Pulsed Electromagnetic Fields in Preventing Physical Deconditioning in Patients Undergoing Prolonged Hospitalization. A case match control study.

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STUDY PROTOCOL

PROTOCOL TITLE:
Pulsed Electromagnetic Fields in Preventing Physical Deconditioning in Patients Undergoing Prolonged Hospitalization. A case match control study.

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STUDY PROTOCOL

1. BACKGROUND AND RATIONALE

Prolonged bed rest, physical inactivity and mechanical unloading is associated with health deficits and functional impairment due to muscle atrophy and loss of muscle function [1]. With a persistency beyond the acute period of inactivity accompanied by long recovery periods [2], physical deconditioning has gained socioeconomic importance in contemporary societies, increasingly raising scientific debates about time courses and underlying mechanisms [3]. Studies in adults documented that skeletal muscle size and function are already reduced after a few days of bed rest [4] and continue to decline with the length of exposure [5].

To intervene, early physical therapy intervention has been initiated in hospitalized patients to increase mobility and reduce muscle weakness from immobility. However, in certain cases, physiotherapy may not be possible due to patient's illness or other circumstances such as isolation due to their medical condition. Haematology patients undergoing induction chemotherapy or stem cell transplant are kept under neutropenic precautions. This includes being isolated in their hospital room for the duration of their treatment which usually lasts 4-6 weeks. At the same time, these patients have limited physiotherapy intervention due to medical reasons (fever, thrombocytopenia, anaemia), compounding their risk for physical deconditioning. Time and again, the post hospitalisation, these previously fit patients are now in a deconditioned state. As the next cycle of treatment begins within the next 10 days, there is little time for the patients to undergo rehabilitation therapy before the next treatment cycle begins and the patient suffers from further deconditioning leading to a vicious cycle. Once treatment is completed, patients are usually deconditioned and the need for rehabilitation prolongs recovery. There is an economic impact as patients need further use of hospital services. There is no current active intervention to prevent such deconditioning in previously fit patients.

Immobilisation also compromises systemic metabolic balance in association with depressed mitochondrial respiration [6]. One manner in which muscle mitochondrial function influences whole-body metabolism is via actions of the muscle secretome [7]. In response to activity dependent activation of mitochondrial respiration, skeletal muscle secretes into the systemic circulation a myriad of regenerative, inflammation and metabolic regulatory factors [7]. Immobilization-induced ectopic accumulation of adipose tissue into muscular and extramuscular sites is associated with increased circulating levels of toxic lipid metabolites, such as the palmitate-derived ceramides. Ceramides are fatty acid derivatives of sphingoid bases, and formed not only through the de novo biosynthetic pathway, but also from the degradation of glycosphingolipids (GSLs) and ceramide-1-phosphate. Ceramides are powerful tumour suppressors that regulate cell proliferation, differentiation, senescence, and apoptosis, which have attracted tremendous attention in combination therapy for cancer treatment [8, 9]. Chemotherapeutic drugs, cytotoxic drugs, hypoxia microenvironment, malnutrition, radiotherapy and hyperthermia can promote the apoptosis of tumour cells by promoting the activity of ceramide synthesis related enzymes and increasing the level of intracellular ceramide [10-12].

Recent studies have shown that the intervention in ceramide production and metabolism will have a significant effect on the treatment of cancer, indicating that ceramides are signal molecules, and have efficiencies of anti-proliferative and pro-apoptotic [13, 14]. These findings raise considerable interest in targeting ceramide metabolism pathways for cancer therapy. Brief exposures to pulsed electromagnetic fields (PEMFs) were previously shown capable of promoting in vitro [15] and in vivo [16] murine myogeneses via the activation of a calcium-mitochondrial axis promoting mitochondriogenesis, oxidative muscle maintenance, systemic metabolic balance, enhanced fatty acid oxidation as well as produced microbiome shift characteristic of leanness [16]. The implicated PEMF-induced calcium pathway pertained to that mediated by the Transient Receptor Potential Canonical 1 (TRPC1) channel commonly implicated in load-bearing oxidative muscle development and linked to PGC-1α transcriptional pathways underlying mitochondrial mitohormetic responses
[16]. Studies carried out in senior in the community have demonstrated its effectiveness in increasing skeletal muscle mass and decreasing body fat mass as well as increasing their functional aptitude. PEMFs exposure demonstrated inhibition of growth, migration and invasiveness in breast cancer cells and in treated mice [17].

Klotho and HTRA1 has been shown to inhibit the in vitro growth of breast cancer cells [18] and both of these candidates are downregulated in several cancers in correlation to cancer severity [19, 20]. The PEMF induced secretion of both Klotho (and HTRA1) may hence serve as manner to manage cancer progression.

This study aims to examine a direct benefit of PEMFs on the patient's muscle mass and physical functioning and indirect benefit on the patient's cancer management. If this pilot study is successful in demonstrating our specific aims, we plan to extend the study to other patient populations specifically targeting the elderly cancer patients.

1.1. General Introduction

Low frequency and low amplitude pulsed electromagnetic field (PEMF) provides many benefits of exercise by activating many of the same cellular second messenger cascades activated by mechanical input (exercise) yet, without imparting a physical stress on the cells. Through a series of *in vitro* and *in vivo* experiments we have shown that at field strengths of 1-2 mT amplitude, this PEMF system stimulates muscle without stressing the tissues and delivers the benefits of slowing muscle loss, improving muscle strength and releasing important myogenic factors. The PEMF leg coil device is designed to provide low amplitude (1.5 mT) magnetic fields for a period of 10 minutes per exposure. The device is tuned and optimised to activate mitochondria in the muscles. Activated muscles are stimulated to produce myogenic factors that are involved in bodily metabolic processes.

1.2. Rationale and justification for the Study

This study is important in looking at how to prevent deconditioning in patients as a result of prolonged bed rest during inpatient hospitalisation.

a. Rationale for the Study Purpose

This study aims to examine a direct benefit of PEMFs on the patient's muscle mass, physical functioning and indirect benefit on the patient's cancer management.

b. Rationale for Doses Selected

Study participants will receive PEMF by alternating between left or right upper thigh, twice per week for 4 consecutive weeks. The recommended doses for this treatment is based on another community study that was already been published by the laboratory [21].

c. Rationale for Study Population

For this study, we would like to validate our hypothesis in haematology patients who required isolated long hospital stays and undergoing induction chemotherapy or stem cell transplant. Healthy volunteer will also be recruited and undergo the same PEMF treatment as the haematology patients. The blood biomarkers from both cohorts will help us assess the direct and indirect benefits of PEMF.

d. Rationale for Study Design

A prospective, double-blinded randomised control study design is the "gold standard" of interventional studies, minimising bias, and ensuring that the effects of the intervention can be accurately evaluated.

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

The hypothesis for this study is that PEMF can prevent or decrease physical deconditioning by producing myogenic factors that are favourable of muscle proliferation and regeneration, as well as anticancer factors that may help in cancer management.

2.2. Primary Objectives

The objective is to examine if pulsed electromagnetic fields can prevent or decrease physical deconditioning associated with prolonged hospitalisation and immobility of patients by evaluating the changes in muscle secretome at baseline and after exposure to pulsed electromagnetic fields, specifically examining the changes in anticancer factors ceramide, Klotho and HTRA1 in patients and healthy volunteers.

2.3. Secondary Objectives

Understanding the blood biomarkers changes in response to PEMF exposure in both cancer and healthy cohorts can help us discover important circulating proteins that may have a role in cancer treatment.

2.4. Potential Risks and benefits:

a. End Points - Efficacy

Patients may require less time for rehabilitation and recovery, reduction in the use of hospital services and lessen economic burdens on them.

Hospital can consider PEMF as part of the cancer treatment regime if prove to be effective in slowing cancer progression. They can become better at utilising the resources to provide service and care for others if this cohort of patients have less demand of the hospital services such as physiotherapy.

b. End Points - Safety

Risks associated with the fields
The risks associated with the application of the fields per se are minimal. We get optimal results with as little as 10 minutes of exposure to PEMFs per week. Since synonymous pathways are activated as by exercise, muscles are only stimulated for as long as the fields are on; PEMF stimulation is as safe as exercise, or possibly even more so as durations of exposure are so brief.

On the other hand, exercise often causes micro-damage to the muscle membrane that must be repaired before physical adaptations can be implemented. Additionally, patient compliance to exercise regimes will be hard to enforce. PEMFs do not impart a physical stress on muscle; that is, PEMFs exert less wear and tear in muscles than exercise.

The non-mechanical attributes of PEMFs pose a benefit here as well. In other words, there would be no overhead to pay, all the gains are directed towards the metabolic and functional adaptations that normally accompany exercise, rather than repairing or replacing damaged muscle – a process that is most notably stymied in the elderly. That is likely the reason that we see such dramatic improvement in metabolic indices with brief PEMFs exposition.

In 2011, we were contacted by the Swiss Health Agency to determine the safety and efficacy of other PEMF-producing apparatuses on the markets. Like ours, none of the commercial apparatuses we tested increases the resting rate of apoptosis or provoked their transformation into a malignant status. Our results agree with the position of the World Health Organization that has deemed fields of this characteristic to be harmless to human health.

World Health Organization: Electromagnetic fields and public health (2007) Exposure to extremely low frequency fields. Accessed 8 April 2024: https://www.who.int/teams/environment-climate-change-and-health/radiation-and-health/non-ionizing/exposure-to-extremely-low-frequency-field

The frequency of the applied pulsed is in the extremely low range (non-heating) and the amplitudes are in the 1-3 mT range (3K to 5K smaller than that applied with an MRI). Our PEMF parameters would exert less damage than conventional MRI treatments.

Risks associated with the apparatus
The risk of harm from the PEMF leg coil device is very low as the entire device is completely isolated and grounded to earth. The risk of inductive heating of metallic implants is low since the applied magnetics flux density applied (< 2 mT) is small, and the frequency of the applied field is in the kHz-range. The fields at this frequency and amplitude range will not affect titanium screws and pins. Moreover, as the induced electric field strength is very low (< 1 mV/m), inductive heating of the tissue is very unlikely.

The controls implemented against possible harm to the subject are that the coils are securely enclosed in a poly carbonate case that completely isolates the coils from the user. All electronics are not assessable without completely disassembly of the apparatus with specialised tools. Moreover, any technical malfunction of the control unit of coil setup will result in a leakage current, so that the earth leakage circuit breaker is triggered and the device is powered down, protecting the user.

Finally, the fields are too low strength to cause muscle contraction and accordingly, none have ever been reported. The risk pf allergic reaction to the PVC composing the chassis of the coil holding structure is very low.

3. STUDY POPULATION

3.1. List the number of subjects to be enrolled.

36 healthy volunteers age from 30 to 45 will be recruited and randomized to undergo PEMF treatment or no treatment.

3.2. Criteria for Recruitment

Investigational Medicine Unit will look through their database to identify prospective study participants based on the inclusion/exclusion criteria set by the study team. Clinical trial coordinator will contact them to assess their interest in joining the study. Prospective study participants will be given ample time to make the decision. Consent will be obtained from eligible participants in accordance with Singapore Guideline for Good Clinical Practice. Participants who are unable to consent would not be recruited for this study.

3.3. Inclusion Criteria

For inclusion in this study, the following criteria must be fulfilled:

a. Age between 30-45 years old
b. Ability to provide informed consent
c. For healthy volunteer, no prior medical history

3.4. Exclusion Criteria

If subjects meet any of the following criteria, they will be excluded from the trial:

a. Exercise more than 150 minutes of moderate activity and 45 minutes of vigorous activity per week
b. Medical history of chronic diseases
c. On long-term medication/dietary supplementation due to nutritional deficiency
d. Electronic or electrical metal implants
e. Existing pregnancy

3.5. Withdrawal Criteria

Study participants will be withdrawn if unexpected adverse events arise through the course of the study. Participants who have missed more than 2 PEMF sessions will be withdrawn.

3.6. Subject Replacement

Participants withdrawn will be replaced.

4. TRIAL SCHEDULE

Week	Blood	Treatment Leg 1	Treatment Leg 2	Activity and Diet Questionnaire
1	✓	✓	✓	✓
2		✓	✓	
3		✓	✓	
4		✓	✓	
5	✓			✓
6				
7				
8	✓			✓

Figure 1: The breakdown of the events that will be happening on each week. Blood will be collected on Week 1, 5 and 8 with a set of questions found in the questionnaire will be assessed on Week 1, 5 and 8.

Early Week (Mon/Tue) recruitment					
Mon	Tue	Wed	Thu	Fri	Sat
Leg 1	Leg 1		Leg 2	Leg 2	
Visit 1			Visit 2		

Late Week (Thu/Fri) recruitment					
Thu	Fri	Sat	Sun	Mon	Tue
Leg 1	Leg 1			Leg 2	Leg 2
Visit 1				Visit 2	

Figure 2: The PEMF treatment schedule depending on the recruitment days as a minimum of two days gap is required in between each treatment with alternate legs.

5. STUDY DESIGN

The study is designed as a double-blinded, randomised, controlled pilot study. Recruitment will be in groups of 10 study participants. In each group of 10, participants will randomized to either sham or treatment group based on the RFID card that they will be assign to. Subject randomisation ID will coincide with RFID card number. Each participant will use the assigned RFID card to tap onto the RFID reader in order to activate the PEMF leg coil. Randomization and blinding is assigned by QuantumTX, the company that develops the PEMF leg coil device together with the RFID system.

5.1. Summary of Study Design

Participant will receive either PEMF or no PEMF twice in a week for 4 consecutive weeks. In each week, the participant will place their upper thigh into the PEMF leg coil to receive the treatment. A minimum of two days of rest is required before the next treatment is administered. The participant will also alternate their legs for every treatment session.

6. METHODS AND ASSESSMENTS

Blood sample collection
Blood from study participants will be collected at Week 1 (before the start of the PEMF treatment as a baseline), Week 5 (one week after completion of 8 sessions of PEMF treatment) and Week 8 (4 weeks after completion of 8 sessions of PEMF treatment). Blood will be collected in EDTA tubes and processed for multiplex and ELISA to assess the blood biomarker levels changes before and after PEMF treatment. Blood collected in normal red serum tubes will be used to assess anticancer potency in human breast cancer cells in vitro.

Activity and Diet Questionnaire
Study participants will be answering a set of questions on the day of blood collection (Week 1, 5 and 8) to help us gain insights about the changes to their daily routine activities or dietary intake which may contribute to the changes in the blood biomarkers levels.

6.1. Randomisation and Blinding

Prospective study participant will be given a subject ID (patient initials) by the clinical trial coordinator and a pre-screening questionnaire will be conducted to confirm the suitability. Personal data such as NRIC, date of birth are not collected using the questionnaire. A subject randomization ID (based on available RFID card number) will be assigned in addition to their subject ID. On the day of treatment, based on the subject randomization ID, the correct RFID card will be used to activate the PEMF leg coil. However, both parties will be blinded by the PEMF treatment administered to the upper thigh when the machine is switch on.

6.2. Study Visits and Procedures

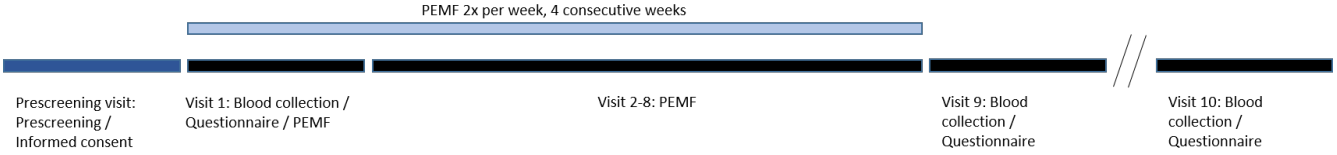

Figure 3: Summary of study visits and procedures

a. Screening Visits and Procedures (Prescreening Visit)

Clinical trial coordinator will perform the recruitment screening. Eligible participants will be recruited and progress to Visit 1.

After participant has given the consent, assign the Subject Randomization ID which can be found on the RFID card.

b. Study Visits and Procedures (Visit 1-10)

Visit 1:

- Activity and diet questionnaire to be completed by the participant
- Blood will be collected from the participant into 2 EDTA tube and 1 red cap tube
- Verify the Subject ID and Randomization ID again before proceeding to use the assigned RFID card to activate the PEMF leg coil

Visit 2-8:

- Verify the Subject ID and Randomization ID again before proceed to use the assigned RFID card to activate the PEMF leg coil

Visit 9:

- Activity and diet questionnaire to be completed by the participant
- Blood will be collected from the participant into 2 EDTA tube and 1 red cap tube (one week after completion of Visit 1-8)

c. Final Study Visit (Visit 10):

Visit 11:

- Activity and diet questionnaire to be completed by the participant
- Blood will be collected from the participant into 2 EDTA tube and 1 red cap tube (four weeks after completion of Visit 1-8)

d. Post Study Follow up and Procedures

Should subjects experience any unlikely discomfort or irritation after treatment, they are free to report it to the study team.

e. Discontinuation Visit and Procedures

Should subjects experience any unlikely discomfort or irritation during treatment or blood collection procedure, they are free to report it to the study team and may ask to stop the treatment. Should subjects are already into the trial for 4 consecutive PEMF therapy (2 weeks, 4 visits), and if withdrawal occurs, subjects are required to return for a final study visit the following week for a final blood withdrawal. No other obligations required.

Subjects may withdraw voluntarily from participation in the study at any time.

7. TRIAL MATERIALS

7.1. Trial Product: PEMF Leg Coil

The PEMF leg coil is a machine that produces low frequency electromagnetic fields in a defined area within a given amount of time. It uses electrical energy to direct a series of magnetic pulses through the skin and each magnetic pulse induces a tiny electrical signal in the cells and tissues. The machine consists of cylindrical PEMF coil apparatus, and a controller. The coils are enclosed in a polycarbonate case that completely isolates them from the user. All electronics are not assessable without complete disassembly of the apparatus with specialised tools. Any technical malfunction of the control unit or coil setup will result in a leakage current which triggers the earth leakage circuit breaker, protecting the user. The exposure time can be controlled by the user. The amplitude of magnetic fields used in this device is set at 1.5mT.

8. TREATMENT

8.1. Rationale for Selection of Dose

PEMF doses was recommended based on another study that was previously published where there were beneficial effects on participants who had received PEMF for 8-12 weeks. In this study, and to match the trial on oncology patients, subjects will be exposed to PEMF twice a week for 4 weeks.

8.2. Blinding

Double blinding will be performed using the RFID cards assigned to the study participants. The treatment details will be stored away by QuantumTX.

8.3. Concomitant therapy

All medications (prescription and over the counter), vitamin and mineral supplements, and / or herbs taken by the participant will be recorded in the questionnaire on Week 1, 5 and 8. Subjects requiring chronic dosing of any clinical drugs/prescriptive nutritional supplementations are excluded from the study. If subjects were given prescriptive drugs/supplements during trial intervention, they must be reported to the trial study team.

9. SAFETY MEASUREMENTS

9.1. Definitions

An adverse event (AE) is any untoward medical occurrence in subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) or reaction is defined as any untoward medical occurrence that at any dose:

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalization or causes prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. May have caused a congenital anomaly/birth defect
6. Is a medical event that may jeopardize the patient and may requires medical or surgical intervention to prevent one of the outcomes listed above.

9.2. Collecting, Recording and Reporting of "Unanticipated Problems Involving Risk to Subjects or Others" – UPIRTSO events to the NHG Domain Specific Review Boards (DSRB)

UPIRTSO events refers to problems, in general, to include any incident, experience, or outcome (including adverse events) that meets ALL of the following criteria:

1. **Unexpected**
   In terms of nature, severity or frequency of the problem as described in the study documentation (eg: Protocol, Consent documents etc).
2. **Related or possibly related to participation in the research**
   Possibly related means there is a reasonable possibility that the problem may have been caused by the procedures involved in the research; and
3. **Risk of harm**
   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.

Reporting Timeline for UPIRTSO Events to the NHG DSRB.

1. Urgent Reporting: All problems involving local deaths, whether related or not, should be reported immediately – within 24 hours after first knowledge by the NHG investigator.
2. Expedited Reporting: All other problems must be reported as soon as possible but not later than 7 calendar days after first knowledge by the NHG investigator.

9.3. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

1. **For Industry sponsored Trials**
   All SAEs will be reported to HSA according to the HSA Guidance for Industry "Safety Reporting Requirements for Clinical Drug Trials."

2. **For Principal Investigator initiated Trials**
   All SAEs that are unexpected and related to the study drug must be reported to HSA.

"A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death.
- Is life-threatening (immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly/birth defect.
- Is a Medically important event.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious."

All SAEs that are unexpected and related to the study drug will be reported. The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

9.4. Safety Monitoring Plan

The study team shall review study data quarterly. Adverse events and serious adverse events will be monitored for safety.

9.5. Complaint Handling –

When a complaint is received, a meeting will be set up by the study team to review the complaint and discuss if any action is required.

10. DATA ANALYSIS

10.1. Data Quality Assurance

The study team members will review the data collection forms periodically to ensure that the forms are signed and dated, writings are eligible, results are logical, and no missing data. Any change or correction had to be dated and initialled without obscuring the original data.

10.2. Data Entry and Storage

Study-related documents, data and information collected during this study are strictly confidential. All data used in analyses and summaries of this study will be anonymous, and without reference to specific subject names. Subject identifiers will not be collected for study purposes, with consent forms being the exception. Any subject identifiers (e.g. name and contact information in consent form) will be kept securely under lock and key in a card-access only facility, separate from data collected for the research study. All other coded research data will be stored in a password-protected laptop, locked in a secure facility. Only the research team will be granted access to study data. The PIs and study participants will remain blinded till study completion.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

As this is a pilot study, there is no power calculation. The sample sizes of 40 for cancer patients and 36 for healthy volunteers were chosen based on feasibility of completing the study within 1 year with the given funding for the healthy volunteer limb. As the study is underpowered, the case matched control cohort is to mitigate some of the confounding factors to identify a trend in the data.

11.2. Statistical and Analytical Plans

Not applicable.

12. ETHICAL CONSIDERATIONS

12.1. Informed Consent

Informed consent will be taken during the first visit. Recruitment of subjects will be predominantly from Investigational Medicine Unit's database. Prospective study participants will be contacted study team to assess their interest in participating in the study. If eligible, participants will be given ample time to decide whether to participate. Consent will be obtained in accordance with Singapore Guideline for Good Clinical Practice, in an isolated room. He/She will be given ample time to read the consent form, ask questions, and consider participation in the study. Subjects who are unable to consent would not be recruited for this study.

12.2. IRB review

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by the IRB / NHG DSRB.

12.3. Confidentiality of Data and Patient Records

Information collected for this study will be kept confidential. Participants' record, to the extent of the applicable laws and regulations, will not be made publicly available. Records will be stored in a password-protected computer in a secure location. Only the investigation team will have access to the data. In the event of any publication, all participants' identities will remain confidential.

13. PUBLICATIONS

The results from this study will be put together for submission and publication in a peer-reviewed journal of the highest impact possible.

14. RETENTION OF TRIAL DOCUMENTS

Information collected for this study will be kept confidential. Participants' record, to the extent of the applicable laws and regulations, will not be made publicly available. Records will be stored in a password-protected computer in a secure location. Only the investigation team will have access to the data. In the event of any publication, all

participants' identities will remain confidential.

List of Attachments

Appendix 1 **References**

Appendix 2 **Informed consent form**

Appendix 3 **Data Collection Form**

Appendix 1: References

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INFORMED CONSENT FORM (FOR HEALTHY VOLUNTEERS)

1. Study Information

Protocol Title:
Pulsed Electromagnetic Fields in Preventing Physical Deconditioning in Patients Undergoing Prolonged Hospitalization. A case match control study.

Principal Investigator & Contact Details:

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Conflict of Interest
A/Prof Alfredo is the owner of the Background IP on PEMF signatures, developed at National University Hospital Singapore.

Title: System and method for applying pulsed electromagnetic fields to subjects.
SG Provisional Application Number: 10201503520V
Filing Date: May 5, 2015
International Publication Number: WO 2016/178631 A1
Filing Date: May 5, 2016

2. Purpose of the Research Study

You are invited to participate in a research study. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part in this research study, the study will be explained to you and you will be given the chance to ask questions. After you are properly satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited because you are a healthy individual who fits the criteria as a study participant and currently does not regularly see/consult any physician/medical specialist for any disease indication, or under any long-term medication.

Cancer patients often experience physical difficulties that can contribute to the state of frailty. Frailty is a condition characterized by the weakening of the physical body with decreased strength, endurance, and ability to recover from illness.

This study is carried out to determine whether preventative treatment for muscle weakness and loss in hospitalized patients can be prevented. This study will investigate the benefits of pulsed electromagnetic fields (PEMFs) on cancer treatment. Low-energy magnetic treatment (PEMF) has been demonstrated to inhibit growth and invasiveness in breast cancer cells, in both tissue culture as well as treated laboratory animals. PEMF has also been shown to improve mobility function and metabolic indices in the elderly.

Your baseline clinical data in the form of blood withdrawals will be collected at the beginning, during, and at the end of the study. Your participation as a healthy volunteer is important to establish the baseline and ascertain the alterations to selected beneficial biomarkers

associated with PEMF treatment. This pilot randomized control trial will recruit 36 healthy participants from NUH over a period of 1 year. 18 participants will be randomized to undergo PEMF treatment. A further 18 participants will serve as the untreated control group (placebo) who will undergo a mock PEMF treatment.

3. What procedures will be followed in this study

If you take part in this study, we will collect some blood (20 ml = 4 teaspoons) at three (3) different time points throughout the study. Blood withdrawals will take place at the beginning, after week 4, and at week 8 of the trial.

We will investigate biomarker changes related to frailty and cancer, and correlate their levels to those of cancer patients, at baseline as well as after PEMF treatment.

You will be randomly assigned to either the group who receives PEMF treatment or the group who does not. The assignment will not be made known to you.

PEMF treatment is a safe and low-energy magnetic treatment. You should feel no sensation during the procedure, which will last for 10 minutes. You will undergo the treatment twice a week for 4 weeks. Your active participation in the study will last 12 weeks.

To protect your identity and privacy, your data will be de-identified/coded. Your identity will be labeled with a unique study number or 'code', without any personal identifiers such as your name or date of birth. Your data may be shared with other collaborating institutions or researchers in a de-identified/coded manner. The NUH study team may include specific information (such as your age, your gender, certain clinical, pathological, or demographic data, etc.); however, this information would likely not allow you to be identified or traced.

The code linking your identifiers to the data will be kept by the study team in a secure and confidential location at the study site. Decoding can only be done by the study team or individual(s) authorized by the Principal investigator. If you change your mind about participating in this future research, this link will be used to locate and destroy any of your remaining samples.

Blood samples obtained during this study will be stored and analyzed only for this study for a period not exceeding 6 years and will be destroyed after completion of the study. The blood samples will not be used for restricted human biomedical research involving human-animal combinations. Any individually identifiable data obtained during this study will be stored and analyzed for this study and will not be used for future biomedical research.

"Incidental findings" are findings that have potential health or reproductive importance to research participants like you/your child and are discovered in the course of conducting the study, but are unrelated to the purposes, objectives or variables of the study. There will not be any incidental findings arising in this research.

There is no additional cost for donating data or biological samples.

4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to undergo all the procedures that are outlined above.

5. What Is Not Standard Care or is Experimental in This Study

The blood test collected would be experimental. The PEMF treatment would be experimental.

6. Possible Risks and Side Effects

There are minimal risks or side effects associated with this study. Blood taking will be associated with bruising and pain. The PEMF device has been tested for safety. You may experience discomfort in your thigh/leg during the 10 minutes in the device as you would have to keep still. You will be allowed sufficient time to answer the questions asked in the questionnaire. If there are any questions that you do not feel comfortable answering, you may choose not to answer these questions.

7. Possible Benefits from Participating in the Study

There is no known benefit from participation in this study. Your participation in this study will allow us to better understand how we can help alleviate muscle weakness and muscle loss in hospitalized adults like yourself or your loved ones in the future.

8. Alternatives to Participation

If you choose not to take part in this study, we will respect your decision.

9. Costs & Payments if Participating in the Study

There will be a nominal transportation cost reimbursement of SGD50 for every visit to all participants of the study.

10. Voluntary Participation

Your participation in this study is voluntary. Even if you consent to participate in this study, you can decide to take up or decline the interventions recommended. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the Principal Investigator.

If you withdraw from the study, you should inform the Principal Investigator or any study team member.

However, the data that have been collected until the time of your withdrawal will be kept and analyzed. The reason is to enable a complete and comprehensive evaluation of the study.

The biological samples collected for the study will be deemed to be gifted to NUH, Singapore, and will not be returned to you. You will also not have any right or claim to any share in the commercial gain derived from the research (if any). However, you retain your right to ask the Principal Investigator to discard or destroy any remaining samples if the biological samples are individually identifiable and have not been used for the research or it has been used for research but it is practicable to discontinue further use of the biological samples for the research.

Your doctor, the Investigator, and/or the Sponsor of this study may stop your participation in the study at any time if they decide that it is in your best interests. They may also do this if you do not follow the instructions required to complete the study adequately. If you have other medical problems or side effects, the doctor and/or nurse will decide if you may continue in the research study.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you will be informed promptly by the Principal Investigator or his/her representative.

11. Compensation for Injury

If you follow the directions of the study team in charge of this study and you are physically

injured due to the procedures given under the plan for this study, the NUH will pay the medical expenses for the treatment of that injury.

Payment for management of the normally expected consequences of your treatment, if any, will not be provided by the NUH. By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

NUH without legal commitment will compensate you for the injuries arising from your participation in the study without you having to prove NUH is at fault. There are however conditions and limitations to the extent of compensation provided. You may wish to discuss this with your Principal Investigator.

12. Confidentiality of Study and Medical Records

Your participation in this study will involve the collection of "Personal Data". "Personal Data" means data about you that makes you identifiable (i) from such data or (ii) from that data and other information to which an organization has or is likely to have access. This includes medical conditions, medications, investigations, and treatment history.

Information and "Personal Data" collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available.

However, National University Health System (NUHS), the NHG Domain-Specific Review Board and Ministry of Health will be granted direct access to your original study records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you are authorizing (i) the collection, access to, use and storage of your "Personal Data", and (ii) the disclosure to authorized service providers and relevant third parties.

Data collected and entered into the Case Report Forms are the property of National University Health System (NUHS). In the event of any publication regarding this study, your identity will remain confidential.

Research arising in the future, based on your "Personal Data", will be subject to review by the relevant institutional review board.
By participating in this research study, you are confirming that you have read, understood and consent to the Personal Data Protection Notification available at

https://www.nuh.com.sg/Pages/Personal-Data-Protection-Act.aspx

13. Who To Contact if You Have Questions

If you have questions about this research study, you may contact the Principal Investigator, Dr Melissa Ooi Gaik Ming (Principal Investigator), Department of Haematology-Oncology, NUH, Tel: 6908 2222. The study coordinator's contact information will be made available to you.

The study has been reviewed by the NHG Domain Specific Review Board (the central ethics committee) for ethics approval.

If you want an independent opinion to discuss problems and questions, obtain information and offer inputs on your rights as a research subject, you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. You can also find more information about participating in clinical research, the NHG Domain Specific Review Board and its review processes at www.research.nhg.com.sg.

If you have any complaints or feedback about this research study, you may contact the Principal Investigator or the NHG Domain Specific Review Board Secretariat.

CONSENT FORM

Protocol Title:

Pulsed Electromagnetic Fields in Preventing Physical Deconditioning in Patients Undergoing Prolonged Hospitalization. A case match control study.

Principal Investigator & Contact Details:

Dr. Melissa Ooi
Haematology Oncology Senior Consultant
Department of Hematology-Oncology
Tower Block Level 7, NUHS
1E Kent Ridge Road, Singapore 119228

Tel: 6908 2222

I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction. I have also been informed and understood the alternative treatments or procedures available and their possible benefits and risks.

_____	_____	_____
Name of Participant	Signature	Date

Translator Information
The study has been explained to the participant / legally acceptable representative in

_____ by _____

Witness Statement
I, the undersigned that:

- I am 21 years of age or older.
- To the best of my knowledge, the participant/ the participant's legally acceptable representative signing this informed consent form has the study fully explained in a language understood by him/ her and clearly understands the nature, risks and benefits of his/ her participation in the study.
- I have taken reasonable steps to ascertain the identity of the participant/ the participant's legally acceptable representative giving the consent.
- I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

_____	_____	_____
Name of Witness	Signature	Date

1. In accordance with Section 6(d) of the Human Biomedical Research Act and Regulation 25 of the Human Biomedical Research Regulations 2017, appropriate consent must be obtained in the presence of a prescribed witness who is 21 years of age or older, and has mental capacity. The witness must be present during the entire informed consent discussion, and must not be the same person taking the appropriate consent. The witness may be a member of the team carrying out the research.
2. However, if the participant/ the participant's legally acceptable representative is unable to read, and/ or sign and date on the consent form, an impartial witness should be present instead. The impartial witness should not be a member of the study team.

Investigator Statement

I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his / her participation in the study.

Name of Investigator / Person administering consent	Signature	Date

CLINICAL TRIAL DATA COLLECTION FORM

(DCF Form)

Study Title: **Pulsed Electromagnetic Fields in Preventing Physical Deconditioning in Patients Undergoing Prolonged Hospitalization. A case match control study.**

Principal Investigator (PI): **Dr Melissa Ooi**

Study ID: **NHG DSRB Ref: 2022/00928**

(NHG DSRB Study Amendment ID: 2022/00928-AMD0003)

Study Site: **National University Hospital (NUH)**

Subject ID (initials) ☐☐☐☐

Subject Randomization ID ☐☐☐

DCF Version Number: 2.0
Date: 04 April 2024

Subject ID: ☐☐☐☐-☐☐☐

Screening Assessment

1. General Demographics

Age (As of 2024): ☐☐ Year of birth: ☐☐☐☐			
Gender	Male ☐ Female ☐	Race	Chinese ☐, Malay ☐, Indian ☐, Caucasian ☐, Others ☐ Specify:
Height (cm)	☐☐☐	Weight (kg)	☐☐☐
Smoking	Yes ☐ No ☐		

2. Clinical History

Do you have any of the following conditions: **(If ☑ yes, please specify)**	
a. Diabetes	Yes ☐ No ☐
b. Hypertension	Yes ☐ No ☐
c. High blood cholesterol	Yes ☐ No ☐
d. Cardiovascular disease	Yes ☐ No ☐
e. Liver / Kidney disease	Yes ☐ No ☐
f. Arthritis / Gout	Yes ☐ No ☐
g. Inflammatory diseases e.g. Asthma, lupus, psoriasis, eczema, colitis, celiac disease	Yes ☐ No ☐
h. Metal implants	Yes ☐ No ☐ Year: Location of implant: Comment:
i. Major surgery in the past	Yes ☐ No ☐ Year: Comment:
j. Allergies	Yes ☐ No ☐
k. Others	Yes ☐ No ☐

Are you on any long term medication? e.g., NSAIDS, antihistamines etc.
Yes ☐ No ☐
If ☑ yes, please specify:

3. Dietary Supplementation

Are you taking any of the following natural/ergogenic supplements regularly (> 4 x a week)?

(If ☑ yes, please specify)

a. Traditional medicine (e.g., herbal remedy, natural supplements)	Yes ☐ No ☐
b. Vitamins D	Yes ☐ No ☐
c. Magnesium	Yes ☐ No ☐
d. Fish Oil	Yes ☐ No ☐
e. Creatine	Yes ☐ No ☐
f. Protein supplements (e.g. whey, casein, soy)	Yes ☐ No ☐
g. Beta-alanine	Yes ☐ No ☐
h. BCAAs (branch chain amino acids)	Yes ☐ No ☐
i. HMB (beta-hydroxy beta-methylbutyrate)	Yes ☐ No ☐
j. Nitric Oxide Precursors (e.g., citrulline malate)	Yes ☐ No ☐
k. Caffeine (e.g., caffeine tablets, daily coffee/tea)	Yes ☐ No ☐

4. Physical Activity

a. On average, how many steps do you take daily?	0 – 4999 ☐, 5000 – 9999 ☐, 10,000 – 14,999 ☐, Above 15,000 ☐.
b. Do you engage in more than 150 minutes of "moderate physical activity" a week? Yes ☐ No ☐	**Moderate physical activity** noticeably increases your heart rate and breathing but still allow you to carry on a conversation. These activities are more intense than light activities. E.g., Brisk walking, cycling, dancing, hiking, tennis (doubles), recreational sports.
c. Do you also engage in more than 75 minutes of "vigorous-intensity physical activity" a week? Yes ☐ No ☐	**Vigorous-intensity activity** will leave you saying no more than a few words without pausing for a breath. E.g., Race walking, running, swimming laps, badminton singles.

If ☑ yes to (B) and/or (C), please indicate the activities below:
e.g. Activity: Brisk walking, running, cycling, swimming, dancing, hiking, tennis, recreational sports etc.
Frequency: (e.g. times per week); Duration: (minutes per session)

Activity:	Frequency:	Duration:
Activity:	Frequency:	Duration:
Activity:	Frequency:	Duration:

d. How many sitting hours per day? ☐☐

Visit 1 – Screening

Based on screening questionnaire, subject is included into study: Yes ☐, No ☐

(page 2 for screening assessment)

Remarks:

Completed by:

Name of Coordinator:

Signature: Date:

Signature: Subject ID: ☐☐☐☐-☐☐☐

Week 1 Visit 1

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Week 1 Visit 2

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Week 2 Visit 1

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Week 2 Visit 2

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Week 3 Visit 1

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Week 3 Visit 2

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Week 4 Visit 1

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Week 4 Visit 2

Date of Therapy: ☐☐/☐☐/☐☐; Day of therapy: _____ ; Time of therapy:☐☐:☐☐

Leg assignment: Left ☐ Right ☐; Name of Coordinator:

Mid-Assessment – Week 5 (2nd Blood Collection)

Subject ID: ☐☐☐☐-☐☐☐

Date of Assessment: ☐☐/☐☐/☐☐

Are you on any long term medication? e.g., NSAIDS, antihistamines etc.
Yes ☐ No ☐ If ☑ yes, please specify:

1. Dietary Supplementation

Are you taking any of the following natural/ergogenic supplements regularly (> 4 x a week)?
(If ☑ yes, please specify)

a. Traditional medicine (e.g., herbal remedy, natural supplements)	Yes ☐ No ☐
b. Vitamins D	Yes ☐ No ☐
c. Magnesium	Yes ☐ No ☐
d. Fish Oil	Yes ☐ No ☐
e. Creatine	Yes ☐ No ☐
f. Protein supplements (e.g. whey, casein, soy)	Yes ☐ No ☐
g. Beta-alanine	Yes ☐ No ☐
h. BCAAs (branch chain amino acids)	Yes ☐ No ☐
i. HMB (beta-hydroxy beta-methylbutyrate)	Yes ☐ No ☐
j. Nitric Oxide Precursors (e.g., citrulline malate)	Yes ☐ No ☐
k. Caffeine (e.g., caffeine tablets, daily coffee/tea)	Yes ☐ No ☐

2. Physical Activity

a. On average, how many steps do you take daily?	0 – 4999 ☐, 5000 – 9999 ☐, 10,000 – 14,999 ☐, Above 15,000 ☐.
b. Do you engage in at least 150 minutes of "moderate physical activity" a week? Yes ☐ No ☐	**Moderate physical activity** noticeably increases your heart rate and breathing but still allow you to carry on a conversation. These activities are more intense than light activities. e.g., Brisk walking, cycling, dancing, hiking, tennis (doubles), recreational sports. .
c. Do you also engage in at least 75 minutes of "vigorous-intensity physical activity" a week? Yes ☐ No ☐	**Vigorous-intensity activity** will leave you saying no more than a few words without pausing for a breath. e.g., Race walking, running, swimming laps, badminton singles.

Mid-Assessment – Week 5 (2nd Blood Collection)

Completed by:

Name of Coordinator:

Signature: Date:

Final Assessment – Week 8 (3rd Blood Collection)

Subject ID: ☐☐☐☐-☐☐☐

Date of Assessment: ☐☐/☐☐/☐☐

Are you on any long term medication? e.g., NSAIDS, antihistamines etc.
Yes ☐ No ☐ If ☑ yes, please specify:

1. Dietary Supplementation

Are you taking any of the following natural/ergogenic supplements regularly (> 4 x a week)?
(If ☑ yes, please specify)

a. Traditional medicine (e.g., herbal remedy, natural supplements)	Yes ☐ No ☐
b. Vitamins D	Yes ☐ No ☐
c. Magnesium	Yes ☐ No ☐
d. Fish Oil	Yes ☐ No ☐
e. Creatine	Yes ☐ No ☐
f. Protein supplements (e.g. whey, casein, soy)	Yes ☐ No ☐
g. Beta-alanine	Yes ☐ No ☐
h. BCAAs (branch chain amino acids)	Yes ☐ No ☐
i. HMB (beta-hydroxy beta-methylbutyrate)	Yes ☐ No ☐
j. Nitric Oxide Precursors (e.g., citrulline malate)	Yes ☐ No ☐
k. Caffeine (e.g., caffeine tablets, daily coffee/tea)	Yes ☐ No ☐

2. Physical Activity

a. On average, how many steps do you take daily?	0 – 4999 ☐, 5000 – 9999 ☐, 10,000 – 14,999 ☐, Above 15,000 ☐.
b. Do you engage in at least 150 minutes of "moderate physical activity" a week? Yes ☐ No ☐	**Moderate physical activity** noticeably increases your heart rate and breathing but still allow you to carry on a conversation. These activities are more intense than light activities. e.g., Brisk walking, cycling, dancing, hiking, tennis (doubles), recreational sports. .
c. Do you also engage in at least 75 minutes of "vigorous-intensity physical activity" a week? Yes ☐ No ☐	**Vigorous-intensity activity** will leave you saying no more than a few words without pausing for a breath. e.g., Race walking, running, swimming laps, badminton singles.

Final Assessment – Week 8 (3rd Blood Collection)

Completed by:

Name of Coordinator:

Signature: Date: