UNIVERSIDAD DE COSTA RICA

EM Escuela de Medicina

EM-878-2015
29 de setiembre de 2015

Dr. Luis Bernardo Villalobos Solano
Decano
Facultad de Medicina

Estimado señor:

UCR FM 16:28 29/09/15

De la manera más atenta, me permito indicar algunas preocupaciones en relación con la solicitud que están haciendo, tanto el Dr. Sixto Bogantes como el Dr. Gabriel Torrealba, ambos profesores de nuestra unidad académica, en relación a un curso, que según indica está inscrito en la Facultad de Medicina, del cual la Escuela de Medicina no tiene ningún conocimiento, al igual que se menciona que hay un coordinador, de un Centro UCR-Harvard PPCR-2015, y que se asocia con "La Catedra de Medicina UCR, del Hospital Rafael Angel Calderón Guardia", como es de su conocimiento hace mucho tiempo no se usa los términos de "Catedra" sino de Departamentos.

En este marco, se está haciendo invitación para estos docentes y solicitudes de viáticos de más de 1000 dólares, los cuales según usted nos ha indicado por normativa se deben justificar. Debido a que se hace referencia en toda la documentación, que dicho curso está en la Facultad de Medicina, para efectos de transparencia y en búsqueda de dar una respuesta adecuada a estas solicitudes me permito solicitarle la siguiente información:

a- En cuál comisión de la Facultad de Medicina se aprobó este curso, y en cuál vicerrectoría está inscrito.
b- Si fue en el Consejo Asesor de la Facultad, también indicarme en qué sesión y en cuál acta está. O en el caso que fuera en una comisión de la Facultad, si le es posible enviarme el acta donde dicha comisión aprobó este curso, o acta, para tener conocimiento en qué términos está y la posible utilidad para nuestros docentes.
c- Si existe algún componente, en estos cursos, de financiamiento externo, sea apoyo de entes externos a nuestra institución y en general cómo se financia este curso.
d- Si cuenta con las autorizaciones de la Universidad de Harvard para utilizar los logos de esta institución y quiénes dieron este aval.
e- Quién autorizó el uso del logo de la UCR, que no está cumpliendo con la normativa institucional actual, que usted conoce.

f- Dónde está inscrito el Centro UCR-Harvard PPCR, y a que vicerrectoría pertenece, y como se eligen, en este centro, los directores y qué calidades tienen, en cuál acta está dicha elección. Puesto, que revisando la base de datos de nuestros profesores, es de nuestro conocimiento que el Dr. Miguel A. Barboza Elizondo cuenta con un grado de licenciatura y una Especialidad, y recién se nombró (2015), por parte de la Escuela de Medicina, dentro del Departamento del Hospital Calderón Guardia, por lo tanto no está en régimen académico aún.

g- Dentro de la participación que menciona el Dr. Torrealba, en su solicitud, en la actividad que desea asistir en Brasil, indica que va a presentar un proyecto cuyo acrónimo es PETKO, *Pilates excercise Training before Knee arthroplasty in patients with Osteoarthrosis-A two-arm, randomized, open-label phase-II clinical trial,* donde indica una fuente de financiamiento y todo el proyecto, en el que se reclutan seres humanos y no se indica en que comité ético se aprobó, tampoco se indica si se ha presentado ante la Vicerrectoría de Investigación y demás aspectos institucionales, que no tiene relación con su especialidad y cursos que imparte.

h- Si existe, algún convenio entre la Universidad de Harvard y la Facultad de Medicina de la UCR, que avale este curso, ya que revisando la página institucional de Asuntos Internacionales no se indica nada al respecto.

Realmente, le agradecería si usted puede facilitarme toda esta información, lo antes que le sea posible, para tener conocimiento de esta y valorar la aprobación de esta solicitud de viáticos, siguiendo la normativa de nuestra institución.

Sin otro particular, se despide atentamente,

Dra. Lizbeth Salazar Sánchez
Directora

UNIVERSIDAD DE COSTA RICA DIRECCION ESCUELA DE MEDICINA

C: Vicerrectoría de Docencia
Vicerrectoría de Acción Social
Vicerrectoría de Investigación
Oficina de Asuntos Internacionales
Dr. Marco Zuñiga M., Director Departamento de Anatomia
Dr. José A. Mainieri, Director Departamento Clínico HRCG

Adj. Documentos indicados
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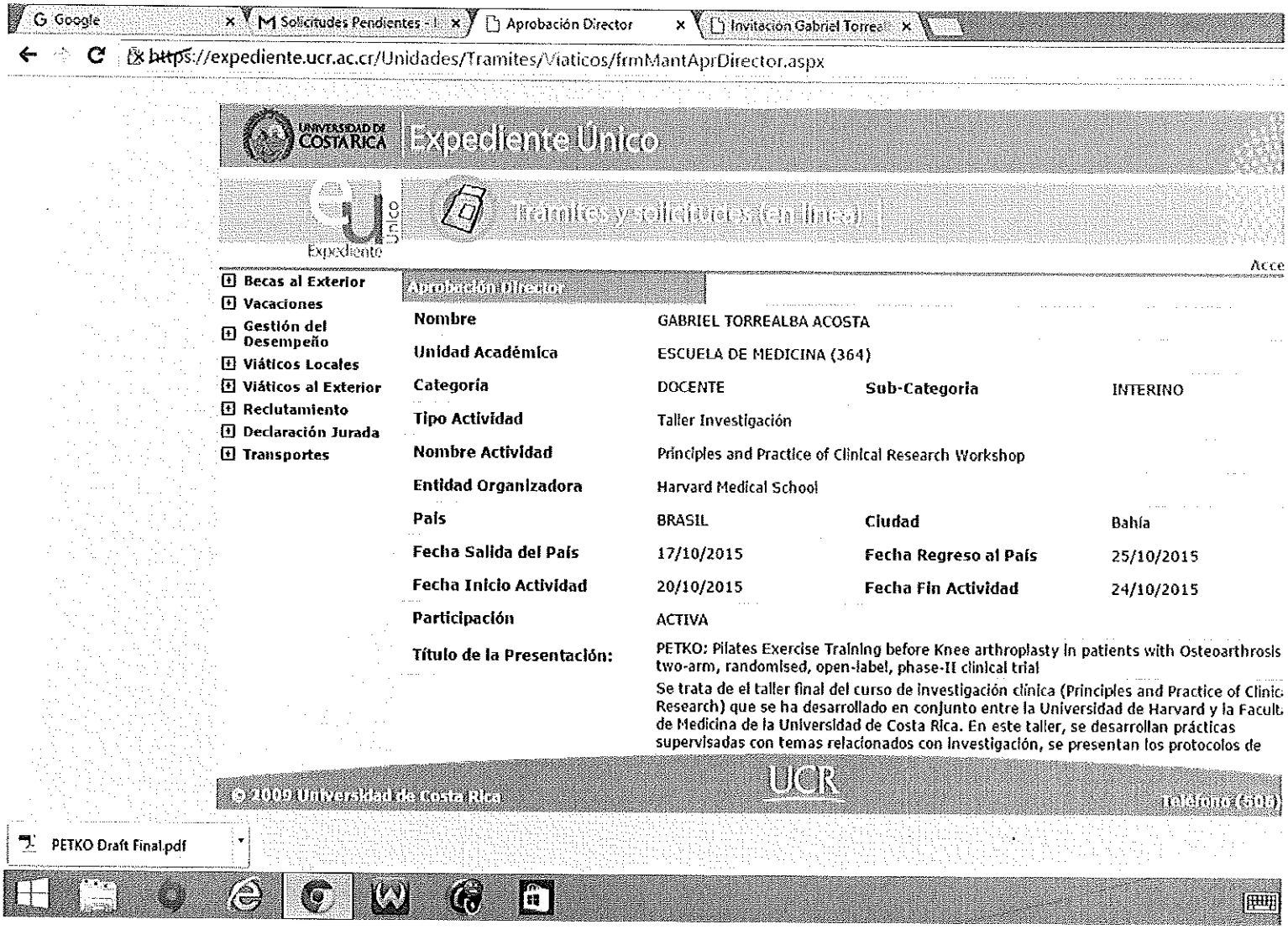
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Nombre GABRIEL TORREALBA ACOSTA
Unidad Académica ESCUELA DE MEDICINA (364)
Categoría DOCENTE
Sub-Categoría INTERINO
Tipo Actividad Taller Investigación
Nombre Actividad Principles and Practice of Clinical Research Workshop
Entidad Organizadora Harvard Medical School
País BRASIL
Ciudad Bahía
Fecha Salida del País 17/10/2015
Fecha Regreso al País 25/10/2015
Fecha Inicio Actividad 20/10/2015
Fecha Fin Actividad 24/10/2015
Participación ACTIVA
Título de la Presentación:
PETKO: Pilates Exercise Training before Knee arthroplasty in patients with Osteoarthrosis two-arm, randomised, open-label, phase-II clinical trial
Se trata de el taller final del curso de investigación clínica (Principles and Practice of Clinic Research) que se ha desarrollado en conjunto entre la Universidad de Harvard y la Facult de Medicina de la Universidad de Costa Rica. En este taller, se desarrollan prácticas supervisadas con temas relacionados con investigación, se presentan los protocolos de
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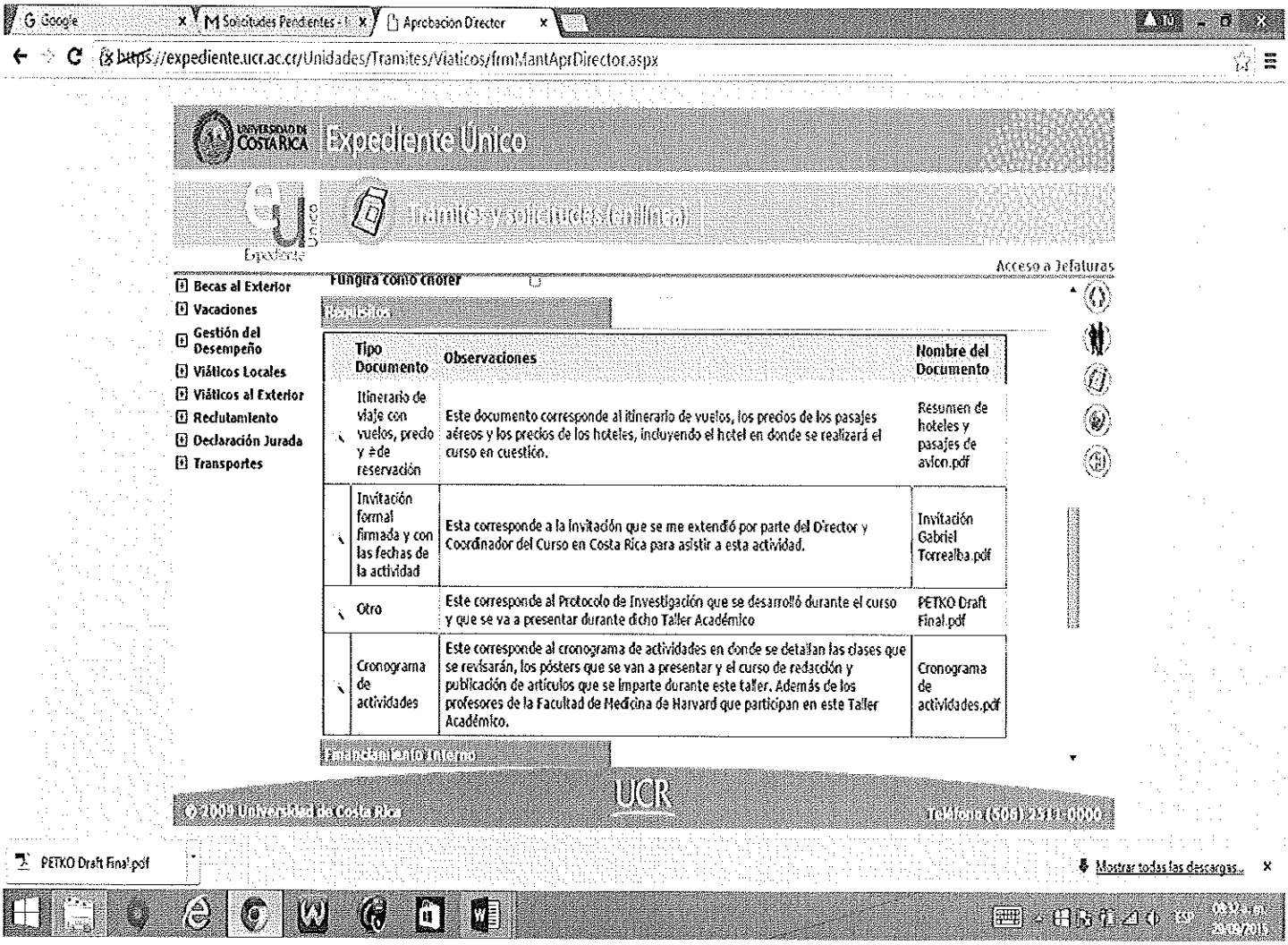
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Nombre del Documento
Itinerario de viaje con vuelos, precio y # de reservación
Este documento corresponde al itinerario de vuelos, los precios de los pasajes aéreos y los precios de los hoteles, incluyendo el hotel en donde se realizará el curso en cuestión.
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Invitación formal firmada y con las fechas de la actividad
Esta corresponde a la invitación que se me extendió por parte del Director y Coordinador del Curso en Costa Rica para asistir a esta actividad.
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Otro
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Este corresponde al cronograma de actividades en donde se detallan las clases que se revisarán, los pósters que se van a presentar y el curso de redacción y publicación de artículos que se imparte durante este taller. Además de los profesores de la Facultad de Medicina de Harvard que participan en este Taller Académico.
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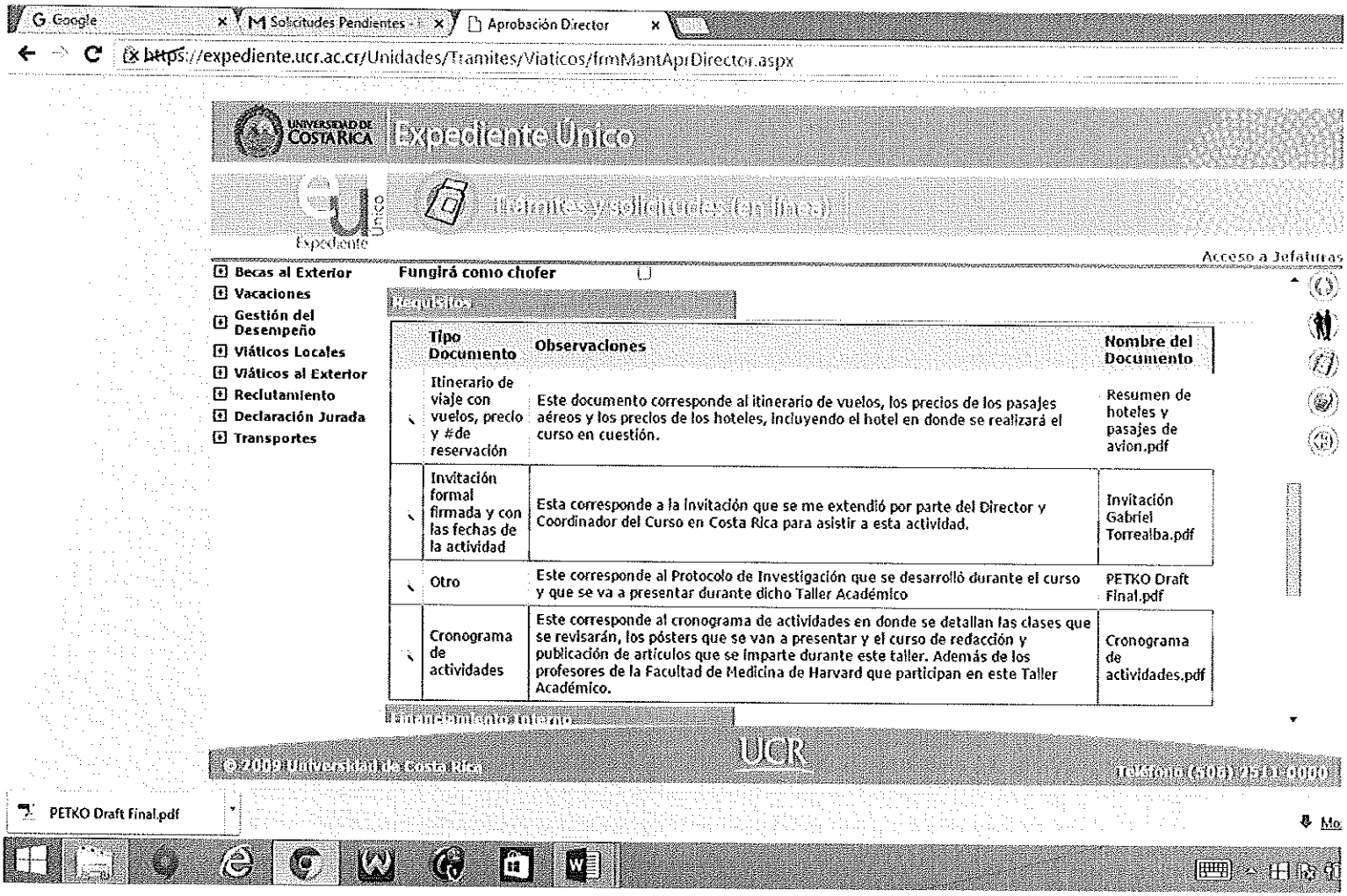
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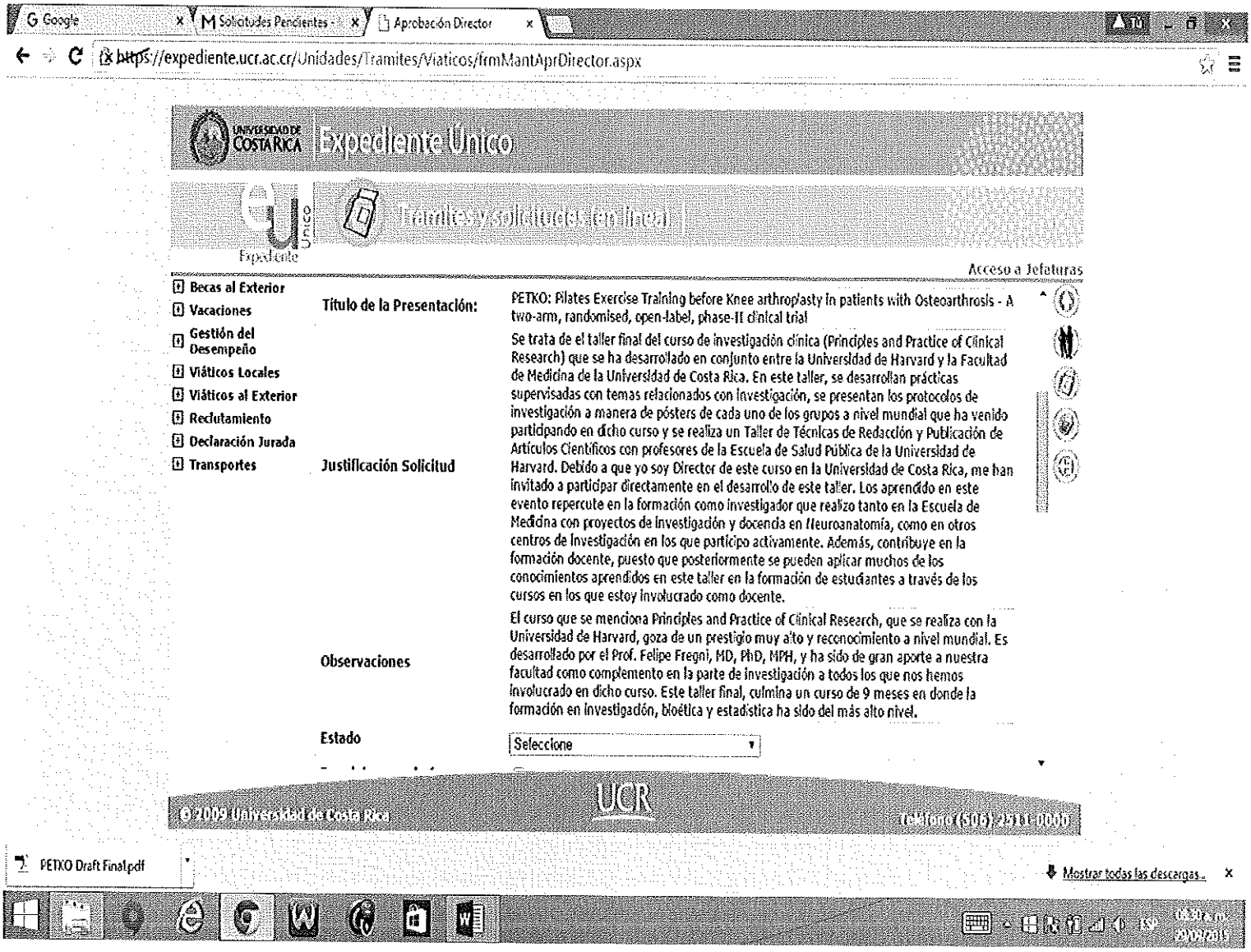
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Título de la Presentación:
PETKO: Pilates Exercise Training before Knee arthroplasty in patients with Osteoarthrosis - A two-arm, randomised, open-label, phase-II clinical trial
Justificación Solicitud
Se trata de el taller final del curso de investigación clínica (Principles and Practice of Clinical Research) que se ha desarrollado en conjunto entre la Universidad de Harvard y la Facultad de Medicina de la Universidad de Costa Rica. En este taller, se desarrollan prácticas supervisadas con temas relacionados con investigación, se presentan los protocolos de investigación a manera de pósters de cada uno de los grupos a nivel mundial que ha venido participando en dicho curso y se realiza un Taller de Técnicas de Redacción y Publicación de Artículos Científicos con profesores de la Escuela de Salud Pública de la Universidad de Harvard. Debido a que yo soy Director de este curso en la Universidad de Costa Rica, me han invitado a participar directamente en el desarrollo de este taller. Los aprendido en este evento repercute en la formación como investigador que realizo tanto en la Escuela de Medicina con proyectos de investigación y docencia en Neuroanatomía, como en otros centros de investigación en los que participo activamente. Además, contribuye en la formación docente, puesto que posteriormente se pueden aplicar muchos de los conocimientos aprendidos en este taller en la formación de estudiantes a través de los cursos en los que estoy involucrado como docente.
Observaciones
El curso que se menciona Principles and Practice of Clinical Research, que se realiza con la Universidad de Harvard, goza de un prestigio muy alto y reconocimiento a nivel mundial. Es desarrollado por el Prof. Felipe Fregni, MD, PhD, MPH, y ha sido de gran aporte a nuestra facultad como complemento en la parte de investigación a todos los que nos hemos involucrado en dicho curso. Este taller final, culmina un curso de 9 meses en donde la formación en investigación, bioética y estadística ha sido del más alto nivel.
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HARVARD MEDICAL SCHOOL

Principles and Practice of Clinical Research

26 de agosto de 2015

Dr. Marco Antonio Zúñiga Montero
Dirección
Departamento de Anatomía
Escuela de Medicina

Estimado doctor,

En este año, a través de la Decanatura de la Facultad de Medicina y con ayuda de la Oficina de Asuntos Internacionales de la Universidad de Costa Rica, se coordinó el establecimiento de un Centro Académico asociado a la Universidad de Harvard para desarrollar el Curso Principios y Prácticas en Investigación Clínica (PPCR 2015). Este curso se imparte mediante una modalidad virtual de forma semanal y es acompañado de talleres que se realizan en las instalaciones de dicha universidad. El Dr. Gabriel Torrealba, estudiante del sistema de posgrado, es estudiante activo del presente del año en curso y colabora como parte de la coordinación del mismo, además.

Como parte de las actividades propias del curso, el mismo organiza un taller de optimización de conocimientos, basado en talleres de estadística presencial, redacción de manuscritos y diseño de estudios clínicos, el cual forma parte de la nota del curso para aquellos estudiantes que puedan asistir, el cual es impartido por académicos del Departamento de Salud Pública y Epidemiología de la Universidad de Harvard, así como de otros colaboradores internacionales del curso. Este taller se llevará a cabo en la ciudad de Bahía, Brasil con fechas del 20 al 24 de octubre del presente año (puede ver la referencia del curso en la siguiente dirección: http://www.ppcr.hms.harvard.edu/index.php?option=com_content&view=article&id=207&Itemid=2369).

Resulta relevante recalcar la importancia de la participación del Dr. Torrealba a esta actividad, con el fin de fortalecer el conocimiento adquirido en el presente curso, y adicionalmente el beneficio que puede devengar en las labores investigativas que el doctor realice en su centro académico y laboral. La interacción con profesores expertos en el área, así como el apoyo para el proyecto de investigación que está realizando en este momento en el curso, resultan muy importantes para el crecimiento en investigación que está realizando el Dr. Torrealba

Le agradezco de antemano su apoyo a esta importante actividad académica. Se despide cordialmente,

Dr. Miguel A. Barboza Elizondo
Director del Centro U.C.R-Harvard PPCR 2015
Cátedra de Medicina UCR, HRACG
Email: miguel.barboza_e@ucr.ac.cr

Title

PETKO: **P**ilates **E**xercise **T**raining before **K**nee arthroplasty in patients with **O**steoarthrosis - A two-arm, randomized, open-label phase-II clinical trial.

1. Trial Registration

DATA CATEGORY	INFORMATION[32]
Primary registry and trial identifying number	ClinicalTrials.gov NCT00000004
Date of registration in primary registry	November 20th, 2015
Secondary identifying numbers	BNI-2014-01.
Source(s) of monetary or material support	National Institutes of Health
Primary sponsor	National Institutes of Health
Secondary sponsor(s)	Balanced Body®
Contact for public queries	*Group4,* MD, [(005) 0000-000] [Fantastic4@gmail.com]
Contact for scientific queries	*Group4,* MD, [(005) 0000-000] [Fantastic4@gmail.com] Principles and Practice of Clinical Research, Harvard University, Boston, MA, USA
Public title	PETKO: Pilates Exercise Training before Knee arthroplasty in patients with Osteoarthrosis.
Scientific title	PETKO: Pilates Exercise Training before Knee arthroplasty in patients with Osteoarthrosis - A two-arm, randomized, open-label phase-II clinical trial.
Countries of recruitment	Brazil

2. Budget/Funding

PETKO Budget

For this project there is an estimated total budget of $110,000, having a per-patient cost of $3400 and a per-control subject cost of $1000. The total estimate cost of the trial was calculated using an estimate number of 20 patients with 20 control subjects. The total budget breaks down in the following categories:

1. **Startup Costs**: This budget category includes all one-time expenses needed for the setup of the trial, before applying the protocol. In this category we have the following items:
   - **IRB fees**: this includes payment for the protocol elaboration and evaluation from the IRB assigned to the trial center. There is a designated fee of $5,000 for this purpose.
   - **Pilates equipment**: although the center where the trial is going to be conducted already has physical therapy installations, there is the need to buy the specialized Pilates equipment for the physical sessions of the intervention arm of the trial. There is a designated fee of $1,500 for the acquisition of this equipment.
   - **Patients' binders, paperwork and office supplies**: this budget item includes the office supplies for the elaboration of the allocation sequence envelopes, the CRFs employed on each patient and control, and any other paperwork needed for the conduction of the trial. There is a designated fee of $500 for this purpose.
   - **Advertising and recruitment activities**: this item includes costs for advertising on newspapers, Metro stations and radio for increasing public awareness of the trial. There is a designated fee of $5,000 for this purpose.
   - Hidden costs: there is an estimate budget of $5,000 for hidden and unexpected costs before and during the conduction of the trial.

2. **Trial implementation costs**: This budget category includes expenses per patient and per control for the implementation of the trial. For this category we have the following items:
   - **Patient travelling/parking**: There is an estimated cost of $20 that is given to each patient, for attending each of the pre-operatory physical sessions, and post-operatory physiatrist consults for this trial. For each patient that completes the whole set of physical sessions and physiatrist consults the total costs on this category would be of $400 per patient.
   - **Patient and companion feeding**: There is an estimated cost of $15 that is given to each patient and the companion that comes with the patient for feeding for each session and physiatrist consult of the trial. For each patient that completes the whole set of physical sessions and physiatrist consults the total costs on this category would be of $300 per patient.

- **Control travelling/parking**: There is an estimated cost of $20 that is given to each subject control, for attending each of the post-operatory physiatrist consults for this trial. For each of the subject controls that complete the whole set of physiatrist consults, the total costs on this category would be of $60 per subject control.
- **Control and companion feeding**: There is an estimated cost of $15 that is given to each subject control and the companion that comes with him for feeding for each of the physiatrist consults of the trial. For each subject control that completes the whole set of physiatrist consults, the total costs on this category would be of $45 per control.

3. **Personnel costs**: This budget category includes the payment for each of the personnel members of the trial, and has the following items:

- **PI salary per patient/control**: Budget category related to the payment given to the Principal Investigator for each patient/control recruited. It includes the patient evaluation, application of inclusion and exclusion criteria. allocation assignment and signing of informed consent. There is an estimated payment of $150 for each patient/control recruited in the trial.
- **Study coordinator salary per patient/control**: Budget category related to the payment given to the Study Coordinator for each patient/control recruited. It includes filling of patient's CRF, physical sessions assignment, monitorization of each patient/control travelling arrangements, monitorization for adverse effects of trial sessions, IRB reports. There is an estimated payment of $150 for each patient/control recruited in the trial.
- **Research assistant salary per patient/control**: Budget category related to the payment given to the Research Assistant for each patient/control recruited. It includes filling of patient's CRF, organizing patients/controls schedule, monitorization for patient's trial sessions, organizing advertising and patient/control recruitment. There is an estimated payment of $100 for each patient/control recruited in the trial.
- **Pilates certified instructor**: Budget category related to the payment given to the Pilates Certified Instructor for each session given to patients on the intervention arm of the trial. There is an estimated payment of $75 for each session given to the patients on the intervention arm of the trial.
- **Physiatrist per patients/controls**: Budget category related to the payment given to the Physiatrist for the evaluation of each patient/control after the surgery, in order to register the modifications on the scale ratings outcome for the trial. There is an estimated payment of $150 for each postoperatory consult given to the patient/control from both arms of the trial.
- **Biostatistician for allocation sequence generation and sealed envelope elaboration**: Budget category related to the payment given to the Biostatistician for the generation of allocation sequence of block randomisation and envelope elaboration. There is an estimated payment of $500 for this purpose.
- **Biostatistician for data analysis (including interim analysis)**: Budget category related to the payment given to the Biostatistician for the data analysis

(including interim analysis) of the results obtained after trial execution. There is an estimated payment of $5,000 for this purpose.

PETKO Funding

Funding for the PETKO trial research project will be based on a grant by National Institutes of Health (NIH). This will cover patient transportation services, salaries of researchers and a biostatistician, also one computer for data analysis and office supplies.

Balanced Body ® (California, USA) is funding the training of the two certified instructors and one physiatrist; it also gives advertising, an educational small talk for patients and the equipment for the exercises needed for the PETKO trial.

The knee joint prosthesis will be manufactured by Zimmer, Inc (Indiana, USA). The main objective is to achieve the monetary support required for obtaining the prosthesis needed for all the patients.

The design, management, analysis and reporting of the study are entirely independent of the manufacturer of the knee joint prosthesis.

3. Background and Rationale

3.1 Background

Osteoarthrosis (OA) is the most common joint disease around the world. It affects millions of people worldwide and it is responsible for considerable disability even at younger ages and its costs are estimated to be over 100 billion dollars a year in USA (1).

It is defined as a degenerative inflammatory disease of the hyaline cartilage in the synovial joints, but recent evidence shows that OA involves all the joint complex, including bones (2). OA typically affects individuals after 40 years, and its prevalence increases with aging. Age, race and sex influences OA epidemiology. In individuals over 65 years, at least 50% have radiographic findings of OA. The prevalence increases sharply after 50 years, probably because of age-related diminished blood supply and cartilage matrix alterations. Women are more affected than men, and the prevalence of knee OA is 70% higher in women (2).

OA is more frequent in white people after 65 years, but black women seem to have a much higher incidence of knee OA (3). Knee joint is by far the most affected site, but other joints may also be compromised. Once thought to be a condition caused by aging only, OA pathophysiology is now considered multicausal. Evidence points to more than one cause acting in the same individual, and genetic, environmental, infectious and immune factors play distinct roles (4). Basic pathophysiology of OA consists of an excessive burden in a healthy joint, or normal loading on an already diseased joint. Main risk factors for OA are: age, race, sex, genetics (family history), trauma, infections,

previous bone and/or joint disease, sickle cell disease, metabolic diseases, menopause and obesity.

The concept of OA as a degenerative disease has been modified recently because of increasing evidence that OA has an important inflammatory pathway. OA seems to be part of a spectrum lying between a normal joint and rheumatoid arthritis (5) (4). Importantly, the pattern of immune response in joints of OA is different from that of rheumatoid arthritis (5).

3.2 Mechanisms

A complex interplay of genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation have lead to articular cartilage failure and the development of OA. Chondrocytes are the most important cells responsible for the development of the osteoarthritic process. Two principal mechanisms are thought to initiate osteoarthritis, the first involves damage to normal articular cartilage by physical forces, which can be either a single event of macrotrauma or repeated microtrauma, and the second relates to chondrocyte reaction to injury caused by degradative enzymes and by elaborating inadequate repair responses. (Peyron JG, Altman RD. The epidemiology of osteoarthritis. In: Osteoarthritis: Diagnosis and Management, Second Edition, Moskowitz RW, Howell DS, Goldberg VC, Mankin HJ (Eds), WB Saunders, Philadelphia 1992. p.15.)

Multiple risk factors have been associated in the pathogenesis of osteoarthritis. There are several studies that suggest the presence of a genetic contribution to the risk of developing OA. Loughlin J. Genetic epidemiology of primary osteoarthritis. Curr Opin Rheumatol. 2001 Mar;13(2):111-6. Intrinsic factors involving joint repair have identified metalloproteases, a class of zinc-containing enzymes, as active components in the development of osteoarthritis. Inhibitors of these enzymes are produced by connective tissue cells, and it is thought that an imbalance between the level of these inhibitors and the enzymes leads to an overall catabolic effect and to cartilage degradation. Other protease such as plasminogen is believed to activate collagenase and to lead to cartilage destruction as well. Kim JH, Jeon J, Shin M, et al. Regulation of the catabolic cascade in osteoarthritis by the zinc-ZIP8-MTF1 axis. Cell 2014; 156:730.

The role of cytokines has also been studied, although OA is not considered an inflammatory disease, there is evidence suggesting the effect of catabolic cytokines, such as interleukin 1, and anabolic cytokines such as insulin-like growth factor I, involved in cartilage degradation. Fernandes JC, et al. The role of cytokines in osteoarthritis pathophysiology. Biorheology. 2002;39(1-2):237-46. The association between aging and osteoarthritis is very strong and may be related to systemic changes with aging, such as loss of muscle mass, declining hormone levels, and impairments in proprioception, also it appears to be a stress response with aging which promotes a proinflammatory state and an age-related decrease in the number of chondrocytes in the articular cartilage.Loeser RF. The effects of aging on the development of osteoarthritis. HSS J 2012; 8:18.

Regarding the role of exercise, evidence has shown different aspects of its effect in development and progression of OA. The direct effect of exercise or mechanical loading likely relates to the magnitude and duration of the physical stimulus that is sensed by the chondrocytes within the cartilage. Several influences inside and outside

of a weightbearing joint may considerably alter the impact created by a given activity or exercise prior to its perception by the chondrocytes within that joint. Davis AM. Osteoarthritis year in review: rehabilitation and outcomes. Osteoarthritis Cartilage. 2012 Mar;20(3):201-6.

A sufficient degree of joint loading appears to be a critical factor for cartilage health, since similar changes have been observed with experimental disuse atrophy. Weakness of the quadriceps group may be etiologically related to the initiation and/or progression of osteoarthritis of the knee. The mechanism may include a deficit in the terminal portion of the swing phase of gait, thereby creating an increased in contact force. Proprioceptive deficits may slow protective periarticular muscular reflexes and, therefore, may increase the risk to cartilage integrity imposed by mechanical loads.

However, prospective, controlled trials of exercise versus equivalent medical attention are needed to provide direct visualization of the impact of exercise on cartilage integrity both in those at risk for osteoarthritis and in those with early osteoarthritis.

3.3 Existing knowledge

Since 2010 over 600.000 total knee arthroplasties (TKA) were being performed annually in the United States and the number of total knee replacements is expected to grow by 673 percent to 3.48 million procedures by 2030 (6). Modern TKA is performed by means of the resection of the diseased articular surfaces of the knee and later resurfacing with metal and polyethylene prosthetic components, and if the patient is selected well, significant pain relief, improved function and quality of life is seen (7).

Pilates method combines the faculties of strength gymnastics, boxing, self defense, instruction, dance and fitness training and was developed by Joshep Hubertus Pilates in New York from the late 1920s to 1960 (8) (9).

Although Pilates method is an integrative approach that involves a complete body workout, this form of exercise is very flexible and can be individualized to meet postoperative rehabilitative needs as that concerned to TKA (8) (9) (10).

Levine (8, 10) reported promising results in a retrospective analysis of 38 patients that followed specific Pilates protocols based on a preoperative regimen of 2-6 weeks with an apparently improved compliance among female joint replacement patients with 73% maintaining and active role in Pilates at one year.

Pre-surgical Pilates routines are aimed at: a) Establishing muscle memory and b) improving strength, mobility and range of motion of the involved and adjacent joints. Pilates also helps patients to adopt a way to tolerate their symptoms and to stimulate function and participation in activities despite preoperative pain and stiffness.

Pilates mechanics help patients in improving his pre and post-surgical recovery by improving the following basic principles (8, 10).

a) Improves core muscle stabilization prior to initiating arm or leg movements
b) Improves control as the ability to monitor movements while performing them with the correct mindful intent.

c) Improves precision as the ability to focus on completing an exercise in a proper way.
d) Improves concentration creating "concentration places"
e) Allows a better breathing control crucial to performing these kind of exercises
f) Improves flow, that means the connection of one movement to the next.

Pilates preoperative routines also maximize function and flexibility, are easily implemented into a home-based program, allows the formation of a strong relationship with a certified instructor that can be maintained postoperatively and also accommodate to known pre and post-surgical precautions and range of motion restrictions.

3.4 Need for a trial (innovation aspects)

Benefits of pre-operative Pilates routines in the elderly had become evident in retrospective and observational patient data analysis as the ones reported by Levine (8, 10). Pilates is a potential useful tool in rehabilitation and prevention programs in the elderly population, a large randomized trial is therefore needed because of the potential benefits of Pilates intervention to increase muscle strength, flexibility, autonomy and quality of life and decrease pain in elderly patients with other osteomuscular conditions. In spite of the previous mentioned benefits and advantages of the pre-surgical Pilates routines in TKA there is a certain need for prospective randomized studies using Pilates based methods that validate the theoretical benefits of Pilates routines in TKA.

3.5 Significance/impact of study

Even though there have been improvements in surgical techniques in minimally invasive procedures, there is a lack of evidence regarding studies and standardized interventions concerning preoperative care for patients suffering severe primary OA with indication of TKA. It´s necessary to search for methods to decrease the average length of hospital stay and to perform an earlier post operative discharge and recovery. Consequently, reducing the costs, ratio of health related infections and hospital stay. (11) (12)

Since 1990 to 2000, a decrease in the average length of hospital stay was noted from 9,7 to 5,3 days (Ganz et al., 2003), mainly regarding development in minimal invasive techniques, aggressive pain management, rehabilitation and regional anesthesia. The main issue of this project is to demonstrate that this choice of physical therapy may maximize the preoperative function, abbreviate the patient´s timeline to return to daily activities and to prepare the whole body to a better post-operative rehabilitation (10).

Thus, this may be the first study of a series of others regarding non pharmacological therapeutic interventions and move its frontier forward towards a new field of knowledge in the pre-operative area, extrapolating the interventions to others surgeries not orthopedics, with a relatively non expensive nor invasive and reproducible method.

4. Choice of Comparators

Pilates exercise is a common technique in physical training. However, experience in the elderly population is limited. In addition, there is no strong evidence to support preoperative exercise in patients over 60 years undergoing TKA and Pilates may be a useful technique in order to improve the knee injury and Osteoarthritis Outcome Score (KOOS). Therefore, due to exploratory nature of the intervention in our study the control group will not be intervened (no exercise) only usual activity will be documented before surgery.

5. Objectives

5.1 Research question

Does six-weeks of pre-operative Pilates routine program (3 times a week) in patients over 60 years with severe primary ostheoarthrosis (defined as Kellgren-Lawrence grade 3 and 4) with indication of total knee arthroplasty improve the Knee injury and Osteoarthritis Outcome Score (KOOS) Activities of Daily Living (ADL) compared with standard pre-operative therapy, on follow-up at 30, 60 and 90 days?

P: Patients over 60 years, with severe primary knee ostheoarthrosis (defined as Kellgren-Lawrence grade 3 and 4) with indication of total knee arthroplasty.
I: Six weeks of pre-operative Pilates routine program (3 weekly sessions)
C: Pre-operative standard care.
O: Primary outcome: improvement in the Knee injury and Osteoarthritis Outcome Score (KOOS) Activities of Daily Living (ADL).

- Secondary outcomes improvement in Western Ontario and McMaster Universities Arthritis Index (WOMAC), pain, walking capacity, range of motion, and hospital length of stay.

T: 30, 60, and 90-day follow-up after surgery.

5.2 Primary and Secondary Aims

- Primary Aim

Determine the effect of pre-operative Pliates routine on increasing the knee injury and osteoarthritis outcomes of patients with severe osteoarthritis who undergo total knee arthroplasty.

- Secondary Aim

Determine the effect of pre-operative Pliates routine on improving WOMAC, pain, walking capacity, range of motion, and hospital length of stay for patients with severe osteoarthritis who undergo total knee arthroplasty.

5.3 Hypotheses

It is hypothesized that a Pilates routine, previous to a total knee arthroplasty for severe osteoarthritis, would improve post-operative KOOS ADL scale, compared to standard treatment.

As secondary hypothesis, pre-operative Pilates routine will allow post-operative improvement in WOMAC, pain measured with VAS and KOOS Pain score, walking capacity measured using KOOS score, range of motion and length of stay for patients with severe OA with TKA

6. Trial Design

Parallel group, two-arm, open-label, unicentric, superiority trial with 1:1 allocation ratio, performed in all patients undergoing unilateral TKA for primary OA within the orthopaedic department of a hospital with expertise in TKA surgeries, and with physical medicine and rehabilitation departments available for compliance with the study needs.

6.1 Trial Design

The study will be a two-arm, open-label, parallel group, unicentric, superiority trial with 1:1 allocation ratio, including all patients with sustained mechanical pain from severe primary knee OA, as defined by radiological grade 3 and 4 following Kellgren-Lawrence's classification, undergoing unilateral TKA.

Patients will be randomly assigned to a pre-operative Pilates routine, with an exercise schedule of 3 times a week sessions for six weeks before surgery, or no pre-operative training, followed by usual physiotherapy after surgery.

Patients will be evaluated by physiatrist, who will assess the KOOS score, WOMAC, visual analog scale for pain and range of motion at baseline, 30, 60 and 90 days after surgery. Length of hospital stay will also be assessed for each patient.

6.2 Study Setting

The study will be performed in an academic hospital with orthopaedic department that performs a minimum of 3 TKA weekly, thereby with expertise on this type of surgery and facilitating the enrollment of patients. The setting must have available physical medicine and rehabilitation, physiotherapists and Pilates expert professionals, for the intervention, follow up and collection of data.

The study setting must create or adapt a space for Pilates training sessions, with adequate equipment and materials.

7. Eligibility Criteria

Inclusion Criteria

1. Primary Knee Osteoarthritis
2. Presence of radiologic OA signs at grade 3 and 4 according to Kellgren and Lawrence
3. Older than 60 years
4. Guidelines indication for total knee arthroplasty
5. Preserved ambulation
6. Availability for scheduled visits

Exclusion Criteria

1. Previous surgical interventions on the affected knee
2. Postoperative complications
3. Medical comorbidities that restrain Pilates routine
4. Not completing at least 16 of 18 sessions programmed

8. Recruitment Strategy

Patients will be recruited through convenience sampling in a prospective consecutive way, obeying inclusion and exclusion criteria, until the calculated sample size is reached.

9. Interventions

9.1 Interventions

Included patients in the trial will be randomised via computer software in equal proportions between patients that will receive pre-surgical intervention and patients with no different intervention than the standard care of the Medical Center prior to the surgery.

The intervention will be over 6 weeks of pre-operative Pilates routine, three times per week under direction of Pilates certified physical therapist. Each patient's program will be individualized according to their baseline physical capacity and reevaluate and advance accordingly after 3 weeks. The sequence consists of an individual Pilates routine 3 times a week (18 sessions in total). The materials needed for this exercises will include a resistance bands, physioballs, a mat and foams.

The routine will be as follows:

Table 1. Routine of Pilates Exercise designed for the intervention of PETKO Trial

Step	Pilates Exercise	Repetitions/time
1.	Modified Hundred	50 repetitions
2.	Rest	3 minutes
3.	Modified Hundred	50 repetitions
4.	Roll-Down	8 repetitions
5.	Single Leg Circle Left clockwise	8 repetitions
6.	Single Leg Circle Right clockwise	8 repetitions
7.	Single Leg Circle Left counterclockwise	8 repetitions
8.	Single Leg Circle Right counterclockwise	8 repetitions
9.	Single Leg Stretch	8 repetitions (4 repetitions each leg)
10.	Double Leg Stretch	8 repetitions
11.	Rest	5 minutes
12.	Single Straight Leg Stretch Right	8 repetitions
13.	Single Straight Leg Stretch Left	8 repetitions
14.	Spine Stretch Forward	5 repetitions
15.	Rest	5 minutes
16.	The Saw	16 repetitions (8 repetitions each side)
17.	The Swan Prep	4 repetitions
18.	Single Leg Kick	10 repetitions (5 each leg)
19.	Side Kick Left side	6 repetitions
20.	Side Kick Right side	6 repetitions
21.	Teaser Prep 1	6 repetitions

22.	Single Leg Stretch (with resistance band)	8 repetitions (4 repetitions each leg)
23.	End of the session	

(Adapted from: Levine B, Kaplanek B, Scafura D, Jaffe WL. Rehabilitation after total hip and knee arthroplasty: a new regimen using Pilates training. Bull NYU Hosp Jt Dis. 2007;65(2):120–125)

The surgery will be scheduled exactly one week after the last session of Pilates. Both groups will receive same medical follow-up and standard physical therapy established for this kind of procedure after the surgery.

The KOOS and the WOMAC will be assessed in the physiatrist post-operative control appointments at 30, 60 and 90 days after the surgery in both groups. Also, the pain level, range of motion of the knee will be evaluated the same days.

9.2 Modification/discontinuation

Any patient can discontinue his/her participation in the trial at any moment he/she decides. Patients will be encouraged to keep in the trial.

A patient that gets an injury during any of the sessions that doesn't allow him/her to execute the routine will be withdrawn from the trial.

If a patient has limitations reproducing the complete routine, it would be accepted as a completed if the patients does at least 50% of the proposed repetitions in every stage.

A completed intervention will be accepted if the patient completes at least 16 of the 18 programmed sessions. A patient that fails to complete at least 16 sessions will be withdrawn from the trial. This cut-offs for a completed routine were chosen arbitrarily.

10. Adherence

In order to increase adherence of the patients in PETKO Trial, professional support will be given during the routines by two Pilates certified physical therapists that will have the task to educate the patients during the execution of the routines and give advice about the importance to keep attending the scheduled physical sessions; they will also clarify any doubts the patients have regarding the intervention.

The Study Coordinator will be the 24/7 professional contact for any doubt, issues or potential adverse effects that may appear during the conduction of the trial.

The Research Assistant will call the patients the day before every session and will confirm the attendance of the patients or will reschedule them for another available day in order to fulfill the required amount of sessions.

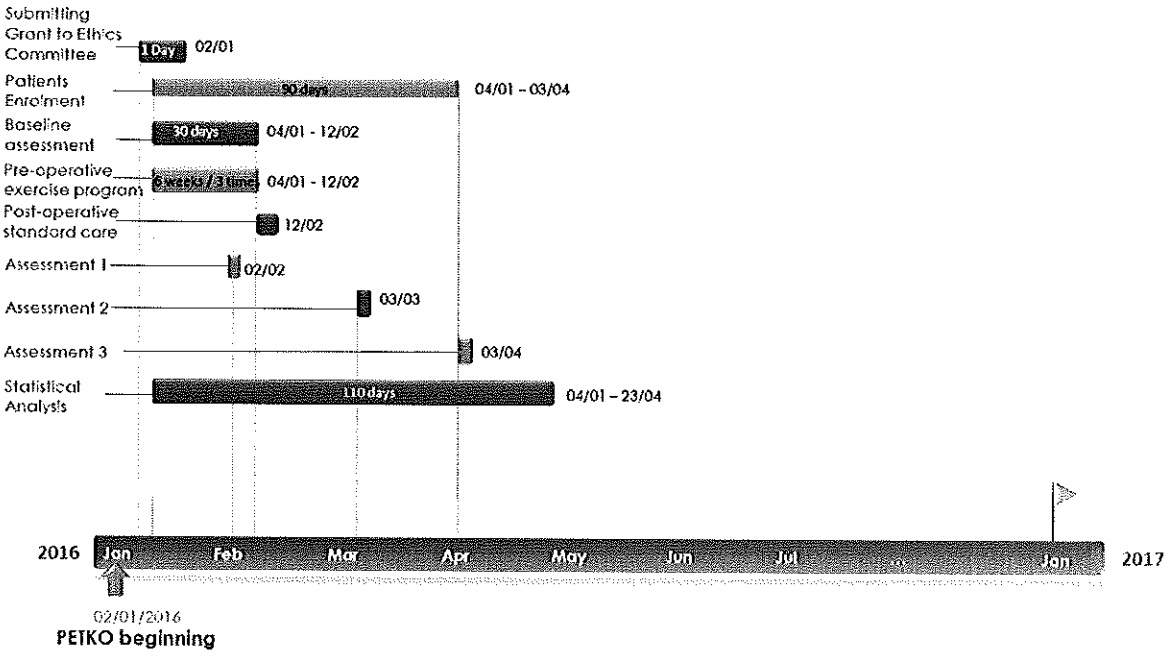
Patients and their companions will be receiving transportation or parking fees to attend each therapy and the follow-up session. They will also receive a healthy snack for each session attended.

11. Outcomes

Considering what is expected from a TKA, the primary outcome of choice will be KOOS-ADL subscale. All remaining KOOS subscales (symptoms, stiffness, pain, sports and recreational activities and quality of life), as well as passive and active articular range of motion (ROM) and total hospital length of stay (LOS) will be considered as secondary outcomes.

For KOOS subscales, we opted for a minimal clinically important change of 10 points (Roos and Lohmander 2003). A 10-degree difference in ROM and a one-day hospital LOS reduction will be accepted as clinically relevant. All outcomes will be measured in time frames of 30-, 60-, 90 post-operative days.

12. Timeline



13. Randomization

Participants will be randomly assigned to either a control group (standard care before TKA) or an experimental group (Pilates therapy before TKA), with a 1:1 randomization, using permuted blocks of random sizes.

The sequence for the permuted blocks will be generated using a computerized random numbers generator. Participants will be randomized on an allocation ratio of 1:1. The randomization process will be based on a permuted block randomization, without stratification. This was the chosen method because the patients included in the study are expected to be homogenous based on the inclusion and exclusion criteria proposed. Because using a stratification randomization may require a larger sample, it was preferred a block randomization for this purpose. Also, there is the possibility of adjusting by age, weight and severity of disease on the statistical analysis after the results are obtained.

The block sizes will be defined on a 4 and 6 random permuted sizes, this sequence and the sizes of the blocks will be hidden from the recruitment staff as well as from the patient, only the person that generated the sequence and elaborated the envelopes knows is, in order to keep and adequate allocation concealment.

14. Randomization - allocation concealment

14.1 Randomization – allocation concealment

Allocation sequence is going to be concealed from the PI by a Biostatistician. The mechanism of implementing allocation sequence will be done by sequentially numbered, otherwise identical, sealed envelopes, each containing a 2-inch by 2-inch paper with a written code designating intervention or control. These papers are going to be placed in a folded sheet of aluminum foil fitted inside the envelope. There are not detectable differences in size or weight between intervention and control envelopes. Envelopes will be opaque and lined inside with carbon paper. Once done, envelopes will be given to the Principal Investigator.

Possible patients will be refered to the PI, who is in charge of running inclusion and exclusion criteria. After doing this, the PI will explain and ask for the inform consent to the patient. Once obtained the informed consent, the patient name will be written on the envelope and then open by the Principal Investigator in front of the patient in order to know his allocation. After this, envelopes will be sent to the Study Coordinator, whom will be in charge of the arrangements with the patients.

14.2 Implementation

The allocation sequence is going to be a computer generated random number list prepared by a Biostatistician, also responsible for assigning participants to interventions by the method of allocation concealment described before. Subjects meeting eligibility criteria will be referred to the Principal Investigator, the one in charge of applying the inclusion and exclusion criteria.

15. Blinding

15.1 Blinding

An open label trial was chosen as the best design for our trial, so blinding won't be necessary. The final data analysis and the interim analysis will be performed by a blinded statistician.

15.2 Emergency unblinding

As there is no blinding mechanism in the trial, there is no need for emergency unblinding plan.

16. Data Management

In order to maintain confidentiality of participant information, all subjects will be assigned a unique ID number that is not related to their name, social security number or other personal identifier. Documents for data collection will include ID only and the list of subjects names, addresses or phone numbers and corresponding ID codes will be kept separate. As part of informed consent, subjects will be assured that their personal information, data from medical records and data collected as part of the project will only be accessed as necessary for research, safeguarding the security and confidentiality. There will be records of all subjects recruited and not eligible, also for those who agreed to participate and how many eventually did participate.

KOOS questionnaire will be given to the patient by the physiatrist in a paper form, followed by checking by the research assistant to make sure all the questions are answered. When data is missing, the reason will be specified. Next, the hole case report form (CRF) will be double checked by the research assistant and the study coordinator. CRF information will be entered in a computer database with double typing and data checking.

Paper forms will be organized in files in a locker and computer database will have restricted access with login and password.

Before analyses are run data will be checked against the raw data to be sure there are no discrepancies or coding errors.

17. Sample Size Calculation

The sample size was calculated on the basis of the primary hypothesis. Sample size was calculated from a previous study (E. Huber et al 2015), where values for expected means differences (an estimated effect size of 2 points) and sample standard deviation (1.7) were obtained. Sample size was estimated with a power of 0.8, and an alpha level of 0.05. In addition a 15% was added to the sample size in order to compensate for study dropouts.

Stata software was used to calculate sample size, obtaining an approximate number of 20 patients and 20 controls, giving a total sample of 40. Sample size was also increased in terms of compensating any given underestimation of standard deviation values, which were obtained through the literature review.

18. Statistical Analysis for primary and secondary outcomes

The intervention group will be compared with the control group in the primary and all secondary outcomes. For continuous variables analysis we will use T-tests when data is normally distributed and the Wilcoxon rank-sum (Mann-Whitney) test in the setting of non-parametric distribution. For categorical variables, Chi-square test or Fisher's exact test will be performed when appropriate.

Table 2. Variables, Outcomes and Methods of Analysis

Variable/Outcome	Hypothesis	Outcome measure	Methods of Analysis
Primary KOOS Activities of Daily Living (ADL) subscale	Improvement occurred	KOOS ADL subscale at baseline, 30-, 60-, and 90-day follow-up after surgery (continuous variable)	Unpaired T-test or Wilcoxon rank-sum test
Secondary KOOS Subscales (the other 4 of them): Pain, other Symptoms, Sport and Recreation Function Sport/Rec) and	Improvement occurred	KOOS Questionnaire score in each Subscale at baseline, 30-, 60-, and 90-day follow-up. Values ranging from 0 - worse -	Unpaired T-test or Wilcoxon rank-sum test

knee-related Quality of Life (QOL).		to 100 - better) (continuous)	
WOMAC score	Improvement occurred	WOMAC Questionnaire score at baseline, 30-, 60-, and 90-day follow-up (continuous)	Unpaired T-test or Wilcoxon rank-sum test
Pain (Visual Analog Scale - VAS)	Improvement occurred	VAS measured at baseline, 30-, 60-, and 90-day follow-up (continuous)	Unpaired T-test or Wilcoxon rank-sum test
Range of Motion (ROM)	Improvement occurred	Degrees, measured with a goniometer. (Continuous)	
Hospital Length of Stay	Decreased occurred	Number of days after surgery (continuous)	Unpaired T-test or Wilcoxon rank-sum test Unpaired T-test or Wilcoxon rank-sum test

19. Missing Data

For handling missing data, a Last Observation Carried Forward (LOCF) method will be used as a simple imputation approach.

20. Data Monitoring/Interim Analysis

20.1 Data Monitoring

As FDA's Guidance for Establishment and Operation of Clinical Trial Data Monitoring Committees states (14), a data monitoring committee (DMC) is most commonly used in studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such a cardiovascular event, cancer recurrence or fatal hemorrhage. Rates of mortality and/or rates of major mobility are well studied and reported by DMC (15). In that order of ideas and based in FDA recommendations the the following factors must be addressed when defining the viability and need of a DMC:

1) Risk to trial participants
2) Practicality of DMC review
3) Importance of DMC review in assuring scientific validity of the trial.

Also, the European Medicines Agency (EMEA) recommends to set a DMC in trials expected to take a long term even in non-life threatening diseases or in cases were the intervention or treatment has the potential to harm patients. For credibility purposes if the trial design contemplates a modification in the protocol during the process based on the interim analysis then a DCM is indicated to be constituted. (European Medicines Agency. Guideline on Data Monitoring Committes. EMEA, London. 2005)

PETKO trial has an inherent low risk to its participants given that the intervention is based on a predefined Pilates routine with clear inclusion criteria and specific contraindication profiles. A DMC reviewing task is not strictly needed in order to ensure the scientific validity of this trial. Because rating (KOOS scale definition) will be made by a trained and blinded statistician this will avoid the need of a whole committee that also would result impractical and will end with an increased cost of our whole trial.

PETKO trial's patients will have a six weeks intervention and then will be evaluated in their post-operative state at 30, 60 and 90 days. Taking in count that the sample for the trial is small (20 patients in the intervention group) and the fact that there are no plans of modifying the protocol regardless of the interim data, in addition to a short period of observation, a non-critical condition evaluated and an open-label trial design the establishment of a DMC won't represent an added benefit for the trial, besides it could signify a delay and unnecessary extension of the trial (Sydes M, et al. Data Monitoring Committees in Clinical Trials, Guidance for Research Ethics Committees, NHS, May 2010 // Lin, J et al. Establishing a data monitoring committee for clinical trials. Shanghai Arch Psychiatry. 2014 Feb; 26(1): 54–56).

20.2 Interim Analysis

An interim analysis will be performed when 75% of the subjects included in the trial complete the 90 days follow-up. This analysis will be held by a blinded for the allocation statistician, and the report will be given in a PDF file format locked for modifications (only allowed for the statistician to access).

The Haybittle-Peto boundary approach will be used for this analysis, a difference in the main outcome between the intervention and control groups with a $p<0.001$ will be

considered as statistically significant and thus, proof beyond reasonable doubt that the difference exists and the trial could then be stopped. (Freidlin, B et al. Stopping clinical trials early for benefit: impact on estimation. Clin Trials 2009;6:119-125 // Pocock, S. When (Not) to Stop a Clinical Trial for Benefit. JAMA, November 2, 2005—Vol 294, No. 17)

Since PETKO is an open-label trial, after the data of the interim analysis is obtained by the statistician, a copy of the data obtained will be given to the IRB (in order to keep proof that the data won't be altered) and simultaneously the principal investigator (PI) will get another copy. The Steering Committee, conformed by the PI, the study coordinator and the research assistant, will make the decision if the trial will continue or will be stopped and will report to the IRB about it.

21. Ethics

21.1 Consent or Assent

All study subjects must consent before being randomized. The study protocol and the inform consent must be approved by the institution review board. The principal investigator will be responsible to conduct the informed consent process. Any relevant change in the study protocol and/or the informed consent will be sent to the independent review board as a protocol amendment. After its approval, it will be informed to the study subjects and only then it will be implemented.

This protocol is going to be submitted to the Clinical Trials Data Bank http://www.clinicaltrials.gov. The principal investigator will be responsible to submit all the information necessary to fulfill these requirements.

21.2 Confidentiality

All the subjects' identities will be protected by a code and only the principal investigator and the primary study coordinator will have access to this information. The confidentiality of the subject´s data will be kept before, during and after the development of this trial and no personal information will be shared with the sponsor or any other institution that is not related directly to the patient care. Information will be provided to regulatory authorities according to current laws.

21.3 Authorship

This trial is intended for publication, even if terminated prematurely.

Authorship credit will be guided by ICMJE recommendations considering the following criteria:

1) Substantial contributions to conception and design, or revising it critically for important intellectual content

2) Drafting the article or revising it critically for important intellectual content

3) Final approval of the version to be published

- ICMJE. International Committee of Medical Journals Editors. Retrieved from http://www.icmje.org/icmje-recommendations.pdf on August 2nd 2015

22. Study Summary

WHO Trial Registration Data Set	**INFORMATION**
1. Primary Registry and Trial Identifying Number	ClinicalTrials.gov NCT00000004
2. Date of Registration in Primary Registry	November 20th, 2015
3. Secondary Identifying Numbers	UTN-01020304, BBC-2015-001
4. Source(s) of Monetary or Material Support	NIH
5. Primary Sponsor	NIH
6. Secondary Sponsor(s)	Balanced Body ®
7. Contact for Public Queries	*Group4,* MD, [(005) 1234-567] [Fantastic4@gmail.com]
8. Contact for Scientific Queries	*Group4,* MD, [(005) 1234-567] [Fantastic4@gmail.com] PPCR, Harvard Medical School, USA

9. Public Title	PETKO: Pilates Exercise Training before Knee arthroplasty in patients with Osteoarthrosis.
10. Scientific Title	PETKO: Pilates Exercise Training before Knee arthroplasty in patients with Osteoarthrosis - A two-arm, randomized, open-label phase-II clinical trial.
11. Countries of Recruitment	Brazil
12. Health Condition(s) or Problem(s) Studied	Primary Knee Osteoarthrosis
13. Intervention(s)	Name: Pilates routine training Active comparator: Pilates routine training six weeks previous to knee arthroplasty Placebo comparator: no exercise previous knee arthroplasty
14. Key Inclusion and Exclusion Criteria	Ages eligible for study: >60 years old Sexes eligible for study: both Accepts healthy volunteers: no Inclusion criteria: - Adult patient older than 60 years, with severe primary osteoarthrosis (Kellgren-Lawrence grade 3-4) with indication of total knee arthroplasty, and who accept the informed consent to participate on the study. Exclusion criteria: - Previous surgical interventions on the affected knee - Postoperative complications - Medical comorbidities that restrain Pilates

	routine - Not completing at least 16 of 18 sessions programmed
15. Study Type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: open-label Primary purpose: improving in KOOS-ADL Phase II
16. Date of First Enrollment	January 2016
17. Target Sample Size	40
18. Recruitment Status	Pending
19. Primary Outcome(s)	Outcome name: KOOS-ADL improvement Timepoint: 30, 60 and 90 days after surgery
20. Key Secondary Outcomes	-Outcome name: WOMAC Metric/method of measurement: Self-administered test Timepoint: 30, 60 and 90 days after surgery -Outcome name: post-operative pain Metric/method of measurement: Visual Analog Scale and KOOS Scale Timepoint: 30, 60 and 90 days after surgery -Outcome name: Other KOOS subscales (Sport/Rec, QOL, Pain, other symptoms) Metric/method of measurement: Self-administered test

	Timepoint: 30, 60 and 90 days after surgery -Outcome name: hospital length of stay Metric/method of measurement: statistics report Timepoint: date of surgery and date of hospital discharge -Outcome name: ROM Metric/method of measurement: Physiatrist assessment Timepoint: 30, 60 and 90 days after surgery

23. Diagram Flow

24. References

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