questions, reflections, and facilitate discussions to check in on participant goals, encourage participant self-monitoring of progress, foster a sense of community, and help to build participant self-efficacy.

The EI is a 12-week intervention consisting of 2 exercise classes per week. The first week of the intervention involves one-on-one exercise sessions with the CEP over Zoom. These sessions allow the CEP to check in, introduce exercises that will be used in the group sessions, and tailor activities. Following the introduction period, participants are then invited to join the group exercise classes held on Zoom. The TWP uses rolling recruitment, so the one-on-one exercise sessions help to ensure that participants feel supported and prepared when they enter a class with participants who may be more advanced. The individual sessions also allow the CEP to be aware of any modifications or safety concerns to be aware of before joining in a group setting.

The TWP exercise sessions are up to 60 minutes in length and consist of aerobic, resistance, balance, and flexibility exercises. Participants are instructed to have a clear, flat space where the camera on their device can see their entire body when both seated and standing. A rating of perceived exertion (RPE)[47] between 3 and 5 is targeted during aerobic activities, and participants will be encouraged to engage in aerobic activity daily in bouts of 10 minutes or more with a target of 30 minutes daily. Walking will be suggested; however, modifications will be provided to suit the needs and abilities of all participants. Resistance exercises will begin with a focus on bodyweight functional movements (eg, sit-to-stand, knee extensions, wall planks). Progressions to using resistance bands will be provided when deemed appropriate by the CEP. All participants will be sent resistance bands for their at-home exercise if they do not already have them. The CEP rotates through a set of 5 different circuits over the course of the 12-week intervention (example circuit available in Supplemental file 1). A summary of the EI components is presented using the Template for Intervention Description and Replication (TIDieR) tool (Supplemental file 2).

Once they have completed the EI, participants are also sent a tailored exercise program handout from the CEP to support continued exercise. In addition, participants will be offered TWP maintenance exercise classes, and referred to local community programs. The maintenance classes will follow a similar program to the EI and will be led by a CEP or by a trained qualified exercise professional (ie, group fitness instructor with program specific training).

Behavior Change Support

Prior to starting the EI, all participants receive a TWP Wellness Manual specific to their transplant type with information and worksheets on goal setting, barrier management, and planning for daily movement when joining the EI. They also receive a one-on-one baseline wellness behavior change support session with a behavior change specialist over Zoom to discuss motivations for joining the program, barriers to exercise and strategies to overcome them, and set goals for the program. The behavior change specialists (J.A.P.S. and S.N.C.-R.) hold graduate training and expertise in the field of health behavior change. J.A.P.S. is a PhD student in exercise psychology with graduate-level training in exercise counseling and behavior change. S.N.C.-R. holds a PhD in the field of exercise psychology and is a Professor in the University of Calgary's Faculty of Kinesiology. S.N.C.-R. holds over 20 years' experience in the field of exercise psychology and health behavior change.

At the midpoint of the EI, participants have the option of a short call with a behavior change specialist to review and adjust goals, discuss any challenges with the first half of the program, and develop strategies to mitigate identified barriers. Participants also have the option to join monthly group behavior change sessions. These sessions will take place over Zoom

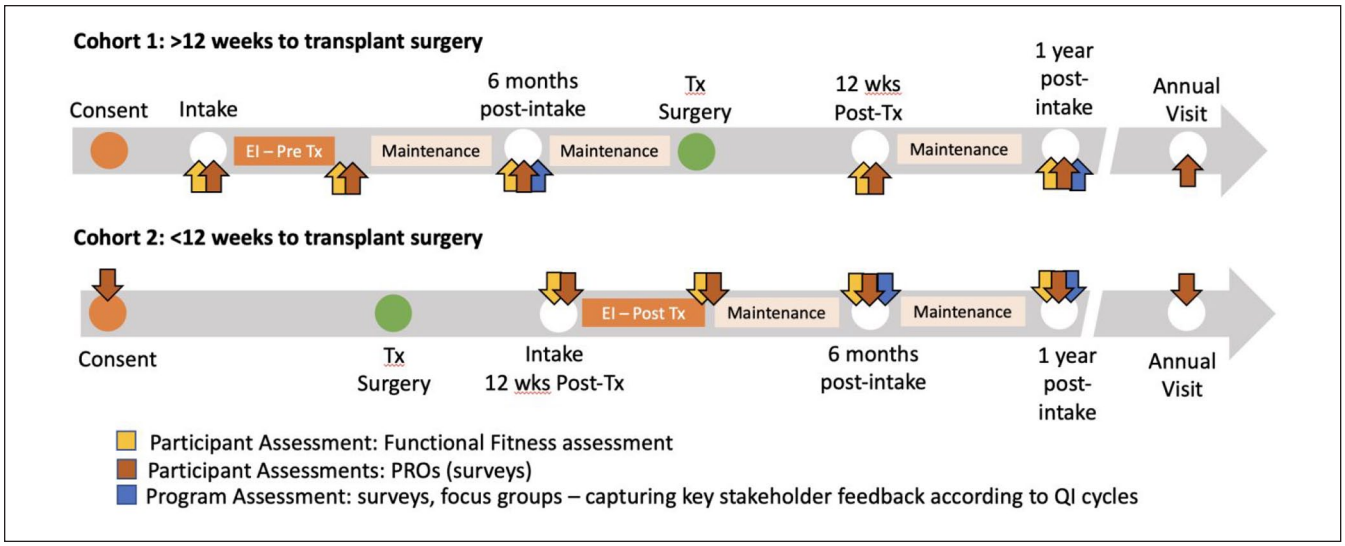

Figure 1. TWP measurement timepoint overview.

and be led by one of the behavior change specialists. They will consist of a brief webinar followed by a discussion period and will cover a variety of topics including goal setting, self-monitoring, barrier management, and self-compassion. Participants will be informed that they can access additional behavior change support throughout the 12-week intervention and maintenance period as needed.

Outcome Measures

The primary outcome measures for the trial are self-reported exercise and QoL. Secondary outcome measures include implementation, functional fitness, and various additional patient-reported outcomes (PROs). Outcome measures are completed at 9 timepoints over the 5-year study period, depending on cohort (see Figure 1). Outcome measures for cohort 1 are taken at (1) study intake, (2) immediately post-EI, (3) 6 months post-intake, (4) 12 weeks post-transplant, (5) 1-year post-intake, and (6-9) annually up to 5 years post-intake. Outcome measures for cohort 2 will be completed at (1) study consent (pre-transplant), (2) study intake (12 weeks post-transplant), (3) immediately post-EI, (4) 6 months post-intake, (5) 1-year post-intake, and (6-9) annually up to 5 years post-intake. Program assessment will occur through quality improvement (QI) cycles every 6 months for the first 2 years of the TWP and annually thereafter.

Patient-Reported Outcomes

The co-primary outcome of self-reported exercise is assessed using the modified Godin Leisure Time Exercise Questionnaire (m-GLTEQ).[48,49] The m-GLTEQ is a validated self-reported measure that asks participants to recall their typical weekly strenuous, moderate, and mild exercise. Each type of exercise is given a score and multiplied by the number of days per week the activity is performed. The sum of the items is then interpreted as either active (>24 points), moderately active (14-23 points), or insufficiently active/sedentary (<14 points).

The QoL is the second co-primary outcome and is assessed using generic measures, EuroQol-5 Dimensions 5 Level (EQ-5D-5L) and EuroQol-Visual Analog Scale (EQ-VAS), as well as disease-specific QoL measures. The EQ-5D-5L is a multidimensional QoL measure consisting of 5 domains, each measured on a scale from 1 to 5, with 1 being no problems and 5 being extreme problems. The responses for the 5 dimensions are then combined into a single index score representing the patient's health status.[50] The EQ-VAS is a measure of patient self-reported health on a vertical scale with endpoints of 100 being "the best health you can imagine" and zero being "the worst health you can imagine." Kidney patients will receive the Kidney Disease Quality of Life 36-item (KDQOL-36), a validated measure of QoL in those with end-stage kidney disease. The KDQOL-36 has 5 subscales that include the 12-item Short Form Health Survey, Burden of Kidney Disease, Symptoms and Problems of Kidney Disease, and Effects of Kidney Disease. The KDQOL-36 is scored using the template by the RAND corporation, which converts the data into a 0 to 100 score, with higher scores representing higher QoL.[51] Liver patients will receive the Chronic Liver Disease Questionnaire (CLDQ), a validated measure of QoL in clinical liver disease populations.[52] The CLDQ has 5 domains, abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry, and is scored from 1 to 7, with higher scores indicating higher QoL. The mean of the 5 domains represents overall QoL in liver disease populations.

Secondary outcomes include nutrition, sleep, mental health, and self-efficacy to engage in exercise. Nutrition is measured with the Mini-Eating Assessment Tool (mini-EAT)

questionnaire,[53] and the Patient-Generated Subjective Global Assessment (PG-SGA).[54] The mini-EAT is a validated brief dietary screener that assesses individuals' consumption of fruits, vegetables, whole grains, refined grains, seafood, legumes/nuts/seeds, low-fat dairy, high-fat dairy, and sweets, with a low-score indicating a poor diet and a higher score indicating a healthier diet. The PG-SGA is a reliable measure assessing nutrition status in hospitalized individuals, allowing for classification of patients as well nourished, moderately or suspected malnourished, and severely malnourished. Sleep is assessed by the Pittsburgh Sleep Quality Index (PSQI),[55] which assesses sleep quality and disturbances over a 1-month period based on subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep mediation, and daytime dysfunction. The sum of the 7 components represents an overall sleep quality score. Mental health is assessed by the Hospital Anxiety and Depression Score (HADS).[56] The HADS includes a 7-point anxiety subscale and a 7-point depression subscale, with a score >8 in either subscale indicating anxiety or depression. Self-efficacy to engage in exercise is measured using an adapted barrier self-efficacy to exercise scale. Existing barrier self-efficacy scales in cancer, cardiac rehab, and older adult populations[57-59] were adapted based on previous research on barriers to engaging in physical activity for SOT recipients.[5,60]

Functional Fitness Measures

Functional fitness measures are completed either online over Zoom or in-person with the CEP at the first 6 measurement timepoints only. All kidney transplant participants will complete online fitness assessments. Liver transplant participants residing within the Calgary area will be invited to complete the fitness assessments in-person at the University of Calgary. Liver participants who reside outside of the Calgary area or who are unable to reach the University of Calgary will complete the fitness assessments online. Functional fitness measures include anthropometrics (height, weight, resting blood pressure, waist and hip circumference), hand grip strength,[61] chair sit and reach,[62] 6-minute walk test,[63] 30 second sit-to-stand,[64] 15-foot walk test, balance tests,[65] and frailty.[66,67] Table 2 shows a breakdown of in-person vs online functional fitness measures.

Hand grip strength. Upper body strength will be assessed using a Jamar hand grip dynamometer (Performance Health, Hydraulic, Illinois, USA), which has been widely used in various chronic illnesses. Participants will complete 3 trials per side, and the highest value in kilograms from each will be taken and added together to get a cumulative value.

Chair sit and reach. Participants begin seated in a chair near the front edge and extend preferred leg in front of hip with foot flexed at approximately 90°. Hands are placed one atop the other, palms down, and are instructed to bend forward at the hip joint, aiming to keep the spine as straight as possible in an attempt to touch their toes. The final position is held for ~2 seconds, and the distance from fingers to toe is measured. A reach short of the toes is recorded as a negative value, and a reach beyond the toes is recorded as a positive value.

Table 2. Summary of Online and in-Person Fitness Assessments.

Summary of fitness assessments	
Online fitness assessment	In-person fitness assessment
Balance • Single-leg stance • Double-leg stance • Tandem-leg stance 30 second sit to stand Timed 5 sit-to-stand[a] 15-foot walk test Modified Fried Frailty Index	Resting vital measures • Heart rate • Blood pressure Anthropometric measures • Height • Weight • Waist circumference Hip circumference Cardiovascular Fitness—6-Minute Walk Test Grip Strength Sit and reach test Balance • Single-leg stance • Double-leg stance • Tandem-leg stance 30 second sit to stand Timed 5 sit to stand[a] 15-foot walk test Fried Frailty Index

[a]Timed 5 sit to stand is only measured in liver patients.

Six-minute walk test. Participants walk as many laps of a set and measured distance as possible during a 6-minute time period. The test is self-paced, with minimal encouragement given. The number of laps of the set distance is counted, and if the participant finishes in between the 2 set points, the distance from the most recent end post is measured. The distance of total laps is added to the final end point for a total distance (meters) walked in 6 minutes.

Fifteen-foot walk test. Participants walk a set 15-foot distance in a straight line. The time to complete the 15 feet is recorded in seconds. The participant completes the test twice, and the lowest time is recorded.

Thirty-second sit to stand. Participants begin in an upright seated position with feet flat on the floor, arms crossed with hands on opposite shoulders, and no contact with the back of the chair. The participant is instructed to complete as many "sit to stands" in the 30-second time period as possible. A full "sit to stand" is considered when the participant rises to a full stand with a straight body, extended hips, and no arm movement. The number of completed sit to stands in the time period is recorded. In addition, specific to liver patients, a

timed measure of 5 sit-to-stands will be conducted to complete the liver frailty index.

Balance tests. Participants will complete 3 different balance tests: single-leg stance, double-leg stance, and tandem-leg stance. The participant first completes the double leg stance test. For this, the participant stands with feet together, hands crossed across chest. The test begins as soon as the participant is in the correct position and is a maximum of 20 seconds. The CEP counts the number of errors such as arms moving away from the body or feet moving. The participant then completes the tandem stance test. The participant stands with 1 foot in front of the other so that feet are in line with each other and arms on hips or crossed across the chest. The test begins as soon as the participant is in the position. The test is a maximum of 20 seconds, and the CEP counts the number of errors within the time period such as arms moving from the body. The test is repeated with the opposite foot in front, and score for each side is recorded. For the single-leg stance participants, the participant places hands on hips and stands with feet shoulder width apart. The test begins when the participant lifts 1 foot off the ground to the height of the ankle. The assessment ends when either the arms leave hips, raised foot touches floor or other leg, raised leg moves from a static position, or 20 seconds have elapsed.

Frailty index. Frailty will be determined using a modified Fried Frailty Index,[66] and in liver patients, the liver frailty index.[67] According to the Fried Frailty Index, frailty is when 3 or more of the following criteria are present: unintentional weight loss (10 or more pounds in the past year), self-reported exhaustion, weakness, slow walking speed, and low physical activity. The CEP will take measures of unintentional weight loss, weakness, walking speed, and physical activity during fitness assessments and then calculate a Fried score. Weakness will be measured using the hand grip strength test, walking speed will be measured using the 15-foot walk test, and physical activity will be measured using the m-GLTEQ. If present, each criterion is given 1 point. A total score of equal to or less than 1 classifies the patient as non-frail, 2 points is pre-frail, and 3 or more points is considered frail. For participants who complete the fitness assessments online, a modified version of the Fried Frailty Index, without a measure of weakness, will be used.

The liver frailty index is a 3-variable model that assesses patient frailty based on hand grip strength, balance, and sit-to-stands. Scores range from 1 to 7, with $\geq$4.4 is considered frail and a score of 3.2 to 4.3 is considered pre-frail.

Quality Improvement

Quality improvement cycles will be used to inform changes to the program and resources in complement to the quantitative data. The QI cycles will assess implementation barriers and facilitators through analysis of bi-annual open-ended surveys and ongoing semi-structured interviews with key program champions. Key program champions will include TWP participants, family members, as well as HCPs. Participant and family member champions will be recruited from the TWP after completion of the 12-week intervention period. The HCP champions will be recruited from referring SOT clinics. Interviews will be conducted online via Zoom or over the telephone. Qualitative description methodology[68] will be used to analyze qualitative data.

Implementation Measures

The reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework will be used to evaluate the implementation of the TWP.[69] This framework has been used extensively to evaluate behavioral interventions.[69-71] Reach and effectiveness will be evaluated at the individual participant level, adoption and implementation will be evaluated at the system level, and maintenance will be evaluated at both a participant and system level. Reach will be assessed by tracking referrals to and enrollment in the TWP. Referrals will be tracked based on referral numbers and sources. Enrollment will be evaluated based on participation rate, with reasons for study ineligibility or refusal tracked. Information from QI cycles will also be used to supplement quantitative data to identify determinants of participation. Effectiveness will be assessed using PROs and functional fitness assessments, which are detailed above. In addition, health economic evaluations will be conducted to determine the cost-effectiveness of the TWP (see the following section). Adoption will be tracked based on the number and characteristics of SOT clinics and HCPs that refer to the TWP. Implementation will evaluate the delivery of the TWP including fidelity checks, time, and expertise to deliver the intervention, number of adverse events, class adherence and reasons for missed classes, and overall delivery cost. Maintenance will be evaluated based on long-term self-reported exercise levels from annual participant surveys up to 5 years post-EI as well as the sustainability of program within the SOT care pathway (see Table 3 for a summary of RE-AIM measures).

Health Economic Evaluation

A health economic evaluation will be conducted to determine the cost-utility of implementing transplant wellness into the care pathway. Personal health numbers (PHNs) will be linked to health service utilization data available from the Alberta Health System's record-keeping system, Connect Care. Patient chart reviews will be conducted to collect health care encounters (inpatient and outpatient), medication use, emergency room visits, hospital admissions, length of hospital stays, intensive care unit admissions (length of stay and days of intubation), patient, and graft survival during the 5-year follow-up period.

Table 3. Summary of RE-AIM Outcome Measures.

RE-AIM outcomes	
Construct	Outcome
Reach	Referrals • Number of patients referred • Source of referral Enrollment • Number or participants enrolled • Number of participants declined enrollment • Demographic characteristics of enrolled and not enrolled participants
Effectiveness	Self-reported exercise Patient reported outcomes • Generic and disease-specific QoL • Sleep • Nutrition Functional fitness outcomes • Musculoskeletal fitness • Frailty index • Balance • Flexibility • Aerobic fitness
	Cost-effectiveness • Health economic evaluation
Adoption	Number of referring HCPs Number of referring SOT clinics Characteristics of referring HCPs Characteristics of referring SOT clinics
Implementation	Fidelity checks • Delivery of exercise intervention • Delivery of behavior change techniques Safety • Number and reporting of adverse events Acceptability • Program adherence • Reasons for non-attendance Cost • Training, delivery, and administrative costs • Time and expertise to deliver intervention
Maintenance	Long-term exercise • Self-reported exercise at annual follow-ups years 1-5 • Sustainability • Number of participants in maintenance programming

Sample Size

Sample size was calculated based on a minimally clinical important difference of an increase of 0.076 from baseline on the EQ-5D-5L index score, based on work within a dialysis population.[72] Based on an alpha of 0.05 and an attrition rate of 25%,[6,73,74] we would need to enroll 150 individuals to evaluate the effectiveness of the EI on our co-primary outcome of QoL. Given the interest in assessing additional outcomes including changes in PA levels, functional fitness measures, comparisons between organ groups, and implementation markers, and an anticipated enrollment rate of 60% of eligible kidney and liver patients into the EI over the 5-year trial period, recruitment of 250 individuals will be required to enroll and retain 150 participants.

Statistical Analyses

Multilevel modeling will be used to assess differences among organ groups in relation to the primary outcomes and adherence to the EI. To determine program participation and adherence rates, a single proportion inference test and confidence interval will be performed. Generalized linear mixed models will be used to determine changes over time in outcome measures. Cohort 1 and 2 data will be analyzed separately and then compared at all timepoints to understand the impact of intervention timing (pre-transplant vs post-transplant) on all outcome measures. Descriptive statistics will be used to report on participant demographic characteristics as well as RE-AIM components. Sample size, clinical and demographic characteristics, and PRO descriptives will be reported on annually through newsletters to the clinical team and participants, as well as via web site updates. In addition, an interim analysis of the first 100 participants or 1 year of intervention implementation (whichever occurs first) will be conducted. This analysis on implementation factors and PROs (effectiveness) will be used to inform any implementation changes. The health economic evaluation will use a decision analytic model to translate the clinical benefits of the TWP into potential cost savings and increases in Quality-Adjusted Life Years. We will collaborate with an experienced health systems research team to conduct the cost-effectiveness analysis using clinical, QoL, and resource data collected in participant surveys.

Dissemination

Semi-annual newsletters will be shared with participants and the larger transplant community to provide study updates, changes, and feedback from QI cycles. Outreach to share findings and work to date with transplant groups and HCPs will also occur through Zoom or in-person meetings. The TWP research team plans to present findings from the TWP to local clinicians and the broader academic community at local, national, and international scientific meetings. Conference presentations and manuscripts will focus on interim effectiveness results and ongoing implementation progress over the course of the study period.

Conclusions

Exercise is an evidence-based supportive care tool for SOT patients[42,43] and large national organizations have called for

the inclusion of exercise in pre-transplant and post-transplant care. Despite this evidence, exercise and wellness programs rarely exist in practice.[8] The TWP aims to address this gap through the hybrid effectiveness-implementation study. To the best of our knowledge, this is the first large-scale trial that will evaluate multimodal wellness as prehabilitation and rehabilitation for SOT recipients. Findings from this study will inform how to integrate exercise and wellness for SOT patients within the clinical care pathway. The effectiveness-implementation design will allow for findings to not only determine what exercise and wellness supports are most effective for SOT patients but also inform future sustainability and scale-up so that all Canadian SOT patients have access to evidence-based exercise and wellness programming during their transplant journey.

Ethics Approval and Consent to Participate

Ethics approval for the Transplant Wellness Program was received from the University of Calgary Conjoint Health Research Ethics Board (REB23-0281). All participants complete a written informed consent form, which has been approved by the University of Calgary Conjoint Health Research Ethics Board.

Consent for Publication

Not applicable.

Availability of Data and Materials

Data will be made available upon request to corresponding author.

Declaration of Conflicting Interests

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ORCID iDs

Jenna A. P. Sim https://orcid.org/0000-0001-8035-691X
Kathryn Wytsma-Fisher https://orcid.org/0000-0002-7823-542X

Supplemental Material

Supplemental material for this article is available online.

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