

**Examining the Efficacy of a Novel Method of Creatine Delivery for Improving
Human Exercise Performance**

by

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ABSTRACT

EXAMINING THE EFFICACY OF A NOVEL METHOD OF CREATINE DELIVERY FOR IMPROVING HUMAN EXERCISE PERFORMANCE

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This thesis is an investigation of the effects of acute and chronic application of a novel topical creatine cream prior to performing five sets of 15 maximal leg extensions (per leg) to evaluate the changes in peak power (W), average power (W) and muscle fatigue index (%). Sixty-two healthy participants (23 ± 3 yr, 71 ± 11 kg, 172 ± 8.4 cm) were randomized into either an acute (study 1) and/or chronic application (study 2) of the experimental creatine cream. Effects were observed over time for peak power ($p=0.01$) and muscle fatigue index ($p=0.007$) for all groups in study 1 by null hypothesis testing. An effect of time was also observed for muscle fatigue index ($p=0.04$) in study 2 for all groups. Using a magnitude-based inference (MBI) approach, *negligible* increases were observed in peak power and muscle fatigue for both studies. The results provided suggest limited effect of the experimental topical creatine cream with acute and chronic application.

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List of Abbreviations

ADP – adenosine diphosphate

AGAT – arginine:glycine amidinotransferase

Akt – protein kinase B

AP – average power

ATP – adenosine triphosphate

ATPase – adenosine triphosphatase

BMI – body mass index

Ca²⁺ - calcium ions

CK – creatine kinase

CRE1 – single creatine application group

CRE2 – double creatine application group

CRT – creatine transporter

CSEP – Canadian Society for Exercise Physiology

DBP – diastolic blood pressure

DNA -deoxyribonucleic acid

FI – fatigue index

GAMT – guandinoacetate N-methyltransferase

GI – gastrointestinal

IGF-1 – insulin growth factor 1

MBI – magnitude-based inferences

Mrf – myogenic regulatory factor

mRNA – messenger ribonucleic acid

mTOR – mammalian target of rapamycin

OC + CRE – oral creatine supplement with experimental topical creatine cream

OC + PLA – oral creatine supplement with topical placebo cream

OP + CRE – oral placebo supplement with experimental topical creatine cream

OP + PLA – oral placebo supplement with topical placebo cream

P13K – phosphoinositide 3-kinase

p70S6K – ribosomal protein S6 kinase

PARQ+ - physical activity readiness questionnaire

PCr - phosphocreatine

PLA1 – single placebo application group

PLA2 – double placebo application group

PP – peak power

RPM – revolutions per minute

SAM – S-adenosyl methionine

SD – standard deviation

SBP – systolic blood pressure

TCr – total creatine

W - watts

Chapter 1

Introduction

1.1 Significance

Individuals that perform maximally strenuous activities (ex: power and strength athletes) in extremely short time intervals (<10 seconds), commonly consume substances to augment performance outcomes. Ergogenic aids (e.g. branched-chain amino acids, beta-alanine, creatine, caffeine) provide athletes with benefits such as: increased protein synthesis ^{1,2}, enhanced buffering capabilities ^{3,4}, elevated immune function ^{5,6}, enhanced mental alertness ⁷, and increased energy ^{8,9}. Creatine is a widely consumed ergogenic aid, with a vast amount of evidence supporting its use in sports by providing additional phosphates (when in its phosphorylated form) to be available for the rapid replenishment of adenosine triphosphate (ATP) ^{10,11}. This benefit allows power athletes to be able to perform more exhaustive training protocols for an extended period of time from the additional energy phosphocreatine is able to contribute, thereby increasing time to fatigue and lengthening the time to which an increase in lean mass and power can be achieved. However, creatine use has mostly been limited to select athletes as it has been reported to increase intracellular water retention ^{12,9} and elicit gastrointestinal (GI) irritation ^{9,13,14}. This discourages individuals who are involved and compete in endurance or weight-dependent and gravity affected events to supplement with creatine, even with its substantiated benefits of prolonging time to fatigue.

As creatine is commonly consumed orally, it must be passed through the GI tract then released and absorbed systemically through the blood stream ¹⁵. Plasma creatine concentrations can reach up to 1000 $\mu\text{mol/L}$ in one hour after 5g of creatine monohydrate supplementation ¹⁶, stimulating the creatine transporter to facilitate the transfer of creatine into the muscle; increasing total creatine content in the muscle by 20% after 20g of creatine for 4-6 days or with 3g/day for 28 days ^{16,17}. This amount of creatine consumption brings average baseline levels of approximately 120 mmol/kg dm to a potential ceiling of 160 mmol/kg dm in the muscle ¹⁶. However, supplementing with creatine orally can provoke GI irritation (with prolonged and excessive use) ¹⁴ and overall weight gain ^{18,19}, as previously mentioned. A topical drug delivery system (through means of a cream) offers an interesting and novel approach to potentially avoid systemic water retention and GI distress. The method in which the topical drug delivery system works, is through dermal penetration of certain substances to an area of interest (i.e. muscle), thereby administering a localized effect. This could allow molecules, such as creatine (and beta-alanine), to potentially localize and concentrate in a muscle that would provide the greatest increase in performance outcomes (ex: quadriceps to generate maximal power while performing squats), reaping the same benefits as oral supplementation, but potentially bypassing the negative side effects.

DelivraTM developed a sport cream called LivSportTM that contains creatine as its main medicinal ingredient and beta-alanine incorporated as a non-medicinal ingredient. Beta-alanine was integrated into the formulation as it could potentially aid as a complimentary substance when paired with creatine, contributing to a delay in fatigue while performing

exhaustive exercise ²⁰. The expectation is to deliver creatine (and beta alanine) through Delivra™'s unique topical drug delivery system to enhance the user's performance. Pilot testing was conducted at the University of Prince Edward Island in recreational athletes, applying a similar formulation on the quadriceps (contained creatine and capsaicin) before performing repeated sprints on a cycle ergometer ²¹. Exclusive of initial pilot testing, there is limited information and research conducted on the use of any ergogenic aid delivered by a topical formulation that has proven beneficial effects ^{22,23}, with no literature evaluating a creatine cream formulation on exercise performance.

While conducting sport performance research, the smallest change can be of importance, but may not reach statistical significance. It is crucial to be able to identify clinical and meaningful changes that are observed within a sample size that may have a large variation. Therefore, inclusion of magnitude-based inferences (in combination with null-hypothesis testing) was incorporated within the analysis of the current study to provide context of the results generated from null-hypothesis testing.

1.2 Objective

Primary Objectives: a) To investigate the effects of an experimental topical creatine cream to a topical placebo cream applied immediately prior to performing maximal leg extensions on peak power, average power and muscle fatigue index; and b) to investigate the effects of chronic application of an experimental topical creatine cream to a topical placebo cream for 7 days prior to performing maximal leg extensions on peak power, average power and muscle fatigue index.

Secondary Objectives: a) To compare two dosing applications for the experimental topical creatine cream prior to exercise; b) To compare the effects of chronic application of the experimental topical creatine cream in addition to oral creatine supplementation prior to exercise; c) To examine the difference in performance between chronic application of the experimental topical creatine cream to oral supplementation of creatine for 7 days; and d) to examine the difference in leg girth subsequent chronic to application of the experimental topical creatine cream.

1.2.1 Hypotheses

Primary Hypotheses: A performance-enhancing effect will be observed while performing maximal leg extensions, such that peak power and average power will improve (increase) and muscle fatigue will also improve (decrease), immediately post application of the experimental topical creatine cream. Improvement (decrease) in muscle fatigue, peak and average power (increase) will be observed through maximal leg extensions, following chronic supplementation of the experimental topical creatine cream.

Secondary Hypotheses: a) Two consecutive applications of the experimental topical creatine cream will be more effective than a single application for improving muscular performance, such that muscle fatigue index decreases; b) chronic application of the experimental topical creatine cream will provide an additional improvement in peak power, average power and muscle fatigue in combination with oral creatine supplementation; c) chronic application of the experimental topical creatine cream will

elicit performance-enhancing effects (improvement in peak power, average power and muscle fatigue) similar ($R > 0.8$) to the oral creatine supplementation; and d) leg girth will increase subsequent chronic application of the experimental topical creatine cream.

Chapter 2

Literature Review

2.1 Introduction

There are many factors that directly influence athletic ability, with specific nutrition regimens, training protocols and genetic pre-disposition having the greatest impact on exercise performance²⁴. At the elite, and sometimes sub-elite, level there is a consistent drive to obtain even marginal advantages over opponents, as events can be won or lost by the smallest of margins. Alongside traditional training methodologies, one such tactic to create and maintain performance advantages is the use of legal ergogenic aids.

Ergogenic aids are substances or techniques, which function through a variety of physiological mechanistic pathways, and are intended to augment exercise performance²⁵. Anabolic steroids, for example, have the ability to stimulate muscle hypertrophy²⁶, while recombinant human erythropoietin can drastically improve oxygen delivery by upregulating erythrocyte production²⁵. While these examples are both banned from all competitive sport leagues, many others are not. Creatine, is a widely-used and legal ergogenic aid used by recreational^{27,28} to top-level athletes²⁹. The allure of creatine is primarily in its ability to accelerate recovery between intense bouts of exercise by allowing a greater ATP provision from PCr during the event, which allow for greater training volume and could promote more effective training outcomes (i.e. act as an anabolic stimulus), such as increased muscle mass, over time^{30,31}.

The human body produces about 1g/d of creatine endogenously ³¹, however, when supplemental (exogenous) creatine is introduced (20g/d for approximately 6 days), greater quantities (~20g creatine retention, which represents ~17% of total amount of creatine ingested) can be taken up and stored mainly in skeletal muscle ^{16,17}. Stored creatine is phosphorylated once it has crossed the cell membrane; this storage of phosphocreatine (PCr) can be used in the resynthesis of adenosine diphosphate (ADP) to ATP – which is energy used in the body for powering various functions including muscle contraction ³². PCr effectively prolongs the period in which maximal work can be performed using the ATP/PCr metabolic pathway; by keeping this energy supply in a useable form ³². In short, PCr plays an important role in providing a readily available energy source to ATP during the first 10 seconds of maximal effort; thereafter a majority of ATP needs are met by anaerobic glycolysis ³³. Phosphates are shuttled from PCr to ADP to form ATP when there is a heavy depletion in ATP stores during short-duration, high-intensity exercise ^{33,34}. This phosphorylation of ATP is dependent on the abundance of PCr and how quickly it is able to be replenished ³⁴. With increased stores of PCr, there is the ability to prolong the creatine/PCr system, increasing time to fatigue ^{33,35} and generating high force and power production ³⁴. Owing to the fact that creatine consistently increases time to fatigue ^{36,35}, enhances muscular strength and hypertrophic gains ^{8,37,38}, has a few side effects and interactions with other supplements and is easy to access and use, it is one of the most widely used supplements in the world. Consequently, it is also a thoroughly researched supplement and there is a large literature base regarding its purported ergogenic effects through oral administration ^{16,18,39-43}.

The exercise performance literature examining creatine efficacy commonly focuses on lower limb activities such as intermittent, high-intensity sprints on a cycle ergometer^{11,40,44}, prolonged submaximal cycling⁴⁴⁻⁴⁶ and maximal leg extensions^{47,48}. In leg extension or resisted “kicking” studies, measures of peak and mean power⁴⁷⁻⁴⁹, are commonly improved, and the rate of fatigue slowed during high intensity or repeated bouts of exercise³⁶. These changes in exercise capacity, which can occur in a relatively short time-course, are driven by improvements in anaerobic metabolism and ATP regeneration; whereas more chronic creatine supplementation may also work to improve lean muscle mass through adaptation to a higher training volume, increased intracellular water thereby increasing protein synthesis, or other mechanisms, such as decreased myostatin^{30,42}.

Owing to the ease of administration, a majority of sports supplements on the market today are ingested orally and absorbed into the body through GI tract; however, other methods of administration (transdermal/topical drug delivery and intravenous injection) have also been reported⁵⁰⁻⁵². At present, oral ingestion of a powdered form of creatine is by far the most common method for supplementation⁴². While effective, oral ingestion can be problematic as passage and incomplete absorption in the GI tract can evoke discomfort (stomach distress, nausea, diarrhea) in some individuals¹². Many studies have also reported increased water retention with creatine supplementation^{12,33,53}. Two theories accompany this observation – the first one suggesting that there is intracellular swelling due to creatine increasing cellular osmolarity because of its high polarity and inactive exchange of ions¹², and the second proposing that there is a concomitant

increase in glycogen content (also driven by resistance training) that allows for the increased water retention in the cell ^{12,54}. With every 1g of glycogen in skeletal muscle, 2-3g of water follows ¹². As oral consumption is the most common route of administration, creatine must be taken up through the gut and transported in the plasma via the circulatory system to arrive at the site of action, the muscles. This allows for creatine to be distributed throughout the body, producing systemic accumulation of additional intracellular water volume in all muscles (1-3 kg) ^{8,12,53,55}. These side effects could be viewed as potentially negative for athletes in body weight sensitive sports, however, the effect could theoretically be localized through an alternative method of administration. The technology used to deliver drugs or other biological agents through topical creams has progressed to a point that more and more substances may be able to be transported locally to underlying tissues. An industry has developed a range of topical creams that have the ability to penetrate the skin and provide pain relief specific to the localized area in which the product is applied. A recent addition to the products of our collaborative industry partner (Delivra™), is a sport performance cream that contains 1% creatine (active ingredient) and 0.3% beta-alanine as a valuable non-active ingredient (containing an amount that is not considered to be a medicinal ingredient).

The incorporation of beta-alanine within the formulation was pertinent because hydrogen ions (H⁺) accumulate during moderate to intense exercise and beta-alanine facilitates the buffering of these H⁺ ions ^{4,20}. It does so by increasing muscle carnosine levels which increases intramuscular pH, leading to a potential attenuation in fatigue (i.e. delaying

metabolic acidosis) that has previously been shown in trained sprinters performing maximal knee extensions ⁵⁶. The administration of creatine and beta alanine in the cream formulation may be of potential value as an alternative delivery method to oral ingestion, allowing localized administration and negating the aforementioned issue of systemic delivery through the circulatory system, while by potentially executing the same benefits as oral consumption. A pilot study conducted at the University of Prince Edward Island assessing the use of a topical cream (formulated by DelivraTM) containing creatine as the active ingredient ²¹ has shown initial potential efficacy. However, it must be noted that the pilot work contained a small number of subjects and only a single dose of the experimental topical creatine cream (or topical placebo cream) was applied immediately prior to a repeated maximal cycling test. Building on this evidence, the main objectives of this literature review are to assess the potential of a novel supplementation administration method with leg extension exercise protocols on mean power, peak power and muscle fatigue index.

2.2 Creatine Background

Creatine is a naturally occurring amino acid-derived metabolite produced in the body ^{1,33}. Synthesis of creatine begins in the kidneys with assembly of arginine and glycine catalyzed by arginine:glycine amidinotransferase (AGAT) ^{33,57}. This yields guanidinoacetate where it is then transferred to the liver to accept a methyl group from S-adenosyl methionine (SAM) :guanidinoacetate N-methyltransferase (GAMT), producing the end product creatine ^{33,57}. The body is capable of producing creatine at approximately

1-2g/d which enough to maintain normal human function, however, creatine is commonly ingested in an omnivore diet ^{31,42,58}. Sources of dietary creatine include animal products such as red meat and fish, providing about 1-2g/d of creatine ^{9,33,34}. Ingestion of exogenous sources of creatine leads to a downregulation of endogenous creatine production due to decreased levels of AGAT and guanidinoacetate ⁵⁴; but biosynthesis rates of creatine return to baseline once supplementation has ceased ^{34,57}.

2.2.1 Transportation and Uptake

Transportation of endogenous creatine occurs in the bloodstream from the liver to the skeletal muscle fibers by the Na⁺-K⁺ ATPase pump ⁵⁷. The influx of creatine activates the Na⁺-K⁺ ATPase pump, increasing the sodium gradient across the cell membrane ⁵⁹. This leads to a rise of the electrochemical gradient ⁶⁰ which initiates the Na⁺-Cl⁻ dependent creatine transporter (CRT) ^{31,59}, allowing for the transfer of creatine into the skeletal muscle ⁶¹. There is a direct relationship of the amount of CRT and creatine in skeletal muscle; if there is a low concentration of CRT in the muscle fibres this indicates a low concentration of creatine storage as well ⁵⁷. In terms of exogenous transit, creatine is absorbed in the bloodstream by intestinal mucosa and taken up by skeletal muscle (or any other creatine-required tissues) through assistance of Na⁺ K⁺ ATPase and CRT ⁶²; which has a binding affinity to creatine of 15-30 μmol/L, which is lower than the 50-100 μmol/L circulating plasma creatine in a healthy, omnivore individual ⁵⁷. Once creatine crosses the lipid bilayer, it is rapidly phosphorylated in the cytosol by creatine kinase (CK) to form PCr ^{33,57}; in which the concentration is contingent on the equilibrium

constant of the reaction ^{51,63}. PCr is essentially stored (60%) within the cytosol as it is not a substrate of the plasma membrane creatine transport system ⁶⁴. This facilitates additional creatine (40%) to be absorbed by the plasma membrane, contributing to the creatine concentration gradient ^{51,64}.

Certain factors such as initial creatine concentration ⁶⁵, presence of insulin ^{31,66}, exercise ^{31,33}, and fiber type profile ^{9,31} are believed to influence the uptake of creatine into the cell. The amount of baseline creatine can determine the additional amount of creatine to be utilized and stored within the body ⁹. As such, individuals with a lower initial concentration of creatine (<120mmol/kg dry mass) respond with improvement of muscle creatine compared to their counterparts with higher initial concentration (>130mmol/kg dry mass) ^{16,18,57}. Lower amounts of creatine are commonly seen in those who are vegetarians (i.e. individuals who do not consume meat products) and, can thus, theoretically increase plasma creatine levels up to 40% beyond the normal increase ⁹. When carbohydrates are ingested by a healthy individual, there is a release of insulin that indirectly stimulates muscle blood flow ^{57,66} and promotes an increase in the availability of creatine in the muscle through insulin mediated creatine uptake ^{46,67}. Insulin is also reported to permit the entry of creatine in the muscle against the concentration gradient by translocation of Na⁺ K⁺ ATPase subunits ^{57,66,68}. Similarly promoting creatine delivery and uptake, exercise enhances stimulation of muscle blood flow ¹⁶, indirect activation of mammalian target of rapamycin (mTOR) ⁶⁹ and possible alteration of transport kinetics ^{46,57,16}. It has been shown that there is a greater extent of PCr in Type II fibers (5-30% more compared to Type I) ^{70,71}, especially in younger individuals compared to the elderly

⁵⁷. This could be explained by the energy system predominately used for different types of exercise, with reliance on fast twitch fibers for the most explosive movements supported by the ATP-PCr system, and more of a reliance on slow twitch fibers in combination with oxidative metabolism ^{57,72}.

2.2.2 Storage

The majority of total creatine (TCr) (95%), which includes both PCr and creatine, is found within the skeletal muscle, with the remainder in several other parts of the body ^{30,57}. In a 70 kg individual, there is roughly 120-140g dry mass of creatine in the body, 40% in the form of free creatine and 60% in the phosphorylated form ³⁰. Individuals who do not consume meat products (i.e. vegetarians) store about 80g of creatine, as dietary sources are limited ⁷³. The volume of TCr stored in the body varies with muscle mass and fiber type distribution ^{30,31}. Males often hold a higher reserve of TCr than females due to the increased muscle mass ⁵⁷; with both sexes having Type II fibers permitting a larger increase TCr storage than Type I ⁵⁷. Eventually, creatine is degraded to creatinine through a spontaneous and irreversible process ⁷⁴ and eliminated from the body through glomerular filtration³¹. This reaction is pH and temperature dependent, with both dietary and endogenous production of creatine matching the degradation of PCr and creatine to creatinine at a rate of 2.6% and 1.1% per day ^{31,57}.

2.3 Proposed Mechanism of Action

There are several important mechanisms for the uptake of creatine in the body. Upon consumption or release of endogenous creatine in the blood, creatine is actively delivered

through a Na⁺ and Cl⁻ dependent transporter, CRT, into the skeletal muscles^{30,75,76}.

Within the cytosol of the muscle cell (where conversion of creatine to PCr is performed)⁵¹, creatine is also potentially able to be transported into the mitochondria by CRT^{54,64,77,78}, suggesting that it may play a greater role in creatine transportation than initially proposed^{64,76}. This would indicate that the mitochondria may regulate intracellular storage of creatine, while also participating in energy metabolism, leading to the ergogenic effects of creatine such as lengthening time for maximal effort to be performed and increasing time to fatigue^{30,58,75}.

The phosphorylation of creatine and ATP to PCr and ADP by CK, primarily serves as a temporal, energy and pH buffer³¹. High energy phosphates from PCr are shuttled between mitochondrial sites of ATP production to cytosolic sites of ATP utilization⁵⁴. Creatine is then bound within the muscle by the charge associated with PCr, preventing its exit through the biological membrane^{31,57}, creating a large phosphate pool¹. The additional phosphates (released with ADP during the “power stroke”, allowing ATP to attach to the myosin head) promote the cross-bridging of the actin myofilaments and myosin binding sites¹. With elevated creatine stores, there is an ability to sustain ATP supply during anaerobic exercise^{1,31,58,79}. During recovery periods, ATP is resynthesized more rapidly due to the raised initial creatine levels prior to exercise^{1,31}.

Creatine plays a large role in the accretion of lean mass, with the current theory suggesting its beneficial effects acting through either optimization of protein synthesis⁸⁰ or a decline in protein catabolism^{28,31}. Intracellular storage of creatine creates an osmotic

pressure gradient across the cell membrane, permitting the migration of water into the cell ⁸¹. With this change in osmotic pressure and the resultant movement of water, there is speculation as to whether hyperhydration acts as an anabolic stimulus to synthesizing protein ², or the hypo-osmolarity allows for the reduction of protein degradation ^{31,39,82}. This alteration in protein turnover (from increased water stores) could conceivably cause increased muscle development with heavy resistance training ⁵⁸. A related and supported mechanism which creatine is proposed to increase protein synthesis is by modulating components of the mTOR pathway ². Evidence has shown *in vitro* and *in vivo* the increased phosphorylation of p70S6K in C₂C₁₂ murine skeletal muscle myoblasts ⁸³ and increased resting muscle mRNA expression of insulin growth factor 1 (IGF-I) in young males ⁸⁴. Augmented activity of both these components, p70S6K and IGF-I, play a key role in stimulating the P13K/Akt/mTOR pathway, leading to an enhancement in muscle growth. Muscle fiber size is also a critical aspect when considering muscle growth. In the process of muscle hypertrophy, surrounding dormant satellite cells donate nuclei (providing a new source of DNA) to the enlarging muscle fibers stimulated by an inflammatory response (i.e. resistance training) ^{2,37,38}. This increase in satellite cell mitotic activity has been observed in response to creatine supplementation and resistance training and could potentially be mediated by the creatine-facilitation of myogenic regulatory factors (Mrf) ⁸⁵. These factors (Mrf4 and myogenin) are expressed during differentiation (i.e. change of myoblasts to myotubes) and are upregulated with creatine supplementation in combination with heavy resistance training ^{2,86}. Strong proposed

mechanisms are rational and supported in the literature, however, uncertainty in how creatine directly increases muscle mass remains.

Creatine has the ability to stabilize cellular membranes and preserve ATP to prevent tissue damage³¹, which is crucial to maintaining the capacity to perform work. More specifically, PCr binds to phospholipid head groups, decreasing membrane fluidity, therefore minimizing the amount of effusion of intracellular enzymes (e.g. CK)³¹. In studies with induced ischemia, ATP production through oxidative pathways is reduced which typically causes cellular damage³¹. However, with greater levels of PCr, there is a higher reserve of ATP, thereby prolonging the time to cell necrosis³¹.

2.4 Creatine Supplementation

Creatine monohydrate is the most studied form of creatine due to its retention, bioavailability and energy supplying properties in the muscle; making it a supplement of interest to researchers hoping to observe an augmentation in athletic/muscle performance³³. There are other forms of creatine, however, their use is primarily focused on muscle degenerative diseases or anti-cancer treatment³⁰, which is why, this review, focuses specifically on the use of creatine monohydrate.

Creatine supplementation is most commonly accomplished through oral consumption^{87,88} as intestinal absorption of creatine is close to 100%⁹ when there is sufficient room to store the molecule. To achieve the greatest effect in creatine supplementation, a dosing protocol of 20g/d for 3-7 days (equates to approximately 0.3g/kg of body weight) taken 4-5 times a day^{9,17}; is often prescribed and referred to as the *loading phase* or “high-

dose” protocol. During this time, there is a substantial (15-20 fold) increase in plasma creatine levels ^{9,16}, followed by a rise (0-40%) of total creatine content in skeletal muscle content ^{9,16,17,49}. However, with continuation of large “loading” doses of creatine (longer than 7 days) the muscles become quickly saturated (as little as 2 days) ¹⁶ and the excess creatine is excreted in the urine ⁹. Retention of creatine can be prolonged using a *maintenance phase* (or initiated with a “low-dose” protocol), which involves continued supplementation with 2-5g/d (of a minimum 5 weeks to a maximum of 12 weeks has been documented), equating to approximately 0.03-0.07g/kg of body weight ^{17,33,79}. Once supplementation ceases, baseline creatine levels (pre-supplementation) are maintained 30 days after termination of exogenous creatine ^{9,31,42,57}. During the supplementation period, water is retained within the myocytes resulting in a subtle weight gain of 1-3 kg ⁹. This phenomenon is more prevalent in males, potentially a result of higher initial muscle mass compared to their female counterparts ⁹. However, once supplementation has stopped, original water weight will return to baseline.

While the majority of creatine supplementation is accomplished via oral administration it can also be delivered intravenously ^{31,52,89}, albeit a highly uncommon practice. These studies have largely focused on creatine turnover rate in healthy males ⁵² and in those with muscle wasting diseases ⁸⁹. In addition, administration of intravenous PCr has been suggested to play a role in prevention of necrotic events during cardiac surgery due to the rapid source of energy it transfers to the production of ATP ^{90,91}.

More recently, a topical drug delivery approach has been used for a variety of applications such as providing anti-nociceptive treatment for knee osteoarthritis ⁹², relief of delayed onset muscle soreness ²³ and improving aerobic and anaerobic performance ²². The topical drug delivery system comprises of penetration enhancers that have the ability to alter the stratum corneum (outermost layer of the skin) permeability in order to access the dermal layers to deliver treatment through a gel or cream vehicle ^{93,94}. This method is advantageous when targeting a specific location to provide localized effects, thereby avoiding massive systemic absorption and utilization ⁹³. Recently, Delivra™ has incorporated creatine monohydrate into their line of topical creams, which has been utilized in pilot testing to observe an increase in power output on a cycle ergometer ²¹. One of the proposed benefits of supplementing locally with creatine is bypassing some of the unwanted side effects of oral administration such as increased systemic water retention ^{12,9} and GI distress ^{95,96}. The Delivra™ formulation contains lecithin (an amphiphilic phospholipid, which aids in the transport of drugs through the skin) which has been used successfully in transporting ketoprofen to the muscle where it has relieved self-reported delayed onset muscle soreness ^{23,97}. Low molecular weight and concentration are additional key aspects in transportation through the skin. Molecules (ketoprofen, ibuprofen and carnosine) used in other topical creams, which have a higher molecular weight than creatine (>200g/mol compared to ~130g/mol for creatine) – albeit in higher concentrations (>4% compared to 1% creatine), have previously elicited effective responses in athletic performance and recovery outcomes ^{22,23,98}. Therefore, the

creatine-containing Delivra™ topical cream presents as a viable candidate for potential localized delivery.

2.5 Ergogenic Effects

Creatine supplementation is primarily recognized for increasing time to fatigue^{9,57,99–101} and enhancing power output during short duration high-intensity exercise^{47,102,103}. These benefits are a result from the addition of available phosphates at the site of use (myofibrils) from the site of ATP production (cytosol)⁹. The elevated phosphate availability increases the duration in which the ATP-PCr system can contribute efficiently and rapidly to energy production⁹. High-intensity activities with intermittent rest periods are able to utilize creatine most effectively, as the short rest periods provide sufficient recovery time to allow for the transfer of phosphates from PCr to ADP, replenishing ATP stores^{9,104}. Following a “high dose” protocol, enhanced fatigue resistance was observed in healthy males after completing multiple anaerobic bouts on a cycle ergometer¹⁰¹. A more gradual percent decline in pedaling frequency (compared to baseline) was attributed to a smaller decline of ATP stores that was offset by the additional availability of PCr¹⁰¹. Additional research suggests that creatine supplementation shortens muscle relaxation time, which allows contractions to be performed more efficiently^{105,106}. There is evidence of shortened muscle relaxation time between maximal isometric elbow flexions¹⁰⁵ and intermittent isometric contractions of the quadriceps¹⁰⁶. This outcome is speculated to be caused through the increased Ca²⁺ - ATPase activity in the sarcoplasmic reticulum and the higher rate of cross-bridging

detachment due to increased CK activity from creatine supplementation ^{58,105,107}. The Ca²⁺ - ATPase pump is able to shuttle more Ca²⁺ from the cytosol to the sarcoplasmic reticulum by use of ATP, facilitating muscle relaxation ^{108,109}. Creatine has also been shown to upregulate satellite cell proliferation ⁸⁵, myonuclei concentration ^{85,110}, and collagen mRNA ¹¹¹ which can lead to an overall gain in lean mass. Due to the anabolic effects of creatine, intense training can consistently be performed at greater volumes which also contributes to the muscle building abilities of creatine.

Most studies primarily focus on reporting creatine supplementation benefits with respect to leg exercises, as lower limb use is most relevant for the majority of sporting activities ^{32,103,112,113}. Improvements are commonly observed in high-intensity intermittent peak power activities. After three bouts of 30-s cycling (80 rpm) with 4 minutes of passive recovery in healthy males consuming 20g/d of creatine monohydrate for 5 days; an increase of peak power in the first bout as well as mean power output in bouts 1 and 2 was shown ⁴³. This increase in power was hypothesized to be due to the augmented re-synthesis rate of ATP ⁴³. Similar results were reported by Tarnopolsky *et al.* ²⁸ after supplementing 20g of creatine for 4 days.

Creatine supplementation has shown the greatest improvements in performance through repeated leg extensions. A notable study by Greenhaff and colleagues ⁴⁹, demonstrated an increase in muscle torque-production of the quadriceps after creatine supplementation. This rise in torque-production was also revealed through work by Rossouw *et al.* ¹¹⁴ and Kambis *et al.* ¹¹⁵; both employing a similar loading (5-6 days) and exercise protocol

(maximal leg extensions) in both men and women. These studies restricted additional training during the investigation, suggesting that the increased torque production is mainly a result of creatine supplementation. Performance benefits are even further increased through protocols that included resistance training through the duration of the study. A two-fold increase in torque production was observed during maximal concentric leg extensions after a short-term creatine supplementation protocol (8 days) in combination with a resistance training program ⁴⁷. When combining creatine supplementation with an existing training protocol, the supplementation allows for greater volumes of high-intensity work to be performed, leading to a greater increase in muscle mass.

Enhancement in performance is generally not seen in aerobic-oriented activities when supplementing with creatine ^{44,116,117}; however, there are select studies that demonstrate otherwise ^{99,118,119}. Aaserud and colleagues ⁹⁹ investigated the effects of creatine supplementation in well-trained athletes with repeated sprint runs, eliciting an endurance aspect in the study. The exercise performance was implemented multiple times throughout the study, at baseline, after loading creatine monohydrate (15g) for 5 days and after a maintenance phase (2g for 9 days) ⁹⁹. Sprint times were significantly lower during the last three sprints in the second and final test compared to baseline ⁹⁹. Repeated sprint intervals observed on land (Aaserud *et al.*) ⁹⁹ and sprint cycling (Vandebuerie *et al.*) ¹²⁰ demonstrated the ability of creatine to provide individuals with an additional energy reserve during the final legs of intermittent sprints, displaying endurance capabilities.

2.6 Practical Applications/Conclusion

The available literature suggests that individuals ingesting creatine monohydrate can increase strength, body mass and time to fatigue during short-term high intensity bouts of exercise when compared to baseline or placebo. The method of consumption that has consistently achieved positive outcomes is oral consumption of 0.3g/kg of body weight per day for 5-7 days, but topical application has come into the spotlight offering similar potential benefits as oral, however bypassing some of oral supplementation's negative consequences (i.e. systemic water retention, gastrointestinal irritation). This new approach of the delivery of creatine can potentially offer other types of athletes who are weight-conscious (i.e. endurance runners) the same advantages as power or strength athletes receive; optimizing the last few 100m of a race. However, the efficacy of this new delivery system still needs to be demonstrated. Duration and doses of the cream may affect the ability of the creatine to be delivered to the muscles, thus determination of these variables is of primary interest.

Chapter 3

Methods

3.1 Participants

To ensure accurate and well-supported evidence for the stated hypotheses, two studies were conducted over a period of 8 months (October 2016 – May 2017). Overall, 62 healthy, recreational through to varsity level athletes (m=33/f=29) participated in the study, with 22 participants completing both studies (detailed schematic of participant allocation and dropouts, refer to Figure 1). Inclusion criteria required participants to be between the ages of 18 and 45; ostensibly healthy; with a BMI \leq 30; able to maintain current physical activity throughout the duration of the trial; literature in English and thus willing and able to give informed consent; and able follow the assigned protocol.

Potential participants were excluded from the study if they: were women who were pregnant, breastfeeding or wished to become pregnant during the same time period as the trial; had a presence of a significant medical disorder that could compromise the participant's safety to take part in the trial; had a history of alcohol or drug abuse within the past year; used recreational drugs; used performance enhancing drugs or supplements within the last 2 months including caffeine and creatine in supplement form; current use of topical agents for treatment of pain or inflammation; or if the participant was allergic to any of the ingredients of the LivSport pre-workout cream, placebo cream, creatine powder and/or placebo. Recruitment was primarily conducted through poster advertisements at the University of Guelph and through word of mouth in the community.

Participants were instructed to maintain their regular eating and physical activity habits throughout their participation in the study. Participants were instructed to avoid intense physical activity 2 days prior to testing and to restrict the ingestion of caffeine, nicotine and heavy meals (3 hours prior to testing) and alcohol consumption 12 hours prior to testing. Ethical approval was obtained from the University's Research Ethics Board (REB#16MY014) (Appendix A) at the University of Guelph and from Health Canada (File# 217760) (Appendix B).

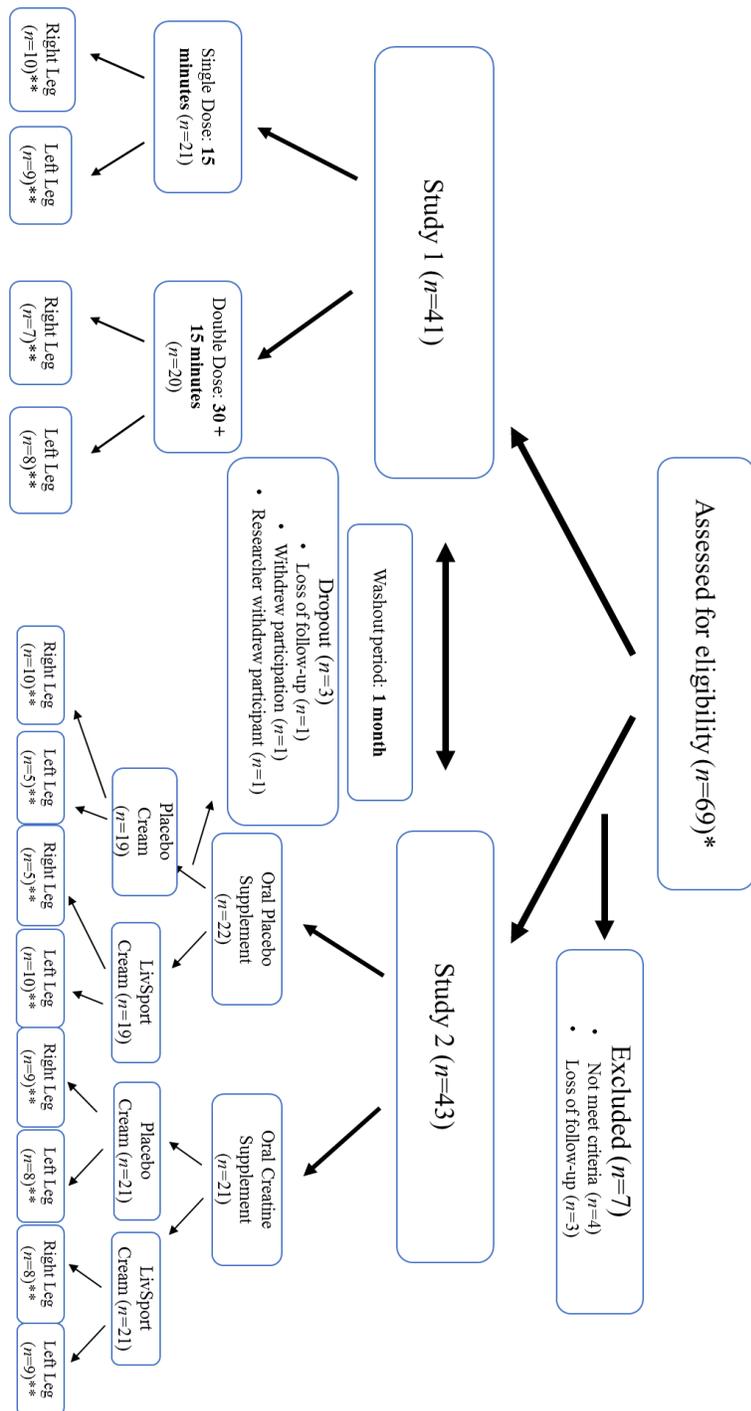


Figure 1. Flow of participant allocation and dropouts for both study 1 and 2

* With twenty-two participants (out of the sixty-eight) completing both studies separated with a 1-month washout in between studies. ** Indicates the number of participants who were analyzed for each arm. The remainder of the participants within that arm were removed as outcomes were higher than 2 standard deviations above or below the mean.

3.1.1 Screening and Accommodation

Upon initial contact, all potential participants received a copy of the Informed Consent (Appendix C), a Physical Activity Readiness Questionnaire (PARQ+) (Appendix D) and a Godin Leisure-Time Exercise Questionnaire (Appendix E) via e-mail. Potential participants were encouraged to review all documents prior to participation and enrollment in the study to determine if they were eligible and able. If the participants met all enrollment criteria, they were asked to arrive at the Human Performance and Health Research Laboratory for initial screening and accommodation procedures with study restrictions applied. The informed consent, PARQ+ and Godin-Leisure Time Questionnaire was completed during the initial visit. If the participant answered “yes” to any of the questions within the PARQ+ (and were not screened back in by a CSEP certified member) or met any of the exclusion criteria, they were removed from the study. The PARQ+ form is a screening tool used by health professionals to assess patient/participant readiness for physical activity¹²¹. Female participants were given a pregnancy test to ensure they were not pregnant prior to enrollment. Once all information was presented, participants were encouraged to ask any further questions and were informed they may remove themselves from the study at any time.

Participants were then required to complete the anthropometrics and accommodation portion of the visit. Measurements of blood pressure, leg girth (both right and left thigh), body mass, height, and body fat percentage (specific protocols of each measurement are outlined in the Appendices G-J). Leg girth was specifically measured to assess localized growth from baseline to post values, where body mass was measured to assess systemic

(overall) gain from baseline to post values. Once anthropometric measures were conducted, participants warmed-up on a cycle ergometer (Monark (Ergomedics 874 E, Monark, Sweden)/Velotron (Racer-Mate Inc., Seattle, WA)) for 5 minutes (100W for males and 60W for females at a cadence of 80-100 revolutions per minute (RPM)), prior to data collection on the newly invented Quantum dynamometer. This device (Quantum dynamometer) was specifically constructed for the current study as it is a part of a large, multi-centre trial, where it was unaffordable to equip each facility with a state-of-the-art Humac Norm isokinetic dynamometer (schematic of machine is provided in Figure 3). A *priori* investigation was performed to assess the reliability and comparability of the Quantum dynamometer for which a comprehensive analysis is available in Appendix K. Calibration and set-up of the machine was in accordance to the 1080 Quantum SOP, located in Appendix L. Participants sat with their knees at 90° on the Quantum dynamometer, performing knee extensions until they were prepared to perform 2-3 maximal practice knee extensions against resistance. The familiarization exercise protocol consisted of 1 set of 15 maximal effort knee extensions per leg at a metronome controlled 2-s beat, with a 1-second no load eccentric return. Between repetitions, participants were assisted to passively bring their lower leg back by having a member of the research team controlling the load on the device, as participants were only required to perform the concentric portion of each leg extension. A 10-minute rest period was allotted between legs to avoid any fatigue related cross-over artifact. Throughout all trials, strong verbal encouragement and visual feedback was available to promote

maximal power production. This familiarization procedure was performed during the initial screening visit to reduce the potential learning effect ¹²².

3.2 Study Design and Data Collection

It was originally planned that, if willing, the majority of participants would do both Study 1 and Study 2. Participants who only completed one study (either study 1 or study 2), came to the laboratory for a total of three visits (one accommodation and familiarization visit, one baseline testing day and one experimental testing day). If the participant completed both study 1 and 2, a total of five visits were completed (one accommodation and familiarization visit, one baseline testing day for each study (2) and one experimental day for each study (2)). Each visit was separated by one week; and one month (washout) between study 1 and study 2, if the participant chose to complete both. Each visit lasted approximately 60 minutes, and was held at the same time of day to reduce circadian differences. The efficacy of the topical creatine cream was assessed through measures in muscular strength (peak and average power output) and muscle fatigue index using repeated leg extensions. Peak power was recorded on the 1080 Motion software as the highest value obtained within 15 repetitions of a set, for all 5 sets, for each individual leg. Average power was calculated by taking the sum of the contractions and dividing it by the number of contractions performed (i.e. 15), per set, per leg. Fatigue index was determined across individual contractions as:

$$\text{Fatigue index} = \left(\frac{\bar{\chi}_{\text{first 5 contractions}} - \bar{\chi}_{\text{last 5 contractions}}}{\bar{\chi}_{\text{first 5 contractions}}} \right) \times 100.$$
 The timeline and procedure is

displayed in Figure 2. The detailed study protocol for each visit is described below in **Section 3.3.1 and 3.3.2.**

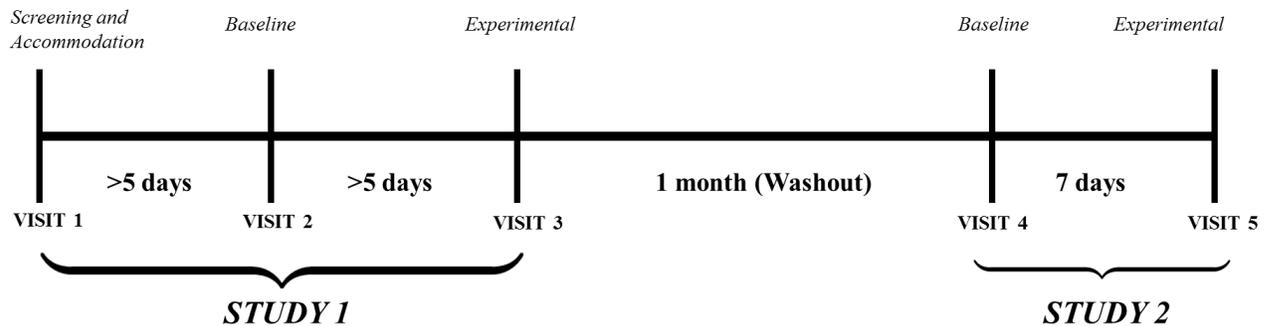


Figure 2. Timeline of events of study 1 and study 2

The structure of the study allowed the researchers to examine two general research questions:

- 1) does the topical creatine cream provide an acute ergogenic performance effect and;
- 2) does the topical creatine cream provide greater enhancement of strength following a week-long supplement period

We examined the acute effects of topical creatine cream 15 minutes and 30 minutes prior to exercise on the Quantum dynamometer (Study 1) and the chronic effects of the topical creatine cream with consumption of oral supplementation for 7 days pre- and post-exercise bouts on the Quantum dynamometer (Study 2).



Figure 3. Configuration of the 1080 Quantum attached to Model A leg extension. The power outputs (W) would be presented on the tablet (A), calculated from the 1080 Quantum (B). The participant would sit in the leg extension machine, and kick the movement arm (C) outwards to complete the leg extension. The range of motion apparatus (D) was in place to suspension the extension, bringing the participant's leg back to the neutral position to be prepared for subsequent extensions. Finally, the participant was secured with a harness (E). (Adapted from *Reliable results of a custom-built robotically controlled dynamometer*, located in Appendix K).

3.2.1 Study 1 (Acute Supplementation)

At least five days after the screening and accommodation visit, participants returned to the lab for baseline testing, with the same restrictions applied. Upon arrival, blood pressure, body mass and leg girth were recorded. Participants then warmed up on the cycle ergometer (with same protocol stated in **Section 3.2**) before initiation of the exercise protocol on the Quantum dynamometer. Calibration was completed and appropriate settings of seat inclination and ankle position were adjusted and recorded on the machine. The participant was then strapped to the dynamometer, where low-intensity knee extensions were performed until participants felt comfortable with the movement, progressing to 2-3 maximal knee extensions. Participants then completed baseline testing of 5 sets of 15 maximal concentric knee extensions at $0.5 \text{ m}\cdot\text{s}^{-1}$ ($180^{\circ}\cdot\text{s}^{-1}$) per leg, at a controlled pace of a 2-second beat metronome. Sets were separated by a 60-s rest, with a 10-minute rest allotted between legs.

On the participant's third visit (≥ 7 days after the baseline visit), participants were placed into one of two different dosing groups (Group 1: single dose or Group 2: double dose) with randomized allocation determined by a research assistant who was separated by the rest of the research team using (<https://www.random.org/sequences/>). In a double-blinded fashion, Group 1 applied 3.5mL of placebo cream (PLA1) to both quadriceps 30 minutes prior to activity and then applied 3.5mL of additional PLA1 to one quadriceps and 3.5mL of experimental cream (CRE1) to the other quadriceps 15 minutes prior to activity (providing a single dose of the creatine cream). Group 2 participants applied 3.5mL of experimental cream (CRE2) and placebo creams (PLA2) 30 minutes and 15 minutes prior

to activity but applied the same cream to the same quadriceps both times (providing a double dose of the creatine cream). For a schematic showing the administration of the creams, refer to Figure 4. The time (of 15 and 30 minutes) at which the cream was applied was implemented due to the manufacturer's instructions and previous pilot testing with the same amount of cream applied ²¹. Additionally, the amount of cream that was applied to the quadriceps was determined through pilot testing ²¹ where 3.5 mL was the maximum absorbable amount that could be applied to the quadriceps surface area in the given amount of time. Once application had been performed, the participant performed the warm-up previously described. With completion of practice leg extensions (submaximal and maximal) on the Quantum dynamometer, 5 sets of 15 maximal concentric knee extensions from 90° flexion at 0.5 m·s⁻¹ was performed, per leg, with the same rest protocol as described previously.

Measurements of power output (peak and average watts (W)) were immediately provided through the 1080 Motion software and assessed through maximal leg extensions on the Quantum dynamometer.

STUDY 1

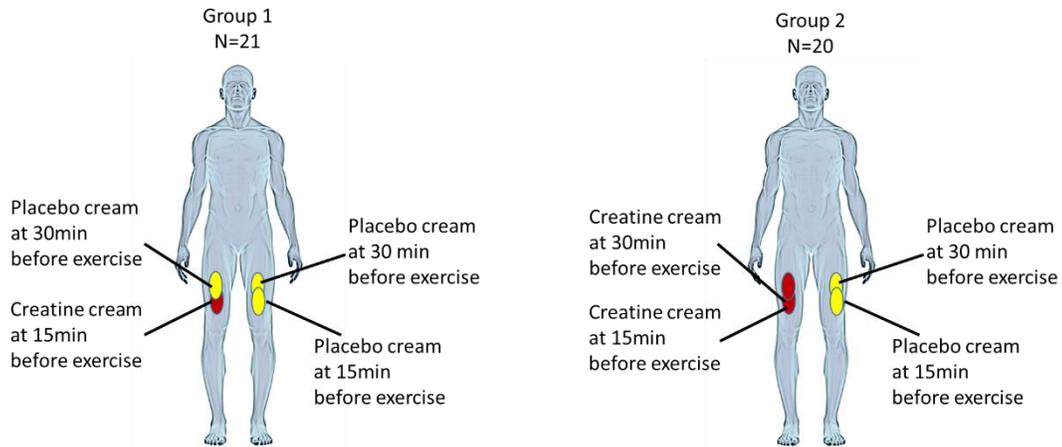


Figure 4. Area of the quadriceps that the either placebo cream (indicated by the yellow circles) or creatine cream (indicated by the red circles) was applied at the 30-minute and 15-minute mark prior to exercise in study 1.

3.2.2 Study 2 (Chronic Supplementation)

Participants reported to the lab on two separate occasions (baseline and experimental testing) if they completed study 1; if not, they had to come in for a screening and accommodation visit, with the same protocol as outline in **Section 3.2**

Following one month after participation in study 1 (washout period), or at least five days after screening and accommodation, blood pressure, body mass and leg girth were measured after the participant had changed into their exercise attire. Warm-up on the cycle ergometer was performed for 5 minutes at a minimum cadence of 80 RPM before the exercise protocol on the Quantum dynamometer (same protocol as outline in Study 1). After completion of the exercise test, participants were randomized into 1 of 2 supplement groups, and within that group legs were randomized for cream application (detailed schematic is provided in Figure 5):

- 1. Oral creatine supplementation
 - experimental cream (additive) (OC + CRE)
 - placebo cream (typical control) (OC + PLA)

- 2. Oral placebo supplementation
 - experimental cream (LivSport cream) (OP + CRE)
 - placebo cream (full control) (OP + PLA)

STUDY 2

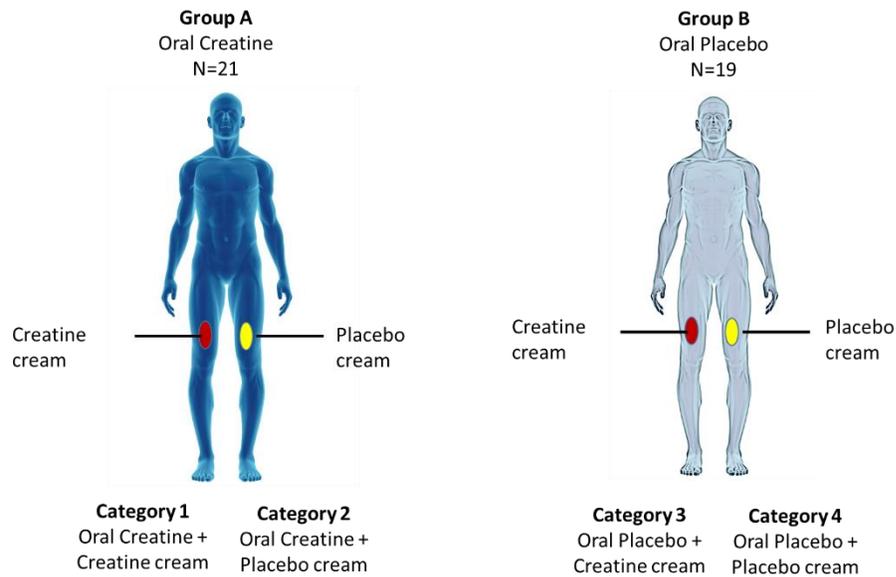


Figure 5. Area of the quadriceps that the either placebo cream (indicated by the yellow circles) or creatine cream (indicated by the red circles) was applied once, every day for 7 days in combination with consuming an oral supplement 3 times a day in study 2.

The participants were instructed to chronically “load” both the oral supplement and the cream. The loading phase for oral supplementation was 7 days of 21g of either placebo or creatine, split into 3 separate doses, combined with 250mL of water. The oral supplement was taken at equal intervals throughout the day (i.e. breakfast, lunch and dinner). In addition, the application of the creams (one bottle per leg), was administered the same time as the second consumption of oral supplementation (i.e. lunch); at 3.5mL per leg, once per day.

After seven days of supplementation, participants returned to the exercise lab where anthropometrics (blood pressure, body mass and leg girth) were taken and supplement containers and tubes were returned. Completion of the warm-up on the cycle ergometer and exercise test on the Quantum dynamometer was performed, as per the protocol administered during the baseline testing.

3.3 Statistical Analysis

Results are presented as mean \pm SD. A factorial 2 (time) x 4 (condition) repeated measures ANOVA was used to compare pre- and post- values of peak power, average power and muscle fatigue for all groups (CRE1, PLA1, CRE2, PLA2) in study 1. This was also repeated for study 2 groups (OP+CRE, OP+ PLA, OC + CRE, OC+PLA). An *alpha* level of $p < 0.05$ was selected, *a priori*. All analyses were performed using SPSS statistical software package v.20.0 (SPSS Inc., Chicago, IL).

A magnitude-based inference approach was performed simultaneously to provide more interpretive analysis of specific results; when analyzing peak power and muscle fatigue

index (because main effects of time and group were observed using null hypothesis testing), a more in-depth interpretation was desired to determine the magnitude and likelihood of a true change. Change scores derived from pre- and post- within group measures were calculated. Using a publicly available spreadsheet¹²³, 90% confidence intervals were calculated to provide a range of uncertainty of the true value. To provide relevance to the uncertainty, a three-level scale of magnitude (*beneficial*, *negligible* and *harmful*) was used by taking the smallest most important value and providing real-life context to that value. Quantitative descriptors were calculated¹²³ of the likelihood of the true value and associated magnitude and were defined as: 0-0.5% - *most unlikely*, 0.5-5% - *very unlikely*, 5-25% - *unlikely*, 25-75% - *possibly*, 75-95% - *likely*, 95-99.5% - *very likely* and 99.5-100% - *most likely*. To further distinguish the outcome, qualitative probabilities (effect sizes) were defined as, small, moderate and large and were calculated based on 0.2-0.6, 0.6-1.2, and 1.2-2.0 of the baseline control standard deviation and probability of each magnitude was calculated.

Chapter 4

Results

The results reported within this thesis are a sub-section of results from a multi-centre study. Inferences of the current (Guelph) data are solely based on this sub-set and are not necessarily indicative of complete results of the greater clinical trial. We wish to recognize that the results herein reported are thus not complete and do not fully or conclusively demonstrate the efficacy of the topical creatine product, and should not be interpreted as such.

4.1 Participant Characteristics

The study population initially included 81 participants to be analyzed completely (study 1 $n=41$, study 2 $n=43$, study 1+2 $n=22$) aged 18-36 years residing in the township of Guelph-Wellington. In total, 15 participants (from either Study 1 or Study 2, 8 females and 7 males) were excluded from data analysis due to inexplicable outlying data, defined as outcomes lying over 2 standard deviations of the mean and likely biasing the overall data. This left a combined total of 66 participants (study 1 $n=34$, study 2 $n=32$, study 1+2 $n=13$). Matched baseline characteristics for both study 1 and study 2 are shown in Table 1 and Table 2, respectively.

Table 1. Baseline characteristics of participants in study 1

Anthropometric Measure	Single Application (n=19)	Double Application (n=15)
Age (yr)	23 ± 3	24 ± 4
Height (cm)	173.3 ± 8.9	171.3 ± 8.6
BMI (kg/m ²)	23.4 ± 3.2	24.2 ± 2.9
Total body fat composition (%)	17.3 ± 7.1	19.7 ± 5.8
Godin-Leisure Score	56 ± 34	68 ± 24
Weight (kg)	70.6 ± 11.6	70.9 ± 13.6
SBP (mmHg)	110 ± 11	110 ± 12
DBP (mmHg)	72 ± 8	74 ± 10
Leg girth, placebo application (cm)	47.6 ± 3.5	49.6 ± 3.4
Leg girth, creatine application (cm)	47.5 ± 3.3	49.5 ± 3.2

Table 2. Baseline characteristics of participants in Study 2

Anthropometric Measures	Oral Placebo (n=15)	Oral Creatine (n=17)
Age (yr)	23 ± 3	22 ± 2
Height (cm)	172.4 ± 8.4	170.7 ± 9.9
BMI (kg/m ²)	23.2 ± 1.9	23.2 ± 2.2
Total body fat composition (%)	17.6 ± 7.3	18.9 ± 7.7
Godin-Leisure Score	63 ± 22	52 ± 25
Weight (kg)	69.2 ± 8.4	68.0 ± 11.5
SBP (mmHg)	108 ± 11	113 ± 12
DBP (mmHg)	71 ± 10	76 ± 9
Leg girth, placebo application (cm)	49.3 ± 3.6	47.8 ± 3.4
Leg girth, creatine application (cm)	49.0 ± 3.4	47.9 ± 3.6

4.2 Study 1 – Acute Intervention

4.2.1 Experimental topical creatine cream vs. Topical placebo cream

Objective: To investigate the effects (peak power, average power and muscle fatigue index) of an experimental topical creatine cream compared to a topical placebo cream applied immediately prior to performing maximal leg extensions.

Mean differences and standard deviations of peak power, average power and muscle fatigue index produced on the Quantum dynamometer at pre- and post- application of each topical cream, are provided for each group (Table 3). Main effects of time for peak power ($p=0.01$) and muscle fatigue index ($p=0.007$) were observed, with no differences between groups. However, there was a significant interaction (time x group) seen of the average power production in PLA2 ($p=0.01$), which was not seen in the other groups, such that PLA2 decreased from baseline.

Table 3. Mean and SD of peak power, average power and fatigue index prior and following application of either PLA1, CRE1, PLA2, or CRE2.

	Group 1				Group 2				P value
	PLA1		CRE1		PLA2		CRE2		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
PP (W)	268 ± 77	262 ± 72	275 ± 95	277 ± 94	296 ± 72	284 ± 72	298 ± 87	286 ± 86	<0.001*
AP (W)	228 ± 67	222 ± 65	231 ± 81	234 ± 81	252 ± 62	239 ± 60**	246 ± 70	238 ± 69	0.04**
FI (%)	27.3 ± 7.4	26.0 ± 6.9	27.7 ± 6.9	27.2 ± 6.2	31.5 ± 8.5	30.4 ± 7.7	30.5 ± 7.7	27.3 ± 8.4	<0.01*

*Presence of a significant main effect of time post administration of topical cream for all groups

**Presence of a significant group x time interaction

P value of F ratio of either significant main effect of time or interaction (time x group)

PP – peak power; AP – average power, FI – fatigue index

As improvement was observed with overall changes in peak power and muscle fatigue (Figure 6), analysis of MBI was reported on those outcomes in the results hereon in. MBI revealed that there was a *possibly negligible* increase observed in peak power when CRE1 was compared to its placebo counterpart, PLA1 (Table 5). A *likely negligible* increase was observed in peak power when CRE2 was compared to its placebo counterpart, PLA2 (Table 5). Analysis of CRE1 effects on peak power within and between sets was conducted; a *moderate, possibly beneficial* increase in power was observed in set 1 (first set), however, digressing to a *likely negligible* increase, observed in set 5 (last set) (Table 5). A *likely negligible* improvement was seen in muscle fatigue when comparing CRE1 to PLA1, however, there was a *small, possibly negligible* increase in muscle fatigue when comparing CRE2 to PLA2 (Table 5). Within and between sets, there was a *small, possibly negligible* improvement in muscle fatigue index of CRE2 to PLA2 in set 1, but in set 5, a *likely negligible* improvement was observed (Table 5).

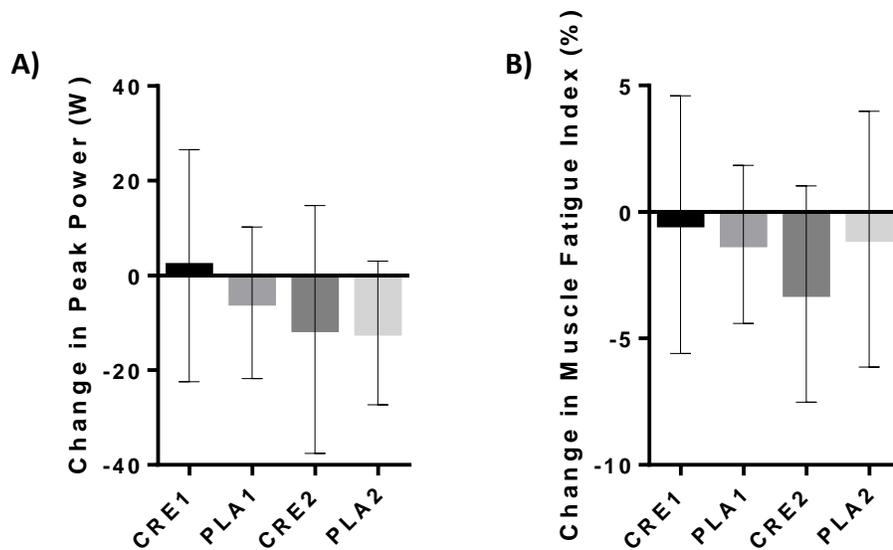


Figure 6. Change scores of A) peak power (W) and B) muscle fatigue index (%) pre- and post- immediate administration (study 1) for all groups after completing five sets of 15 maximal knee extensions per leg at $0.5 \text{ m}\cdot\text{s}^{-1}$ ($p>0.05$). A decrement in muscle fatigue index indicates an improvement in performance.

4.2.2 Single dose vs. Double dose

Objective: To compare two dosing applications (single = 15 minutes prior to exercise, double = 30 and 15 minutes prior to exercise) of the experimental topical creatine cream.

When comparing the difference between CRE1 and CRE2 on all performance measures (peak power, average power and muscle fatigue index), no significant differences were observed ($p > 0.05$) (Figure 6).

A *small, possibly negligible* increase was observed in both peak power and muscle fatigue when comparing CRE1 and CRE2 (Table 5). This continued for peak power in set 1 of a *moderate, possibly negligible* increase seen in CRE1 when compared against CRE2, however, calculating a *small, possibly negligible* improvement for set 5 (Table 5).

Muscle fatigue index reported a *moderate, unlikely negligible (likely beneficial)* improvement of CRE2 when compared to CRE1 in set 1, but a *small, likely negligible* improvement was reported at set 5 (Table 5).

4.2.3 Anthropometric Measures

Descriptive measures including weight, systolic blood pressure and leg girth (right and left legs) revealed no significant changes observed between single and double experimental application ($p > 0.05$). Though a main effect of time was observed on the change in diastolic blood pressure, exhibiting a significant decrease in the double application of creatine group (4 ± 6 mmHg; $p=0.03$; Table 4).

Table 4. Mean and SD of weight, SBP, DBP, and placebo and creatine treated leg girth before and after either a single or double application of topical cream (study 1).

	Single		Double	
	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>
Weight (kg)	70.7 ± 11.5	70.6 ± 11.8	72.2 ± 12.4	72.4 ± 12.5
SBP	111 ± 9	104 ± 24	111 ± 13	108 ± 11
DBP	73 ± 8	72 ± 7	75 ± 11	71 ± 8*
Leg girth, placebo (cm)	47.8 ± 3.5	48.1 ± 3.9	49.6 ± 3.4	49.7 ± 3.3
Leg girth, creatine (cm)	47.5 ± 3.3	47.9 ± 3.5	49.5 ± 3.2	49.5 ± 3.2

*Significant ($p<0.01$) main effect of time post administration of double application of the topical creatine cream

Table 5. Complete MBI approach results for Study 1

Study 1 - Single (n=19); Double (n=15) ¶¶						
	Δ PP(W) \pm SD	ES; \pm 90% CL	Inference	Δ MFI (%) \pm SD	ES; \pm 90% CL	Inference
Single vs. Placebo	2 \pm 25; -6 \pm 16	0.38; \pm 0.6	Negligible*	0.5 \pm 5.1; -1.3 \pm 3.1	0.18; \pm 0.5	Negligible**
Single vs. Placebo Set 1	4 \pm 28; -9 \pm 15	0.60; \pm 0.5	Beneficial*	2.3 \pm 5.4; -1.0 \pm 7.3	0.51; \pm 0.5	Negligible*
Single vs. Placebo Set 5	-3 \pm 19; 0 \pm 20	-0.12; \pm 0.5	Negligible**	-0.97 \pm 8.5; -1.3 \pm 7.8	0.04; \pm 0.5	Negligible**
Double vs. Placebo	-12 \pm 26; -12 \pm 15	0.03; \pm 0.6	Negligible**	-3.2 \pm 4.3; -1.1 \pm 5.1	-0.46; \pm 0.6	Negligible*
Double vs. Placebo set 1	-15 \pm 29; -12 \pm 16	-0.13; \pm 0.7	Negligible**	-1.6 \pm 5.4; 0.9 \pm 5.4	-0.47; \pm 0.6	Negligible*
Double vs. Placebo set 5	5 \pm 21; -2 \pm 35	0.22; \pm 0.6	Negligible*	2.8 \pm 9.0; -1.3 \pm 12.5	-0.14; \pm 0.6	Negligible**
Single vs. Double	2 \pm 25; -12 \pm 25	-0.53; \pm 0.6	Beneficial*	-0.5 \pm 5.1; -3.2 \pm 4.3	-0.58; \pm 0.6	Beneficial*
Single vs. Double Set 1	4 \pm 28; -15 \pm 29	-0.69; \pm 0.6	Beneficial*	2.3 \pm 5.4; -1.6 \pm 5.4	-0.73; \pm 0.6	Beneficial**
Single vs. Double Set 5	-3 \pm 19; 5 \pm 21	0.35; \pm 0.6	Negligible*	-1.0 \pm 8.5; -2.8 \pm 9.0	-0.21; \pm 0.6	Negligible**

¶¶ total of 41 participants included in study 1, only 34 participants analyzed.

*Possibly

**Likely

REMINDER: likelihood of true value and associated magnitude were defined as: 0-0.5% - *most unlikely*, 0.5-5% - *very unlikely*, 5-25% - *unlikely*, 25-75% - *possibly*, 75-95% - *likely*, 95-99.5% - *very likely* and 99.5-100% - *most likely*.

4.3 Study 2 – Chronic Intervention

Mean differences and standard deviations of peak power, average power and fatigue index produced on the Quantum dynamometer prior to and proceeding both oral and topical supplementation are provided in Table 6. There was no 2-way interaction for average power (time x group; $p=0.8$), nor main effects following supplementation. A time x group interaction was observed in peak power ($p=0.02$), such that there was a decrement ($8 \text{ W} \pm 16 \text{ W}$) in the OP + PLA group, whereas the other groups increased or the decrement was less ($<3 \text{ W}$) (Figure 7). However, a main effect of time was seen in muscle fatigue index ($p=0.04$; Table 6) in all conditions (improving from pre- to post-). Overall changes for each condition for peak power (W) and muscle fatigue index (%) are presented in Figure 7.

Table 6. Mean and SD of peak power, average power and fatigue index before and after supplementation of either oral placebo (with topical placebo (OP+PLA) and creatine cream (OP+CRE)) or oral creatine (with topical placebo (OC+PLA) and creatine cream (OC+CRE)).

	Oral Placebo				Oral Creatine				<i>P</i> value
	Placebo Application		Creatine Application		Placebo Application		Creatine Application		
	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	
PP (W)	288 ± 94	280 ± 96	277 ± 105	281 ± 100	243 ± 69	248 ± 72	249 ± 81	255 ± 84	0.02**
AP (W)	234 ± 82	234 ± 86	232 ± 94	232 ± 93	202 ± 61	207 ± 64	208 ± 71	211 ± 69	<i>N.S.</i>
FI (%)	26.7 ± 6.1	25.8 ± 6.7	27.5 ± 5.8	27.2 ± 7.2	31.1 ± 10.2	28.2 ± 9.7	30.3 ± 8.0	28.7 ± 7.7	0.04*

*Presence of a significant main effect of time post supplementation for all groups

**Presence of a significant group x time interaction

P value of F ratio of either significant effect of time or interaction (time x group)

PP – peak power; **AP** – average power, **FI** – fatigue index

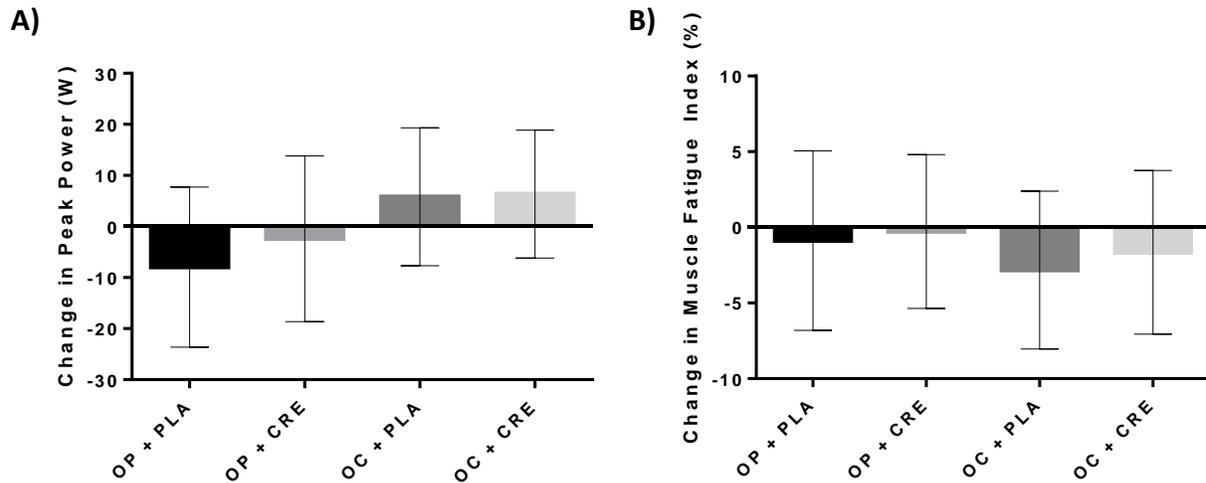


Figure 7. Change scores of A) peak power (W) and B) muscle fatigue index (%) pre- and post-supplementation in study 2 for all groups after completing five sets of 15 maximal knee extensions per leg at $0.5 \text{ m}\cdot\text{s}^{-1}$ ($p>0.05$). A decrement in muscle fatigue index indicates an improvement in performance.

4.3.1 Chronic use of OP + CRE vs. OP + PLA

Objective: To investigate the effects (peak power, average power and muscle fatigue index) of chronic application of an experimental topical creatine cream to a topical placebo cream for 7 days prior to performing maximal leg extensions.

When examining all performance outcomes (peak power- creatine cream: $-2\text{W} \pm 16\text{W}$, placebo cream: $-8\text{W} \pm 16\text{W}$; average power – creatine cream: $0\text{W} \pm 19\text{W}$, placebo cream: $0\text{W} \pm 21\text{W}$; and muscle fatigue – creatine cream: $-0.27\% \pm 5.1\%$, placebo cream: $-0.87\% \pm 5.9\%$) for OP + CRE and OP + PLA, no significant differences were found ($p > 0.05$).

Specific analysis using MBI for peak power between treatments (OP + CRE vs. OP + PLA) revealed a *small, possibly negligible* increase seen with OP + CRE when compared to OP + PLA (Table 8). Observing peak power values of set 1, a *small, possibly*

negligible increase was observed in OP + CRE, however a *likely negligible* increase was observed in set 5 in OP + CRE (Table 8). In addition, muscle fatigue index revealed a *likely negligible* improvement when comparing OP + CRE to OP + PLA (Table 8). Sets 1 and 5 showed a *likely negligible* improvement in muscle fatigue of OP + CRE (Table 8).

4.3.2 Chronic use of OC + CRE vs. OC + PLA

Objective: To compare the effects (peak power, average power and muscle fatigue) of chronic application of the experimental topical creatine cream in addition to consumption of oral creatine supplementation for 7 days prior to exercise.

Differences were not found when comparing the combination of oral creatine supplementation and the experimental topical creatine cream to only the oral creatine administration (topical placebo cream applied) for any outcome measure (peak power – creatine cream: $6W \pm 13W$, placebo cream: $6W \pm 13W$; average power – creatine cream: $3W \pm 11W$, placebo cream: $4W \pm 9W$; or muscle fatigue index – creatine cream: $-1.7\% \pm 5.4\%$, placebo cream: $-2.8\% \pm 5.2\%$) ($p > 0.05$).

A *likely negligible* increase in peak power when comparing OC + CRE and OC + PLA and a *small, likely negligible* improvement observed in muscle fatigue index when comparing OC + CRE and OC + PLA (Table 8). Changes in peak power between sets 1 and 5 showed a *likely negligible* improvement seen between treatments (Table 8).

Changes in muscle fatigue followed similar suit with a *likely negligible* improvement observed in set 1 and set 5 between OC + CRE and OC + PLA (Table 8).

4.3.3 Chronic application of OP + CRE vs. OC + PLA

Objective: To examine the difference in performance (peak power, average power and muscle fatigue index) between chronic application of the experimental topical creatine cream to consumption of oral creatine supplementation for 7 days prior to exercise.

Assessment of topical creatine supplementation in the oral placebo supplement group to only oral creatine administration with topical placebo cream application, did not reach statistical significance for any outcome measure (peak power – creatine cream: $-2\text{W} \pm 16\text{W}$, oral creatine: $6\text{W} \pm 13\text{W}$; average power – creatine cream: $0\text{W} \pm 19\text{W}$, oral creatine: $4\text{W} \pm 9\text{W}$; or muscle fatigue index – creatine cream: $-0.27\% \pm 5.1\%$, oral creatine: $-2.8\% \pm 5.2\%$) ($p > 0.05$). In addition, correlations of < 0.8 were observed for all outcome measures when comparing OP + CRE to OC + PLA.

A small, possibly negligible, but possibly beneficial effect was seen in OC + PLA compared to OP + CRE, regarding changes in peak power (Table 8). When looking between changes in sets of OP + CRE and OC + PLA, a likely negligible increase was seen in set 1 with a small, possibly negligible increase seen in set 5 (Table 8). A small, possibly negligible improvement was observed in changes in muscle fatigue between conditions (Table 8). Similarly, a small, possibly negligible improvement was seen in set 1 and set 5 (Table 8).

4.3.4 Leg Girth

Objective: To examine the localized differences in leg girth subsequent chronic application of the experimental topical creatine cream after 7 days of application prior to exercise.

Regarding anthropometric measures taken pre- and post- supplementation, there was no 2-way (time x group) interaction or main effects for weight and blood pressure measurements ($p > 0.05$). However, a significant main effect of time ($p < 0.001$) was observed in leg girth with an increase in size between pre- and post- measurements for both oral placebo and creatine groups (Table 7).

When completing a MBI approach, specifically for weight, there was a *moderate, possibly beneficial* increase in weight when comparing the oral creatine group to the oral placebo group.

Table 7. Mean and SD of weight, SBP, DBP, and placebo and creatine treated leg girth before and after either oral placebo or creatine supplementation for 7 days prior to exercise.

	Oral Placebo		Oral Creatine	
	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>
Weight (kg)	69.7 ± 8.3	69.7 ± 8.2	68.1 ± 11.0	68.6 ± 11.2
SBP (mmHg)	109 ± 7	110 ± 8	109 ± 12	113 ± 12
DBP (mmHg)	70 ± 6	74 ± 8	74 ± 8	74 ± 9
Leg girth, placebo (cm)	49.3 ± 3.6	49.5 ± 3.3*	47.8 ± 3.4	48.2 ± 3.5*
Leg girth, creatine (cm)	49.0 ± 3.4	49.6 ± 3.8*	47.9 ± 3.6	49.0 ± 3.6*

*Significant ($p < 0.001$) time effect post oral supplementation of creatine and placebo in both legs

Table 8. Complete MBI approach results for Study 2

Study 2 - Oral Placebo (n=15); Oral Creatine (n=17) +

	Δ PP(W) \pm SD	ES; \pm 90% CL	Inference	Δ MFI (%) \pm SD	ES; \pm 90% CL	Inference
OC+PLA vs. OP+CRE	6\pm13; -2\pm16	-0.55; \pm0.6	<i>Negligible*</i>	-2.8\pm5.2; -0.3\pm5.1	0.50; \pm0.6	<i>Beneficial*</i>
OC+PLA vs. OP+CRE set 1	3 \pm 18; 3 \pm 24	-0.04; \pm 0.6	<i>Negligible**</i>	-2.6 \pm 7.2; 0.4 \pm 5.9	0.45; \pm 0.6	<i>Negligible*</i>
OC+PLA vs. OP+CRE set 5	0 \pm 17; -4 \pm 17	-0.22; \pm 0.6	<i>Negligible*</i>	3.9 \pm 6.8; -1.8 \pm 7.9	0.28; \pm 0.6	<i>Negligible*</i>
OP+PLA vs. OP+CRE	-8\pm16; -2\pm16	0.35; \pm0.6	<i>Negligible*</i>	-0.9\pm5.9; -0.3\pm5.1	0.11; \pm0.6	<i>Negligible**</i>
OP+PLA vs. OP+CRE set 1	-6 \pm 17; 3 \pm 24	0.42; \pm 0.6	<i>Negligible*</i>	1.3 \pm 7.4; 0.4 \pm 5.9	-0.14; \pm 0.6	<i>Negligible**</i>
OP+PLA vs. OP+CRE set 5	-1 \pm 39; -4 \pm 17	-0.09; \pm 0.7	<i>Negligible**</i>	-0.7 \pm 8.1; -1.8 \pm 7.9	-0.13; \pm 0.6	<i>Negligible**</i>
OC+PLA vs. OC+CRE	6\pm13; 6\pm13	0.04; \pm0.6	<i>Negligible**</i>	-2.8\pm5.2; -1.7\pm5.4	0.22; \pm0.6	<i>Negligible**</i>
OC+PLA vs. OC+CRE set 1	3 \pm 18; 1 \pm 15	-0.12; \pm 0.6	<i>Negligible**</i>	-2.6 \pm 7.2; -1.2 \pm 8.5	0.17; \pm 0.6	<i>Negligible**</i>
OC+PLA vs. OC+CRE set 5	0 \pm 17; -4 \pm 26	-0.18; \pm 0.6	<i>Negligible**</i>	-3.9 \pm 6.8; -4.6 \pm 8.7	-0.09; \pm 0.6	<i>Negligible**</i>

+ total of 40 participants included in study 2, only 32 participants analyzed.

**Possibly*

***Likely*

REMINDER: likelihood of true value and associated magnitude were defined as: 0-0.5% - *most unlikely*, 0.5-5% - *very unlikely*, 5-25% - *unlikely*, 25-75% - *possibly*, 75-95% - *likely*, 95-99.5% - *very likely* and 99.5-100% - *most likely*.

4.4 Adverse Events

There were reported side effects after application of the creams in Study 1 and after the week-long supplementation period in Study 2, specifically regarding the cream application. In study 1, 68% of the participants (23/34) experienced some degree of adverse reaction to the creams (both placebo and creatine). Twenty participants felt mild sensations and various combinations of irritation (3), burning (4), warmth (6), numbness (2), stinging (1), redness (7), itching (3) and tingling (1). One participant felt coldness in one leg with another participant experiencing moderate burning. In study 2, 86% of the participants (28/32) experienced an adverse reaction to the application of the creams throughout the week. There were 12 counts of irritation (7 mild, 5 moderate), 6 counts of itching (5 mild, 1 moderate), 5 counts of redness (4 mild, 1 moderate), 20 counts of burning (8 mild, 10 moderate, 2 severe) and 5 counts of heat (3 mild, 1 moderate, 1 severe). These sensations were exacerbated with exercising, sweating or applying hot water on the area. With one participant dropping out of the study due to severe burning experienced with the application of the cream.

Chapter 5

Discussion

For the first time, we examined the potential performance-enhancing effects of topically absorbed creatine monohydrate. No significant improvements were observed in overall peak and average power; however, a reduction in fatigue index was demonstrated in repeated leg extensions after immediate and short-term application; which suggests a potential ergogenic effect of the topical cream. In addition, the magnitude and likelihood components of a MBI statistical approach were used to enhance the interpretation of the findings. Within the literature, creatine has typically been administered orally in exercise performance studies, likely due to its efficient cost, high bioavailability and consistent results^{9,124,125}. However, certain negative side effects (e.g. GI irritation and water retention) are common when consumed orally¹², which has led to the avoidance of the supplement for individuals who respond to oral supplementation with GI discomfort or those who participate in weight-sensitive activities.

5.1 Effectiveness of experimental topical creatine cream

No performance-enhancing capabilities of the novel topical creatine cream were observed in a mixed group of subjects consisting of recreational and varsity level athletes. Peak and average power values generally declined (peak: $-11\text{W} \pm 26\text{W}$, average: $-9\text{W} \pm 18\text{W}$) with two consecutive applications of the experimental topical creatine cream and placebo topical creams (Study 1) or displayed no to very minimal change (peak: $-2 \pm 16\text{W}$, average: $0\text{W} \pm 19\text{W}$) within the oral placebo group (Study 2) during a short-term (7-day)

application of the cream. These findings were described as *negligible* for peak and average power (peak: $-11\text{ W} \pm 26\text{ W}$, average: $-9\text{ W} \pm 18\text{ W}$); which is further supported by previous studies observing an increase of $>20\text{ W}$ following 7 days of oral creatine supplementation^{47,48,126}.

Furthermore, an improvement in muscle fatigue was observed in both studies with application of the experimental topical creatine cream (Study 1: $>0.27\%$, Study2: $>0.5\%$). These changes are minimal compared to the few muscular fatigue improvements with creatine supplementation^{99,100}. However, the experimental topical creatine cream provided consistent enhancement of muscle fatigue index, whereas Cottrell *et al.*¹⁰⁰ observed changes in muscle fatigue that ranged from a decrement of 2.3% to an improvement of 5.1% in repeated bouts of cycling after 7 days of oral creatine supplementation. While changes in fatigue index in the current study are less than what has previously been reported^{99,100}, this slight gain may be of clinical or practical value simply due to the difference in administration of creatine (topical vs. oral).

5.1.1 Similarities between current study and previous research

The current study analyzed all groups (composed mainly of recreationally active individuals) for homogeneity, displaying no difference between groups. Francaux and Poortmans¹² reported that recreational individuals seem to respond equally to oral creatine supplementation when compared to sedentary or even trained athletes. Therefore, it was expected that individuals who participated in leisurely exercise would respond similarly to those who are athletically inclined, allowing for a greater population to

recruit from. Results from Harris *et al.*¹⁶ demonstrated that only 20g of creatine monohydrate for two or more consecutive days would elicit a 20% increase in total creatine concentration, which is why a seven-day loading protocol was implemented. Although direct muscle creatine and PCr concentrations were not measured in the current study, Greenhaff *et al.*⁴⁹ and Rawson *et al.*³⁶ have demonstrated an improvement in muscle fatigue without blood or tissue collection with a similar repeated leg extension design. However, studies using a short-term dosing protocol (<7 days) uncommonly see a change in peak or average power in exercise performance^{101,126–128}, which corroborate our null findings in regards to peak and average power. Significant improvements in power outputs are mainly observed in those with long-term use of creatine supplementation or those that incorporate a resistance training program^{129,130,55}. It is possible that short-term creatine supplementation (<7 days) is insufficient time to elicit significant improvements in muscle hypertrophy or strength.

5.1.2 Delivery of creatine

There was an improvement in muscle fatigue index immediately and shortly after chronic application of both placebo and creatine cream, however, the mechanism in which the experimental topical creatine cream is absorbed and transported through the body is unknown. Both the topical experimental and placebo creams contained the same formulation (except the active ingredient, creatine monohydrate). Even though no blood samples or biopsies were collected, with the assumption the cream was delivered to the muscle, it is possible that the inclusion of the 0.3% beta-alanine possibly contributed to the observed fatigue-resistant effects. Penetration is feasible as the company's

(Delivra™) delivery system works through the liposomal carrier system which incorporates various penetration enhancers that disrupt the outer epidermis to allow for transportation of a targeted bioactive (i.e. creatine and beta-alanine). Fatigue resistance has been observed with a similar design, employing a topical carnosine cream (LactiGo™) that correlated with an average improvement in 1000m time by 4.13% ²². The enhancements detected in muscle fatigue in the current study with a double application of the experimental topical creatine cream are within a similar range (3.2%) as Sharpe and Macias ²² reported, along with the timeframe of application (Whinton: 15 or 30 minutes prior to exercise; Sharpe and Macias: 45 minutes), and absence of blood samples. This rapid augmentation in performance suggests that the administration of carnosine (and for the purpose of our results, beta-alanine) could be an important factor when considering potential, viable and safe avenues of improvement in sport, due to its buffering capabilities it provides topically ²² and orally ⁵⁶.

5.1.3 Formulation of the topical cream

Another component (vanillyl butyl ether) combined in the topical formulation can affect performance by chemical interplay of sensory neurons ¹³¹. This ingredient could interact with certain skin receptors such as touch and pressure (cutaneous mechanoreceptors), temperature (thermoreceptors), and pain/itchiness (nociceptors) that could ultimately influence absorption into the skin ¹³². Vanillyl butyl ether was incorporated into all creams which can bind to the vanilloid receptor subtype 1, therefore allowing passage through the cell membrane and providing similar sensations as excessive heat or irritation ¹³¹. This intense feeling of warmth could be related to the decrement or absence of

significance in power production with immediate (26% participants experienced warmth of those who reported an adverse event) and short-term (71% of those with side effects, felt sensations of burning, with 18% feeling heat) application of the cream prior to exercise if it affected the participant's motivation or perception of effort. Studies performed in individuals who require pain relief such as those with diabetic neuropathy, arthritis and postherpetic neuralgia have a relatively large (30%) dropout rate with most reporting severe burning sensations in a low dose (0.075%) topical capsaicin formulation¹³³. This could influence an individual's performance either positively, negatively or not at all, depending on how one reacts to this stimulus. Zinner *et al.*¹³⁴ experimented with the application of a topical formulation containing nonivamide (capsaicinoid, part of the vanilloid family) and nicoboxil (increases blood flow)¹³⁵, where there was no change in average power nor any cardiovascular parameters (heart rate, cardiac output, perceived exertion or oxygen uptake)¹³⁴.

5.1.4 Concentration of creatine

A main contributor to which a substance can penetrate multiple layers depends on the concentration and molecular weight of that desired substance. Creatine monohydrate has a molecular weight of 132 g/mol, making it relatively smaller in comparison to other molecules that have been successful at accessing the muscle (ketoprofen: 254 g/mol, nicoboxil: 223 g/mol, nonivamide: 293 g/mol)¹³⁶. If other agents of larger weight are able to penetrate and enter the muscle successfully, it stands to reason that creatine monohydrate should be able to as well. Although a single application of the topical absorption of the creatine cream (0.035 mg) likely caused some systemic circulation of

creatine metabolites, it is also fair to suggest that the majority of the absorbed creatine (0.035 mg, if 100% absorbed), would be concentrated at the site of application (i.e. quadriceps – approximately 1 kg of muscle mass). This theory is based on a similar study with a topical ketoprofen cream (10% active ketoprofen) revealing minimal systemic absorption 24 hours post absorption ²³. However, 10% of the topical formulation was ketoprofen; the current study contains 1% of the active ingredient (creatine monohydrate) with a protocol of applying the cream at a minimum of 2 times (immediate application) or a total of 7 times (short-term application). It is certainly possible that the amount of active ingredient within the formulation and amount of times it is applied, plays a major role in determining whether the active ingredient is able to penetrate deep enough to elicit any performance effect in a short timeframe that is commonly observed with oral creatine supplementation.

5.2 Limitations

Contrary to the reported benefits of oral creatine supplementation in relation to exercise performance, the current study did not observe any significant advantageous changes. Oral creatine supplementation best elicits effects when paired with high-intensity, short duration exercise (i.e. maximal leg extensions) ^{49,114,115}. This is because these short, repeated movements (<10 seconds of activity) have a greater response to the 2.5 – 5% increase in energy supply that may be provided with creatine supplementation ⁹. It is of critical importance that participants perform maximally to garner the benefits of creatine supplementation, which is why researchers implement techniques for this reason.

Individuals are more likely to perform closer to their true maximum when motivation is

provided by researchers or peers and is confirmed through interpolated twitches^{19,137} or practice movements beforehand^{49,114}. Multiple studies report that “verbal encouragement was provided” but fail to describe and explain the details of events^{127,138,139}. This qualitative factor to motivate participants becomes hard to quantify and determine how “much” motivation someone needs or what kind of motivation helps participants perform maximally. Standardized phrases such as “you’ve got this, kick a little harder” and “let’s go, keep pushing, get to your maximum again” were implemented throughout the current exercise protocol so that every participant encountered the same motivation from all researchers. Furthermore, in order to truly quantify whether or not an individual is performing maximally, interpolated twitches are occasionally employed prior to the actual exercise performance to establish an upper limit. Although this technique was not incorporated in the current study, others have shown that even with verification of maximal effort, creatine supplementation does not improve peak power production or maximal voluntary contraction strength^{19,137}. Familiarization visits and practice “kicks” were implemented prior to the actual performance test, so that we were able to assess, to the best of our knowledge, the participant was performing maximal knee extensions and to void any learning effect. Lastly, an important limitation to be noted, is the absence of blood measures or muscle biopsies. Incorporation of these measures would confirm the presence of the experimental topical creatine cream systemically and locally.

5.3 Future Direction

Current research is delving into fine tuning how oral supplementation induces muscle hypertrophy², how other supplements in combination with creatine can stimulate or

influence uptake ¹³⁹ and how different exercises improve with supplementation ¹⁴⁰. While we have incorporated an exercise (i.e. leg extension) that is well-documented in the literature, we have encompassed the first two new areas of creatine research within the current study. The way in which creatine stimulates muscle growth is up for debate and has many valid hypotheses including creatine's osmosensing effects ^{2,42}, stimulating components of the mTOR pathway ^{2,83}, and decreasing myostatin ^{42,111}. Administering creatine topically, potentially provides another avenue in which creatine can influence muscle growth locally and offers future opportunity to pursue further investigation, especially in a clinical setting (i.e. muscular dystrophy). In addition, incorporating beta alanine (as a non-active ingredient) to the formulation of the experimental topical creatine topical cream allows for the examination of the two ergogenic aids working simultaneously, similarly to Crisafulli's ¹³⁹ work. From the results reported in the current study, suggests beta-alanine could have played a potential role in combination with creatine supplementation (providing an additive effect) in decreasing muscle fatigue. Whereas, the combination of the experimental topical creatine cream and oral creatine supplementation revealed *likely negligible* improvements. There is large interest in exploring how different combinations of supplements work in order to test if there is an additive, synergistic, negative, or null effect to be able to enhance overall performance.

Chapter 6

Conclusion

The current study demonstrated positive but *likely negligible* changes in muscle fatigue; however, no real or beneficial clinical changes in peak or average power when supplementing with topical and oral creatine were observed. This was the first study to apply a topical creatine cream to examine power production and muscle fatigue with leg extensions on a novel isokinetic dynamometer. Topical application of ergogenic aids, specifically creatine (or those that influence muscle growth or recovery), are on the cusp of advancing research. This study provides an entrance into the world of topical creatine supplementation with sound techniques and evidence paving the way for future research in this area. Topical application is trending as it bypasses the GI tract that can cause many individuals distress and even sometimes, severe complications⁵³, and provide localizing effects. Future direction should employ the use of topical creatine cream with a high concentration of the ergogenic aid, with more frequent applications to a greater sample size. Potentially using a different exercise protocol (e.g. repeated short sprints of varied distances, or weightlifting) may provide insight on real-life application of its use.

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Appendix A

Ethics Approval from REB of the University of Guelph



RESEARCH ETHICS BOARDS

*Certification of Ethical Acceptability of Research
Involving Human Participants*

APPROVAL PERIOD: July 28, 2016
EXPIRY DATE: July 28, 2017
REB: NPES
REB NUMBER: 16MY014
TYPE OF REVIEW: Full Board
PRINCIPAL INVESTIGATOR: Burr, Jamie (burrj@uoguelph.ca)
DEPARTMENT: Human Health & Nutritional Sciences
SPONSOR(S): NSERC Industrial Postgraduate Scholarships
TITLE OF PROJECT: Randomized, Double-Blind, Placebo-Controlled, Short Term Trial of Delivra™ LivSport PreWorkout Cream with or without Oral Creatine for Improved Power Output and Reduction of Muscle Fatigue During Resistance Training

The members of the University of Guelph Research Ethics Board have examined the protocol which describes the participation of the human participants in the above-named research project and considers the procedures, as described by the applicant, to conform to the University's ethical standards and the Tri-Council Policy Statement, 2nd Edition.

The REB requires that researchers:

- Adhere to the protocol as last reviewed and **approved** by the REB.
- Receive approval from the REB for any **modifications** before they can be implemented.
- Report any **change in the source of funding**.
- Report **unexpected events or incidental findings** to the REB as soon as possible with an indication of how these events affect, in the view of the Principal Investigator, the safety of the participants, and the continuation of the protocol.
- Are responsible for **ascertaining and complying with all applicable legal and regulatory requirements** with respect to consent and the protection of privacy of participants in the jurisdiction of the research project.

The Principal Investigator must:

- Ensure that the ethical guidelines and approvals of facilities or institutions involved in the research are obtained and filed with the REB prior to the initiation of any research protocols.
- Submit a **Status Report** to the REB upon completion of the project. If the research is a multi-year project, a status report must be submitted annually prior to the expiry date. Failure to submit an annual status report will lead to your study being suspended and potentially terminated.

The approval for this protocol terminates on the **EXPIRY DATE**, or the term of your appointment or employment at the University of Guelph whichever comes first.

Signature:

Date: July 28, 2016

L. Vallis
Chair, Research Ethics Board-NPES

Appendix B

Notice of Authorization from Health Canada pertaining Clinical Trial Application for



Health Canada Santé Canada

Delivra LivSport PreWorkout Cream

NATURAL AND NON-PRESCRIPTION HEALTH PRODUCTS DIRECTORATE

Notice of Authorization

Company Code. 23365
File No. 217760
Submission No. 217760

April 26, 2016

Dr. Joseph Gabriele
c/o Dr. Florence Roulet
Delivra Inc.
1327 Heine Court
Burlington ON
L7L 6A7

Dear Dr. Gabriele:

Re: CLINICAL TRIAL APPLICATION for Delivra LivSport PreWorkout Cream
(Delivra-002) *Natural Health Products Regulations* Section: 67

The Natural and Non-prescription Health Products Directorate is pleased to inform you that the information and material provided to support the above Clinical Trial Application have been assessed and we have no objection to your proposed study. Please consider this as your notice of authorization to sell or import this natural health product for the purposes of this clinical trial in Canada.

Please note that you are responsible for ensuring the appropriate considerations are taken into account in order to comply with the requirements set out in the *Natural Health Products Regulations* (NHPR) and its associated guidance documents. For more information on the expectations and approaches relating to quality requirements and Good Manufacturing Practices for natural health products, please consult the *Quality of Natural Health Products Guide* and the *Good Manufacturing Practices* guidance document (<http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index-eng.php>).

I would remind you of the necessity of complying with the *NHPR*, Part 4, in the sale of this product for clinical testing. In addition, the Regulations (Part 4) impose responsibilities, including commencement notice, record keeping and reaction reporting, on those conducting clinical trials. Please ensure that all systems are compliant in order to meet these responsibilities.

Please note that the mandatory reporting requirements of the NHPR for Serious Adverse Reaction (SARs) that have occurred in Canada will continue to be applied by the Therapeutic Products Directorate (TPD). However, we request that you submit all SAR case reports using the Council for International

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Organizations of Medical Sciences (CIOMS) I Form. This preferred form can be downloaded and printed at <http://www.cioms.ch/index.php/cioms-form-i>. The SAR report should be faxed to the following number: (613)941-2121.

You are also reminded that all clinical trials should be conducted in compliance with the Health Canada Guidance for Industry: Good Clinical Practice: Consolidated Guideline ICH Topic E6.

Should you have any questions concerning this letter, please contact the submission coordinator at nhpd-cta.dec-dpsn@hc-sc.gc.ca.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'BR', with a long, sweeping underline that extends to the right and then loops back down.

Bruce Randall
Director, Bureau of Product Review and Assessment
Natural and Non-prescription Health Products Directorate
2936 Baseline Rd. (A.L. 3302C), Ottawa, ON K1A 0K9

Appendix C
Informed Consent



Randomized, Double-Blind, Placebo-Controlled, Short Term Trial of Delivra™ LivSport Pre-
Workout Cream with or without Oral Creatine for Improved Power Output and Reduction of
Muscle Fatigue During Resistance Training

**Study 1: Isolated single leg exercise (Acute) and Study 2: Repeated high intensity bouts
(Chronic loading)**

Investigators

Rachel Aubry, MSc. Candidate, Department of Human Health and Nutritional Sciences,
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Dr. Jamie Burr, PhD, Assistant Professor, Department of Human Health and Nutritional Sciences,
University of Guelph, Contact: burrj@uoguelph.ca 519-824-4120 ext. 52591

INFORMED CONSENT FORM

I have been invited to participate in a clinical research study at the University of Guelph in the Human Performance Laboratory. The Natural Sciences Engineering Research Council of Canada (NSERC) and Delivra Inc. have provided research funding to conduct this research on enhancing athletic performance. If I decide to participate, I will be asked to sign this consent form to confirm that I understand the nature of the study and my involvement in it. I will be informed of any new information that may affect my willingness to continue participation in this study. My signing of this consent form does not take away any of my rights.

Introduction

The current trial is designed to test sport performance and the elasticity of arteries of a topical cream containing creatine as compared to a placebo in individuals who range from recreationally to professionally physically active. The trial will also confirm the effective dose of the topical creatine cream, and evaluate the application technique that should be considered while using the product. The ingestion of oral supplementation of creatine has been explored thoroughly in the literature. It enhances one's physical performance by increasing muscle structure, strength and fat free mass^{8,42}. However, oral ingestion of creatine has negative side effects such as water retention⁴². Preliminary work done in the laboratory at UPEI with humans has shown a 0.5-1.5% change in overall power of an individual after application of the creatine cream. Although, sounding like a very small percent change, this range of enhancement might represent the difference between a podium finish or even making the final race when considering Olympic standards for many sports. This will be the first study to evaluate the effects of a topical cream with the natural substance (compared to other active ingredients in topical creams on the market such as methyl salicylate or menthol) of creatine. We hope to answer some of these questions and reach the full potential of this system; resulting in an improved athletic performance and potential health benefits to vascular structure.

There are two studies to this proposed research; you are not required to volunteer for both, but the study has been designed to accommodate this. Should you choose to do so, you will not require repeated testing of some measures in the second study if you have already performed them in the

first. Details of each study are included below.

If you are interested in participating in this investigation, please complete and sign the consent form.

Before initiating any physical testing or training, you will be required to complete a Physical Activity Readiness Questionnaire (PAR-Q+) to evaluate your ability to safely complete the proposed testing and a Godin-Leisure-Time Exercise Questionnaire to determine a participant's current physical activity level. Should any areas of concern regarding your current health/risk factors for exercise be identified, you will not be allowed to participate until you have received clearance from your doctor. If you qualify, you will then be asked to complete anthropometric baseline measurements and accommodation tests of the single leg concentric exercise. The appearance of noticeable atrial or ventricular arrhythmias, or otherwise life-threatening conditions (e.g. severe hypertension) will be communicated to you. This data is only experimental and does not constitute a diagnosis. If you have any concerns it is recommended you inquire with a physician.

INCLUSION AND EXCLUSION CRITERIA

6.1 Inclusion criteria

- Females and males between the ages of 18-45
- Ostensibly healthy screened by the PARQ+ and Godin-Leisure-Time Exercise Questionnaire to be safe to perform exercise tests)
- $BMI \leq 30$
- Ability to maintain current physical activity throughout the study period
- Ability to read and write in English
- Willing and able to give informed consent
- Ability to follow protocol

6.2 Exclusion criteria

- Women who are pregnant (female participants will be asked to do a self-administered pregnancy test and use appropriate birth control during trial), breastfeeding, could be pregnant or wish to conceive during this trial
- Presence of significant medical disorder that would compromise the participant's safety to take part in the trial (eg: cancer, immunosuppressed)

- History of alcohol or drug abuse within the past year
- Anyone using recreational drugs (i.e: opium, morphine, belladonna, etc), performance-enhancing (eg: steroids, testosterone, creatine etc) and prescription (eg: beta-blockers, anti-depressants, etc)
- People currently using other topical agents for treatment of pain or inflammation
- Allergic to any of the ingredients of the LivSport pre-workout cream, placebo cream, creatine powder and/or placebo powder (the list has been provided to participant)
- All non-regulated medication use (including natural health products and over-the-counter medications)

The researchers wish to be inclusive in their recruitment process. This project requires:

- The placement of medical sensors placed on the neck and groin
- Measurements of the thigh
- Interaction one on one with a female technician/researcher
- Wearing loose clothing or shorts and a t-shirt
- Removal of articles of clothing including headgear

If for any reason you may feel uncomfortable taking part, please contact the researcher to discuss possible modifications to the procedure to address your concerns.

STUDY PROCEDURE

This study consists of a randomized, double-blind, placebo-controlled evaluation on the efficacy and effect of a topical pre-workout cream containing creatine. The first study will assess the acute effects of the experimental creatine cream and the second study will assess the effects of chronic oral supplementation of creatine in addition to application of the experimental creatine cream.

The study involves the use of experimental (creatine) and placebo cream and oral products (powders) made in such ways that the study treatment identity will remain unknown to both the investigator and the participant for study 1 and 2.

Information regarding the oral supplementation and creams, please refer to the appendices.

The duration of the trial is approximately 2 months and it is planned that there will be 132 participants with a 10% dropout rate, leaving 120 participants fully completing the study.

There will be 2 studies, explained below.

Study 1: Isolated single leg exercise

Procedure

This study will be performed at the University of Guelph in the Human Performance Laboratory, in the HHNS ANNEX, room 271.

Participant preparation. We ask that you arrive at the laboratory having refrained from a heavy meal, caffeine, or nicotine, 3 hours prior to your visit or consumption of alcohol within 12 hours. Please also avoid any intense exercise 48 hours prior. Please wear loose clothing or shorts and a t-shirt for the testing visits. You will be asked to complete a PARQ+ to ensure you're healthy to participate in this study and a Godin-Leisure-Time Exercise Questionnaire to assess your physical activity level. If you are unable to participate, your screening data will be destroyed. Female participants will be given a pregnancy test to take home

Study 1 – Visit 1: Screening and Accommodation

On your first visit to the laboratory we will review the consent form, the Godin-Leisure Time Exercise Questionnaire (for assessment of physical activity level) and the PARQ+. Afterwards, measurements of your height, weight, body fat percentage, resting blood pressure, and the circumference of your thigh muscles (to see if there is a weight change with the use of creatine) (~15 minutes) will be collected. Once this is completed, warm-up on a cycle ergometer for 5-minutes will be initiated. The settings will be standardized throughout the entire study to ensure reliable results. After the warm-up, you will next be accommodated to the testing procedures, by being put on our exercise machine and practicing the leg-kicking procedure so that it feels more natural for the real testing protocol. Accommodation protocol will consist of 1 set of 15 repetitions of maximal concentric knee contraction (one set per leg) at 0.5 m·s with 1 minute in between legs using a 1080 Quantum isokinetic dynamometer (~30 minutes).

For Females: Before you leave, you will be offered a pregnancy test to perform in the comfort of your home. It is essential for this study that you and the research assistants are certain there is no chance of pregnancy. This is important for the health and safety of you and your potential child.

The test should be taken in the morning if possible, for the most accurate results. You can also approach your physician to obtain a pregnancy test. If the test is negative, on your next visit, you will confirm your results by verbally indicating this to the research assistant. If the test is positive, you can inform the research assistant that you will no longer be able to move forward with testing. You do not have to tell the research assistant why you will be dropping out, just that you will not be moving forward. Those choosing to proceed with participation will be given information on how to ensure that pregnancy does not occur during the course of the experiment. Visit 1 will take approximately **45 minutes**.

Seven days of rest will be implemented after the accommodation visit to ensure that you are ready and recovered for your next visit.

Study 1 – Visit 2: Baseline Test (*>7 days after accommodation*)

Prior to testing, measurements of body mass, blood pressure and leg girth will be collected. Once you have changed into your exercise attire and anthropometric measurements have been completed, you will be permitted to warm-up on an exercise bike for 5 minutes. You will then perform 5 sets of 15 repetitions of maximal knee extensions at 0.5 m·s on a standard exercise machine with the 1080 Quantum isokinetic dynamometer providing the resistance and measuring performance. We will ask you to simply stay in a comfortable, seated position throughout the duration of the training. Whichever leg was randomized to go first will be the one you start with (randomization of your legs will be completed before the assessment), completing 5 sets of 15 maximal effort knee contractions with 60 seconds rests in between. After completion of the first leg, the exact same protocol will be performed on the other leg. There will be a 10-minute rest in between legs for recovery. You will be stabilized in the chair with a belt across your legs, waist, and chest.

Visit 2 will take approximately **1 hour**.

Study 1 – Visit 3: Experimental Test (*>7 days rest from the baseline test*)

Upon arriving, you will be assessed for body mass, leg girth and blood pressure and you will be

randomly and blindly designated to one of 2 groups. These groups include: Group 1) creatine cream application 15 minutes (single) prior to exercise and Group 2) creatine cream application 15 minutes and 30 minutes (double) prior to exercise.

If you are in Group 1 (“15”), 30 minutes before exercise you will be asked to apply 3.5ml of the cream B to your upper thigh (quadriceps) on each leg. Fifteen minutes before exercise, you will be asked to apply cream A to your upper thigh (quadriceps) to one leg and cream B to the other leg.

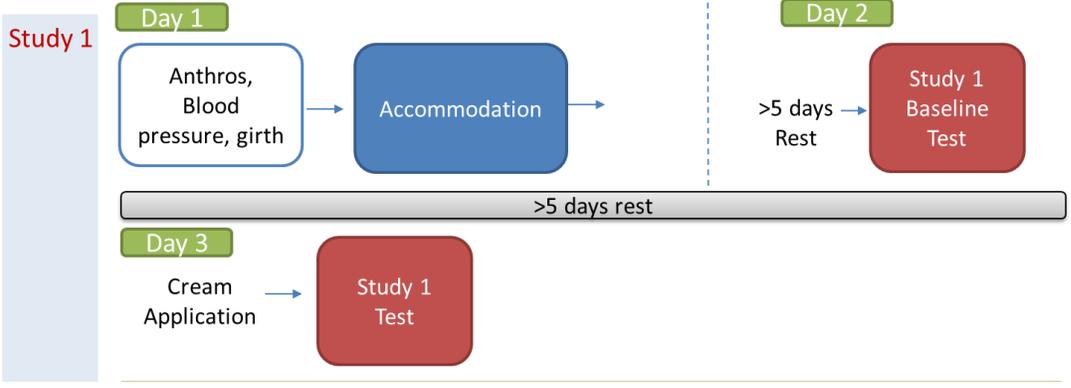
If you are in Group 2 (“15 + 30”), you will be asked to put 3.5 ml of the Cream A or Cream B to your upper thigh of both legs 30 min and 15 min prior to testing. You will be asked to put 3.5ml of cream A to one of your upper thigh (quadriceps), 15 minutes and 30 minutes prior to testing. You will apply 3.5ml of cream B to the contralateral leg at 15 and 30 minutes prior to testing.

You will be randomized to either group 1 or group 2, however you will not be informed as to whether you are assigned to group 1 or group 2, and therefore will not know whether you have applied a single or a double dose of active ingredient creatine cream.

After cream application, you will ride the cycle ergometer for 5 minutes to warm-up before you perform the kicking exercise that you practiced during baseline testing.

Visit 3 will take approximately **1 hour**

The entire study 1 will take approximately **3 hours**.



Study 2: Repeated high intensity bouts (chronic loading)

Procedure

Note: If you are a new participant and have not already participated in Study 1, you will be going through the Screening and Accommodation visit prior to beginning Study 2. If you have already participated in Study 1, you will start directly at the stage “**Study 2 – Visit 4: Baseline Test**” once there has been a **one-month washout period**.

This study will be performed at the University of Guelph in the Human Performance Laboratory, in the HHNS ANNEX, room 271.

Participant preparation. We ask that you arrive at the laboratory having refrained from a heavy meal, caffeine, or nicotine, 3 hours prior to your visit or consumption of alcohol within 12 hours. Please also avoid any intense exercise 48 hours prior. Please wear loose clothing or shorts and a t-shirt for the testing visits. You will be asked to complete a PARQ+ to ensure your healthy to participate in this study and a Godin-Leisure-Time Exercise Questionnaire to assess your physical activity level. If you are unable to participate, your screening data will be destroyed. Female participants will be asked to provide a urine sample in order to test for pregnancy.

Study 2 – Screening and Accommodation

On your first visit to the laboratory we will review the consent form, the Godin- Leisure -Time Exercise Questionnaire (for assessment of physical activity level) and the PARQ+. Afterwards, measurements of your height, weight, body fat percentage, resting blood pressure, and the circumference of your thigh muscles (to see if there is a weight change with the use of creatine, which can alter the amount of stored body water) (~15 minutes) will be collected. Once this is completed, warm-up on a cycle ergometer for 5-minutes will be initiated. The settings will be standardized throughout the entire study to ensure reliable results. After the warm-up, you will next be accommodated to the testing procedures, by being put on our exercise machine and

practicing the leg-kicking procedure so that it feels more natural for the real baseline test. Accommodation protocol will consist of 1 set of 15 repetitions of maximal concentric knee contraction (one set per leg) at 0.5 m·s with 1 minute in between legs using a 1080 Quantum isokinetic dynamometer (~30 minutes).

For Females: Before you leave, you will be offered a pregnancy test to perform in the comfort of your home. It is essential for this study that you and the research assistants are certain there is no chance of pregnancy. This is important for the health and safety of you and your potential child. The test should be taken in the morning if possible, for the most accurate results. You can also approach your physician to obtain a pregnancy test. If the test is negative, on your next visit, you will confirm your results by verbally indicating this to the research assistant. If the test is positive, you can inform the research assistant that you will no longer be able to move forward with testing. You do not have to tell the research assistant why you will be dropping out, just that you will not be moving forward. Those choosing to proceed with participation will be given information on how to ensure that pregnancy does not occur during the course of the experiment. Following the accommodation procedure, there will be a 7-day rest to recover the muscles that were exerted, so maximal effort will be performed at baseline testing.

Study 2 – Visit 4: Baseline Test (*>7 days after accommodation OR one-month after Visit 3*)

You will be asked to attend your study visit between the hours of 8:00am – 4:00pm. Prior to your arrival for the testing visit, you will be asked to avoid alcohol, heavy meal and caffeine for 3 hours prior, alcohol 12 hours prior and intense exercise 48 hours prior. You will be asked to wear loose clothing or shorts and a t-shirt for the testing visits. Resting blood pressure, body mass and leg circumference will be measured before testing. You will be asked to perform a pulse wave velocity (PWV) test that measures arterial stiffness, which is an indicator of overall cardiovascular health. You will be asked to lay down and a tonometer (a pen like stick) will be placed on the carotid artery (neck) and femoral artery (near the groin); this is a non-invasive procedure that takes around 10 minutes. 3M red dots will be placed on 3 sites of your body to measure your heart rate (lower left abdomen within the rib cage frame, suprasternal notch and the xiphoid process). This procedure will be done before exercise, as well as immediately post and 15-minutes post exercise. You will then be permitted to warm-up on an exercise bike for 5

minutes and this should be standardized for all tests. You will perform knee extensions on a standard exercise machine with the Quantum 1080 isokinetic dynamometer providing the resistance and measuring performance. We will ask you to simply stay in a comfortable, seated position throughout the duration of the training. Either the right or left leg will be chosen to go first depending on the randomization that will be determined before you come to the visit. The first leg will be assessed, completing 5 sets of 15 maximum knee contractions with 60 second rests in between. After completion of the first leg, the exact same protocol will be performed on the contralateral leg. There will be a 10-minute rest in between legs for recovery. You will be stabilized in the chair with a belt across the exercising leg, the waist, and the chest. During the exercise test, muscle oxygenation and regional blood flow will be examined using near infrared spectroscopy (NIRS) through a Moxy sensor strapped around the thigh for the duration of the exercise. Immediately after and fifteen minutes after completion of the exercise test, you will be asked to perform PWV test again following the same procedure. The expected time to complete this exercise for both legs is approximately **1 hour**.

At the end of your visit 4, you will be given your portion of the oral supplementation to complete your 7-day loading protocol. These oral products will be labelled with information about dose and timing of intake.

Supplementation protocol:

Once randomized, you will “load” the oral product (creatine or placebo) for 7 days prior to the experimental testing days. The oral product will be administered at a dose of 0.3g/kg of body weight per day, which will be taken for 7 days, split in three intakes per day 1) at breakfast, 2) lunch and 3) dinner. This is an estimate of about 20g/d for 7 days. These oral products (in powder form) will all be provided to you during study 2 Visit 3-Baseline Test, labelled with a reminder of when to take them. During the loading protocol, you will be applying 3.5 ml of the experimental or the placebo cream to one leg and then you will apply 3.5 ml of the experimental or placebo cream (clearly labelled) to the contralateral leg once every day for 7 days, at lunch time.

You will be randomized to one of two oral ingestion groups and each of your legs will be randomized into one of two cream application groups:

1. Oral Creatine + Creatine Cream

1. Oral Creatine + Placebo Cream

2. Oral Placebo + Creatine Cream

2. Oral Placebo + Placebo Cream

Pulse Wave Velocity (PWV) Test: This test is a measure of arterial stiffness, which is a decrease in elasticity and an increase hardness in your arteries. This increases mechanical stress on your heart, leading to heart failure. The reason why we are testing for this is because research has shown that creatine supplementation may decrease arterial stiffness. This procedure measures the speed of the arterial pressure waves from one point of the body to another. A high speed indicates greater arterial stiffness.

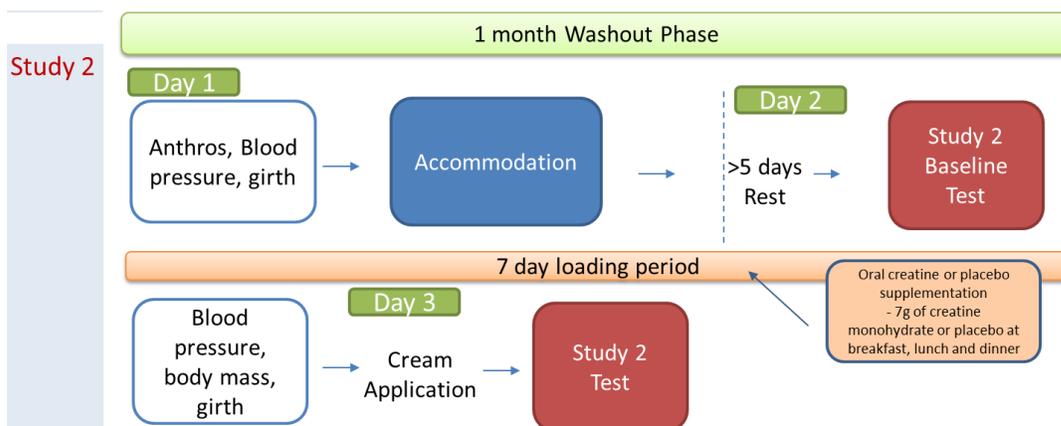
Study 2 – Visit 5: Experimental Test (7 days after Visit 4)

You will be asked to attend the lab between the hours of 8:00am – 4:00pm. Prior to your arrival for the testing visit, you will be asked to avoid alcohol 12 hours prior, caffeine, heavy meals and nicotine for 3 hours prior, and intense exercise 48 hours prior to testing. You will be asked to wear loose clothing or shorts and a t-shirt for the testing visits. Resting blood pressure, body mass and leg girth will be measured before testing. Next, you will also be asked to undergo the PWV test. You will be asked to lay down and a tonometer (a pen like stick) will be placed on the carotid artery (neck) and femoral artery (near the groin); this is a non-invasive procedure that takes around 10 minutes. 3M red dots will be placed on 3 sites of your body to measure your heart rate (lower left abdomen within the rib cage frame, suprasternal notch and the xiphoid process). This procedure will be done before exercise, as well as immediately post and 15 minutes' post exercise. You will then ride a cycle ergometer for 5 minutes to warm-up for the exercise test. You will be asked to simply stay in a comfortable, seated position throughout the duration of the training. The chair will be stabilized with a belt across the exercising leg, the waist, and the chest. During the exercise test, muscle oxygenation and regional blood flow will be examined using near infrared spectroscopy (NIRS) through a Moxy sensor strapped around the thigh for the duration of the exercise. Either the right or left leg will be chosen to go first depending on the randomization that will be determined before you come to the visit. The leg will

be assessed using 5 sets of 15 maximum concentric knee contractions with 60 second rests in between. After completion of the first leg, the exact same protocol will be performed on the contralateral leg. There will be a 10-minute rest in between legs for recovery. Immediately after and fifteen minutes after completion of the exercise test, you will be asked to perform PWV test again following the same procedure.

Visit 5 will take **1 hour** to complete.

The entire Study 2 will take approximately **2 to 3 hours** to complete.



Parameter/ timeline	Accommodation and Screening Visit 1 (Before visit 2 and 4) –	Study 1 Blinded			Study 2 Blinded		
		Baseline Test - Visit 2 (>7 days after accommodation) - 1h	Experimental Test - Visit 3 (>7 days after visit 2) - 1h	Wash-out phase (>1 month after visit 3)	Baseline Test - Visit 4 - 1h	Loading phase - 7 days	Experimental Test – Visit 5 1h

	45 minutes						
Medical history/ <i>PAR</i> - <i>Q</i> +/ <i>Godin</i> Leisure <i>Q</i>	√						
Inclusion/ exclusion criteria	√						
Physical examination (height, weight, body fat %, blood pressure, body mass, leg girth)	√	√	√		√		√
Quantum 1080 dynamomet er accommodat ion (1 set of 15 repetitions)	√						
Creatine cream application			√			√	
Quantum 1080		√ (baseline)	√ (test)		√ (baseline)		√ (test)

dynamometer Physical Performance Test (anaerobic power)							
Oral creatine ingestion						√	
Safety assessment	√		√	√	√	√	√

DRUG ADMINISTRATION

- In Study 1, during the experimental testing you will receive the LivSport Pre-Workout cream and the placebo cream. You will be asked to administer 3.5ml of cream (blinded) to each leg 30 and 15 minutes
- In Study 2, the schedule and dosage of the oral supplementation over the 7 days will be provided to you.
- The cream will be given to you during Visit 4 of Study 2 for the loading protocol.

RISKS AND WARNINGS

The pre-exercise cream that will be used has already been pilot tested on humans, with products of its kind already commercially available and is pending approval by Health Canada for a natural health product number. However, there may be unknown risks with taking the investigational product. The placebo is the same cream, just without the active ingredient- thus there is little risk of an adverse event to either cream. The ingredient list of the creams will be provided upon participation to the study to ensure any potential allergies you may have are avoided. In the unlikely event that you have a reaction to the cream (i.e. allergy), you will be asked to report this to the investigators and seek medical attention from your health professional.

The test of physical fitness may cause you to become tired and short of breath for a short period of time. There are no permanent known adverse side effects that are due to these types of exercise sessions. Data from typically older individuals with or without heart disease indicates that the likelihood of having a heart attack or dying during an exercise stress test is 1 in 10,000 tests during maximal exercise testing. All exercise testing and body composition measures will be performed under the supervision of trained personnel including a certified exercise physiologist (Canadian Society of Exercise Physiology (CSEP)). A CSEP-Certified Exercise Physiologist is a university-trained individual that has obtained the most advanced health and fitness certification in Canada for work with healthy and clinical populations. They are trained, certified, and insured to conduct the appraisals outlined in this proposal.

As all health procedures carry some risk, it is important to disclose these prior to your involvement. There is 1 procedure that may cause you pain or discomfort:

There is a (theoretical) possibility that particularly stressful exercise can lead to excessive muscle trauma and breakdown, leading to a serious condition known as rhabdomyolysis. This condition is extremely rare, only occurs with extensive effort far beyond that which will be employed in the current investigation, and has quite obvious signs and symptoms including intense muscle pain and noticeable darkening of urine, which participants will be warned to inform the researchers or medical help should they experience any of the above.

Performance tests: The concentric knee extension may cause discomfort as a result of muscle fatigue. This may also result in leg muscle soreness and/or soreness in the legs for one to two days after. These feelings are completely normal and should not harm you. Exercise is associated with an increase in breathing rate and perspiration (sweating). Any lasting discomfort should be reported immediately to the researchers.

As a study participant, you will not be giving up any legal rights by participating in the clinical trial and will not release the Investigators from liability for negligence.

In regards to the PWV procedure, there is no known risk to the measurement of arterial stiffness and it is non-invasive.

Reporting an Incident

If there is an emergency, please seek medical attention at the closest emergency department for treatment. Afterwards, or in cases which are not immediate enough to go to emergency, report the incident to Jamie Burr (Contact: burrj@uoguelph.ca 519-824-4120 ext. 52591). You can also contact the qualified investigator, Dr. Joe Pontoriero (Contact: 905-73-1448).

PARTICIPANT COMPLIANCE

- Participation in clinical research studies with any investigational product is not permissible unless it has been longer than 30 days since participating in the last clinical research study.
- I have not taken any drugs of abuse (for example cocaine, marijuana) from the time of screening
- In the event that I start consuming prescription medication included in the Exclusion Criteria, I will notify immediately the investigators of the study.
- I should return the used products for determination of compliance or the degree of non-compliance that will result in premature withdrawal from the trial

COMPENSATION AND BENEFITS

Compensation

You will receive 40 Canadian dollars for full participation in study 1 and 50 Canadian dollars for full participation in study 2. If you decide to withdraw earlier, you will be prorated for your time during the study. In addition, compensation is based on a flat rate and you will not receive additional payment if the study day persists longer than anticipated.

Benefits

You will not benefit directly from participating in this study, however, your data will contribute to advancing our knowledge into the specific topical delivery system that creatine can access, which may lead to the improvement of athletic performance. You may benefit from this study in gaining important information about your current state of fitness, which requires expensive equipment and expertise to operate.

The investigators conducting the study will not be receiving a fee for enrolling participants into this study.

RANDOMIZATION AND BLINDING

Randomization into either group 1 or group 2 will be completed by using an automatic randomization sequencing tool before visit 2. One group will receive a double dose of the experimental cream and the other group will receive a single dose of the experimental cream;

allocation to groups will be unknown by you, the participant, and the researcher. The study involves use of a placebo cream such that the study treatment identity will remain unknown by both the investigator and the participant, ensuring double-blinding. Randomization and blinding information will be held by the Sponsor.

DATA

You may also request to receive a form of aggregate results of the study. You may also request to receive your specific results from the research team.

If you are part of a sports team, no results will be provided to team management, nor will participation decisions (either participating or not participating) be known by team management. Every effort will be made to ensure confidentiality of personal information that is obtained in connection with this study. Confidentiality will be secured by the use of participant ID Codes on all correspondence and all data collection instruments. Coded data will be kept on a password-protected computer and all written material secured indefinitely in a locked cabinet on site. Master lists of participant ID codes will be retained by J. Burr. Your de-identified data will be shared with the other investigators in the multi-center study (University of Guelph, University of PEI and University of Saskatchewan), and with the sponsor.

Data will be retained for 25 years in accordance with Section 76 of the Natural Health Products Regulations. All de-identified data will be stored electronically in databases with access only granted to investigators involved in the use of the data. All personal identifiers will be destroyed following the participants' study completion. Jamie Burr, PhD, Assistant Professor will be in charge of data stewardship.

The general results may be used for commercial purpose. However, identity and individual results will remain confidential.

RIGHTS AND WELFARE OF THE INDIVIDUAL

Your confidentiality will be respected. However, research records identifying you may be inspected in the presence of the Investigator or his or her designate by the University of Guelph Research Ethics Board, the Sponsor, government authorities, such as the Therapeutic Products Directorate and the Natural Health Products Directorate of Health Canada, the US Food and Drug Administration or the funding agency NSERC for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

You have the right to refuse to participate in this study. It is understood that you are free to withdraw from any or all parts of the study at any time without penalty. You may also request the removal of your data from the study until the data are permanently de-identified. The principal investigator may also remove you from the study should circumstances warrant it. Your identity will remain confidential as all individual records and results will be analyzed and referred to by number code only. The master list of codes will be kept in a locked cabinet in the Human Performance Laboratory at the University of Guelph. This lab will remain locked and only those directly involved in the study (namely Dr. Jamie Burr, PhD) will have access to your records and results. You will not be referred to by name in any study reports or research papers. Your individual results will remain confidential as they will not be discussed with anyone outside the research team.

This project has been reviewed by the Research Ethics Board for compliance with federal guidelines for research involving human participants.

Please be assured that you may ask questions at any time. If any information becomes available that may be relevant to your willingness to continue participation in the trial, you will be informed in a timely manner. We will be glad to discuss your results with you when they have become available and we welcome your comments and suggestions. Should you have any concerns about this study or wish further information, please contact Jamie Burr (burrj@uoguelph.ca) at the University of Guelph.

CONTACT NUMBERS

<p>Study-related and medical related questions and medical emergencies:</p> <p>In case of emergency, please refer to your closest hospital emergency department.</p>	<p>For any other concerns, please contact:</p> <p>Dr. Joe Pontoriero (CPSO #100742)</p> <p>2200 Fairview Street, Unit 208</p> <p>Burlington, ON</p> <p>L7R 4H9</p> <p>Office Phone: 905-632-2542</p> <p>Cell Phone: 905-730-1448</p>
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If you have any questions about your rights as a study participant please contact a member of the clinical study staff. If you wish to address your concerns to the committee that reviewed the ethics aspects of the study, you may contact the REB contact line:

Joy Knight
(902) 620-5104

If you have any questions regarding your rights and welfare as a research participant in this study (REB #16MY014), please contact: Director, Research Ethics; University of Guelph; reb@uoguelph.ca; 519-824-4120 ext. 56606

CONFIRMATION OF CONSENT

- I understand that my safety during these studies requires that I answer truthfully all questions put to me during the consent and health screening process.
- I am free to withdraw at any time and will be prepared to answer any questions related to the use of the study product and any health consequences associated with its use.
- I understand that the sponsor receives the right to terminate the study at any time due to adverse reactions from the cream or exercise protocol, non compliance of the study protocol or omission of reporting adverse reactions.
- I understand that I will not be giving up any legal rights by participating in the clinical trial and that I do not release the investigators from liability for negligence.
- I have read all of the sections of the Informed Consent form in the presence of the Principal Investigator, who has satisfactorily answered any questions I may have had. I understand the contents and voluntarily give my consent to participate in the study.

SIGNATURE of RESEARCH PARTICIPANT

I have read the information provided for the study “**Randomized, Double-Blind, Placebo-Controlled, Short Term Trial of Delivra™ LivSport Pre-Workout Cream with or without Oral Creatine for Improved Power Output and Reduction of Muscle Fatigue During Resistance Training**” as described herein. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

Name of Participant (please print)

Signature of Participant

Date

SIGNATURE OF WITNESS

Name of Witness (please print)

Signature of Witness

Date

Appendix D

PARQ+

2015 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1) Has your doctor ever said that you have a heart condition <input type="checkbox"/> OR high blood pressure <input type="checkbox"/> ?	<input type="checkbox"/>	<input type="checkbox"/>
2) Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?	<input type="checkbox"/>	<input type="checkbox"/>
3) Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	<input type="checkbox"/>	<input type="checkbox"/>
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? PLEASE LIST CONDITION(S) HERE: _____	<input type="checkbox"/>	<input type="checkbox"/>
5) Are you currently taking prescribed medications for a chronic medical condition? PLEASE LIST CONDITION(S) AND MEDICATIONS HERE: _____	<input type="checkbox"/>	<input type="checkbox"/>
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer NO if you had a problem in the past, but it does not limit your current ability to be physically active. PLEASE LIST CONDITION(S) HERE: _____	<input type="checkbox"/>	<input type="checkbox"/>
7) Has your doctor ever said that you should only do medically supervised physical activity?	<input type="checkbox"/>	<input type="checkbox"/>

If you answered NO to all of the questions above, you are cleared for physical activity. Go to Page 4 to sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow International Physical Activity Guidelines for your age (www.who.int/dietphysicalactivity/en/).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

⚠ Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at www.aparmedx.com before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.



2015 PAR-Q+

FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. **Do you have Arthritis, Osteoporosis, or Back Problems?**
If the above condition(s) is/are present, answer questions 1a-1c If **NO** go to question 2
- 1a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES NO
- 1b. Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)? YES NO
- 1c. Have you had steroid injections or taken steroid tablets regularly for more than 3 months? YES NO
-
2. **Do you have Cancer of any kind?**
If the above condition(s) is/are present, answer questions 2a-2b If **NO** go to question 3
- 2a. Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck? YES NO
- 2b. Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)? YES NO
-
3. **Do you have a Heart or Cardiovascular Condition? This includes Coronary Artery Disease, Heart Failure, Diagnosed Abnormality of Heart Rhythm**
If the above condition(s) is/are present, answer questions 3a-3d If **NO** go to question 4
- 3a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES NO
- 3b. Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction) YES NO
- 3c. Do you have chronic heart failure? YES NO
- 3d. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months? YES NO
-
4. **Do you have High Blood Pressure?**
If the above condition(s) is/are present, answer questions 4a-4b If **NO** go to question 5
- 4a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) YES NO
- 4b. Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure) YES NO
-
5. **Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes**
If the above condition(s) is/are present, answer questions 5a-5e If **NO** go to question 6
- 5a. Do you often have difficulty controlling your blood sugar levels with foods, medications, or other physician-prescribed therapies? YES NO
- 5b. Do you often suffer from signs and symptoms of low blood sugar (hypoglycemia) following exercise and/or during activities of daily living? Signs of hypoglycemia may include shakiness, nervousness, unusual irritability, abnormal sweating, dizziness or light-headedness, mental confusion, difficulty speaking, weakness, or sleepiness. YES NO
- 5c. Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, OR the sensation in your toes and feet? YES NO
- 5d. Do you have other metabolic conditions (such as current pregnancy-related diabetes, chronic kidney disease, or liver problems)? YES NO
- 5e. Are you planning to engage in what for you is unusually high (or vigorous) intensity exercise in the near future? YES NO



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6. **Do you have any Mental Health Problems or Learning Difficulties?** *This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome*
 If the above condition(s) is/are present, answer questions 6a-6b If **NO** go to question 7
- 6a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? **YES** **NO**
 (Answer **NO** if you are not currently taking medications or other treatments)
- 6b. Do you **ALSO** have back problems affecting nerves or muscles? **YES** **NO**
-
7. **Do you have a Respiratory Disease?** *This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure*
 If the above condition(s) is/are present, answer questions 7a-7d If **NO** go to question 8
- 7a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? **YES** **NO**
 (Answer **NO** if you are not currently taking medications or other treatments)
- 7b. Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy? **YES** **NO**
- 7c. If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week? **YES** **NO**
- 7d. Has your doctor ever said you have high blood pressure in the blood vessels of your lungs? **YES** **NO**
-
8. **Do you have a Spinal Cord Injury?** *This includes Tetraplegia and Paraplegia*
 If the above condition(s) is/are present, answer questions 8a-8c If **NO** go to question 9
- 8a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? **YES** **NO**
 (Answer **NO** if you are not currently taking medications or other treatments)
- 8b. Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting? **YES** **NO**
- 8c. Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)? **YES** **NO**
-
9. **Have you had a Stroke?** *This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event*
 If the above condition(s) is/are present, answer questions 9a-9c If **NO** go to question 10
- 9a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? **YES** **NO**
 (Answer **NO** if you are not currently taking medications or other treatments)
- 9b. Do you have any impairment in walking or mobility? **YES** **NO**
- 9c. Have you experienced a stroke or impairment in nerves or muscles in the past 6 months? **YES** **NO**
-
10. **Do you have any other medical condition not listed above or do you have two or more medical conditions?**
 If you have other medical conditions, answer questions 10a-10c If **NO** read the Page 4 recommendations
- 10a. Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months **OR** have you had a diagnosed concussion within the last 12 months? **YES** **NO**
- 10b. Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)? **YES** **NO**
- 10c. Do you currently live with two or more medical conditions? **YES** **NO**
- PLEASE LIST YOUR MEDICAL CONDITION(S) AND ANY RELATED MEDICATIONS HERE: _____

GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.



2015 PAR-Q+

 If you answered **NO** to all of the follow-up questions about your medical condition, you are ready to become more physically active - sign the **PARTICIPANT DECLARATION** below:

-  It is advised that you consult a qualified exercise professional to help you develop a safe and effective physical activity plan to meet your health needs.
-  You are encouraged to start slowly and build up gradually - 20 to 60 minutes of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
-  As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
-  If you are over the age of 45 yr and **NOT** accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.

 If you answered **YES** to **one or more** of the follow-up questions about your medical condition: You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should complete the specially designed online screening and exercise recommendations program - the ePARmed-X+ at www.oparmedx.com and/or visit a qualified exercise professional to work through the ePARmed-X+ and for further information.

 **Delay becoming more active if:**

-  You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
-  You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at www.oparmedx.com before becoming more physically active.
-  Your health changes - talk to your doctor or qualified exercise professional before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and **NO** changes are permitted.
- The authors, the PAR-Q+ Collaboration, partner organizations, and their agents assume no liability for persons who undertake physical activity and/or make use of the PAR-Q+ or ePARmed-X+. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- All persons who have completed the PAR-Q+ please read and sign the declaration below.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that the Trustee maintains the privacy of the information and does not misuse or wrongfully disclose such information.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact
www.oparmedx.com
 Email: oparmedx@gmail.com

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton, with Dr. Norman Gladisil, Dr. Veronika Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

dates for PAR-Q+
 Warburton DER, Jamnik V, Gladisil N, McKenzie DC, and Shephard RJ on behalf of the PAR-Q+ Collaboration. The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and Revised Physical Activity Readiness Medical Examination (ePARmed-X+). *Health & Fitness Journal of Canada*. 6(2): 25-33, 2011.

PAR REFERENCES
 1. Lovink MK, Warburton DER, McKenzie DC, Shephard RJ, Stone J, and Shephard R. Enhancing the effectiveness of clearance for physical activity participation: development and validation of a process. *APM* 18(1):10-15, 2011.
 2. Warburton DER, Gladisil N, Jamnik V, Gladisil N, McKenzie DC, Stone J, Cheltenham L, and Shephard R. Evidence-based risk assessment and clearance criteria for physical activity clearance. *Consensus Document*. *APM* 18(1):15-24, 2011.



Appendix E

Godin-Leisure Time Exercise Questionnaire

INSTRUCTIONS

In this excerpt from the Godin Leisure-Time Exercise Questionnaire, the individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits.

CALCULATIONS

For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three, respectively. Total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula:

$$\text{Weekly leisure activity score} = (9 \times \text{Strenuous}) + (5 \times \text{Moderate}) + (3 \times \text{Light})$$

The second question is used to calculate the frequency of weekly leisure-time activities pursued “long enough to work up a sweat” (see questionnaire).

EXAMPLE

Strenuous = 3 times/wk

Moderate = 6 times/wk

Light = 14 times/wk

$$\text{Total leisure activity score} = (9 \times 3) + (5 \times 6) + (3 \times 14) = 27 + 30 + 42 = 99$$

Godin, G., Shephard, R. J.. (1997) [Godin Leisure-Time Exercise Questionnaire](#). *Medicine and Science in Sports and Exercise*. 29 June Supplement: S36-S38.

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

**Times Per
Week**

a) STRENUOUS EXERCISE

(HEART BEATS RAPIDLY)

(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE

(NOT EXHAUSTING)

(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE

(MINIMAL EFFORT)

(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN

1.

SOMETIMES

2.

NEVER

3.

Appendix F

Blood Pressure Standard Operating Procedure

Blood Pressure (BpTRU)

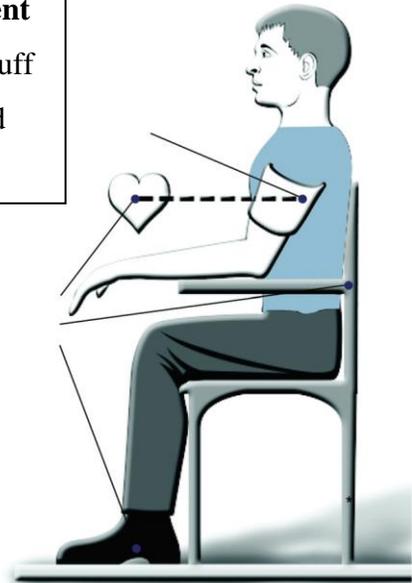
1. Ensure that the participant avoids caffeine for at least three hours before the test.
2. Position the participant carefully into a seated position with an arm-rest
3. Ensure that the participant is comfortable and relaxed sitting down.
4. Ensure that the upper arm is at heart level and supported.

Cuff Selection and Placement

Ensure cuff index is within cuff range markers when wrapped around the upper arm.

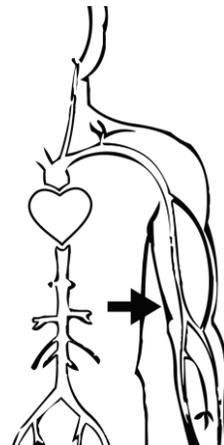
Proper Patient Position

Cuff at heart level, back and arm supported, feet flat on floor.
Stay still during measurements.
Relax



Apply the Cuff

1. Align the artery indicator on the cuff over the brachial artery of the participant's **left** arm (shown in the figure to the right)
2. Wrap the cuff around the arm and check that the white index marking on the edge of the cuff falls within the white range markings on the inside surface of the cuff.
3. Check that the index falls within the range markers. If the index does not fall within the range markers, replace the cuff with a smaller or larger cuff, as indicated.
4. Ensure that the cuff is tight but that it is still possible to insert two fingers between the cuff and the arm.



During the measurement:

- Ensure that the participant’s arm and body do not move
- Avoid talking to other people in the room

Series of Measurements (Automatic Mode)

Individual readings will be displayed after each measurement and the individual and averaged readings can be reviewed during or after the series of measurements.

We will be taking 3 measurements and taking the average of those three.

1. Select the cuff that is appropriate size for the participant.
2. Apply the cuff to the participant
3. Press CLEAR to ensure that any previous measurements are cleared from the BpTRU memory.
4. Select Automatic mode by pressing the CYCLE button until the cycle time you want (i.e., the interval between BP measurements – **1 MINUTE**) shows in the **Cycle** display (“SP” indicates a single measurement)
5. Initiate the series of measurements by pressing the START button.
6. Once **3** readings have been completed, press the REVIEW button and record the ”A” (average) readings.

During each measurement, the cuff will inflate to the minimum required to pre-set pressure level. While inflating and deflating, the **Systolic** display indicates the cuff pressure.

NOTE: Initiate rapid deflation of the cuff at any time by pressing the STOP button or by turning off the power.

It is important for the participant to remain still and not talk during inflation or deflation of the cuff.

During the series of measurements, the **Reading** display shows the number of measurement currently being taken. The most recent **Systolic, Diastolic, and Pulse** measurements are shown in the respective displays until the next measurement begins.

Review Measurements in Automatic Mode

Upon completing a series of measurements in Automatic mode, you can review each measurement in the series by pressing the REVIEW button. As the result of each reading is shown, the reading number is shown in the **Reading** display. The value “A” in the **Reading** display indicates that the average of the last 3 readings is being shown.

If you press the REVIEW button between measurements during an automatic series of measurements, the BpTRU suspends measurement. You can then cycle through the measurements taken to that point using the REVIEW button.

Press START button to resume the automatic series

Pressing the REVIEW button during a measurement has no effect.

**INFORMATION REGARDING DISPLAY REFERENCE,
TROUBLESHOOTING, SETUP INSTRUCTIONS AND MAINTENANCE,
PLEASE REFER TO THE BPTRU MANUAL.**

Appendix G

Leg Girth Measurement SOP

Leg Girth (Health o meter) by Digital Tape Measure

1. Press the POWER button to turn the unit on. Make sure the tape is fully retracted.
2. The screen will automatically prompt a body part to be measured.
3. Pull the tape and wrap it around the thigh.
4. Insert the locking pin into the tape receptacle.
5. Push and hold the ADJUST button until the tape has fully retracted around the thigh.
6. Press “Select” to confirm the measurement. The unit will make an audible beep.
7. Fully retract the tape. This will prepare the unit for the next measurement and ensure accuracy and turn off the unit.

Thigh placement: While standing, measure the midpoint between the iliac crest and the superior patella.

Additional Directions

- It is recommended to take measurements in a relaxed state. Do not flex while taking the measurement.
 - **Position:** The participant should point their toe on the ground, knee bent, not flexing
- Measurement will be taken prior to physical activity
- Measurements should be taken on the **both** sides of the body
- If you want to calibrate the unit, zero out the unit and press and hold the POWER and “Select” buttons. Make sure that the tape is fully retracted when you are doing this

Troubleshooting:

- If the readout is a negative value, “E” will appear on the display:
 - To reset the unit, turn the unit off by pressing and holding the POWER button. Make sure that the tape is fully retracted. Follow steps 1 and 2 to re-start the measurement again.
 - To zero out the unit, follow the calibration technique.

Replacing the Battery

- If the battery is running low, a “Lo” sign will appear on the display
- Locate the battery cover on the back of the tape measure.
- Use a flat head screwdriver or coin to rotate the battery cover counter clockwise to the unlock position

- Remove the used battery and insert a new lithium battery (CR2032-3V)
- Rotate the battery cover clockwise to the lock position.

Appendix H

Weight SOP

1. Using the digital scale in the laboratory, place (if not already placed) the scale on a firm floor.
2. Have the participant remove any heaving clothing and shoes.
3. Ask the participant to stand with both feet in the centre of the scale, upright, when the scale reads **0.0 kg**
4. Record the weight to the nearest **0.1 kg**
 - Ensure that the participant has voided bladder before weight measurement

Appendix I

Height SOP

Height (Seca 217)

1. Ensure that the stadiometer (Seca 217) is positioned comfortably against the wall (where it will not tip) and all the pieces are connected.
2. Direct the participant to stand on the black platform of the stadiometer and to stand straight (no hunching, shoulders back, flat footed, hands to the side, back against the stadiometer and head up).
3. Ensure that the participant's shoes are removed prior to measurement.
4. Ask the participant to inhale and lower the measuring device until it rests gently on the top of the participant's head and record the measurement.
5. Record the height to the nearest 0.1 cm

Repeat this twice.

Appendix J

Body Composition SOP: Body Metrix by IntelaMetrix (Ultrasound)

1. Turn on your computer and insert the CD that has been provided to you by IntelaMetrix. (This should be already installed, if not, please refer to the BodyMetrix Personal Windows User Guide).
2. Plug in the BodyMetrix into the USB port; the green light should be turned on, indicating that the device is connected.
3. To start the software, go to the desktop and double-click on the BodyView Personal icon. After a few seconds, the home page should appear.
4. The home page will have existing profiles or create a new profile (depending on what stage you are with your participant). *To create a new profile:*
 - a. Click on the New Profile button and enter in the participant ID, birth date, gender, weight (kg) and height (cm)
 - b. Select appropriate athletic type:
 - i. **Elite:** individuals generally have good muscle definition (“six pack abs”) and little excess fat, they generally exercise regularly and can include small frame (e.g. marathon runners) to large frame individuals (e.g. body builder). You can always change the athletic type once the profile has been created
 - ii. **Athletic:** individuals do NOT look overweight and generally exercise occasionally. Most people fall into this category.
 - iii. **Non-Athletic:** individuals are visibly overweight.
5. Once the profile has been selected or created, you will need to move over to the Body Composition page.

Note: If this is the first time you use the BodyMetrix System, the software will prompt you to calibrate the device. Simply press and hold the button for a few seconds to complete the calibration process.

- To make a measurement you must first select the formula to use which will be the **7 site Jackson & Pollock**. Simply use the drop down menu to select the formula
- Before starting a new measurement, clean the device with an antiseptic wipe

6. To start, select the anatomical point and then click on **Measure Point** to begin the assessment.

- a. Apply a dime sized amount of ultrasound gel to the centre of the BodyMetrix device as shown. This is usually 2-3 pumps of the small ultrasound dispenser.
- b. Place the device on the measurement site and move the device to spread the gel uniformly over an area of approximately 2 inches. When you have completed doing this, slide the device to the measurement site and press the button for 3-5 seconds while sliding the BodyMetrix device about ¼ of an inch to either side of the start position. When sliding the device back and forth make sure you maintain good contact with the skin. Typically, you would perform the back and forth motion 2-4 times per second or at a rate that is comfortable to do. Performing this during the measurement averages the fat thickness over the scan area and provides more consistent measurements. **WARNING:** Stop use if the participant feels any burning sensation or has adverse skin reaction and seek medical treatment. Report incident to IntelaMetrix asap (925) 606-7044 and to your advisor.
- c. After the 1st measurement you will be asked to repeat the measurements a second time. If the two measurements differ by more than 10% then you will be asked to repeat the measurement for a third time. When completed the measured value is automatically entered into the Points List.
- d. Repeat a-c for each of the measurement sites
- e. After all measurements are complete the software will calculate and display the Body Fat Percentage
- f. After completing the assessment, clean the device with antiseptic wipes.



Measurement Site and Scan Point Guide

Male & Female

Chest – Halfway between the shoulder and the nipple. To scan, place on the axillary line. Press and hold the device measurement button while slowly sliding vertically 3-4 inches towards the nipple.



Abdominal – Locate 1 inch to the side of the belly button. To scan, place on the waist site. Press and hold the device measurement button while slowly sliding horizontally right 3-4 inches towards the hip.



Thigh – The midpoint the front thigh between the knee and in line with the hip joint. To scan, place on the midpoint, press and hold the device measurement button while slowly sliding vertically 3-4 inches towards the knee.



Tricep - The midpoint of the back, upper arm, between the shoulder and the elbow. To scan, place on the midpoint, press and hold the device measurement button while slowly sliding vertically 3-4 inches down towards the elbow.



Subscapular – Located just below the bottom tip of the shoulder blade. To scan, place the bottom tip of the scapula. Press and hold the device measurement button while slowly sliding horizontally 3-4 inches to the right.



Suprailiac – Locate 1 inch above the front side tip of the top of the hip bone. To scan, place 1 inch above the front side tip of the top of the hip bone. Press and hold the device measurement button while slowly sliding horizontally to the right 3-4 inches.



Midaxillary - Located the site below the armpit and level with the bottom of the sternum. To scan, place on the axilla. Press and holding the button while slowly sliding vertically 3-4 inches.



INFORMATION ABOUT: ANALYZING, TRENDS, ACTIVITY AND SCANS CAN BE LOCATED IN THE USER MANUAL.

Appendix K

Reliable results of a custom-built robotically controlled dynamometer

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Abstract

This study sought to assess the reliability and comparability of a custom isokinetic dynamometer and compare it to the gold-standard. The effect of altering the dynamometer with commercially available alternatives was also considered. Twenty subjects (14m/6f, 26 ± 4.8 yr, 176 ± 7 cm, 74.4 ± 12.4 kg) performed repeated concentric knee extensions on both the Quantum and the gold-standard (Humac Norm) isokinetic dynamometers. Fifteen consecutive maximal knee extensions were performed with each leg at $180^\circ\cdot s^{-1}$ ($0.5m\cdot s^{-1}$) from which peak and mean power (W), and fatigue index (%) were determined. The Quantum was tested with leg extension models (A/B) attached to control the exercise movement. The Quantum revealed high reliability for peak and mean power on repeated tests ($ICC>0.88$) irrespective of the leg extension model. Coefficient of variation (CV) and standard error of measurement (SEM) were small when comparing Model A and the Humac Norm (\bar{x} CV=9.0%, \bar{x} SEM=49.4W; peak CV=8.4%, peak SEM=49W). These values differed when Model B was used (\bar{x} CV=13.3% \bar{x} SEM=119.6W; peak CV=14.7%, peak SEM=146W). The Quantum is capable of highly reliable measures, but absolute values may be affected by machine design. Consistent use of a single model offers reliable results for tracking muscular performance over time, or testing an intervention.

Key words: leg extension, 1080 Quantum, isokinetic, muscular power, strength, testing

Introduction

The quantification of muscular strength and endurance is important in clinical testing^{141,142}, athletic capacity assessment^{143,144}, and broadly within human research in the exercise sciences^{145,146}. Reliable and valid measures are required for the assessment of standardized test values with normative data, to track changes over time, and to interpret these effects with reference to a significant and meaningful change.

Using isokinetic dynamometry, the power a muscle group generates, can be quantified throughout its full range of motion by employing an accommodating resistance to a standardized contraction velocity^{145,147,148}. As such, isokinetic dynamometry provides a highly reproducible measure of neuromuscular performance in both health and disease¹⁴⁹. Parameters such as peak force, mean force, power, and angular work can be derived through relatively straight-forward maximal or submaximal protocols^{145,146,150}. Tight controls requiring precise movement and standard operating procedures allows for tracking of differences due to subject variation, rather than inconsistent data capture¹⁵¹. Recently, a novel linear resistance machine, called the 1080 Quantum (1080 Motion, Lidingö, Sweden), has been developed for applications in the sport-training and rehabilitation fields. The 1080 Quantum employs a robotically controlled dynamic cable resistance that permits the targeting of resistive forces to emphasize loading or unloading at different movement phases across fixed or dynamic velocities (concentric and eccentric). To accomplish this throughout a movement, the 1080 Quantum adjusts force and velocity as a cable is wound around an internal drum, and thus, also offers the capability of force/velocity quantification. While the intended application of the 1080

Quantum is targeted toward dynamic multi-joint, or rotational movements, the cable resistance offers the possibility of the attachment to a single-joint resistance exercise machine, allowing the testing of power about a single joint or muscle group. As such, when connected to the appropriate piece of “selectorized” equipment in place of the normal iso-inertial resistance of the machine (weight stack), the Quantum may be capable of measurements similar to those collected using established isokinetic dynamometers, though this has not been previously tested. The application of such a versatile training and testing device could offer many benefits, amongst them being the ability to construct a task-specific dynamometer for a far lower cost.

Our intended aims were three-fold 1) establish the test-retest reliability using the Quantum dynamometer, 2) establish the comparability of measures made using the novel Quantum dynamometer versus gold standard measures, and 3) understand the effect of altering the exercise equipment to which the 1080 Quantum resistance device is connected for measurement. It was hypothesized that irrespective of the exercise equipment used to control the exercise motion, test-retest data would demonstrate a highly reliable measurement using the Quantum as an isokinetic resistance. Secondly, it was hypothesized that measures using the novel Quantum dynamometer would be similar to those collected on a Humac Norm dynamometer, but that there would be some degree of offset between the measurements as the Humac Norm measures torque, while the Quantum measures linear force. Lastly, it was hypothesized that employing two different knee extension machines connected to the 1080 Quantum would alter the degree of offset with the Humac Norm, owing to design differences such as adjustability of lever arms

from the point of rotation, and the shape of the cam around which the cable runs between the point of attachment and resistance.

Methods

Subjects

Twenty healthy, recreationally active males (n=14) and females (n=6) (26 ± 4.8 years, 175.7 ± 7.4 cm in height, 74.4 ± 12.4 kg of body mass) participated in the study, with sample size based on previous reliability literature using knee extensions^{145,150,152}.

Exclusion criteria were limited to the presence of a significant medical disorder that would compromise the subject's safety (e.g. chronic disease, musculoskeletal or cardiovascular complications). Subjects were instructed to maintain their regular eating habits and physical activity, while avoiding intense physical activity during the 2 days prior to testing. All subjects provided written informed consent prior to study participation, and the rights of the subjects were protected throughout the study in accordance with the ethical guidelines of the University of Guelph Research Ethics Board, who approved the protocol (REB#16MY024).

Instrumentation

Two isokinetic dynamometers, the Quantum and the Humac Norm dynamometer (CSMi Solutions, Stoughton, MA), were used for the assessment of isokinetic leg power and fatigue index for both legs in the study. The 1080 Quantum was attached, in turn, to two different leg extension machines, model "A" (the Element Fitness Carbon Dual 9019 Leg Extension/Leg Curl; The Treadmill Factory Mississauga, ON), or model "B" (IT9328 Leg Extension/Leg Curl; Viva Fitness, United States), which were similar in function but

differed in their design. The newly constructed Quantum isokinetic dynamometer has similar features and outcome measures to the Humac Norm, when used for knee extension exercise; and thus allows the Quantum to be compared to the gold standard.

Set-up

To create the custom-built dynamometer, the 1080 Quantum was connected to a commercial leg extension machine by removing the original weight stack and attaching the Quantum dynamometer in its place. More specifically, a custom fit cable was attached to the cam of the leg extension, through the incorporated pulley and connected to a carabiner at the end of the line for the 1080 Quantum, so that the Quantum was able to manipulate the actions of the leg extension (Figs 1 and 2). Subsequently, calibration was completed daily per the manufacturer's instructions. The Quantum was operated with 5 kg (for female subjects) and 8 kg (for male subjects) added to the concentric and eccentric load. Incorporation of these loads was crucial to the operation of the Quantum, to keep the cables taught and in the pulleys and for an initial load against which to push. On both devices, subjects were seated comfortably, restrained using a chest harness and lap cushion to limit any movement other than the leg extension task, and a distal shin pad was placed 2 cm above the lateral malleolus of the exercising leg. The knee joint was aligned with the axis of rotation to the mechanical dynamometer. A goniometer was used to verify the starting position of 90° flexion at the knee, with a stop put in place to control range of motion. Once the subject was positioned correctly, all adjustable variables were recorded for standardization between trials. The unit was set to record maximal contractions performed at a linear velocity of 0.5 m·s⁻¹ for the Quantum and at an

equivalent angular velocity of $180^{\circ}\cdot\text{s}^{-1}$ for the Humac Norm. The linear speed of $0.5\text{ m}\cdot\text{s}^{-1}$ was calculated by using the equation $v=r\omega$, where v represents velocity in metres per second, r represents the average length of the femoral epicondyle to the top of the distal shin pad (radius in metres) and ω represents angular velocity in radians per second.

[INSERT FIGURE 1 HERE]

Fig 1. 1080 Quantum Dynamometer Model A Configuration. The power outputs (W) would be presented on the **A.** tablet, calculated from the **B.** 1080 Quantum. The participant would sit in the leg extension machine, and kick the **C.** movement arm outwards to complete the leg extension. The **D.** range of motion apparatus was in place to suspend the extension, bringing the participant's leg back to the neutral position to be prepared for subsequent extensions. Finally, the participant was secured with a **E.** harness.

[INSERT FIGURE 2 HERE]

Fig 2. Bird's eye view. The leg extension machine (Model A) was attached to the **H.** 1080 Quantum by a **F.** carabiner through a **G.** custom-fit cable wound on the cam.

Exercise Protocol

Subjects performed each knee extension from a 90° neutral starting position to a 180° finishing position. To reduce the potential learning effect, subjects warmed-up with light knee extensions until they were comfortable progressing to 2-3 maximal practice knee extensions, prior to data collection, on both devices¹²². The exercise protocol consisted of 15 maximal effort knee extensions per leg at a metronome controlled pace of 30 contractions per minute, with a 1-second return to the starting point. The Humac Norm was fixed at a controlled $45^{\circ}\cdot\text{s}^{-1}$ eccentric speed, with the Quantum set at $4\text{ m}\cdot\text{s}^{-1}$ eccentric speed. Between repetitions, subjects were assisted to passively return their leg to the starting position with a researcher controlling the load on the device. A 10-minute rest

period was given after the first leg and before testing the second to avoid any fatigue related cross-over artifact, and for sufficient time to adjust the Humac Norm for testing the opposite leg (set-up according to Dalton et al. 2015)¹⁵³. The order in which a subject's legs were tested was randomized preceding the visit, and kept constant for all subsequent visits. Throughout all trials strong verbal encouragement and visual feedback of real-time values was available to encourage maximal power production. Test-retest of the exercise protocol was performed on the Quantum (for each of the two leg extension attachments) using a repeated test separated by at least 48 hours and performed at the same time of day.

Measures were recorded and analyzed with LabChart (Labchart, Pro Modules 2014, version 8) software for the Humac Norm and integrated 1080 Motion software for the Quantum. Torque, position and angular velocity data were sampled at 2500 Hz and digitized by a 16-bit analog-to-digital system (PowerLab Data Acquisition Unit 16/35, AD Instruments, Bella Vista, New South Wales, Australia) on the Humac Norm. Force, power, speed and work were sampled at 111 Hz and computed on the 1080 Motion (Version 3, Lidingö, Sweden). Power was calculated as the product of torque multiplied by angular velocity on the Humac Norm. The values obtained were taken at the highest point of the single contraction and was recorded as peak power, for each device. Mean power was calculated by taking the sum of the contractions and dividing it by the number of contractions performed (i.e. 15), per leg. Fatigue index was determined across

individual contractions as: $fatigue\ index = \left(\frac{\bar{\chi}_{first\ 5\ contractions} - \bar{\chi}_{last\ 5\ contractions}}{\bar{\chi}_{first\ 5\ contractions}} \right) \times 100$.

Statistical Analysis

For assessment of reliability; peak power, mean power and fatigue index were compared between the two repeated tests of the Quantum using a 2 (variation of Quantum: Model A and Model B) x 2 (test: first test and second test) ANOVA with *post-hoc* tests. Reliability of measures for repeated tests on the Quantum were further examined using intra-class correlation coefficient (ICC_{2,1}) and was classified according to the categories of Sole and colleagues (2007)¹⁵⁰. All procedures were reproduced for the Quantum using a second leg extension attachment, and additional comparisons were drawn between Quantum Model A and Model B using the same statistical tests. As raw values only indicate precision, comparability of the Quantum (both models) vs the Humac Norm was further assessed by examining the coefficient of variation (CV) and through standard error of measurement (SEM), indicating the standard deviation of scores between the two tests of the Humac Norm and the associated model. CV values of <15% or below are considered acceptable based on Stokes (1985)¹⁵⁴ and Santos and colleagues (2013)¹⁵⁵. All statistical procedures were performed with SPSS 24 statistical software (SPSS Inc., Chicago IL, USA), or publicly available spreadsheets (sportsci.org) for verification of reliability and comparability and an *alpha* of $p < 0.05$ was set *a priori*.

Results

Reliability

Repeated tests on the Quantum dynamometer did not differ in measures of peak power, mean power or fatigue index (Table 1). These findings were consistent whether attachment A or B was connected for the leg extension test. Also, irrespective of which

attachment was used with the Quantum, ICC for both peak and mean power were high.

Significant differences were found between the leg extension models (A and B) for both peak power ($\Delta 225\text{W} \pm 88\text{W}$) and mean power ($\Delta 202\text{W} \pm 79\text{W}$), with higher raw values consistently generated on model B ($p < 0.0001$).

Table 1. Reliability of measures between two tests (pre and post) of 15 leg extensions per leg on two variations of a custom-built isokinetic dynamometer, the 1080 Quantum.

	Mean \pm SD (W)	<i>p</i>	ICC	SEM (W)	95% CI (W)	Correlation
Peak Power (W)						
Model A ₁	344 \pm 110	0.1 [†]	0.88 (0.78- 0.93)	38.3	32.5 - 47.1	98*
Model A ₂	339 \pm 110					
Model B ₁	569 \pm 187 [§]	0.96 [‡]	0.91 (0.82- 0.95)	55.7	47.4 - 68.7	97*
Model B ₂	569 \pm 177					
Mean Power (W)						
Model A ₁	296 \pm 96	0.06 [†]	0.88 (0.78- 0.93)	34.1	28.8 - 41.7	98*
Model A ₂	286 \pm 99					
Model B ₁	498 \pm 163 [§]	0.6 [‡]	0.91 (0.83- 2395)	47.8	40.7 - 59	98*
Model B ₂	501 \pm 155					
Fatigue Index (%)						
Model A ₁	17.8 \pm 6.2%	0.14 [†]	0.09 (-0.36 - 0.5)	5.50%	4.4 - 7.4%	17
Model A ₂	20.3 \pm 5.2%					
Model B ₁	14.2 \pm 3.8% [§]	0.7 [‡]	0.51 (0.08- 0.76)	2.80%	2.2 - 3.8%	48*
Model B ₂	14.6 \pm 4.3%					

A₁= test 1 on the first leg extension attachment (Model A) of the Quantum; **A₂**= test 2 on the first leg extension attachment (Model A) of the Quantum; **B₁**= test 1 on second leg extension attachment (Model B) of the Quantum; **B₂**= test 2 on the second leg extension attachment (Model B) of the Quantum; **SD**= standard deviation; **ICC**= intra-class correlation coefficient; **CI**= confidence interval; **SEM**= standard error of measurement; **p**= between tests within each model; * = <0.05; †= comparison between Model A₁ to Model A₂; ‡= comparison between Model B₁ to Model B₂; §= <0.05, difference between Model A₁ to Model B₁

Comparability

Comparison of both models of the Quantum to the Humac Norm were significantly different for all assessments of peak power, mean power and fatigue index ($p < 0.0001$; Table 2). Log-transformed Bland-Altman plots are presented in Fig 3, displaying the agreement between Model A₁ and the Humac Norm, and Model B₁ and Humac Norm.

Table 2. Comparison of measures using the first test of 15 leg extensions per leg between a gold standard dynamometer (Humac Norm) and two variations of a custom-built isokinetic dynamometer (1080 Quantum)

	Mean ± SD (W)	<i>p</i>	CV (%)	SEM (W)	Correlation (R)
Peak Power (W)					
Humac Norm	361± 116				
Model A ₁	344 ± 110	0.015	8.4	48.5	93 [*]
Model B ₁	570 ± 187	<0.0001 [¶]	14.7	146.1	90 [*]
Average Power (W)					
Humac Norm	333 ± 107				
Model A ₁	296 ± 96	<0.0001	9.0	49.4	93 [*]
Model B ₁	498 ± 163	<0.0001 [¶]	13.3	119.6	92 [*]
Fatigue Index (%)					
Humac Norm	5.7 ± 4.7%				
Model A ₁	17.8 ± 6.2%	<0.0001	41.86	7.7%	21
Model B ₁	14.2 ± 3.8%	<0.0001 [¶]	46.01	6.0%	-16

A₁= test 1 on Model A of the Quantum; B₁= test 1 on Model B of the Quantum; SD= standard deviation; CV= coefficient of variation; SEM= standard error of measurement; CI= confidence interval; *p*= Comparison of each model of the Quantum to the Humac Norm; ^{*}= <0.05; ^{||}= comparison between the Humac Norm and Model A₁; [¶]= comparison between the Humac Norm and Model B₁

[INSERT FIGURE 3 HERE]

Fig 3. Difference in individual and peak power outputs (W) between both models of the Quantum and the Humac Norm expressed as Bland-Altman plots. To the left, difference in individual power outputs (W) between A) Model A₁ and the Humac Norm and B) Model B₁ and the Humac Norm are shown. Differences in peak power (W) between C) Model A₁ and the Humac Norm and D) Model B₁ and the Humac Norm are located on the right. The horizontal lines represent the mean bias (solid black line) and

upper and lower 95% limits of agreement (dotted black lines). The y axis is the difference of scores between machines and the x axis display the mean differences of those scores.

Discussion

The 1080 Quantum has recently garnered the attention of sports scientists for its notable versatility, and reliability of movements as a solo system ¹⁵⁶. The 1080 Quantum provides measures of force, velocity and power for specific isolated movements to track progressions and create individualized training programs. However, there is no previous research conducted to compare the 1080 Quantum in combination with a movement controlled exercise machine. The purpose of the present study was to demonstrate reliability and comparability of the newly constructed Quantum isokinetic dynamometer. We confirmed our hypothesis that it was both reliable and comparable.

The major finding of the present study was that the pairing of a single-joint leg extension machine with the 1080 Quantum (Model A) showed strong consistency of test-retest (A_1 - A_2) power outputs. This consistency was further indicated through ICC of high reliability of >0.88 for peak and mean power, which aligned with peak torque results of Gross and colleagues (1991) (ICC=0.87) when assessing concentric knee extensions at 180° s on the Cybex II ¹⁵⁷. These results demonstrate that the Quantum can be used as a reliable and cost-effective dynamometer when completing test-retest measurements, making it a desirable machine to provide consistent power measures.

The comparability of power outputs between the Humac Norm and Quantum (Model A, test A_1) revealed acceptable values of variation ($<15\%$) and error (Table 2) ¹⁵⁰. The calculated indices of comparability, CV% and SEM, further substantiate the intra-

machine reproducibility for peak and mean power of both tests. When comparing high quality, commercially available dynamometers, a variance of 6.25%-9.5% is typically observed^{145,155,158}, with low SEM values demonstrating more precise power output values when comparing between machines¹⁵⁹. Model A compared to the Humac Norm was within the typically observed variation (A-Humac Norm: peak power= 8.4%, \bar{x} power=9.0%) (Table 2). SEM revealed the same peak (49 W) and mean power (49 W) values between Model A and the Humac Norm. This same amount of error indicates a strong parallel alignment and clear consistency of the Model A apparatus and the Humac Norm, even with different absolute values computed. The Bland-Altman plots (Figure 3) illustrate the variability and systematic bias between the power outputs of Model A and the Humac Norm. It is apparent that the agreement between Model A and the Humac Norm is strong, as the differences in individual power outputs are clustered around the mean and close to zero.

Comparison of peak power, mean power and fatigue index between Model A and the Humac Norm, displayed clear differences. These findings were expected as the Humac Norm and the Quantum are relatively distinct in respect to mechanical structure, adjustability, requirement for a baseline load and interfacing software, which influence force producing lever arm capabilities and data sampling rates. Furthermore, the addition of a crescent shaped cam (incorporated in the leg extension) provides a potential mechanical advantage by distributing varied resistance throughout the range of motion to all for maximum development production of the muscle^{149,160}. Different cam structures

can result in dissimilar peak and mean power between machines depending on where the cam applies resistance and assistance ¹⁶⁰ and, thus, may also alter fatigue index.

To verify the differences of power outputs as a result of different design and cam shapes, a second leg extension machine (Model B), manufactured with an oval-shaped cam, was attached to the 1080 Quantum, following the same design and statistical analysis as used with Model A. Findings of reliability between pre and post-tests ($B_1 - B_2$) of Model B of the Quantum, mimicked Model A's consistency and ICC. Both peak and mean power output from the first test of Model B (B_1) were within an acceptable range of variation, according to Stokes (1985) ¹⁵⁴, when compared to the Humac Norm (CV% - peak= 14.7%; \bar{x} = 13.3%), albeit at the higher end. In addition, the error of measurement between Model B_1 and the Humac Norm was larger compared to Model A_1 and the Humac Norm. Of importance, higher raw values for peak and mean power were produced in Model B_1 compared to Model A_1 . This observation can be attributed to the different cam design, which allowed the muscles to be stressed in a different manner; making the exercise easier to perform at the weakest joint angles and applying maximized force wherein the muscle is the strongest, for equal relative loading ¹⁶¹.

Despite small differences between the custom built and commercially available dynamometer, it is apparent that the 1080 Quantum combined with an existing exercise machine allows reliable determination of power production. While the power outputs of the Quantum (attached to the leg extension machine) were not found to be specifically equivalent to the Humac Norm, it stands to reason that a mathematical adjustment, individualized to the mechanics of each machine, could be introduced to provide

comparison across instruments (Model A: $y=0.8359x+18.654$; Model B: $y=0.5688x+49.252$). This would, of course, only be necessary for comparisons of data collected using different devices. Future directions include, assessment of the reliability and comparability of the 1080 Quantum with other fitness equipment, such as upper body exercise, to understand the applicability for testing different movements.

The Quantum dynamometer demonstrated reliable peak and mean power measures of concentric knee extension at a commonly employed testing speed. While raw outputs differed from the gold-standard, the differences were strongly correlated and consistent for within-machine comparisons, suggesting the variation was introduced by the design of the leg extension machine. This was confirmed by our follow-up, showing a differently designed leg extension model altered this relationship. The test-retest reliability when using a single device was high, indicating potential for use in most typical test-retest applications, including research.

Appendix L
1080 Quantum Dynamometer SOP

Standard Operating Procedure

Equipment/Procedure: *1080 Quantum Isokinetic Dynamometer*

Filename: 1080QuantumSOP

Assessor's name & date: *Jamie Burr*

Reviewer's name & date:

Review date:

1080 Quantum Isokinetic Dynamometer

Getting Started

Always use the 1080 Quantum under the supervision of a trained instructor if you have not received the training yourself. Ensure you have acquired adequate instruction of how to operate the 1080 Quantum in a safe manner before use. 1080 Motion offers a wide range of training for 1080 Quantum users worldwide.

General Operation:

1. *Turn on the master power switch (located on the back of the 1080)*



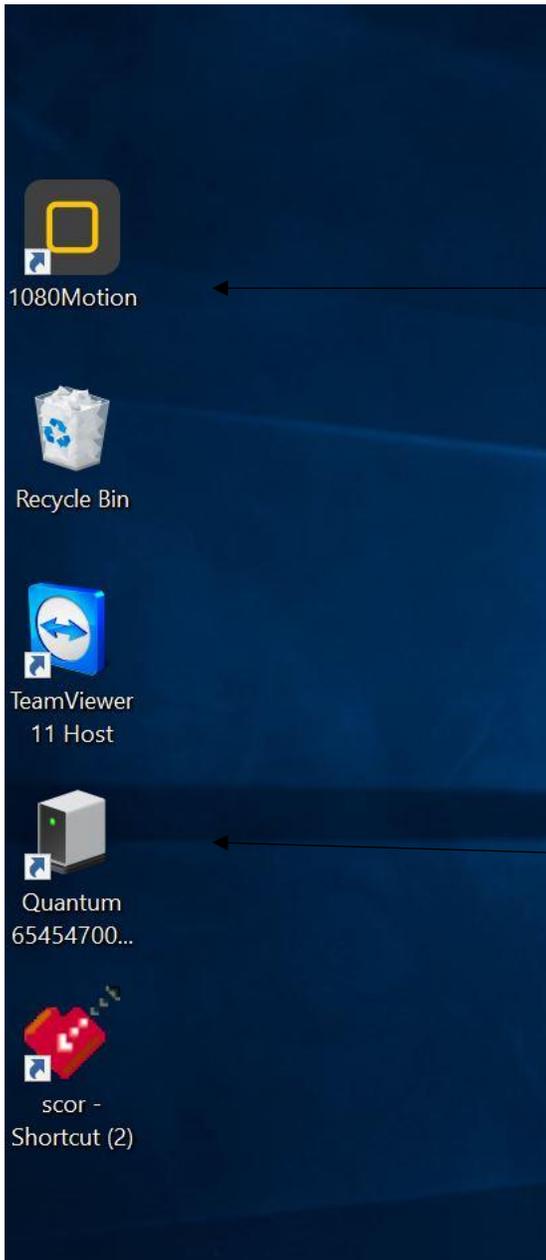
2. *Turn on the tablet*



3. *Connect to WiFi*

4. *Press and hold the Quantum Desktop Icon until you see “connect to Bluetooth” which will connect the tablet to the 1080 Quantum*

5. *Run the program by double clicking on the 1080 Quantum icon on your Desktop*



[Click this icon to start the Quantum machine](#)

[Click this one first to connect with Bluetooth](#)

6. Login with your username and password (1080 Quantum allows for up to 9 users to be logged in at the same time)

1080 QUANTUM

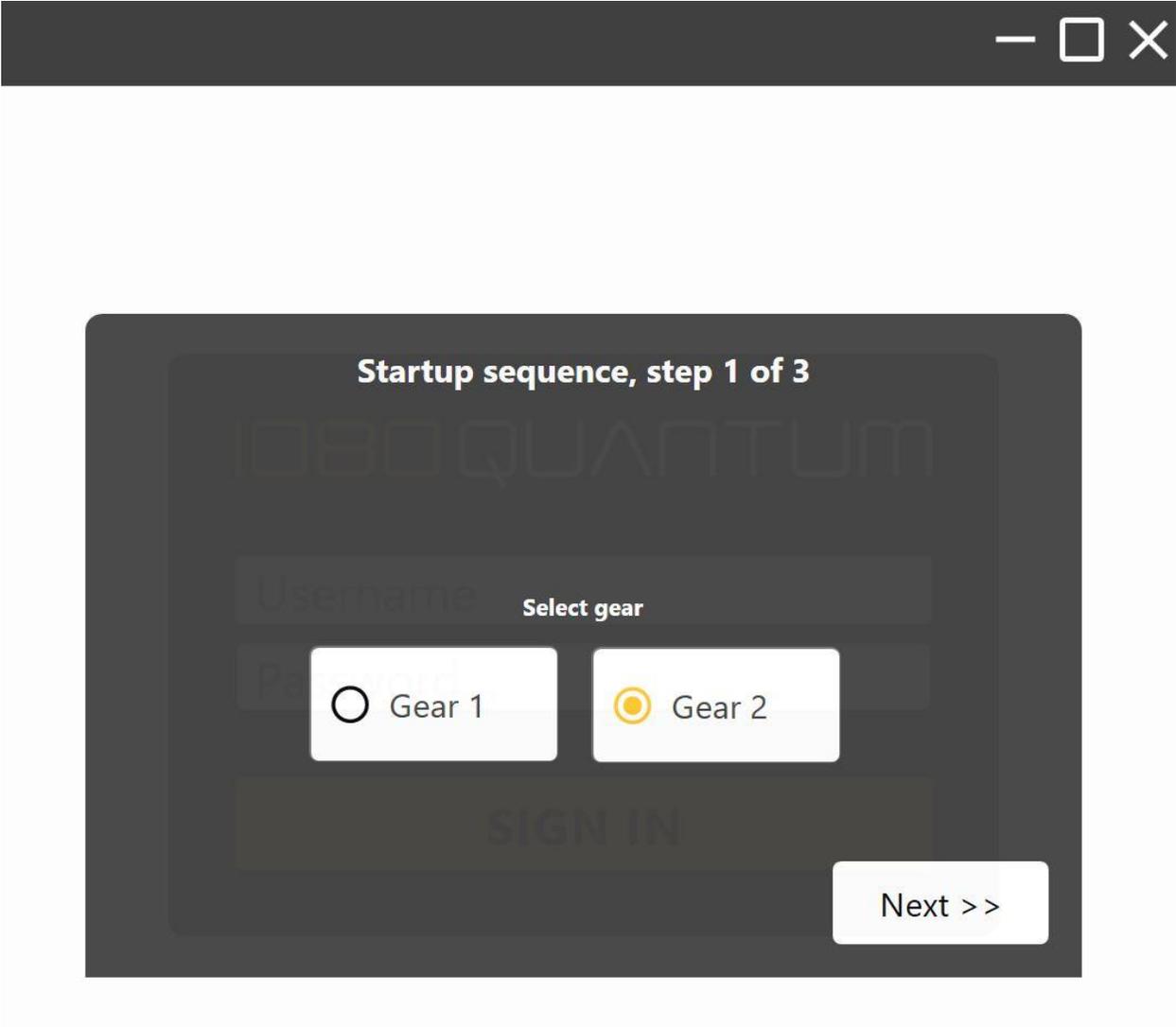
Username

Password

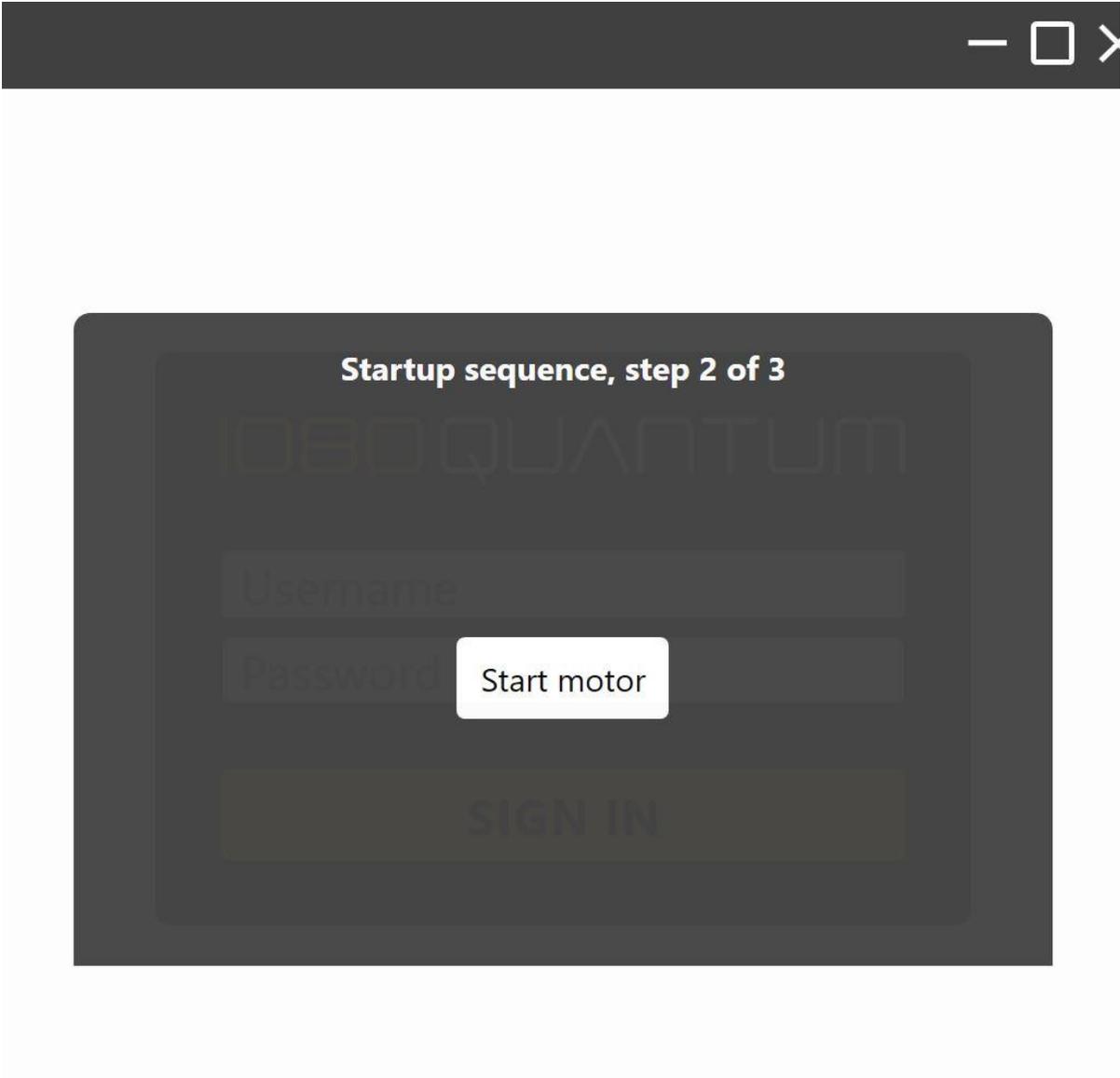
SIGN IN

Con/Ecc Load (kg) 8 Mode Isotonic Gear Second Con/Ecc Speed Limit (m/s) 0.5 4

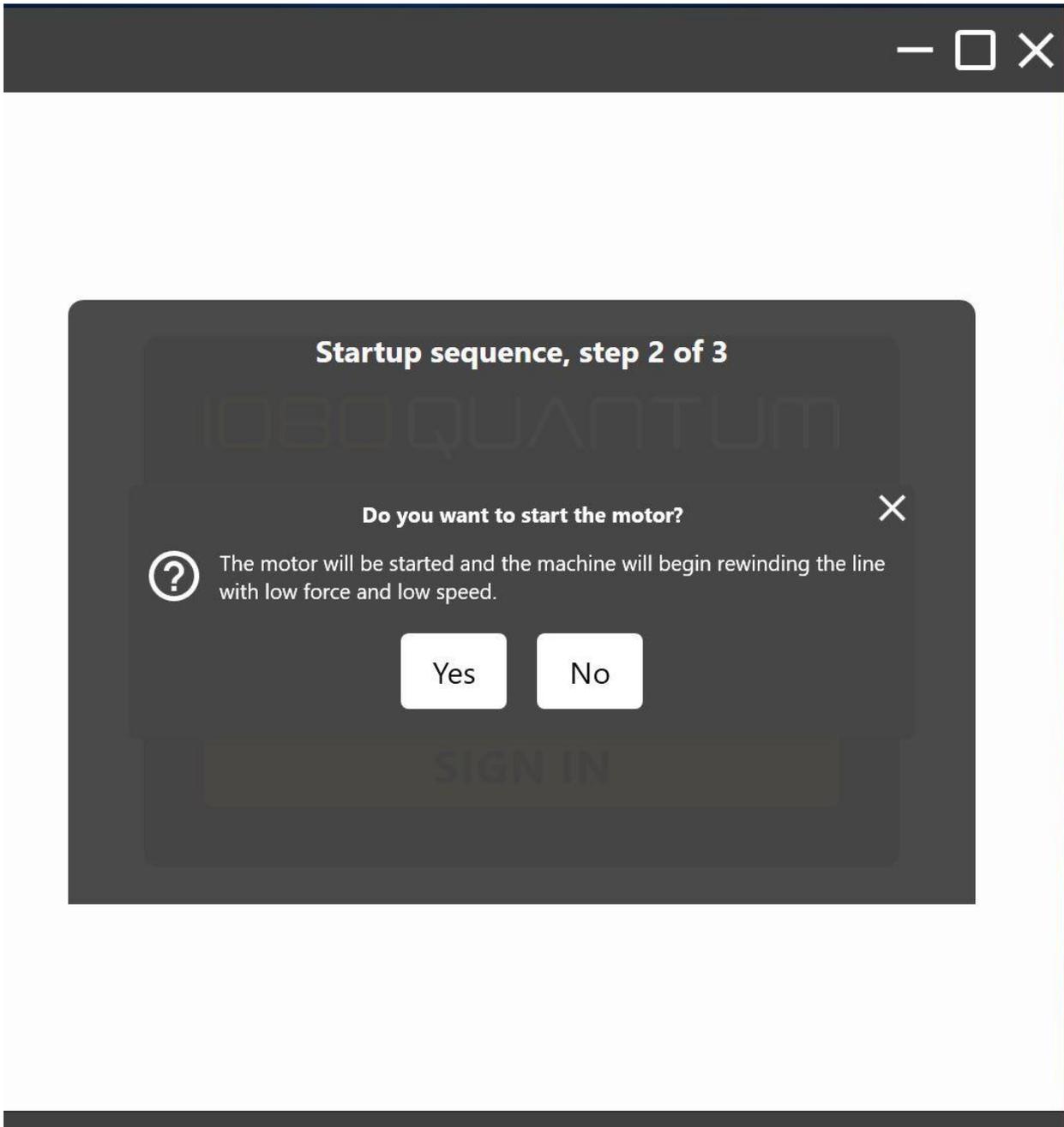
7. Select "Gear 2" and press "Next"



8. Click on "Start motor"



9. *When the dialog box comes up, select OK (the machine will now start and begin rewinding the line using low force and speed)*

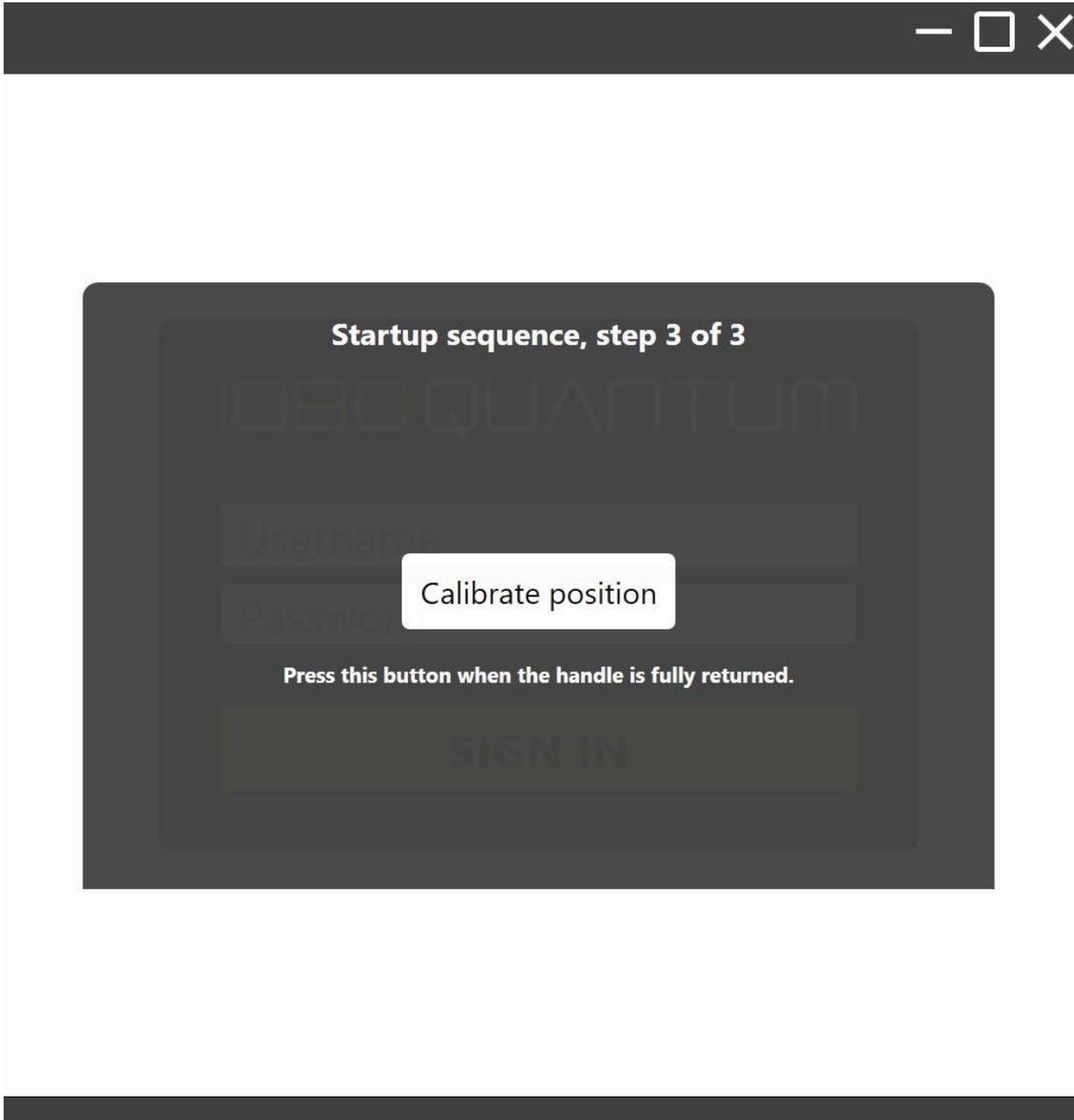


10. The 1080 Quantum lever arm will be secured at the fourth notch from the top of the machine, as shown below.



11. The carabiner should be detached from the wire (the wire that is integrated with the cam) before calibration so it will be tight when performing the extensions.

11. Once the carabiner is released, press “**Calibrate Position**”. The carabiner should be at the very top of the lever.





12. You may then take the carabiner and attach it to the looped wire. This should feel tight; indicated by the leg extension being very close to the chair.
13. Select “Groups & Users” on the ribbon menu on the right
 - a. Select “Add Group” for participants that are included in the first phase of the study and add a second group for the second phase of the study.

ACTIVE CLIENTS
← Add client ✓ ⚙ Delivra1
— □ ×

MY CLIENTS >

No clients are activated.

New client
× [icon] CANCEL SAVE

Name

Please enter 2 to 25 characters

Lastname

Please enter 2 to 25 characters

1/1/1986

Please enter a value between 30 and 250

Male Female

Length (cm)

Please enter a value between 30 and 250

Weight (kg)

Please enter a value between 10 and 500

Email

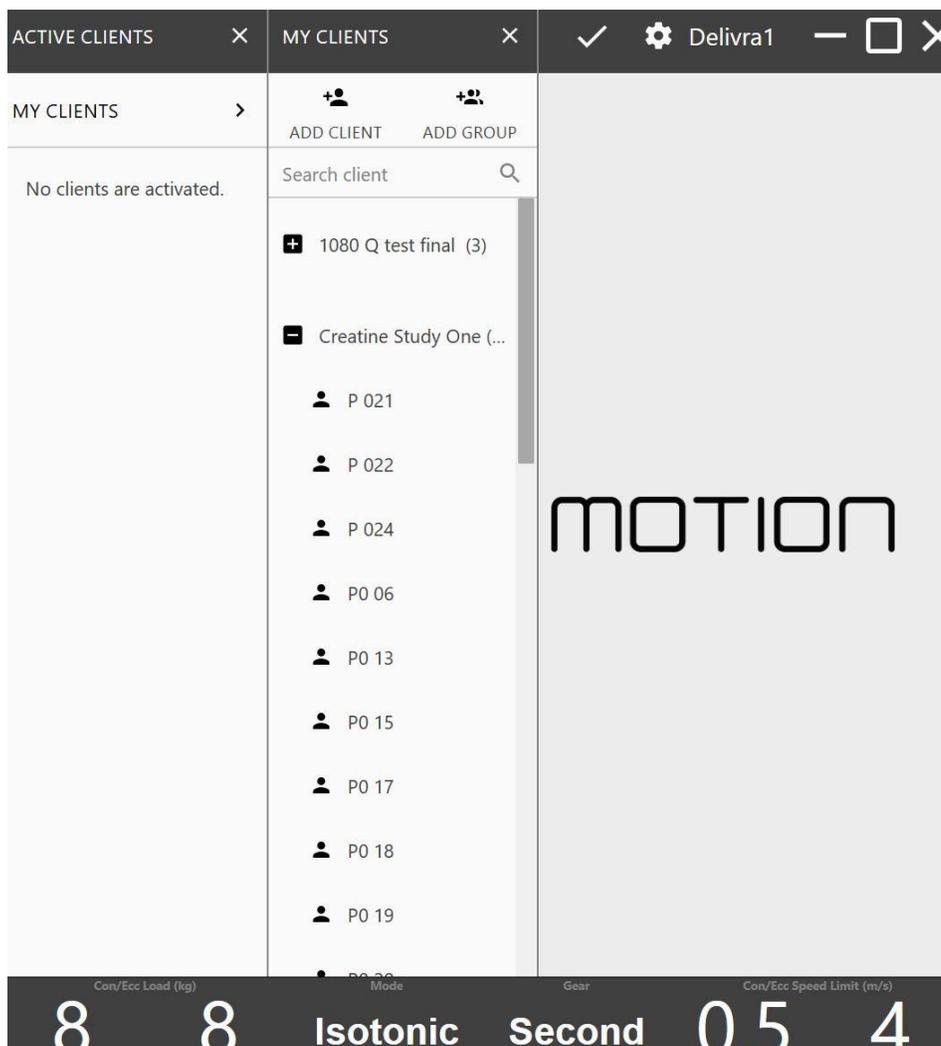
▾

Control Speed (kg) 8 8
Mode Isotonic Second
Gear Control Speed Limit (km/h) 0.5 4

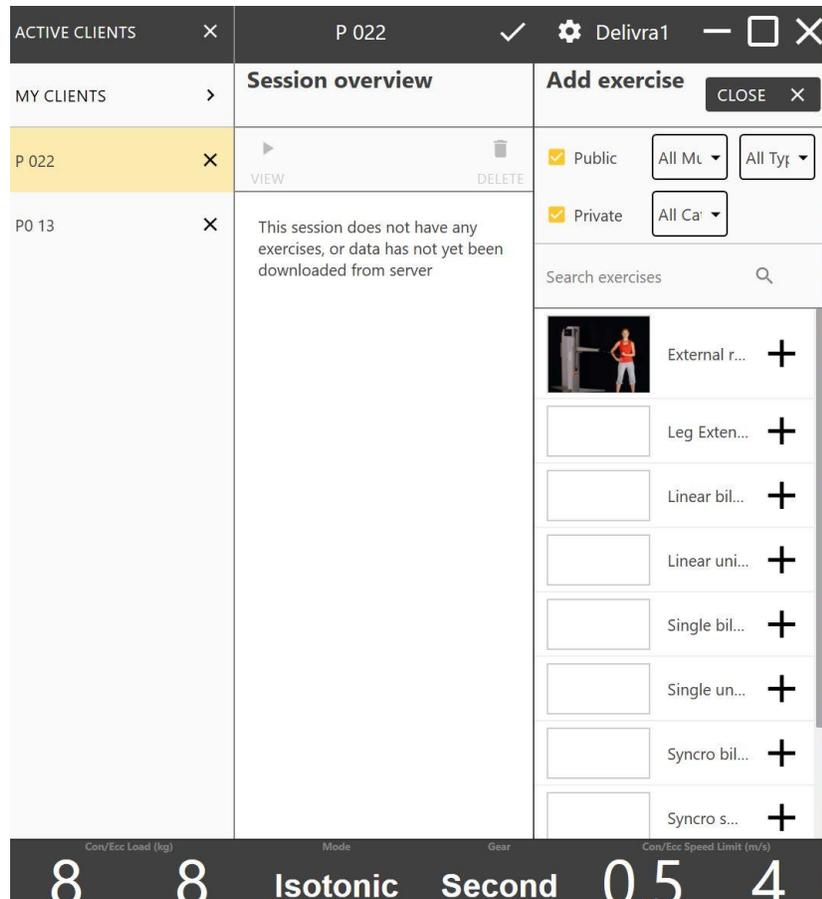
- b. Once a group has been made, add User
- i. Note that participants should have an ID number as opposed to their actual name for research project confidentiality
 - ii. Add as many other patient details as required. The system only requires the name box to be completed.
 - Have extensive participant details (height, weight, BP, body fat %, leg girth and blood pressure) recorded in another secured location (ie: secured excel file)

14. Select a client from **My Clients** from the ribbon on the left.

- a. Select the add client on the top of the screen and choose the appropriate group (ex: Creatine Study One)



b. Press the participant you would like to test and select “Leg Extension”



c. Select Leg Extension Exercise

i. **Add Exercise:** Navigate the right ribbon and select “Exercises”. Press the Create button to add an exercise to the list of exercises. The “Select exercise” dialog appears. Select an exercise from the list.

ii. **Leg Extension**

1. To edit an exercise, navigate to the middle menu of the exercise tab. The “Edit exercise settings: dialog opens.
2. Enter your preferred settings for training and/or testing (in our case it will be **8 kg** for **con/ecc load** (for MALE) and **5 kg** for **con/ecc load** (for FEMALE), **Isotonic** mode (which will eventually say “Vibration” mode, but there will be zero vibration), **Gear 2**, and **0.5 m/s con speed** and **4 m/s ecc speed**.

3. The name of the exercise should be “Leg Extension”, **Pressing** should be selected in the Category section; the muscle group you should select is **Quadriceps** (you could also include lower leg) and select **con-ecc**.

The screenshot displays the 'Session overview' for client P 022. The interface is divided into several sections:

- Client List (Left):** Shows 'P 022' and 'P0 13' with expand/collapse icons.
- Session Overview (Middle):** Displays 'P 022' with 'VIEW' and 'DELETE' options. Below, a table shows 'Set 1' with the note 'This set is empty'. The table headers are 'Set', 'Side', 'Reps', 'Max', 'Min', and 'Avg'.
- Add exercise Panel (Right):** Includes a 'CLOSE' button, checkboxes for 'Public' and 'Private', and dropdown menus for 'All Mt', 'All Tyf', and 'All Ca'. A search bar is labeled 'Search exercises'. A list of exercise options is shown, with 'Leg Exten...' highlighted.
- Status Bar (Bottom):** Shows session parameters: 'Con/Ecc Load (kg) 8', 'Mode Isotonic', 'Gear Second', and 'Con/Ecc Speed Limit (m/s) 0.5 4'.

- d. Once the exercise has been added, set 1 will appear on the left. The Quantum will start measuring outputs once the exercise has been

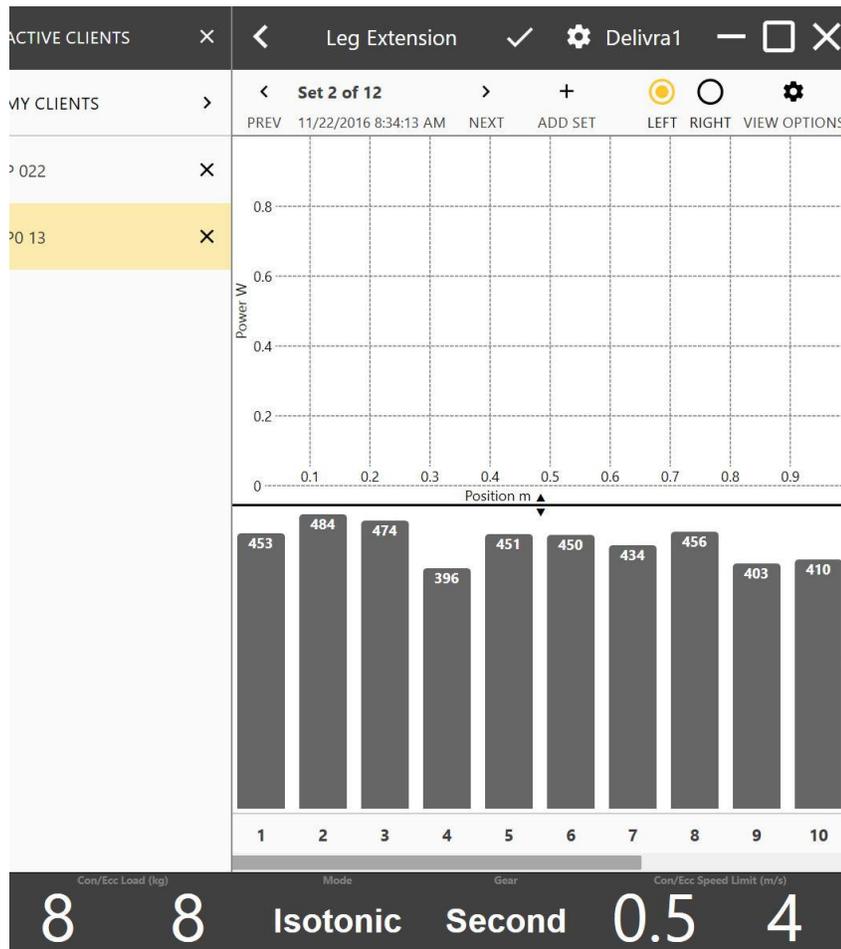
selected. This is O.K, but do not use this data. You can add sets on the right (picture below) and view in the larger mode with the **VIEW** button

The screenshot shows a mobile application interface for a fitness program. At the top, there's a header with 'ACTIVE CLIENTS' and a close button. Below that, a client profile for 'P 022' is shown, including birth date (1986-01-01), height (179cm), and weight (64kg). The main area is split into two columns. The left column lists clients, with 'P 022' selected. The right column shows a 'Session overview' for 'P 022' with options to add exercises, view, or delete. Below this is a table of sessions for 'Leg E...' with columns for Date, Exercises, Set, Side, Reps, Max, Min, and Avg. The bottom of the screen features a large display showing resistance modes: '8 8 Isotonic Second 0.5 4'.

Date	Exercises	Set	Side	Reps	Max	Min	Avg
2016-12-01	Leg Extension (12)	1					This set is empty
2016-11-30	Leg Extension (12)	2					This set is empty
2016-11-24	Leg Extension (4)	3					This set is empty
		4					This set is empty
		5					This set is empty
		6					This set is empty
		7					This set is empty
		8					This set is empty
		9					This set is empty

i. You have the option to delete numbers/sets which were erroneous, measurement error, or outliers

15. On the bottom of the screen certain resistance modes will appear. These are always visible and available for changes once the machine has started AND during the exercise protocol.



- On the far left, the concentric load will be set at **5 or 8 kg** (dependent on sex of participant) and the eccentric load will be set at **5 or 8 kg** as well
- Mode of the protocol should be set to **“Isotonic”** and should be in **“Second”** gear
- On the far right on the bottom of the screen should be concentric and eccentric speed. Set the parameters to **0.5 m/s** for concentric speed and **4 m/s** for eccentric speed.

DANGER!

When participant is completing maximum exercise, **ENSURE** and **DOUBLE-CHECK** that **ECCENTRIC** speed is at **4 m/s**. If it is lower than this, the cord will create slack, which will still be there when the participant is about to complete another concentric extension. This could potentially cause hyperextension of the knee

16. Select right or left limb

- a. Left is indicated with the yellow colour and right is indicated with the grey (make sure to label these once the participant has completed the protocol so when you need to go back and remember which leg they did first it will be on the tablet).*
 - i. This cannot be done when you have exited the software*

17. Patient setup

- a. Position the participant on the chair by adjusting the back support with the level lever. Secure with upper body straps (5-point harness) and lap belt. Ensure that the participant is positioned on the chair in such a way that they have full comfortable range of motion to be tested.*
- b. Adjust the participant so that their range of motion is at 90° with the goniometer*

18. Set Range of Motion

- a. Ask the participant to move to the full extent of their range of motion in one direction of the plane of motion being tested (from 90° to 180°)*
 - i. The knee will not extended 180° at the top. Encouragement of full extension of the knee joint will be administered without hyper extension*
- b. The foam block will be adjusted accordingly on the Velcro strips so that at a 90° flexion the participant's heel will strike the block, indicating that they have reached the desired ROM on returning from each kick.*
 - i. This will be put in place so that the participant completes a full extension and contraction*

19. Ensure that the participant follows the specific methodological requirements for consistency of testing, i.e. hands holding onto the side hand bars during contractions

20. When testing is complete assist the participant with the seatbelt straps from the dynamometer and relax.

21. Once the participant is rested, assist the individual off of the dynamometer and begin to wipe the machine down with Lysol wipes.

Shutting down 1080 Quantum:

- 1. Exit the software*
- 2. Shut down the tablet*
- 3. Switch off the 1080 Quantum*

Appendix

User Qualifications

Users of 1080 Quantum must be physically fit to use the machine. Talk to your physician prior to starting a new exercise program.

This product shall only be used by persons who have undergone the required training, or are under supervision of a trained instructor.

Users should not be under the influence of drugs, alcohol, or be very tired.

This product is not intended for use by those who lack basic knowledge of how the product is used safely.

Keep children away from product. Children must be supervised when present and never be allowed to operate the equipment.

Before use

Do not use machine if service access covers are open or missing.

Do not attempt to fix a broken or jammed machine. Notify facility staff or 1080 Motion.

Inspect machine including power cable, pull cord, swivels and attachments prior to use. DO NOT use if anything appears to be damaged or inoperable.

A broken fuse may be an indication of a serious malfunction. Do not replace the fuse until machine has been inspected by authorized personnel.

During use

DANGER!

When participant is completing maximum exercise, **ENSURE** and **DOUBLE-CHECK** that **ECCENTRIC** speed is at **4 m/s**. If it is lower than this, the cord will create slack, which will still be there when the participant is about to complete another concentric extension. This could potentially cause hyperextension of the knee

DANGER! Do not remove the side or back service cover of the machine as this poses an extreme risk for electrical shock or mechanical injury to hands and fingers. All maintenance inside the machine must be performed by certified service personnel.

Extreme caution must be used when increasing resistance and speed setting during exercise. Do not use resistance and speed settings beyond the physical capacity of the user.

Use the machine only for the intended use. Do not modify the machine.

Never use the machine alone. Ensure Emergency Stop is within reach by user or spotter/assistance.

If user unintentionally gets entangled or otherwise stuck in an unwanted position, press the Emergency Stop to deactivate the machine.

Do not release the handle from a distance when the machine is pulling.

Keep the line away from sharp edges. Do not place any sharp or heavy objects on top of the line.

If the Quantum is used with a Smith press, always position mechanical safety stops on the Smith press in proper position to avoid injury if losing control or bar.

Do not insert body parts or objects into the machine.

Disconnect power before servicing.

Do not remove warning labels on product. Refrain from using product and contact 1080 Motion to order replacement labels if necessary.

Intended Use

1080 Quantum is a powerful training and testing device for musculoskeletal conditioning. Improper use, installation and maintenance of the product can cause severe injury or death.

This product is intended to be used for:

- *Performing exercise sessions of all the major muscle groups in the body with the purpose of improving muscular strength and speed*
- *Evaluating strength, speed and power output during a concentric/eccentric motion at various levels of resistance*
- *Detecting muscular imbalances when comparing left vs. right and front vs. back side of the body*
- *Monitor progress over time for a user following a training program*
- *The product is intended for indoor commercial use in gyms and training facilities*
- *The product is NOT intended to provide medical diagnoses or therapy*

Safety Information

- *Due to the complex operation of this machine and its application you as the operator must have read and understood the operator's manual (the "?" (right hand of the screen) on the tablet/system) and have had the required induction training before using this machine.*
- *Ensure that the machine (anything that has to do with electrical problems)*
- *Please discuss and confirm with the participant that they do not have any underlying joint or mobility issues.*
- *Loose clothing should be avoided by both operator and participant (exception for "gym" shorts and t-shirts). Do not place items of clothing, towels, etc. near or on the dynamometer.*
- *Ensure there is clear enough area around the machine so that the controls and items can be easily assessed.*
- *When altering the height of the lever arm, ensure that correct manual handling practices are undertaken and that the area is clear.*

IMPORTANT SAFETY INSTRUCTIONS

DANGER – to reduce risk of electric shock:

- 1) *Always power down and unplug this appliance from the electrical outlet immediately after using and before cleaning.*

WARNING – To reduce the risk of burns, fire, electric shock, or injury to persons:

- 1) *An appliance should never be left unattended when plugged in. Power down and unplug outlet when not in use and before putting on or taking off parts.*
- 2) *Do not cover machine. Excessive heating can occur and cause fire, electric shock or injury to disabled persons.*
- 3) *Close supervision is necessary when this appliance is used by, on, or near children or disabled persons.*
- 4) *Use this appliance only for its intended use as described in this protocol. Do not use attachments not recommended by the manufacturer.*
- 5) *Never operate this appliance if it has a damaged cord or plug, if it is not working properly, if it has been dropped or damaged, or submerged into water. Return the appliance to a service center for damage and repair.*
- 6) *Do not lift or carry this appliance by supply cord or use cord as a handle.*
- 7) *Keep the cord away from heated surfaces.*
- 8) *Never operate the appliance with air openings blocked. Keep the air openings free of lint, hair and the like.*
- 9) *Never drop or insert any object into the opening.*
- 10) *Do not use outdoors.*
- 11) *Do not operate where aerosol (spray) products are being used or where oxygen is being administered.*
- 12) *To disconnect, power down the machine, then remove plug from the outlet.*

Additional Notes:

Set up 1080 Quantum to Leg Extension

REFER TO JEFF BOWSER’S ASSEMBLY DOCUMENT FOR FURTHER INSTRUCTIONS ON SPECIFIC SET-UP OF CHAIR, HANDLE AND WIRE.

The lever on the 1080 Quantum should be at a 90° angle and should look like this



The wire (with the green plastic casing) will be secured and fastened with a U-bolt and attached to the carabiner.



A second gear will have to be added to the Quantum to allow for more force to be generated

- *Attach the second gear onto the cord (orange) from the 1080 Quantum and secure (pinch together).*
- *Once secured, take the black plastic knob (at the end of the orange cord on the Quantum) and file it through the small magnetic bar at the top of the lever of the Quantum*

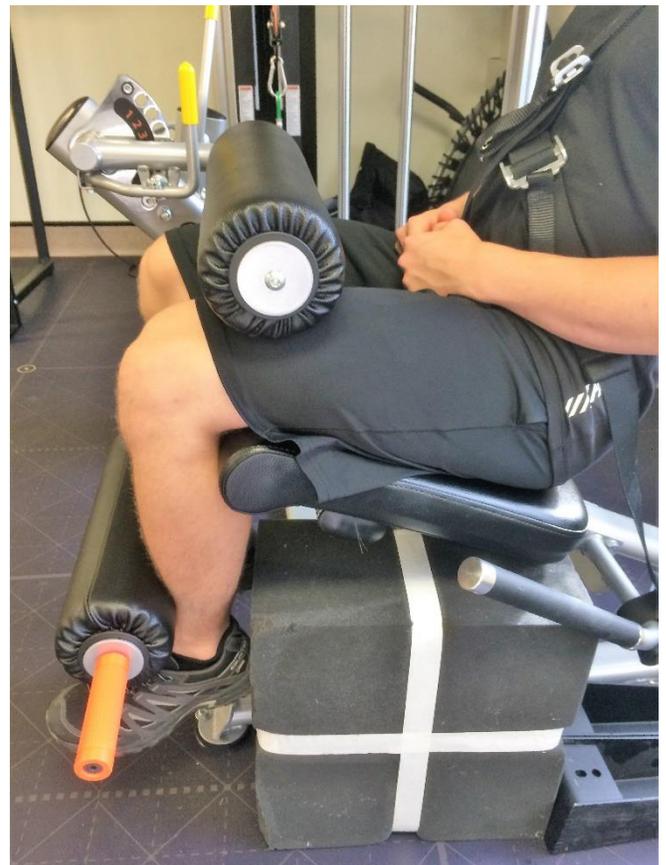


- *Attach the carabiner to the loop hole on the second gear, and then attach the carabiner to the exposed, looped wire with the “U-bolt”*

Top of the Chair



Bottom of the Chair



Emergency Stop Button

For participant safety and reassurance, we will have a researcher/volunteer near the emergency stop button.

If this button is pressed during the actual protocol ensure the participant is O.K. and react as necessary.

If the participant is fine, release the emergency stop button and add another set.

Data will not be erased, however a subsequent set may have to be completed.

Exercise Protocol

1. *Once set-up is complete, the participant can start performing the exercise protocol*
2. *5 sets of 15 maximal concentric knee extensions on both legs*
 - a. *Concentric speed of 0.5 m/s*
 - b. *60 second rest between sets*
 - c. *10-minute rest between legs*

Testing Adjustments

- *When performing the testing there is a **Curves section** – this displays the repetitions where the curve is selected to be shown. The graph automatically scales to best fit on the screen*
- **Repetitions** - *this section shows all repetitions as bar graphs with a numerical value for each repetition.*
 - **Del:** *Press this button to delete all selected repetitions (marked with orange border). This action cannot be undone*
 - **Show/Hide:** *This button shows or hides the curve for all selected repetitions*
- **Average Repetitions** – *The average repetitions are calculated for each colour by averaging the curve for each repetition in that colour where they overlap in position. This method has some implications*
 - *All repetitions in the same colour must have roughly the same start and stop position for an average repetition to be defined.*

- *The peak and average values of an average repetition will not necessarily be exactly the same as the average peak and average values of single repetitions of the same colour.*
- **Trim tool** - *use this tool to adjust the start and stop point used to calculate the peak and average values of the curve*
- **History** – *This tab contains a calendar of all training and test sessions performed*
 - *This will be useful when assessing when the participant came and performed the exercise protocol*

Concentric and Eccentric Adjustments – Background Information

- a. *For concentric and eccentric load (kg) set the parameters to 5 or 8 kg (concentric) and 5 or 8 kg (eccentric)*
 - i. **Concentric Load** – *if the concentric load is set to 0kg the machine will turn off and all other settings will have no effect. Maximum load on gear 1 is 0-25kg*
 - ii. **Eccentric Load** – *depends on the current selected concentric load and eccentric speed limit. This load is always greater than the concentric load. A greater concentric load allows for a smaller relative difference between eccentric/concentric load. A greater eccentric speed limit allows for a smaller relative difference between eccentric/concentric load. Maximum eccentric load range: 0-37kg*
 - iii. **Concentric speed limit** – *the machine limits the speed to the set limit by temporarily increasing the amount of resistance, thus decreasing the speed. The concentric speed limit creates an isokinetic resistance mode. Minimum – Maximum speed: 0.1 m/s – 8.0 m/s*
 - iv. **Eccentric speed limit** – *the eccentric speed limit prevents the handle from returning faster in the eccentric direction than the set limit, even if the user releases the handle completely. The machine reduces eccentric speed by temporarily decreasing the amount of resistance. Minimum – Maximum speed: 0.1 m/s – 8.0 m/s*

Installation, Maintenance and Calibration

- *The 1080 Quantum itself is essentially a fixed piece of equipment that cannot be easily moved to a new location without considerable intervention.*

- *Calibration system checks are performed every time the program starts and electrical safety testing is carried out*
- *Inspection and maintenance should be performed on a regular basis to ensure safe and trouble free operation of 1080 Quantum*

Regular Inspection

- ***Look for malfunctions of any kind.*** *The inspection must be made when the machine is being used. Signs of a malfunction could be a strange noise or a jerky feeling when using the machine. See Troubleshooting section in the 1080 Quantum Manual if unsure of what the problem may be*
- ***Ensure that bolts securing machine to the floor are secure.*** *If the machine shows signs of rocking during use, stop using and contact authorized service personnel.*
- ***Inspect the line.*** *The line is inspected by visually checking for excessive wear and tear along its full length.*
- ***Inspect the power cord.*** *The power cord must not have any visible damages to prevent electric shock.*

WARNING! *Risk for electric shock. Disconnect machine from power source and contact authorized service personnel if the power cord shows any sign of damage.*

- ***Inspect the emergency stop***

Check the Emergency Stop function. When the button is pressed, the resistance should be turned off immediately and an error message will occur on the screen. Deactivate the Emergency Stop by lightly twisting the knob so it pops out into the outward position.

Regular Maintenance

The following maintenance must be performed on a regular basis:

- ***Cleaning*** – *clean the touch screen only using a soft cloth and cleaning agent designed for PC touch screens. Use of any other cleaning material may cause permanent damage to the screen. Suitable cleaning cloths and liquids are available in stores selling computers and office supplies. Clean other surfaces with a soft cloth and detergents suitable for painted surfaces. Do not use any strong chemical detergents that may damage the paint or plastic components. Disinfectants must be suitable for cleaning gym equipment.*

- **Lubrication** – *Lubrication of 1080 Quantum is not normally required*
- **Tightening of bolts and fasteners** – *Over time some of the bolts and fasteners on 1080 Quantum may become loose when used frequently. Please inspect all bolts at regular intervals and re-tighten if necessary. Pay extra attention to the area around the tilting mechanism of the display and the swivel assembly*