The **V**irgin Puls**E** **G**lobal Ch**A**llenge **S**tudy (VEGAS):

A Single-Blind, Randomised Controlled Trial to Evaluate the Health Outcomes of the Virgin Pulse Global Challenge (VPGC) Programme

Protocol Number:

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Sponsor: Virgin Pulse

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Summary of Changes from Previous Version:

|  |  |  |
| --- | --- | --- |
| **Affected Section(s)** | **Summary of Revisions Made** | **Rationale** |
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# **Statement of Compliance**

The trial will be carried out in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and in compliance with the Australia National Statement on Ethical Conduct in Human Research issued by the Australia National Health and Medical Research Council (NHMRC). As this study is an intervention trial without involving any therapeutic goods, it is not subjected to requirements of the clinical trial notification (CTN) or clinical trial exemption (CTX) schemes.

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB, in this case it refers to the Swinburne University of Technology’s Human Research Ethics Committee (HREC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# **1. PROTOCOL SUMMARY**

## Synopsis

|  |  |
| --- | --- |
| **Title** | The **V**irgin Puls**E** **G**lobal Ch**A**llenge **S**tudy (VEGAS): A Single-Blind, Randomised Controlled Trial to Evaluate the Health Outcomes of the Virgin Pulse Global Challenge (VPGC) Programme  |
| **Study Description** | This study aims to conduct a single-blind randomised controlled trial to evaluate health outcomes of the Virgin Pulse Global Challenge (VPGC) programme across several Australian organisations. A comparison of the VPGC programme with a control treatment in terms of physical activity, sleep, psychological well-being, cognition and overall health outcomes will be assessed. It is hypothesised that the VPGC will improve both physical and mental health of participants. The project will contribute to filling a gap in the literature (rigorous evaluation of the health benefits of programmes similar to the VPGC and the development of a heart age measure that quickly responds to behavioural change) while providing Virgin Pulse with tools, insights, models and recommendations for improving the Global Challenge programme. |
| **Objectives** | 1. To determine the health benefits of the VPGC programme among participants (employees from various organisations).
2. To evaluate the effects of physical activity, sleep, mental health and cognition on estimates of heart age.
3. To determine the sustainability of health benefits post-VPGC programme among participants.

  |
| **Endpoints** | Assessment will be done at baseline, at within 20 days after programme completion, and 3 months post programme completion. 1. Emotional symptoms assessment using the *Depression Anxiety Stress Scale (DASS-21)*
2. Quality of Life assessment using the *Personal Wellbeing Index – Adult version (PWI-A)*
3. Sleep quality assessment using the *Pittsburgh Sleep Quality Index (PSQI)*
4. Daytime sleepiness assessment using the *Epworth Sleepiness Scale (ESS)*
5. Cognitive assessment using computerised *CogState* battery
6. Blood pressure assessment
7. Anthropometric assessment including BMI, waist & hip circumference, body muscle to fat mass ratio
8. Self-reported serum lipid and glucose level assessment
9. Lifestyle and behaviour changes including smoking, alcohol consumption, and physical activity
 |
| **Study Population** | 420 male and female employees aged 18 and over from 30 organisations based in Victoria (Australia) participating in the VPGC programme. Each organisation will recruit and enrol 14 employees who have consented to participate in both the VPGC programme and study. 210 participants will be randomised into the VPGC intervention group and 210 participants will be randomised into the control group (waitlisted for the next VPGC programme intake).Eligible subjects must be aged 18 years and over at the time of enrolment and have not previously participated in the VPGC programme. The following subjects are excluded from the study:* Persons who are pregnant or planning to become pregnant for the duration of the 100-Day VPGC programme
* body weight of 150kg or greater
* unable to follow the VPGC programme due to physical limitation or language barrier
 |
| **Phase** | Not Applicable |
| **Description of sites** | 30 organisations based in Victoria (Australia) who have signed up onto the VPGC programme and agreed to participate in the VPGC study. |
| **Intervention** | Intervention and control participants will both enrol in teams of seven, and all participants will receive the same activity tracker. However, whereas participants in the Global Challenge condition will receive the full Global Challenge programme, participants in the control condition will be wait-listed. The control participants will have no form of intervention except a facility to sync/enter daily step counts. Participants in the VPGC programme will be encouraged to commit to at least one of the following modules i.e. Balance, Sleep, and Nutrition.The VPGC programme is a 100-day wellbeing solution that equips employees with the knowledge, tools and support required to improve lifestyle behaviour.  |
| **Study Duration** | February 2019 – December 2021 |
| **Participant Duration** | First Batch May 2019 – January 2020Second Batch September 2019 – May 2020 |

## Schema

|  |  |
| --- | --- |
| 6 weeks prior to VPGC | N = 420. Subject eligibility screening. Obtain informed consent. Request subjects to obtain blood panel results from their General Practitioner. |
|  |  |
|  | Randomisation. Minimum 14 participants per organisation. |
|  |
| VPGC Intervention ArmN=210 (30 teams) |  | Control ArmN=210 (30 teams) |
|  |  |  |  |
| Visit 12-3 Weeks Prior to VPGC commencementApril 2019 / August 2019(Baseline Assessment) | * Complete CRF

⭘ Subject Demographics⭘ Social Activity⭘ Medical History⭘ Cognitive Assessment (CogState)⭘ Emotional Assessment (DASS-21)⭘ Quality of Life Assessment (PWI-A)⭘ Sleep Assessment (PSQI & ESS)* Blood Pressure Measurement
* Height, Weight, Hip & Waist Circumference, Body Fat Measurement
 |
|  |  |
| May 2019 / September 2019 | 100-Day VPGC. After the programme ended, subjects in control arms will join the next VPGC programme in September 2019 and May 2020, respectively |
|  |  |
| Visit 2Within 2 weeks Immediately after VPGC completionSeptember 2019/ January 2020 | * Complete CRF

⭘ Social Activity⭘ Medical History⭘ Cognitive Assessment (CogState)⭘ Emotional Assessment (DASS-21)⭘ Quality of Life Assessment (PWI-A)⭘ Sleep Assessment (PSQI & ESS)⭘ Programme Participation Satisfaction Survey* Blood Pressure Measurement
* Height, Weight, Hip & Waist Circumference, Body Fat Measurement
 |
|  |  |
| Visit 3  3 Months Post VPGC completionJanuary 2020 / April 2020 | * Complete CRF

⭘ Social Activity⭘ Medical History⭘ Cognitive Assessment (CogState)⭘ Emotional Assessment (DASS-21)⭘ Quality of Life Assessment (PWI-A)⭘ Sleep Assessment (PSQI & ESS)* Blood Pressure Measurement
* Height, Weight, Hip & Waist Circumference, Body Fat Measurement
 |

## Schedule of Activities (SoA)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Procedures** | Screening & Enrolment Day -35 to -28  | Team Allocation & Randomisation Day -28 to -21 | **Visit 1** (Baseline Assessment) Day -21 to 0  | VPGC May 2019 Day 0 to Day 100 | Screening & Enrolment Day 68 to 75 | Team Allocation & Randomisation Day 68 to 75 | **Visit 1** (Baseline Assessment) Day 75 to 95 | **Visit 2** (Post VPGC Assessment)Day 101 to 119 | VPGC September 2019 Day 120 to Day 220 | **Visit 3** (3 months post VPGC)Day 190 to Day 200^ | **Visit 2** (Post VPGC Assessment)Day 221 to 234#  | **Visit 3** (2 months post VPGC)Day 260 to Day 290# |
| **Special Note** | N=210Apr 19 | N=210Apr 19 | N=210May 19 | N=210Aug 19 | N=210Aug 19 | N=210Aug 19 | N=210Sep 19 | N=105Nov 19 | N=315Jan 20 | N=315Feb 20 |
| Screening | X |  |  | X |  |  |  |  |  |  |
| Informed Consent | X |  |  | X |  |  |  |  |  |  |
| Randomisation |  | X |  |  | X |  |  |  |  |  |
| Demographics |  |  | X |  |  | X |  |  |  |  |
| Social Activity |  |  | X |  |  | X | X | X | X | X |
| Medical History |  |  | X |  |  | X | X | X | X | X |
| Cognitive Assessment |  |  | X |  |  | X | X | X | X | X |
| Emotional Assessment |  |  | X |  |  | X | X | X | X | X |
| QoL Assessment |  |  | X |  |  | X | X | X | X | X |
| Sleep Assessment |  |  | X |  |  | X | X | X | X | X |
| Programme Participation Satisfaction Survey |  |  |  |  |  |  | X | X | X | X |
| Pathology report |  |  | X |  |  | X | X | X | X | X |
| Blood Pressure |  |  | X |  |  | X | X | X | X | X |
| Height |  |  | X |  |  | X | X | X | X | X |
| Weight |  |  | X |  |  | X | X | X | X | X |
| Waist & Hip circumference |  |  | X |  |  | X | X | X | X | X |
| Body Fat Mass  |  |  | X |  |  | X | X | X | X | X |
| AE Review & Evaluation |  |  | X |  |  | X | X | X | X | X |
| Complete CRFs |  |  | X |  |  | X | X | X | X | X |

# These visits will include all the participants in the September 2019 batch and control arm from the May 2019 batch.

^ Intervention arm only as the control arm subjects have already joined the next VPGC programme

***Note****: Control arm from the September 2019 batch will be waitlisted for the VPGC programme in May 2020. However, their data from May 2020 onwards will not be used in the study analysis due to time constraint.*

|  |  |
| --- | --- |
|  | May 2019 Batch, N=210 |
|  | September 2019 Batch, N=210 |

# 2. INTRODUCTION

## Study Rationale

The World Health Organisation (WHO) has identified cardiovascular disease (CVD) and type 2 diabetes mellitus as the most severe non-communicable diseases (NCD) resulting in rising problems in today’s Western world [1]. Most NCDs primarily result from unhealthy lifestyles such as consumption of too much or unhealthy food [1-4], excessive alcohol consumption [2-3,5], and smoking [2-3,6], combined with physical inactivity [2-3,7-8]. Specifically, physical inactivity and unhealthy eating habits are associated with weight gain, whilst being overweight or obese are the major underlying causes for modern diseases such as CVD and type 2 diabetes mellitus [9-11].

## Background

Although physical activity appears to have a positive long-term influence on non-communicable diseases, there is still a lack of longitudinal studies to support this argument [12]. In addition, the mechanisms by which physical activity prevents disease and improves health outcomes are poorly understood [13].

Programs that promote better sleep and mental health are also a priority. Previous studies have shown that insomnia is associated with significant morbidity in terms of health problems and health-care utilization, work absenteeism and reduced productivity, and risk of non-motor-vehicle accidents [14]. A recent survey suggests approximately 33% to 45% of Australian adults experience inadequate sleep on a daily basis or several times a week [15]. The effects of lack of sleep include lapses in attention and inability to stay focused; reduced motivation; compromised problem solving; confusion, irritability, and memory lapses; impaired communication; slowed or faulty information processing and judgement; diminished reaction times; and indifference and loss of empathy [16]. In addition, an insufficient amount of sleep has an adverse effect on physical health with an increased risk of heart attack, stroke, hypertension, obesity, diabetes, depression, and mortality [17-23]. Apart from the above, inadequate sleep has an economic cost relating to its effect on health, safety and productivity [24].

Emerging wearable sensors and devices offer much promise for improving health and fitness practices [25]. Recent advancement in technology provides an opportunity to gain insight into the naturalistic use and effects of these devices on health outcomes [25].

The Virgin Pulse Global Challenge (VPGC) is a workplace health and exercise program involving a 100-day virtual journey. An activity tracker monitors daily step counts and participants are encouraged to work towards a daily target of 10,000 steps, with their cumulative step entries unlocking new locations (virtual distance and location covered by total calculated steps) along the way. The program also has sleep, nutrition and mental health modules. This study involves a single-blind, randomised control trial to assess the health benefits of the VPGC programme, relative to a control condition, among Australian organisations.

## Risk/Benefit Assessment

### Known Potential Risks

As there is no investigational product or invasive procedures involved in this trial, there is no foreseeable physical, psychological, social, legal, and economic or any other risks to the participants by participating in the study. However, it maybe possible for participants to have increased risk of musculoskeletal injuries with increased physical activity.

### Known Potential Benefits

There are many known potential direct and indirect benefits associated with a workplace health and physical activity (WHPA) programme, such that it is in the VPGC programme. This can be categorised into 4 groups:

1. Individual Health Benefits
* Increased in physical activity
* Improved nutrition
* Reduced smoking rates, alcohol consumption and substance abuse
* Improved physical and mental health
* Reduced risks of NCD
1. Economic Benefits to Organisations
* Improved job performance and productivity
* Reduced absenteeism
* Reduced workplace costs
* Reduced workers’ compensation and disability rates
* Enhanced corporate image
1. Environmental Benefits to Organisations
* Enhanced working conditions and safety
* Decreased accidents and injuries
* Improved working atmosphere
* Reduced job stress
1. Social Benefits to Organisations
* Increased social support
* Increased job satisfaction
* Improved motivation, commitment, morale and loyalty
* Improved communication and teamwork
* Improved recruitment with less staff turnover
* Retention of quality staff

### Assessment of Potential Risks and Benefits

It is possible that during each study visit, a subject may be found to have abnormally high blood pressure, which may or may not be treated by a medical physician. In the event that high blood pressure is detected during the health assessment (e.g. High systolic blood pressure of >140mmHg or diastolic blood pressure of >90mmHg), the subject will be referred to his/her family physician for medical attention. Study subjects may also be referred to mental helpline support e.g. Lifeline if he or she is found to be in severe emotional distress.

# 3. OBJECTIVES AND ENDPOINTS

The study objectives are as follows:

1. To determine the health benefits (composite outcomes of physical, emotional, and quality of life) of the VPGC programme among participants (employees from various organisations).
2. To evaluate the effects of physical activity, sleep, mental health and cognition on estimate of heart age.
3. To determine the programme compliance by analysing the daily step-count data provided by Virgin Pulse.
4. To determine the sustainability of health benefits post-VPGC programme among participants.

In order to achieve the study objectives above, the following endpoints will be captured at baseline (pre-VPGC programme), within 2 weeks and 3 months after the 100-day VPGC programme is completed:

1. Emotional symptoms assessment using the *Depression Anxiety Stress Scale (DASS-21)*
2. Quality of Life assessment using the *Personal Wellbeing Index – Adult version (PWI-A)*
3. Sleep quality assessment using the *Pittsburgh Sleep Quality Index (PSQI)*
4. Daytime sleepiness assessment using the *Epworth Sleepiness Scale (ESS)*
5. Cognitive assessment using computerised *CogState* (Identification test, set-shifting and back tests)
6. Blood pressure assessment especially for hypertensive subjects at baseline
7. Anthropometric assessment including BMI, waist & hip circumference, body muscle to fat mass ratio
8. Self-reported serum lipid and glucose level assessment
9. Lifestyle and behaviour changes including smoking, alcohol consumption, and physical activity

# 4. STUDY DESIGN

## Overall Design

The study aims to assess the health benefit of a workplace health and physical activity (WHPA) programme designed by Virgin Pulse. It is hypothesised that such a programme will improve overall physical and mental health of employees participating in the VPGC. In order to determine the health benefits of the VPGC, a single-blind, multi-site, randomised control trial will be conducted.

A total of 30 organisations based in Victoria, Australia will be recruited by Virgin Pulse. Ideally, only people working in the office should be included as it will be difficult to assess employees who are constantly working in the field. It is the responsibility of Virgin Pulse to ensure that at least 14 participants from each organisation have consented to participate in the VPGC study. The 14 participants will be allowed to choose one of the two study teams, where the team members will work together throughout the 100-day VPGC programme. A simple randomisation (tossing a coin) will be performed within each organisation to determine which team will be allocated to intervention or control arm. The intervention team will be told not to discuss the VPGC programme with the control group for the duration of the study to minimise contamination. The control group will be waitlisted to participate in the next intake of the VPGC programme. Stratified analysis based on work industries may be performed.

## Scientific Rationale for Study Design

A clinical trial design is used to determine the efficacy of the VPGC programme in providing greater health benefits relative to a control arm (with no intervention). Only the investigators will be blinded throughout the trial to minimise bias as it is not possible to blind the participants from allocation to either the intervention or control groups. Randomisation is used to minimise selection bias. Stratification analysis based on work industries may be performed to minimise bias associated with different work requirements and workload (For example, employees from a healthcare organisation will have different work culture and workload from employees working in an accountancy firm).

The control group from the May 2019 intake will be waitlisted to join the September 2019 intake so that they do not miss out on any potential health benefit associated with the programme. In addition, they will also contribute to the overall intervention data at the end of the study.

## End of Study Definition

A participant is considered to have completed the study if he or she has completed all study visits including the last scheduled procedure shown in the Schedule of Activities (SoA), section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial throughout all 30 organisations.

# 5. STUDY POPULATION

## Inclusion criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 and over
4. In good general health as evidenced by self-reported medical history
5. Physically able to participate in the VPGC programme e.g. able to perform step-count
6. Employees of Australian organisations participate in VPGC programme
7. Agreement to adhere to Lifestyle Consideration (see section 5.3) throughout study duration.

## Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

* Participants who have previously enrolled in the VPGC programme.
* Pregnant women or women who plan to conceive during the VPGC programme.
* Participants whose weigh 150kg or more at baseline screening.
* Participants who are unable to follow the VPGC programme due to physical limitations.
* Participants who are unable to follow the VPGC programme due to language barriers.
* Participants who are unable to commit to the study procedures and visits throughout the study duration.

## Lifestyle Considerations

During this study, participants are asked to:

* Not discuss the VPGC programme with the team assigned to the control arm for the duration of the study and vice versa.
* Fast before any blood tests, collected by the participants’ respective physicians or pathologists.
* Abstain from caffeine, alcohol or strenuous exercise 4-6 hours before each study visit assessments.

## Screen failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of possible false positive pregnancy test may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

## Strategies for Recruitment and Retention

The target sample size for this study is 420 subjects of any gender, race, ethnicity and aged 18 years or over. Recruitment of companies participating the VPGC programme will be conducted by Virgin Pulse. The ideal companies to be recruited into the VPGC study are:

1. Based in Victoria, Australia
2. Will be able to enrol at least 14 office-based employees

It is anticipated that 15 organisations (210 participants) will be recruited for the May 2019 programme intake and the remaining 15 organisations and 210 participants will be recruited for the September 2019 programme. Organisations recruitment strategies will be handled by Virgin Pulse. A liaison from Virgin Pulse will be nominated to act as the study coordinator between Swinburne University and the participating organisations.

Each participating company will be required to nominate a site coordinator (ideally a HR personnel), who will disseminate all research related materials, including study information and consent forms to its employees who enrolled onto the VPGC programme. The site coordinator will also liaise with Virgin Pulse study coordinator on all study requirements and visit schedules.

As the study is trying to assess the VPGC programme compliance and its benefits, there will be minimal interference from the research team to encourage participation in the VPGC programme. However, an incentive (lucky draw gift/s, exact gift will be sponsored by Virgin Pulse) will be offered to participants who completed all visits’ case report forms and questionnaires.

# 6. STUDY INTERVENTION

## Study Intervention(s) Administration

### Study Intervention Description

The Virgin Pulse Global Challenge (VPGC) is a 100-day workplace wellbeing solution that equips organisations’ employees with the knowledge, tools and support they need to build healthy habits that can sustain for a lifetime. The programme addresses key elements of employee wellbeing including physical activity, nutrition, sleep and mental wellbeing.

The VPGC is designed for all employees, regardless of geography, age, job profile or level or health. It is easily accessible using the VPGC desktop platform or mobile application. The VPGC helps employees understand their current heath levels and measure improvements along the way. Real-time reports are also available allowing employers to monitor overall health improvements across their workforces. The VPGC programme incorporates professional advice and tools to improve participants’ physical health, mental wellbeing, nutrition and sleep.

An interactive dashboard is available to help participants manage the programme in each organisation workplace. It is available 24/7, 365 days a year and comprised of five modules that highlight key areas for leading a healthy and active lifestyle. For more information on Virgin Pulse Global Challenge, please visit <https://www.virginpulse.com/global-challenge/>

### Administration of Intervention

All participants (intervention arm) who signed up to the VPGC will be working in teams of seven, which creates healthy competition, provides a support network and ensure accountability, which is a critical factor in the behaviour change process. All participants (both intervention and control arm) will be given an activity tracker at the beginning of the programme, which the participants may or may not choose to use. Participants are also allow to use their own personal activity tracker if they wish to. VPGC has developed an application that allows syncing daily activity via a wide range of wearable technology.

The VPGC will transforms employee health and wellbeing one step at a time, building confidence and demonstrating how enjoyable and easy lifestyle changes can be. There are also mini challenges that provide employees with that extra bit of motivation throughout their journey, and some extra fun to keep them going. Other programme highlights include flexible challenges to reinforce healthy behaviours, year-round content, communication, and gamification to continuously engage the participants.

The control arm will not have access to the VPGC support modules or any programme supports other than an activity tracker and the ability to sync their daily activity onto the VPGC desktop platform or mobile application.

All participants will be provided with in-depth analyses and reports of their health, performance and teamwork at the end of the programme.

## Preparation/Handling/Storage/Accountability

### Acquisition and accountability

Each study participants will be provided with a daily activity tracker by Virgin Pulse and access to programme toolkits that aim to improve participants’ physical health, mental wellbeing, nutrition and sleep. The participants can sync their daily activities data and access the toolkits from a desktop platform or by downloading an application to their mobile devices. The study participants will be allowed to keep the daily activity tracker at the end of the study.

### Appearance, Packaging, and Labelling

Virgin Pulse will provide a step tracker (shown below) to each participant. This wireless device is in compliance with the essential requirements and other relevant provisions of the R&TTE Directives 1999/5/EC.



## Measures to Minimise Bias: Randomisation and Blinding

In order to minimise selection bias, study subject randomisation will be conducted by the site coordinator once the organisation has recruited a minimum of 14 participants who consented to the study. The 14 participants will be randomised to either intervention or control group. Randomisation will be conducted according to central randomisation schedule generated from Stata version 14 where each team will have a 50% chance of being allocated to either the intervention arm or control arm (waitlisted for the next VPGC programme).

As it is not possible to blind the participants due to the nature of the intervention, assignment of subjects to either intervention or control arm will only be made known to the site participants, site coordinator and Virgin Pulse study coordinator. Information on randomisation outcome will be kept by the site coordinator. The study investigators and the PhD student who conducts the physical assessment will be blinded from the identification of participants’ study arm. The breaking of randomisation codes will only occur after all study procedures have been completed and data analysed. The blind will not be broken under any circumstances as the study investigators do not anticipate any serious adverse events.

## Study Intervention Compliance

One study outcome is to assess participants’ compliance to the use of an activity tracker. Thus, there will be no special procedure to maintain compliance of programme activities. However, in order to ensure all participants complete their health assessment, case report forms and questionnaires, a lucky draw gift will be given to participants who have completed all 3 visits assessments.

## Concomitant Therapy

Not applicable

#

# 7. STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## Discontinuation of Study Intervention

The investigators anticipate a small chance of discontinuation of study intervention for the duration of the study. However, in the unlikely event that the VPGC programme has been discontinued, discontinuation from the programme does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a significant finding is identified (including, but not limited to changes from baseline) after enrolment, the investigator will determine if any change in participant management is needed. The data to be collected at the of study intervention discontinuation will include the following:

⭘ Social Activity

⭘ Medical History

⭘ Cognitive Assessment (CogState)

⭘ Emotional Assessment (DASS-21)

⭘ Quality of Life Assessment (PWI-A)

⭘ Sleep Assessment (PSQI & ESS)

⭘ Programme Participation Satisfaction Survey

⭘ Blood Pressure Measurement

⭘ Anthropometric Measurement (Height, Weight, Hip & Waist Circumference, Body Fat)

## Participants Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

* Participant becomes pregnant
* Participant resign from the company or take extended leave (more than 30 days)
* If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
* Progression of pre-existing diseases, which requires discontinuation of the study intervention
* If the participant meets an exclusion criteria (either newly developed or not previously recognised) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Subject Withdrawal & Loss to Follow-up case report form. Subjects who sign the informed consent form and are randomised but do not received the study intervention may be replaced. Subjects who sign the informed consent form, and are randomised and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

## Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for the 2nd or 3rd post-VPGC programme visits and is unable to be contacted by the site coordinator. The following actions must be taken if a participant fails to return for required study visit:

* The site will attempt to contact the participant and reschedule the missed visit (within 14 days) and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
* Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant via the Virgin Pulse study coordinator and site coordinator (where possible, three telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s study file.
* Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up, which will be captured in the Subject Withdrawal & Loss to Follow-up case report form.

# 8. STUDY ASSESSMENTS AND PROCEDURES

## Efficacy Assessments

Efficacy of the VPGC programme is determined based on the composite health benefits achieved at the end of the programme and 2 months post programme completion to assess healthy behaviour sustainability. Efficacy is defined as the composite outcomes comprised of the following assessments:

* Emotional symptoms assessment using the *Depression Anxiety Stress Scale (DASS-21)*
* Quality of Life assessment using the *Personal Wellbeing Index – Adult version (PWI-A)*
* Sleep quality assessment using the *Pittsburgh Sleep Quality Index (PSQI)*
* Daytime sleepiness assessment using the *Epworth Sleepiness Scale (ESS)*
* Cognitive assessment using computerised *CogState* Attention and Response Inhibition tests

The Depression, Anxiety and Stress Scale - 21 Items (DASS-21) is a set of three self-report scales designed to measure the emotional states of depression, anxiety and stress [26]. Each of the three DASS-21 scales contains 7 items, divided into subscales with similar content. The depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The stress scale is sensitive to levels of chronic nonspecific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset / agitated, irritable / over-reactive and impatient. Scores for depression, anxiety and stress are calculated by summing the scores for the relevant items.

The DASS-21 is based on a dimensional rather than a categorical conception of psychological disorder. The assumption on which the DASS-21 development was based (and which was confirmed by the research data) is that the differences between the depression, anxiety and the stress experienced by normal subjects and clinical populations are essentially differences of degree. The DASS-21 therefore has no direct implications for the allocation of patients to discrete diagnostic categories postulated in classificatory systems such as the DSM and ICD.

Recommended cut-off scores for conventional severity labels (normal, moderate, severe) are as follows:

**NB** Scores on the DASS-21 will need to be multiplied by 2 to calculate the final score.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Depression** | **Anxiety** | **Stress** |
| Normal | 0-9 | 0-7 | 0-14 |
| Mild | 10-13 | 8-9 | 15-18 |
| Moderate | 14-20 | 10-14 | 19-25 |
| Severe | 21-27 | 15-19 | 26-33 |
| Extremely Severe | 28+ | 20+ | 34+ |

The PWI scale contains seven items of satisfaction, each one corresponding to a quality of life domain as: standard of living, health, achieving in life, relationships, safety, community-connectedness, and future security [27]. These seven domains are theoretically embedded, as representing the first level deconstruction of the global question: ‘How satisfied are you with your life as a whole?’ The PWI-A scale is to be administered with an adult who is at least 18 years of age and should be self-completed by the respondents themselves. The test administrator should allow each respondent to respond in an entirely private manner and assure respondents that their individual data will remain confidential and anonymous.

As the test items are designed to tap life domains which represent the first level deconstruction of life-as-a-whole, the test questions are broadly worded and intended to allow respondents to form their personal interpretation and judgment about them. If the respondent should seek conceptual clarification of these questions (e.g. ask for concrete explanations or examples) from the test administrator, it is important that the test administrator DOES NOT provide them. Rather, reply by re-directing the responsibility of interpreting these questions to the respondent. An example of such responses the test administrator may use is: “Just think of the question you have been asked in the way it makes sense to you. There is no right or wrong answer.” If the person remains unable to provide a response, skip to the next item or terminate. The test administrator should confirm that the required response mode (see below) is understood before proceeding with the index items.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No Satisfaction at all** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **Completely Satisfied** |
| **0** |  | **1** |  | **2** |  | **3** |  | **4** |  | **5** |  | **6** |  | **7** |  | **8** |  | **9** |  | **10** |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Sleep assessments will be conducted using two tools, one to assess sleep quality (PSQI) and the other to assess daytime sleepiness (ESS). In scoring the PSQI [28], seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality. The ESS questionnaire asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, though not necessarily every day [29]. The scores for the eight questions are added together to obtain a single number. A number in the 0–9 range is considered to be normal while a number in the 10–24 range indicates that expert medical advice should be sought.

A selective computerised cognitive assessment using CogState will be performed by the participants. It is designed and validated for clinical trials. Each of the CogState tests (see below) is designed to measure a specific area of cognition:

* Identification Test (Attention and reaction time test)
* Set-Shifting Test (Executive function)
* Two Back Test (Working memory)

For detail description and demonstration of the tests, please visit <https://www.cogstate.com/clinical-trials/computerized-cognitive-assessment/>.

Secondary outcomes include blood pressure assessment especially for pre-hypertensive and hypertensive subjects at baseline, and anthropometric assessment including BMI, waist & hip circumference, body mass composition, self-reported serum lipid and glucose level, as well as lifestyle and behaviour changes including smoking, alcohol consumption and physical activity. Compliance to the VPGC programme will also be assessed using the daily activity tracker data. The sequence of study procedures are outlined in the schedule of activities (SoA), please see section 1.3 of the protocol.

Blood pressure and anthropometric assessments will be performed by the medically trained PhD student. Blood pressure measurement will be done using the OMRON HEM-907 model. Please refer to <https://omronhealthcare.com.au/pdf/HEM-907_Instruction_manual.pdf> for further information. Blood pressure will be measured twice between 3-5 minutes interval. An average value of two readings will be calculated to ascertain the final systolic and diastolic blood pressure results in mmHg.

Body mass index (BMI) will be calculated from weight (kg) and height (m) measurement using the formula kg/m2. Participants’ weight will be measured using TANITA BC545 Bioelectrical Impedance Scale and height will be measured using CHARDER HM200P portable stadiometer.

Waist circumference will be measured using SECA measuring tape at midpoint between the lowest palpable rib and the top of the iliac crest (hipbone), which is roughly in line with the belly button. Hip circumference will also be measured using SECA measuring tape at a level parallel to the floor, at the largest circumference of the buttocks. The measurement will be taken while the participant is standing up and at the end of a normal expiration when the participant is in a relaxed posture after a few deep, natural breaths. Participants will be asked to wear loose clothing during these procedures.

Body mass composition will be measured using the TANITA BC545 Bioelectrical Impedance Scale. Instruction manual can be found here <https://tanita.eu/media/wysiwyg/manuals/home-use-body-composition-monitors/bc-545n-instruction-manual.pdf>. The following data will be captured on the case report form:

* Body weight (kg)
* Body fat (%)
* Muscle mass (kg)
* Total body water (%)
* Visceral fat level

Based on the results, fat mass (kg), lean body mass (kg) and muscle to fat mass ratio will be calculated.

Participants’ serum lipid and glucose level will not be performed by the researcher due to the lack of funding. Thus, participants are encouraged to obtain their serum lipid and glucose results from their respective general practitioner prior to each study visit. This procedure is entirely voluntary.

All questionnaires, physical assessment, blood tests and lifestyle behaviour i.e. smoking, alcohol consumption, physical activity change will be captured in the case report form at baseline prior to programme initiation, within 2 weeks post-VPGC programme completion and 2 months post-VPGC programme completion.

Screening procedures will be conducted by the site coordinator prior to randomisation and re-evaluated by the PhD student prior to baseline assessment. Participants will be encouraged to complete the questionnaires online prior to or during each visit assessment. At the end of the study, participants will be provided with detailed results of their assessment throughout the study.

## Safety and Other Assessments

There will be no specific safety assessment performed during the study. Participants’ safety will be monitored as part of the VPGC programme by Virgin Pulse and any adverse events will be reported to the study investigators by Virgin Pulse or ascertain during study visits using the adverse event reporting CRF.

## Adverse Events and Serious Adverse Events

### Definition of Adverse Events (AE) and Serious Adverse Events (SAE)

Adverse event is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. An adverse event (AE) or suspected adverse reaction is considered “serious” if, in the view of either investigator or sponsor, it results in any of the following outcomes:

* death,
* a life-threatening adverse event,
* inpatient hospitalisation or prolongation of existing hospitalisation,
* a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
* congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm or angina requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation.

### Classification of an Adverse Event

The following guidelines will be used to describe AE severity:

* **Mild** - Events require minimal or no treatment and do not interfere with the participant’s daily activity
* **Moderate** - Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with daily functioning
* **Severe** - Events interrupt a participant’s usual daily activity and may require systemic drug treatment or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

All AEs must have their relationship to study intervention assessed by a qualified clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgement. The degree of certainty about causality will be graded using the categories below.

|  |  |
| --- | --- |
| **Not Related** | There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate aetiology has been established. |
| **Definitely Related** | There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention should be clinically plausible. |
| **Probably Related** | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal. |
| **Potentially Related** | There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate. |
| **Unlikely to be Related** | A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments). |

A clinician will be responsible for determining whether an adverse event (AE) is **expected** or **unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously reported.

### Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the Adverse event reporting case report form. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilisation of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterised as intermittent require documentation of onset and duration of each episode.

The PhD student will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilisation.

### Adverse Event & Serious Adverse Event Reporting

The investigator must record non-serious adverse events and report them to the sponsor and Swinburne Ethics Committee within 30 days after being made aware of the non-serious adverse event.

In the case of serious adverse event, the study investigator shall complete a Serious Adverse Event Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse effect and shall report the results of such evaluation to the appropriate authority and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as requested by the appropriate authority.

### Reporting Events to Participants

Not applicable

### Events of Special Interest

In the event of device malfunction or technical issues with accessing the VPGC webpage or application, the participants will be directed to Virgin Pulse for support.

### Reporting of Pregnancy

Not applicable

## Unanticipated Problems

### Definition of Unanticipated Problems (UP)

The reporting of UPs applies to non-exempt human subject research. Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets ALL of the following criteria:

* Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
* Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
* Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

### Unanticipated Problem Reporting

The principal investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the sponsor. The UP report will include the following information:

* Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
* A detailed description of the event, incident, experience, or outcome;
* An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
* A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

 To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

* UPs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the event.
* Any other UP will be reported to the IRB and to the study sponsor within 30 days of the investigator becoming aware of the problem.

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# 9. STATISTICAL CONSIDERATIONS

## Statistical Hypotheses

**Study Hypotheses**:

* In comparison to the control group, the VPGC program improves the well-being of participants
* In comparison to the control group, the VPGC program improves the emotional symptoms of participants
* In comparison to the control group, the VPGC program improves the overall sleep dysfunction of participants
* In comparison to the control group, the VPGC program improves the participants’ quality of sleep
* In comparison to the control group, the VPGC program improves the cognitive abilities of participants
* The overall effects of physical activity, sleep, mental health and cognition contribute to the estimates of heart age

**Primary Efficacy Endpoints**

The primary endpoint is the change in quality of life (PWI-A measure) from baseline to after participation in the VPGC program (within 20 days after programme completion), as well as from baseline to 3 months post-programme completion.

**Secondary Efficacy Endpoints**

The secondary endpoints are:

* changes from baseline to within 20 days after programme completion for:
* DASS-21 score (emotional symptoms)
* Global score in PSQI (measure of overall sleep dysfunction)
* ESS sore (daytime sleepiness)
* Cognitive abilities including memory, attention and executive function (Cogstate battery)
* Self-reported serum lipid and glucose level
* Blood pressure
* BMI, waist circumference, hip circumference, fat mass
* Social behaviour and activities I.e. smoking, alcohol consumption and physical activity
* sustainability of programme benefits by comparing all endpoints at 3 months post-programme completion against baseline and 20 days post-programme completion.

## Sample Size Determination

Sample size calculation is based on the primary endpoint defined as the change in quality of life score from baseline to 4th month. Previous study revealed on average, well-being improved immediately after the health program (+3.5 units of WHO-5) [30]. Assuming an average change in well-being of 3 units and standard deviation of 10 units from 4th month from baseline between intervention and control groups. With 80% power, 5% level of significance and 20% attrition, a total of 420 participants are needed for this study (210 participants in the control group and 210 participants in the intervention group).

## Populations for Analyses

**Intention-to-Treat analysis of all randomised participants**

In the Intention-to-Treat (ITT) analysis, all participants randomised to either the intervention or control group will be included in the primary analysis. Accordingly, participants who drop out prematurely are included in the primary analysis within the respective group they have been assigned to at randomisation to avoid potential bias due to exclusion of participants.

**Safety analysis**

Participants who experienced adverse events or serious adverse event defined in section 8.3 will be included in the safety analysis if, and only if, they actually participated in the study regardless of control or intervention group. Additionally, participants are grouped for analysis according to the control or intervention group they actually participated in, not according to the allocated group if there is any discrepancy.

**Per-protocol analysis**

Per-protocol (PP) is a subset of participants from the ITT analysis. All participants who do not violate the exclusion criteria stated in section 5.2, will be included for the PP analysis.

## Statistical Analyses

### General Approach

All continuous data will be summarised using mean and standard deviation (SD), whilst frequency and percentage will be used to summarise categorical data.

Repeated Measures Mixed Models (RMMM) will be used to analyse the data and provide comparisons of the intervention group with the control group for all health assessments. Regression analyses will be conducted in order to establish the impact of physical activity, sleep, mental health and nutrition on heart age, using the module engagement data logged on the Virgin Pulse website. All analyses will be adjusted for covariates such as age and gender, as well as variables that differ significantly between two groups at baseline.

Missing data will be checked and explained in individual data tables. In the presence of outlier(s), appropriate justifications will be provided to explain the exclusion of the outlier(s) in statistical analyses.

A p-value < 0.05 will be used to determine statistical significance. Analyses will be performed using Stata version 14 (Stata Corporation, TX).

### Analysis of the Primary Efficacy Endpoint(s)

Change in quality of life after participation in the VPGC program will be assessed by analysing the difference between baseline, within 20 days and 3 months post-VPGC programme completion. The potential magnitude of the regression to the mean effect on the observed changed in quality of life will be estimated using an established method [31]. Additionally, both RMMM and regression analyses will be utilised to examine the change in quality of life between baseline, within 20 days and 3 months post-VPGC programme completion between intervention and control groups. All analyses will be adjusted for covariates such as age and gender, as well as variables that differ significantly between two groups at baseline.

### Analysis of the Secondary Endpoint(s)

The changes of all secondary endpoint measures between baseline, within 20 days and 3 months post-VPGC programme completion, will be evaluated between intervention and control groups. Both RMMM and regression analyses will be utilised to examine the change in measures from baseline, within 20 days and 3 months post-VPGC programme completion between intervention and control groups. All analyses will be adjusted for covariates such as age and gender, as well as variables that differ significantly between two groups at baseline.

### Safety Analyses

If presence, each AE will be counted once only for a given participant. Severity, frequency and relationship of AEs to study intervention will be presented by System Organ Class (SOC). Start date, stop date, severity, relationship, expectedness, outcome and duration about each AE will be reported.

### Baseline Descriptive Statistics

Demographics and baseline characteristics will be summarised for all participants by control or intervention group. Characteristics to be examined are: age, gender, race, ethnicity, marital status, residential postal code, highest educational attainment, employment status, occupation, physical assessments and anthropometric measurements.

### Planned Interim Analyses

Interim analyses will be conducted after 210 participants (equal number of participants from the intervention and control groups) from May 2019 batch have completed all health assessments. This interim analysis will be conducted based on blinded data and done before the commencement of September 2019 batch of participants. Results from the interim analyses will be used to make adjustments to the sample size stated in section 9.2. All investigators will review the results and decide whether we still need 210 participants for the September 2019 batch.

### Sub-Group Analyses

The sub-group analyses will be analysed based on age, gender and allocated group.

### Tabulation of Individual Participant Data

Individual participant data will be listed by measure and time point.

### Exploratory Analyses

Not applicable

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Regulatory, Ethical, and Study Oversight Considerations

### Informed Consent Process

Prior to the beginning of the trial, a written approval of the research protocol, subject study information sheet and written informed consent form will be obtained from the IRB i.e. Swinburne University Ethics Committee.

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant’s comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign and date the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that their job within the company will not be adversely affected if they decline to participate in this study.

A copy of the subject information sheet and informed consent form is submitted with this protocol. The subject information sheet and consent form will be disseminated and collected by the site coordinator. The PhD student will subsequently review the signed informed consent forms to verify each subject’s eligibility during the baseline visit prior to study procedure initiation.

### Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension.

Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. Circumstances that may warrant termination or suspension include, but are not limited to:

* + Determination of unexpected, significant, or unacceptable risk to participants
	+ Demonstration of efficacy that would warrant stopping
	+ Insufficient compliance to protocol requirements
	+ Data that are not sufficiently complete and/or evaluable
	+ Determination that the primary endpoint has been met
	+ Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

### Confidentiality and Privacy

Participants will be allocated a numerical identifier in order to maintain anonymity. After consent is obtained, only these numbers will identify participants. No personal information will be required on all questionnaires and health assessments.

All health assessment data will be entered into the Subject Case Report Form, and subsequently be entered into Qualtrics platform. Directly entered data into Qualtrics platform will consist of the participants’ responses to battery of questionnaires. All data will be kept in Qualtrics platform and they will be securely stored in Swinburne Laptop protected by passwords.

All files containing participants’ name will be kept separately from the questionnaire data in the principal investigator’s office. This information will not be accessible without appropriate justifications. Data will be retained for 15 years (as per Good Clinical Practice requirement) from the date of publication of the results from the study. All data will be destroyed after 15 years. In terms of publications, all participants will remain anonymous.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study coordinator, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator. The study site will permit access to such records.

The study participant’s contact information will be securely stored at each participating site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Swinburne University (Hawthorn campus). This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the participating sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Swinburne University (Hawthorn campus).

### Future Use of Stored Specimens and Data

Not applicable

### Key Roles and Study Governance

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Key Roles** | **Principal Investigator** | **Co-Investigator 1** | **Co-Investigator 2** | **Research Coordinator (PhD Student)** |
| Name | Dr Won Sun Chen | Prof Denny Meyer | Dr Matthew Pase | Wilson HH Low |
| Institution Name | Swinburne University of Technology, Faculty of Health, Arts and Design |
| Department | Department of Statistic, Data Science & Epidemiology |
| Address | John Street, Hawthorn, Victoria 3122 Australia |
| Phone Number | *+613 9214 8437* | *+613 9214 4824* | +613 9214 5243 | +61 451 888 001 |
| Email | wchen@swin.edu.au  | dmeyer@swin.edu.au  | mpase@swin.edu.au  | *To be confirmed* |

### Safety Oversight

Not applicable.

### Study Monitoring

Study site monitoring is conducted remotely to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The research coordinator will conduct the study monitoring on-site and remotely. Monitoring will be conducted at baseline visit, 50th days into the VPGC programme, post-VPGC programme assessment visit and 60 days post-VPGC programme assessment.

Key monitoring activity include:

* 100% data verification
* Safety data

Independent audit of monitoring practices will not be conducted.

### Quality Assurance and Quality Control

Each study site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site’s quality management.]

 Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

### Data Handling and Record Keeping

Informed consent form collection is the responsibility of the site coordinator and research coordinator (PhD student). Data entry will be done online by the participants and research coordinator using Qualtrics platform provided by the Swinburne University of Technology. Any paper data entry will be performed by the research coordinator and subsequently entered into the Qualtrics platform. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

In the event of electricity blackout, internet failure or hardware problems, hardcopies of the study visit CRFs will be provided for use as source document worksheets for recording data for each participant enrolled in the study.

### Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, or International Conference on Harmonisation Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 20 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The investigators are responsible for knowing and adhering to the reviewing IRB requirements.

### Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

All publications must be reviewed and approved by Virgin Pulse, this review and approval process could take up to a maximum of 45 days.

### Conflict of Interest Policy

Conflict or potential conflict of interest must be declared by all researchers. A copy of the Conflict of Interest Guidelines from Swinburne University can be found at the following website.

<https://wiki.swinburne.edu.au/pages/viewpage.action?spaceKey=GAU&title=Conflicts+of+interest>

## Additional Considerations

None

## Abbreviations

|  |  |
| --- | --- |
| AE | Adverse Event |
| BMI | Body Mass Index |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CTN | Clinical Trial Notification |
| CTX | Clinical Trial Exemption |
| CVD | Cardiovascular Disease |
| DASS-21 | 21 Items version of the Depression Anxiety Stress Scale |
| ESS | Epworth Sleepiness Scale |
| HREC | Human Research Ethics Committee |
| ICH GCP | International Conference on Harmonisation Good Clinical Practice |
| IRB | Institutional Review Board |
| NCD | Non-Communicable Disease |
| NHMRC | National Health and Medical Research Council |
| PI | Principal Investigator |
| PSQI | Pittsburgh Sleep Quality Index |
| PWI-A | Personal Wellbeing Index – Adult version |
| QA | Quality Assurance |
| QC | Quality Control |
| QoL | Quality of Life |
| SAE | Severe Adverse Event |
| SoA | Schedule of Activity  |
| UP | Unanticipated Problems |
| VPGC | Virgin Pulse Global Challenge |
| WHPA | Work Health & Physical Activity |

## Protocol Amendment History

# 11. REFERENCES

1. Chai W, Nigg CR, Pagano IS, Motl RW, Horwath C, Dishman RK: Associations of quality of life with physical activity, fruit and vegetable consumption, and physical inactivity in a free living, multiethnic population in Hawaii: a longitudinal study. The international journal of behavioral nutrition and physical activity. 2010, 7: 83-10.1186/1479-5868-7-83.
2. Dishman RK, Washburn RA, Heath GW: Physical Activity Epidemiology. 2004, Champaign, IL: Human Kinetics
3. World Health Organization: Global Health Risks - Mortality and burden of disease attributable to selected major risks. 2009, World Health Organization, <http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf>,
4. Astrup A, Dyerberg J, Selleck M, Stender S: Nutrition transition and its relationship to the development of obesity and related chronic diseases. Obes Rev. 2008, 9: 48-52. 10.1111/j.1467-789X.2007.00438.x.
5. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J: Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet. 2009, 373: 2223-2233. 10.1016/S0140-6736(09)60746-7.
6. Ambrose JA, Barua RS: The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004, 43: 1731-1737. 10.1016/j.jacc.2003.12.047.
7. Schuit J: Physical activity, body composition and healthy ageing. Sci & Sports. 2006, 21: 209-213. 10.1016/j.scispo.2006.06.004.
8. Bijnen FCH, Caspersen CJ, Mosterd WL: Physical inactivity as a risk factor for coronary heart disease: a WHO and international society and federation of cardiology position statement. Bull World Health Organ. 1994, 72: 1-4.
9. de Berrington Gonzaley A, Hartge P, Cerhan JR: Body mass index and mortality among 1.43 million white adults. N Engl J Med. 2010, 363: 2211-10.1056/NEJMoa1000367.
10. Vogel T, Brechat P-H, Leprâtre P-M, Kaltenbach G, Berthel M, Lonsdorfer J: Health benefits of physical activity in older patients: a review. The Int J od Clin Pract. 2009, 63: 303-320. 10.1111/j.1742-1241.2008.01957.x.
11. Warburton DE, Nicol CW, Bredin SS: Health benefits of physical activity: the evidence. CMAJ. 2006, 174: 801-809.
12. Reiner M, Niermann C, Jekauc D, Woll A: Long-term health benefits of physical activity – a systematic review of longitudinal studies. BMC Public Health. 2013, 13:813. [doi.org/10.1186/1471-2458-13-813](https://doi.org/10.1186/1471-2458-13-813)
13. Neufer PD, Bamman MM, Muoio DM, Bouchard C, Cooper DM, Goodpaster BH, Booth FW, Kohrt WM, Gerszten RE, Mattson MP, Hepple RT, Kraus WE, Reid MB, Bodine SC, Jakicic JM, Fleg JL, Williams JP, Drugam JK, Koenig JI, Ingraham RH, Krotoski D, Garcia-Gazarin M, McGowan JA, Laughlin MR: Understanding the cellular and molecular mechanisms of physical activity-induced health benefits. Cell Metabolism. 2015, 22:4-11.
14. Daley M, Morin CM, LeBlanc M, Gregoire JP, Savars J, Baillargeorn L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. Sleep Medicine 2009:10(4), 427-438.
15. Adams RJ, et al. Sleep health of Australian adults in 2016: results of the 2016 Sleep Health Foundation national survey. Sleep Health. 2017;3(1):35–42.
16. Joint Commission. Health care worker fatigue and patient safety: the Joint Commission sentinel event alert 48. 2011. https://www.jointcommission.org/sea\_issue\_48/. Accessed December 6, 2017.
17. Cappuccio FP, et al. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32(12):1484–1492.
18. Cappuccio FP, et al. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep. 2010;33(5):585–592.
19. Cappuccio FP, et  al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep. 2008;31(5):619–626.
20. Gangwisch JE. A review of evidence for the link between sleep duration and hypertension. Am J Hypertens. 2014;27(10):1235–1242.
21. Gangwisch JE, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension. 2006;47(5):833–839.
22. Gangwisch JE, et  al. Sleep duration as a risk factor for diabetes incidence in a large U.S.  sample. Sleep. 2007;30(12):1667–1673.
23. Zhai L, et al. Sleep duration and depression among adults: a meta-analysis of prospective studies. Depress Anxiety. 2015;32(9):664–670.
24. Hillman DR, et  al. The economic cost of sleep disorders. Sleep. 2006;29(3):299–305.
25. Fritz T, Huang EM, Murphy GC, Zimmermnaa T: Persuasuve technology in the real world: a study of long-term use of activity sensing devices for fitness. Proceedings of the SIGCHI Conference on Human Factors in Computing Systems, 978-1-4503-2473-1, Toronto, Ontario, Canada. 2014, 487-496.
26. Lovibond, S.H. & Lovibond, P.F. (1995). Manual for the Depression Anxiety & Stress Scales. (2nd Ed.)Sydney: Psychology Foundation
27. International Wellbeing Group (2013). Personal Wellbeing Index: 5th Edition. Melbourne: Australian Centre on Quality of Life, Deakin University (<http://www.deakin.edu.au/research/acqol/instruments/wellbeing-index/index.php>)
28. Buysse, DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research 28:193-213, 1989
29. Johns MW (1991). ["A new method for measuring daytime sleepiness: the Epworth sleepiness scale"](https://web.archive.org/web/20150226064109/http%3A/epworthsleepinessscale.com/wp-content/uploads/2008/12/a-new-method-for-measuring-daytime-sleepiness-the-epworth-sleepiness-scale2.pdf). Sleep. 14 (6): 540–5. [PMID](https://en.wikipedia.org/wiki/PubMed_Identifier) [1798888](https://www.ncbi.nlm.nih.gov/pubmed/1798888)
30. Freak-Poli RLA, et al. Change in well-being amongst participants in a four-month pedometer-based workplace health program. BMC Public Health. 2014;14:953.
31. Linden A. Estimating the effect of regression to the mean in health management programs. Dis Manag Health Outcomes. 2007;15(1):7-12.