TITLE PAGE: **Prevention of Chemotherapy-induced Peripheral Neuropathy with PRESIONA, a Therapeutic Exercise and Blood Flow Restriction Program: A Randomized Controlled Study Protocol.**

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**ABSTRACT**

**OBJECTIVE**: This trial will analyze the acute and cumulative effects of a tailored program called PRESIONA that combines therapeutic exercise and blood flow restriction (BFR) to prevent CIPN in early BC patients undergoing neoadjuvant chemotherapy.

**METHODS**: PRESIONA will be a physical therapy-led multimodal exercise program that uses BFR during low load aerobic and strength exercises. For the acute study, only one session will be performed one day before the first taxane cycle, in which 72 women will be assessed before intervention and 24 hours post intervention. For the cumulative study, PRESIONA will consist of 24-36 sessions for 12 weeks following an undulatory prescription. At least 80 women will be randomized to the experimental or control group. Feasibility will be quantified based on the patient recruitment-acceptance ratio; dropout, retention, and adherence rates; participant satisfaction; tolerance; and program security. In the efficacy study, the main outcomes will be CIPN symptoms assessed with a patient-reported questionary (EORTC QLQ-CIPN20). In addition, to determine the impact on other patient-reported health, sensorimotor and physical outcomes, the proportion of completed scheduled chemotherapy sessions will be examined at baseline (t0), after anthracycline completion (t1), after intervention (t2), and at the 2-month (t3) and one-year follow-ups (t4).

**CONCLUSION**: The proposed innovative approach of this study will have a far-reaching impact on therapeutic options, and the physical therapeutic role could be essential in the oncology unit to improve quality of life in patients with cancer and reduce side effects of cancer and its treatments.

**IMPACT STATEMENT:**

- Physical therapists in the health system could be essential to achieve the planned doses of chemotherapy to improve survival and decrease the side effects of patients with BC.

- The prevention of CIPN would have an impact on the quality of life in patients with BC.

- This protocol could provide an action guide that could be implemented in any healthcare system.

**TRIAL REGISTRATION**: ClinicalTrials.gov, NCT04652609 (October 20, 2020).

**KEYWORDS**: breast cancer, neoadjuvant therapy, peripheral nervous system diseases, physical therapy modalities, therapeutic exercise.

**INTRODUCTION**

Breast cancer (BC) is the most common malignancy in women worldwide1; nevertheless, increasing survival and quality of life in patients with BC remains a challenge. One of the most promising advances in terms of treatment has been the implementation of neoadjuvant chemotherapy protocols2, which typically consist of cyclically administering anthracyclines and taxanes. The aims of this therapy are to reduce tumor size, improve breast conservation rates, eliminate possible micrometastases, recognize poor responders to limit the toxicity of ineffective therapy3, and produce a complete pathological response4. However, despite being very effective for BC, neoadjuvant chemotherapy has a great impact on the peripheral nervous system, which is known as neurotoxicity5. The clinical presentation is chemotherapy-induced neuropathy (CIPN), which is a dose-limiting toxicity for many commonly used anticancer agents. CIPN can lead to dose reductions or discontinuation of cancer therapy6, which may influence survival and quality of life7.

CIPN is generated by axonal and dorsal root ganglion damage8 and predominately is a sensory rather than a motor neuropathy, but the intensity of dysfunction can impair physical functions. Symptomatology is largely subjective, and patients often experience numbness, tingling and pain in their fingers, affecting activities of daily living and manual dexterity9. Moreover, CIPN negatively affects psychological wellbeing and sleep quality10 and can have a significant impact on physical function in patients, thus increasing fall risks11.

In 2019, the National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee concluded that ‘CIPN is a priority area of translational research in cancer care’12. Therefore, many treatments are still being tested without consensus13, and the results have provided new recommendations to be explored, including methods for the prevention of CIPN14. A reduction in neurotoxicity improves quality of life due to not only the decrease in associated symptoms15 but also the longer survival derived from compliance with the planned treatment16.

In recent years, supervised therapeutic exercise (TE) programs have become a widely used tool for patients with BC. Many of the health benefits of TE are thought to be related to its short-term strengthening of the immune system and long-term anti-inflammatory effects17,18, weight control19 and improved control of endogenous sex hormone levels20. TE during chemotherapy has shown neuroprotective effects against CIPN and has a level of evidence and grade of recommendation of IIC21.

Evidence indicating the most successful TE intervention to prevent CIPN remains scarce22,23 due to heterogeneity of studies. The intensities and load of TE usually used in prevention studies during chemotherapy are moderate to high24–26. These features potentially represent a handicap in BC patients given the barriers of perceived exertion effort in this population27. Adherence rates to high-intensity programs tend to be higher among active people28, and many patients are sedentary and even reduce their physical activity at the time of diagnosis29,30.

According to previous evidence, the effects of TE could be complemented with the effects of the blood flow restriction (BFR) method. In this type of training, a limitation of the arterial supply to the muscles of the extremities is generated while individuals are exercising31. The performance of this combination at low intensities [40-50% maximum volume of oxygen (VO2max) or 20-40% repetition maximum (RM)] generates extra physiological and metabolic stimuli that produce cardiorespiratory and neuromuscular adaptations32,33 without causing muscle damage34. This method promotes a marked elevation of hemodynamic variables and a greater demand for energy during and after exercise33 as well as acute activation of the immune system34 and an improvement in the antioxidant barrier35–37. The justification for the innovative approach of TE and BFR in patients with BC involves a systemic view that includes how TE and BFR may mediate oxidative stress38–40, immunity41,42 and fibrinolytic system response43. These mechanisms do not occur in isolation, and the neuromusculoskeletal system may be enhanced40,44,45 to protect against chemotherapy toxicity. In addition, the reported values of perceived exertion and pain in BFR training are not necessarily high compared to those in an equivalent form of higher intensity exercise without BFR46. This method has no remarkable adverse effects47.

Therefore, given the current evidence, our hypothesis is that implementing a tailored program called **PRESIONA** that combines TE and BFR to prevent CIPN, which involves preconditioning of the musculoskeletal and nervous system, will alleviate the stress of chemotherapy.

*Study objectives*

The overall objective is to analyze the acute and cumulative effects of **PRESIONA** in BC patients undergoing neoadjuvant chemotherapy and determine the impact on the onset and severity of CIPN, quality of life, sensorimotor and physical functional outcomes, and proportion of completed scheduled chemotherapy sessions.

**METHODS**

*Study design*

This is a study protocol of a randomized controlled trial that has been developed following the recommendations of the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT)48, the Consolidated Standards of Reporting Trials (CONSORT) Statement49 and the Template for Intervention Description and Replication (TIDieR) checklist50. The **PRESIONA** trial was registered with ClinicalTrials.gov (code: NCT04652609)51.

An efficacy study will be performed based on a randomized controlled trial design of two parallel groups, including an experimental group and a control group, to examine both the acute and cumulative effects of the **PRESIONA** program. The entire protocol of the present study will be performed at the ‘Cuidate Support Unit for Oncology Patients (CUIDATE)’, a research center specializing in oncology rehabilitation that is part of the ‘Sport and Health University Research Institute’ (iMUDS) of the University of Granada, Spain.

Prior to the efficacy study, a feasibility study will be conducted due to the novelty of the study using a prospective, longitudinal, quasi-experimental, prepost, one-arm design to investigate the recruitment, retention, satisfaction, acceptability, and safety of the program.

The study population will be patients diagnosed with early BC identified by oncologists (Figure 1). Patients will be recruited from the oncology unit of San Cecilio University Hospital in Granada, Spain.

[Insert Figure 1]

*Eligibility criteria*

The inclusion criteria will be (1) patients with confirmed HER2+ subtype BC, (2) patients over 18 years of age, and (3) patients waiting to receive neoadjuvant chemotherapy. The exclusion criteria will be (1) previous diagnosis of cancer, (2) pregnancy, (3) cardiac pathology, (4) symptoms or pathology that could be confused with neuropathy or related to diabetes and (5) a recommendation from an oncologist against TE practice.

*Intervention*

**PRESIONA** will be a physical therapy-led multimodal exercise program that applies BFR during concurrent exercise (aerobic and strength exercises). The program consists of 24-36 sessions over 12 weeks following an undulatory prescription based on the physical stimulus assimilation of each patient using the ATOPE+ mobile application52. Each patient must attend at least 2 weekly sessions up to a maximum of 3 on alternate days. **PRESIONA** has been designed by physical therapists with experience in BFR prescription who specialize in TE in patients with cancer.

The sessions will be face-to-face and last approximately 1 hour with three parts: warm-up, main part and cooling-down period (Figure 2). Balance proposals and mobility will be included in the warm-up. The balance proposals will progressively increase the complexity of the task from low to high(**monopedal** position, eyes closed, instability on the surface) for three sets of 20 seconds, allowing for rest between sets (intra- and intersets)53. To avoid injuries, patients will be secured by the physical therapist. The main part involves low-medium intensity physical exercise, including aerobic work at 40-50% heart rate reverse (HRR) using an elliptical machine and eight resistance full-body exercises with a focus on the intrinsic muscle of the hands and feet at 20-40% RM. During this part, patients will wear occlusion cuffs (KAATSU cycle 2.0, KAATSU Global, Inc, California) that will reduce the arterial blood flow up to 60% of arterial occlusion pressure (AOP) of the muscles that are working at that moment. Perfusion will be normal during rest.

Progression will be determined according to ATOPE+, which is a mobile application developed54 and registered by our research group (https://ieeexplore.ieee.org/document/9314150). ATOPE+ recommends physical exercise depending on the recovery assessed with different objective and subjective tools. After registering in the morning, the researcher receives information on the state of recovery. The aim is to ensure that whenever a subject participates in **PRESIONA** is in a state of recovery.

[Insert Figure 2]

To determine the BFR pressure (mmHg), a vascular Doppler ultrasound probe (Samsung HM70A) will be placed acrally over the tibial artery or radial artery of the lower or upper limbs while subjects are in a relaxed standing position55. A KAATSU cuff attached to the proximal portion of the limb will be automatedly inflated to the point at which the auscultatory pulse of the artery is interrupted (10-mmHg precision)56–58.

For ethical reasons, **participants in the control group will be told they can participate in other research studies,** but their information will be recorded for inclusion in the analysis. Importantly, any physical activity performed in the control group will be recorded.

*Outcome measurements*

**Feasibility study**

The recruitment-acceptance ratio will include the number of potentially eligible and recruited patients. Reasons for nonparticipation will be recorded. Additionally, the rate of dropouts, the reasons for not attending the program and the preferences or needs that would drive patients to participate will also be recorded. The retention rate will be calculated based on patients who complete at least 75% of the program59.

Adherence will be assessed using an attendance diary collected by the physical therapist. The threshold will be 75%60.

Participant satisfaction will be registered using a MEDRISK questionnaire61 consisting of 20 items and with a Cronbach’s α of on.90, which will be conducted after discharge from outpatient physical therapy care.

Program tolerance will be quantified by measuring the pain produced by the occlusion using the visual analog scale (VAS, 0-10). BFR may be painful47; the pressure used will be lower (**40-60% of limb occlusion pressure**) to minimize possible pain. Otherwise, if a patient cannot tolerate occlusion will be withdrawn from the study. The analysis will be performed on an intention-to-treat principle.

Program safety will be assessed by recording the incidence and severity of adverse events using Common Terminology Criteria for Adverse Events (CTCAE) v5.0.62. Every week, patients will answer an online questionnaire to report any adverse events that they interpret as concerning. **The answer will be monitored and saved by a medical oncologist, and this person will consider whether the adverse events are related to the intervention.** Adverse events, such as cardiovascular responses (e.g., hypertension, ischemia), exertional symptoms and musculoskeletal symptoms63, could be expected, bearing in mind that we expect some adverse events given the fact that patients are undergoing chemotherapy64.

**Efficacy study**

*Main outcome:*

The Spanish version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20-item scale (EORTC QLQ-CIPN20) will be used to assess patient-reported CIPN across sensory, motor, and autonomic domains. The total questionnaire score ranges from 0 to 100, and a higher score indicates increased symptom burden65. The sensory and motor subscales have good reliability, obtaining Cronbach’s α values of .87 and .83, respectively66.

*Secondary outcomes:*

* Patient-reported health outcomes:

The European Organization for Research and Treatment of Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) will be provided to measure cancer-specific indices of quality of life based on 23 items. The scoring is the same as that noted for the previous questionnaire, and the assessment has a Cronbach’s α between .46 and .9467.

The clinical version of the Total Neuropathy Score (TNSc) will be used to monitor and assess CIPN severity and progression68. The assessment includes muscle weakness and numbness and tingling in the hands and feet as well as pinprick sensibility, vibration sensibility, tendon reflexes, and strength assessments. The total score ranges from 0 to 24 points; a higher score indicates greater neuropathy severity. Its intraclass correlation coefficient (ICC) ranges from .85 to .8769.

To evaluate the quality of sleep, we will use the Spanish version of the Pittsburgh Sleep Quality Index (PSQI)70, which consists of 19 self-reported items and 5 questions reported by a roommate of the patient. Items are grouped into seven subjective dimensions, and the total score ranges from 0 to 21. Higher scores indicate worse sleep quality. In the BC population, the Cronbach α is .8071.

Pain in the hands and feet will be measured using the VAS. Participants will be asked to mark the level of pain felt at that moment on a linear scale with a length of 10 cm. The VAS has been widely used in cancer patients72.

* Sensorimotor outcomes:

Touch detection thresholds will be measured using Semmes-Weinstein filaments (SWMs) (North Coast Medical Inc., Morgan Hill, CA, USA). The fibers (1.65 to 6.65 gauge) will be applied perpendicularly to a skin area following a previously published protocol73. For each point, the smallest monofilament perceived by patients shall be recorded and will be analyzed as frequency and percentages of patients. SWMs are a valid tool to identify subclinical peripheral neuropathy in oncology patients73.

The Purdue Pegboard Test (Lafayette Instrument Co., Lafayette, USA) will be used to evaluate fine manual dexterity and sensorimotor function74. The number of pins a patient can place in the holes using both hands in 30 seconds will be recorded as a function of manual dexterity according to the instructions in the user’s manual. This test is recommended to evaluate patients who suffer from CIPN75.

* Physical function outcomes**76**:

The 6-min walk test (6MWT) is a widely validated measure of general physical functioning and mobility. Patients are instructed to walk between two markers set 30 m apart as many times as possible over 6 minutes. A greater distance covered indicates greater mobility and general functioning77. The 6MWT has been validated in patients with cancer with an ICC of .9378.

We will use the handgrip strength test using a TKK5101 Grip-D dynamometer (Takeya, Tokyo, Japan) to assess the muscle strength of patients following a previously established protocol79. Patients will be asked to grip the device and squeeze it three times as hard as possible, and they will be allowed to take breaks between attempts. Three mean values will be determined in kilograms for both hands. This test has been previously used in BC patients80.

The Mini-Balance Evaluation Systems Test (Mini-BESTest) includes 14 items involving dynamic balance tasks. A maximum of 28 points is possible with higher scores signifying better balance81. This test has been validated in patients with cancer with an ICC of .8682.

* Body composition and anthropometric outcomes:

Muscle mass (kg), body fat (%) and body weight (kg) will be assessed using the InBody720 bioelectrical impedance device (Biospace, Seoul, Korea) following the indications of the user’s manual83. This technique has an ICC of .95 for muscle mass and .93 for body fat in women84.

* Chemotherapy completion:

We will also report the ratio of the number of chemotherapy program sessions and the number of completed sessions.

*Sample size*

For both the acute and cumulative studies, sample sizes were calculated based on patient-reported CIPN using the minimal clinically important difference of the sensory and motor subscales, respectively85. In both analyses, a confidence level of 95%, a statistical power of 85% and **one-sided alpha of 5%** were considered. **The literature on physical exercise and cancer supports the decision to perform a one-sided test for sample size calculation; it is a novel intervention, but physical exercise is also widely employed in the breast cancer population and it is known that participation in this program will be positive.** An effect size of .66 (d) has been reported to detect differences in the first cycle of taxane-based chemotherapy in patients with BC; hence, 34 participants will be needed per group. Considering a dropout rate of 5%, 72 patients will be included in the acute study. For the cumulative study, a .70 effect size (d) is expected in patients one year from the start of chemotherapy85; therefore, 31 participants will be needed per group. Due to a potential dropout rate of 30%59, at least 40 patients will be required for each group with 80 in total.

*Randomization and blinding*

Following successful completion of baseline assessments, patients will be randomized and allocated by a blinded researcher (Figure 3) using two concealed lists generated with random numbers with a 1:1 distribution. Assessments will be performed by a blinded assessor. However, the research staff responsible for delivering the intervention and allocating participants will not be blinded.

[Insert Figure 3]

*Data collection and management*

Patients will be evaluated at baseline 24 hours prior to the first chemotherapy session (t0) and in the next 24 hours after the first chemotherapy session (t1) in the acute study.

With regard to cumulative effects, patients will be assessed at five time periods: at baseline (after diagnosis) (t0), after anthracycline completion (t1), at the end of chemotherapy (t2), and at the 2-month (t3) and one-year (t4) follow-ups (Figure 4).

[Insert Figure 4]

*Ethics*

The study was approved by the Ethics Committee of the Junta de Andalucía (1674-N-20) according to the Helsinki Declaration for biomedical research. All participants will provide informed consent.

*Statistical analyses*

Preliminary descriptive analyses will be used for visualization of sociodemographic and clinical data from the two groups, and the results will be presented as means and standard deviations for continuous data and frequencies and percentages for categorical data. The normal distribution will be assessed using the Kolmogorov or Shapiro Wilk test. For baseline comparisons, Student’s t / Mann-Whitney U tests will be used for continuous variables; **and χ2 / Fisher’s exact tests will be used for categorical variables, as appropriate**. Regarding feasibility, the proportions, percentages, and Student’s t or Mann-Whitney U tests results will be reported, as appropriated. For the efficacy study, acute effects will be assessed by analyzing two assessments (t0 - t1) using a univariate general linear model. For cumulative effects, repeated measures analysis of covariance (ANCOVA) followed by post hoc analysis with Bonferroni adjustment will be used. For both effects, body composition, anthropometric characteristics and age will be considered covariables. Whether anthracyclines produce any effect on CIPN will be analyzed (t0 - t1). Then, the main effect of the intervention will be measured as (t1 - t2). If the main effect is maintained over time, it will be observed as (t1 - t3 and t1 - t4). Potential missing outcomes will be analyzed according to the intention-to-treat principle86, where multiple imputations will be performed87. Calculations of the intergroup effect sizes will be performed to provide magnitude changes; the effect size will be estimated using Cohen d (0-.19, negligible; .20–.49, small; .50–.79, moderate; ≥.8, large)88. All analyses will be performed using IBM© SPSS© Statistics. Significance will be set at p<.05.

**DISCUSSION**

**Many methods tested for the treatment of CIPN have not yet achieved the expected results**89. The prevention of CIPN would have an impact on quality of life and reduce healthcare costs associated with CIPN in patients with BC as a consequence of loss of labor force, outpatient visits and time spent in the hospital90. The most promising nonpharmacological intervention to prevent CIPN is therapeutic exercise12,21. However, there are many gaps in identifying the exercise parameters that provide the greatest benefit for the prevention of CIPN91. Furthermore, it must be ensured that these studies are safe and can be easily performed.

In fragile populations, TE with BFR is a useful and safe method to improve various aspects related to the physical health of the patient, such as cardiorespiratory function, hypertrophy, and weight loss92,93. Given the results demonstrated in other populations, we believe that **PRESIONA** could represent a preconditioning method for patients with BC in which multimodal TE might have beneficial effects beyond CIPN to cancer treatment.

Additionally, this study is one of the first to explore a battery of common clinical measures recommended in prevention trials for CIPN14. It is expected that this study will provide an improved understanding of the role that TE and BFR training can play in providing an efficacious, time-efficient modality of exercise for patients with BC. Our patients will be monitored using the ATOPE+ app to ensure healthy doses of exercise. The main reason to implement **PRESIONA** is to achieve greater therapy success and improve the quality of life during and after medical treatments given the active involvement of the patients in their own health. **PRESIONA** could be easily integrated into public healthcare; in fact, physical activities reduce healthcare costs worldwide94. Given rehabilitation efforts in cancer care, it is possible to develop a clinically integrated physical therapy model95.

*Limitations*

The **PRESIONA** study consists of a primary prevention design, which provides the highest likelihood of success if the therapy cannot reverse or delay the progression of the established damage, but participants will be exposed to unnecessary therapy14. Additionally, it is possible that the impact of diagnosis could cause denial before the trial’s enrollment.

The proposed innovative approach of this study will have a far-reaching impact on therapeutic options. Physical therapists in the health system could be essential to achieve the planned doses of chemotherapy to improve survival and decrease the side effects of BC96. This protocol could provide an action guide that could be implemented in various healthcare settings.

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**CONFLICTS OF INTEREST**

None declared.

**CONSENT**

Written and verbal consent will be obtained from all patients.

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**FIGURE LEGENDS**

Figure 1. Representation of treatment schedule and study inclusion for patients with HER2-positive breast cancer.

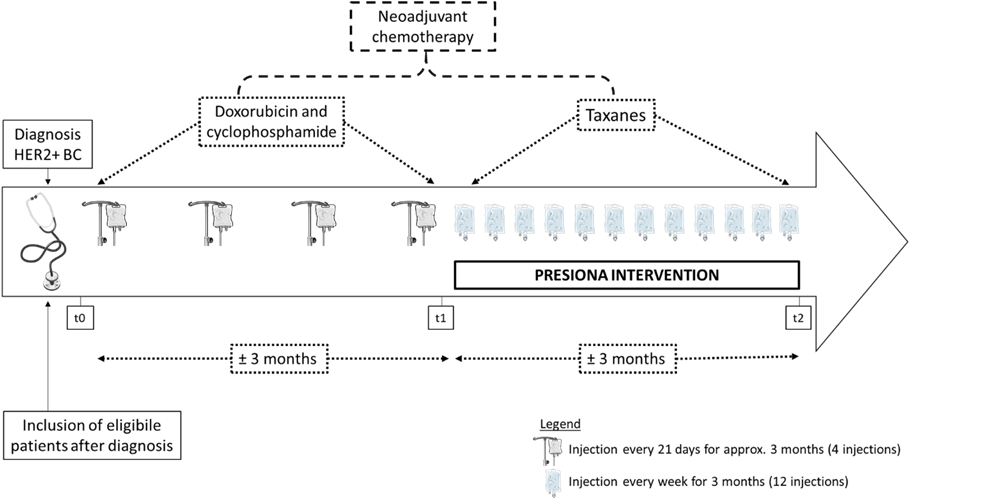
Figure 2. Schematic representation of one session of the PRESIONA program. Each session will have three parts (warm-up, main part and cold down). The main part is composed of 20 minutes of aerobic walking and a strength phase where load will be applied to the upper and lower limbs. The gray color represents when the occlusion cuffs will be applied. % AOP: calculated percentage of arterial occlusion pressure; HRR: heart rate reserve; RM: repetition maximum.

Figure 3. The proposed CONSORT diagram of enrollment, allocation, follow-up and analysis throughout the study for each arm.

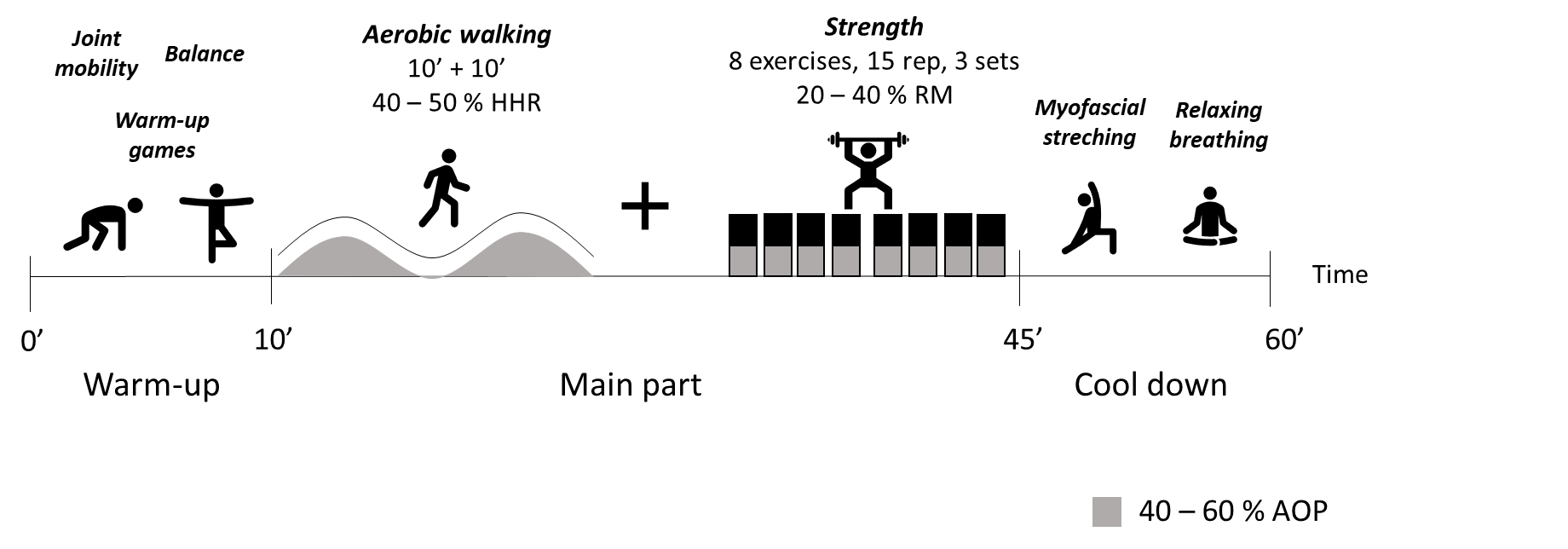
Figure 4. Details of enrollment, intervention and assessments according to the SPIRIT diagram.

**FIGURES**

**Figure 1**. Representation of treatment schedule and study inclusion for patients with HER2-positive breast cancer.



**Figure 2**. Schematic representation of one session of the PRESIONA program. Each session will have three parts (warm-up, main part and cold down). The main part is composed of 20 minutes of aerobic walking and a strength phase where load will be applied to the upper and lower limbs. The gray color represents when the occlusion cuffs will be applied. % AOP: calculated percentage of arterial occlusion pressure; HRR: heart rate reserve; RM: repetition maximum.



**Figure 3**. The proposed CONSORT diagram of enrollment, allocation, follow-up and analysis throughout the study for each arm.



**Figure 4**. Details of enrollment, intervention and assessments according to the SPIRIT diagram.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **STUDY PERIOD** | | | | | | |
| ***Post breast cancer diagnosis*** | | | ***During neoadjuvant chemotherapy*** | | ***End of chemotherapy (follow-up)*** | |
| ***Enrollment*** | ***Baseline*** | ***Allocation*** | ***Pre intervention*** | ***Post intervention*** | ***2-month follow-up*** | ***1-year follow-up*** |
| **TIMEPOINT** | ***-t1*** | ***t0*** | ***0*** | ***t1*** | ***t2*** | ***t3*** | ***t4*** |
| ***ENROLLMENT*** |  | | | | | | |
| Eligibility screening | **X** |  |  |  |  |  |  |
| Informed consent | **X** |  |  |  |  |  |  |
| Allocation |  |  | **X** |  |  |  |  |
| ***INTERVENTIONS*** | | | | | | | |
| PRESIONA |  |  |  |  |  |  |  |
| Control group |  |  |  |  |  |  |  |
| ***ASSESSMENTS*** | | | | | | | |
| *Feasibility* | | | | | | | |
| Recruitment-acceptance ratio | **X** |  |  |  |  |  |  |
| Rate dropouts |  |  |  |  |  | **X** |  |
| Retention |  |  |  |  |  | **X** |  |
| Adherence |  |  |  |  |  | **X** |  |
| Satisfaction |  |  |  |  |  | **X** |  |
| Tolerance |  |  |  |  |  | **X** |  |
| Safety |  |  |  |  |  | **X** |  |
| *Efficacy* | | | | | | | |
| CIPN symptoms |  | **X** |  | **X** | **X** | **X** | **X** |
| Quality of life |  | **X** |  | **X** | **X** | **X** | **X** |
| Severity of CIPN |  | **X** |  | **X** | **X** | **X** | **X** |
| Quality of sleep |  | **X** |  | **X** | **X** | **X** | **X** |
| Mood |  | **X** |  | **X** | **X** | **X** | **X** |
| Pain |  | **X** |  | **X** | **X** | **X** | **X** |
| Quantitative sensory testing |  | **X** |  | **X** | **X** | **X** | **X** |
| Manual dexterity |  | **X** |  | **X** | **X** | **X** | **X** |
| Handgrip strength |  | **X** |  | **X** | **X** | **X** | **X** |
| Physical functioning |  | **X** |  | **X** | **X** | **X** | **X** |
| Balance |  | **X** |  | **X** | **X** | **X** | **X** |
| Body composition |  | **X** |  | **X** | **X** | **X** | **X** |