Cover Page

Title:

The Neurocognitive Effects of Extended-Release Methylphenidate in Healthy Adults: A Review and Placebo-Controlled Randomized Controlled Trial

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Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a clinically diagnosed medical condition. The Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5™) (American Psychiatric Association, 2013) of the American Psychiatric Association is primarily used for the diagnosis of ADHD The International Statistical Classification of Diseases and Related Health Problems (ICD-10) is the tenth edition of a medical classification list published by the World Health Organization (World Health Organisation, 1992). This too includes ADHD in its listings.

Attention Deficit Hyperactivity Disorder is a chronic condition starting in childhood (before age 12 years) and may persist into adulthood. To make the diagnosis there are a minimum number of symptoms that must be present with dysfunction in social and occupation/academic activities.

The mainstay of treatment is pharmacological; and primarily stimulants. Methylphenidate (MPH) is in South Africa, and indeed universally, the drug of choice and is a potent amphetamine-like stimulant drug with similarities to cocaine. Numerous studies have shown the benefit of treatment of ADHD with methylphenidate, with the intent of normalising the underlying central nervous system dysfunction and returning the homeostasis of neurological and social function (Surman, Hammerness, Pion, & Faraone, 2013).

As a stimulant and therefore a substance that has the potential to enhance sporting performance, methylphenidate is a prohibited substance that appears on the prohibited substance list of the Wold Anti-Doping Agency (World Anti-Doping Agency, 2017). This prohibits athletes from using it in competition, unless they have a Therapeutic Use Exemption (TUE) (World Anti-Doping Agency, 2017). A TUE is a concession whereby a competitive athlete is allowed to use a prohibited substance and its issuance is reliant on specific criteria, including that the substance will not unduly enhance performance and is required to return health status to a premorbid state. Despite much research on methylphenidate and its psychosocial effects, there is very little research on the physiological parameters and physical effects of this medication and in particular in sport or exercise. In 2006 of 490 adverse analytical findings (positive tests) of stimulants by WADA, 32 (6.5%) were for methylphenidate (World Anti Doping Agency, 2006). These were the 4th highest following amphetamine, cocaine and ephedrine. In the latest published figures of 2015, of 528 positive stimulant tests, methylphenidate topped the list with 96 (18%), followed by amphetamine

(80[15%]) (World Anti Doping Agency, 2016). In 2009 it was reported that there was a substantial increase in TUEs in American baseball, with almost 8% of players using medication for ADHD (Associated Press, 2009). It is not known whether competitive athletes taking methylphenidate or stimulants do have an advantage and whether their performances are improved whilst taking the medication, than if they were not. Recently a hacking group called Fancy Bear gained access to the therapeutic use exemption database of WADA and started publicising information on international athletes from around the world (Fancy Bears, 2016). Their action is thought to be retaliatory for the exposing of alleged systematic doping by the Russian authorities of their athletes. The intent appears to have been one of exposing doping by athletes that have been legitimised by the TUE process. A number of exposed information revealed that there were some athletes in various sports that were granted TUE's for stimulants. It is not clear for which medical conditions as the TUE certificates do not disclose this information, although a few may have included ADHD under the comments section of the certificates. As elite sportsmen and women, the performances of these athletes have been exceptional and it is impossible to determine what role the stimulants may have had on their individual performances.

Should an athlete be clinically diagnosed as having ADHD and granted a TUE, is there the potential for that athlete to have an undue advantage in sport? This study has relevance on the physical performance of patients diagnosed with ADHD in their daily activities, in their sports participation and on implications for doping control regulations. It will further evaluate a number of physiological parameters that are germane to sport such as cognitive function, balance, and risks, such as for cardiac events. With the apparent widespread use of MPH amongst athletes, whether for legitimate medical reasons or as a performance enhancing substance; and the prevalent concern of sudden cardiac death in athletes, this study will also address the potential harmful effects of MPH on cardiac electrical activity.

Diagnosis of ADHD

The DSM-5™ diagnostic criteria for ADHD lists symptoms of inattention, hyperactivity and impulsivity. It is estimated that 5-12% of children have the condition with up to half persisting into adulthood (Faraone & Antshel, 2008; Faraone, et al., 2000; Faraone & Biederman, 2005). More recent reports are that 2.5% persist into adulthood (Sobanski, et al., 2014).There are three subtypes of ADHD, and persons with ADHD may have multiple symptoms of each type. The

three subtypes of ADHD are: primarily hyperactive-impulsive type, primarily inattentive type, and combined type. (Table1). Persistent life dysfunction is the core clinical presentation, with treatment aims being to reduce impairment (Caci et al., 2014).

Table 1: Subtypes of Attention Deficit Hyperactivity Disorder (Centers for Disease Control and Prevention, 2016)

Symptoms of inattention	Symptoms of hyperactivity and impulsivity
Often fails to give close attention to detail or makes mistakes	Often fidgets with or taps hands and feet, or squirms in seat
Often has difficulty sustaining attention in tasks or activities	Often leaves seat in situations when remaining seated is expected
Often does not seem to listen when spoken to directly	Often runs and climbs in situations where it is inappropriate (in adolescents or adults, may be limited to feeling restless)
Often does not follow through on instructions and fails to finish schoolwork or workplace duties	Often unable to play or engage in leisure activities quietly
Often has difficulty organising tasks and activities	Is often 'on the go', acting as if 'driven by a motor'
Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort	Often talks excessively
Often loses things necessary for tasks or activities	Often blurts out answers before a question has been completed
Is easily distracted by extraneous stimuli	Often has difficulty waiting their turn
Is often forgetful in daily activities	Often interrupts or intrudes on others

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The most common manifestation of ADHD is inattention (Attention Deficit Disorder [ADD]). (Diamond, 2005). Attention Deficit Disorder is developmentally inappropriate inattention and impulsive behaviour without hyperactivity and is implicated in learning disorders. It is diagnosed four times more frequently in boys than in girls. Attention Deficit Disorder with hyperactivity is diagnosed when signs of over activity are obvious. Inattention is described as a failure to finish a task, easy distractibility, seeming lack of attention, difficulty in concentrating on tasks requiring sustained attention, and is described as acting before thinking, difficulty taking turns, problems organising work and constant shifting from one activity to another. Hyperactivity is best described as difficulty staying seated and sitting still, and running or climbing excessively. The American Psychiatric Association's Diagnostic criteria from the DSM-V (American Psychiatric Association, 2013) lists symptoms to be utilised in the diagnosis of the disorder, where symptoms persist in more than one setting, for at least 6 months to such a degree that is maladaptive and inconsistent with the developmental process. These symptoms must be present before the age of 12 years and will interfere with normal functioning at home and at school. A medical assessment must ensure there is no underlying disease or illness that could otherwise account for the disruptive behaviour.

Pathophysiology of ADD/ADHD and stimulant drug actions

Attention Deficit Hyperactivity Disorder is a heritable condition but with influencing factors such as obstetric complications and psychosocial affliction (Biederman, 2005). Rather than as previously thought, small for gestational age and lower birth weight, rather than prematurity may increase risk for ADHD (Heinonen, et al., 2010). Further, preterm children are at risk for both ADHD and autism (Johnson et al, 2010). Other factors that have been considered include lead exposure (Eubig, Aquiar, & Schantz, 2010; Huang, et al., 2016) and zinc deficiency (Lepping & Huber, 2010).

The primary pathophysiology is dysfunction in the frontal-subcortical-cerebellar catecholamine neural circuits (Biederman, 2005) and frontocingulate areas (Rubia et al, 2011). Imaging techniques confirm abnormalities in the frontal brain area in both children and adults with ADHD (Cubillo et a; 2012; Sokunbi et al, 2013). The cerebellar vermis has also been implicated in the pathophysiology of ADHD (Castellanos et al, 2002). Magnetic Resonance imaging (MRI) techniques have shown that children with ADHD have context-specific dissociation, in that with MPH treatment there is up-regulation in fronto-striato-thalamo-cerebellar and parietal-temporal attention networks with down regulation of hyper-sensitive orbitofrontal activation (Rubia, 2009).

Treatment of ADD/ADHD

Satterfield et al (1994) have suggested that hyperactive children suffer from a state of depressed central nervous system arousal. This would be the basis for how stimulant therapy may positively influence symptoms in those with the condition.

Stimulant treatments for the symptoms of ADHD have been used since 1937 (Bradley, 1937). Methylphenidate was synthesized in 1944, and in 1954 was tested on humans. In 1957, Ciba Pharmaceutical Company began marketing MPH as Ritalin® to treat chronic fatigue, depression, psychosis associated with depression, narcolepsy, and to negate the sedative effects of other drugs (Center for Substance Abuse Research: Ritalin, 2015). In a 1995 study by the Drug and Chemical Evaluation Section, Office of Diversion Control within the Drug Enforcement Administration Department in the US Department of Justice, methylphenidate was researched in a background paper. The following was reported: “Methylphenidate is a schedule 11 stimulant which is structurally and pharmacologically similar to amphetamines and is indicated for the

treatment of attention deficit and hyperactivity disorder (ADHD) and narcolepsy. The use of Methylphenidate in the United States has increased dramatically in recent years. Since 1990 there has been an increase in the US production and utilisation of Methylphenidate. According to the UN 1993 statistics on psychotropic medication, the US produces and consumed five times more methylphenidate than the rest of the world combined." (U.S . Department of Justice, 1995).

In South Africa Methylphenidate is classified as a Schedule 6 Drug (Janssen Products , 2013). It is registered as a stimulant in the pharmacological classification of antidepressants for the treatment of ADHD as diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). The package inserts for MPH state that the mode of therapeutic action is not known, but that it is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space (del Campo et al, 2011).

The effects of stimulants are on both the dopaminergic and noradrenergic humoral systems. (Scheel-Kruger, 1971; Solanto, 1998). As far back as the 1990's the neuro-active drug Ritalin®, whose main component is Methylphenidate, had been most commonly prescribed for ADHD. Its effects have been shown to reduce impulsivity and hyperactivity. There are however non-responders with up to 30% not responding to medication (Lee, et al., 2009). In children with symptoms persisting into adulthood, the treatment is the same.

Physiological and physical effects of Methylphenidate

Kim et al (2011) reported the beneficial effects of treating ADHD with both methylphenidate and treadmill based exercise. Other studies have likewise shown the benefits of exercise in those diagnosed with ADHD (White, Harris, & Gibson, 2013; Abramovitch, Goldsweig, & Schweiger, 2013). Little however is known of the effect of MPH on exercise. One of the few reports relating to exercise and the prescription of MPH was that published by Bar-Or (2004) where the aim was to determine the influence of exercise in those with ADHD, and explained the reasoning behind exercise as a treatment for ADHD. Bar-Or also cited in his findings that the use of Ritalin caused sub-maximal heart rate increases of 10 beats per minute without any alteration in the maximal heart rate in the same subject (Bar-Or & Rowland, 2004).

According to Robbins and Sahakian (1979), stimulants exert rate-dependant effects and primarily enhance motor output rather than processing of information; and the overlapping effects in individuals both with and without ADHD implies that stimulants do not act on specific neurobiological deficits (Solanto, 1998). In adults increased motor effects of MPH has been shown in those without ADHD (Rapoport et al 1980).

Cycling cadence was influenced by the stimulant caffeine at lower rates of perceived exertion (RPEs) but not at higher RPEs (Green et al, 2017) . In another cycling-based study using MPH at a fixed RPE in a randomised controlled study, Swart et al (2009) suggested that during endurance activity the central nervous system regulates exercise performance. Thus centrally acting stimulants may have an influence on regulating performance, in contrast to Solantos' findings (Solanto, 1998).

Although motor skills improve in ADHD-diagnosed children with MPH use that were previously drug-naïve, as many as half did not show improvement (Brossard-Racine et al, 2012). Specific sport performance skills and effects of MPH in explosive and endurance activities are unknown.

Methylphenidate: cognitive function and psychometric testing

In addition to methylphenidate having an absence of a specific mode of action, the cognitive performance effects have been reported in children and adults with and without ADHD (Peloquin & Klorman, 1986; Krusch et al, 1996; Klorman et al, 1994).

A variety of psychometric tests are used as aides in diagnosis and monitoring of ADHD in patients. These include Behavior Rating Inventory of Executive Function , Wechsler Intelligence Scales for Children (WISC-IV), the Test of Attentional Performance for Children (KITAP), Test of Variables of Attention (TOVA), and Bender Visual-Motor Gestalt Test (BGT) (Hellwig-Brida et al, 2011; Huang et al, 2007; Huang et al, 2012). Methylphenidate has shown significant improvements in cognitive domains in spatial working memory, rapid visual processing, set shifting, inhibition/vigilance and verbal recognition memory; using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Hammerness et al, 2014). This test has not been reported for use in assessing motor performance.

There are no reports of the use of psychometric tests in ADHD that are used in closed head injury/concussion, commonly used in athletes; such as ImPACT®® (Immediate Post-Concussion Assessment and Cognitive Testing)(ImPACT® Applications, Inc; v4.8.2, 1.4.0, Pittsburgh, United States of America) which have high sensitivity **(Khurana & Kaye, An overview of concussion in sport, 2012)**. This online computer based test for neurocognitive function is validated and the first such medical device to receive approval from the US FDA (Food and Drug Administration) under the category Computerized Cognitive Assessment Aid. Thus the use of the ImPACT® psychometric test may be of value in measuring neurocognitive effects with the use of MPH.

Cardiovascular effects of methylphenidate

The use of MPH has been reported as not having any significant increase in the short term risk of severe cardiac events (Shuster & Olfson, 2012; Winterstein, et al., 2012). Thirteen percent of recreational stimulant users of both 40mg or 80mg MPH developed sinus tachycardia (Koblan, et al., 2016), and treatment with MPH in adolescents has shown increases in heart rate and blood pressure, particularly in the early stages of treatment (Hammerrness, et al., 2009). Olfson et al (2012) reported that it was a rare occurrence for any clinical diagnoses of cardiovascular events and symptoms with stimulant use in treating ADHD. However they did not identify any ECG abnormalities or minor/unreported occurrences, as they defined such events as those that required emergency department or inpatient attention. Electrocardiogram assessments of PR, QRS and QTc showed no changes (Hammerrness, et al., 2009). However clinically “insignificant” cardiovascular effects, including arrhythmias, were reported by Arcien et al (2012).

Stiefel and Besag (2010) also reported no major CVS incidences, despite increases in heart rate and QTc; but suggested that further research is needed, specifically to address CVS risk with ADHD treatment. In a review of psychopharmacologic therapy and cardiovascular side effects, the paper by Potočnjak et al (2016) grouped stimulants as potentially having risk, but did not determine any specific concerns or details for that class of drugs other than illicit stimulants such as cocaine.

The stimulant atomoxetinem, also used for the treatment of ADHD, has shown to produce morbidity and even mortality through CVS side effects (Martinez-Raqa, Knecht, Szerman, & Martinez, 2013).

This was however countered by a paper that suggested there was no increased risk (McCarthy et al, 2009). Animal models have shown that the stimulant caffeine may prolong the QTc via the hERG channel (human ether-à-go-go-related gene (Zheng, et al., 2017). In child populations treated with MPH, similarly the QT interval, QTc and TpTe/QT ratios were affected, and which the researchers advise should be measured in children treated for ADHD (Karpuz et al, in press).

A community-based study by Westover et al (2015) using maximal treadmill testing in adults of prevalent stimulant users (amphetamine or methylphenidate-type) reported decreased peak heart rate and increased risk of chronotropic incompetence. The latter is an inappropriate heart rate response to the demands of physical activity and is associated with cardiovascular disease and heart failure. They measured estimated VO_2max as an outcome, but they did not perform ECG tracings.

Abuse of methamphetamines, with similar biological effects as MPH, as recreational drugs, do however exhibit potentially severe cardiac morbidity (Paratz, Cunningham, & MacIsaac, 2016). Extreme measures producing an acute high dose exposure of MPH may lead to ST-elevation myocardial infarction, as reported in a case of an abuser who concocted a home-made solution from MPH tablets and injected himself intravenously (Hay et al, 2015).

Methylphenidate effects on postural stability

Methylphenidate may have an effect on the cerebellum in addition to other central nerve areas, and may influence postural balance. In older adults a single dose of MPH showed improvement in walking and postural stability, which according to the authors may have been related to an attention effect but also directly on the motor system (Shorer et al, 2013; Jacobi-Polishook, Shorer, & Melzer, 2009). Sway in children with ADHD was significantly higher in those without MPH treatment than with controls (Bucci et al, 2014). The authors measured postural stability using a platform with a strain gauge, consisting of two dynamometric clogs. The centre of pressure (CoP) deviations were recorded.

One tool used in sport science and concussion testing, and management, is the Biodex Balance™ (Intertek, 2010, United States of America). Modified Clinical Test of Sensory Integration of Balance

(mCTSIB) is a dynamic and objective measure of this and uses a force plate to challenge and remove sensory inputs. This equipment consist of a platform with sway strain gauges and tests visual, vestibular and somatosensory feedback systems under four sensory conditions. As the test difficulty increases the degree of balance impairment increases in concussion patients (Guskiewicz, 2011). Recovery of balance changes is used to manage return to play in diffuse brain trauma (concussion). Application of this measurement before and after use of MPH will objectively determine any drug effects on postural balance.

This study therefore aims to assess the physiological and physical effects, if any, of the stimulant methylphenidate in children over the age of 6 years and adults with ADHD. The knowledge gained will add to that in the domain of treating ADHD, and also to the sporting community and authorities with regards to the use of MPH in sport.

Problem statement

The use of methylphenidate is common amongst athletes at all levels, both in those that require the treatment for diagnosed ADHD, and in some that use it for its stimulant effects as a doping agent or to improve cognitive function in work/academics. As a prohibited substance in the stimulant class, the concern of whether it unduly enhances performance in those taking it and thus creating an unfair advantage; or whether it poses cardiac health risks in exercising individuals, has not been clearly established. To further determine whether there are physical and physiological deficiencies in persons with ADHD that are corrected with MPH treatment, and thus clearly defining the therapeutic use exemption concept can enhance the tasks of WADA and TUE committees in their management of MPH TUE applications.

Aims:

To determine whether participants diagnosed with ADHD and using methylphenidate have significant changes in:

a. physiological parameters
b. neurocognitive function
c. balance

d. physical performance

Objectives:

The objectives of the study are to measure the effects of methylphenidate before the use of and whilst on treatment, on:

a. heart rate, blood pressure, maximum oxygen consumption, electrocardiography
b. psychometric tests
c. balance
d. muscle strength

HYPOTHESIS:

H0: there is no meaningful clinical difference between pre dosage and post dosage tests.

H1: there is a relevant difference between the pre dosage and post dosage tests.

METHODS

RESEARCH DESIGN

This is a prospective longitudinal descriptive and intervention randomised double-blind cross over control study of the effect of Methylphenidate Hydrochloride in drug-naïve children and adults diagnosed with ADHD. Testing will comprise assessments to ascertain if MPH affects the outcomes as per the aims and objectives of the study, over a 4 week period (Appendix A), using participants as their own controls

STUDY POPULATION

The study population are people based in Johannesburg. Psychiatrist and paediatric practices based in Johannesburg that specialise in ADHD conditions will be approached and their patients will comprise the population to be invited to participate. These practices will primarily be identified through the Attention Deficit Hyperactivity Disorder Support Group of South Africa (ADHASA). The study population will include children and adults. The last reported data are that In 2004 in the suburban Johannesburg area there were over 13 000 patients on treatment for ADHD with

stimulant medication looking at prescriptions/dispensed medication; but did not confirm the diagnosis of ADHD as it did not depend on ICD10 coding (Truter, 2009). In addition the study population will target healthy adults, who will be invited to participate.

Sample size

The study will consist of an analysis of continuous response variables within participants during treatment with methylphenidate or placebo. To determine differences between two-tailed independent means of two groups with a probability (power) of 0.8 (80%), an effect size of 0.5 and α-error probability of 0.05, the sample size was determined using G*Power to be 64 (Faul et al, 2007). To account for drop-out and non-compliance, the sample size will be 35 in each group; with 35 in the children ages and 35 in adult age groups.

Selection of participants

Patients being treated by specialist psychiatrists or paediatricians treating patients with ADHD in the Johannesburg area will be invited to participate in the study. The study groups will be as follows: group 1 grades 8-12 aged 14-17 years (n=35), and adults (over 18 years) (n=35) who are MPH-naïve, or at first diagnosis and have not yet started on treatment will be informed of the study by the psychiatrists or paediatricians, and if interested will be contacted by the researcher. Otherwise healthy adults, especially staff and students at the university will be invited to participate through university email channels and posters and social media. Details of the study will be provided, in addition to written information (Appendix B). If agreeable, the participants or parents/guardians of child participants will sign informed consent before participating in the study (Appendix C). Children will sign informed assent (Appendix D). Participants in the different age groups will randomly be given either active MPH drug or placebo to take for a 2-week period, followed by 3 day washout and then the other substance, either placebo or active MPH. The time frames have been formulated on the short half-lives and clinical responses of the drug. The participants will act as their own controls and outcome measures will be assessed whilst on placebo or MPH and compared. The placebo will be manufactured with the assistance of the Department of Pharmacy and Pharmacology in such a way that the placebo will look identical to the active drug, or both active and placebo ingredients will be formulated into capsules to look identical.

Inclusion criteria

Newly diagnosed ADHD children or adults who have not yet started taking the prescribed methylphenidate, or have been drug-naïve for at least 6 months

1. Between the ages of 14- 30 years
2. Participants will be willing to accept that placebo/inactive formulation will be administered for 2 weeks
3. Participants will be willing to volunteer to undergo non-invasive investigations and assessments

Healthy adults with no contraindications to taking stimulants.

Exclusion criteria

1. The use of any other medication that may affect physical performance, electrocardiogram tracings or balance
2. Any physical or other affliction that may affect the successful completion of the physical performance tests

Site of study

The site of study will be at the Centre for Exercise Science and Sports Medicine, on the Wits Education Campus in Parktown, Johannesburg.

Measuring tools/instruments

After the participants have signed informed consent they will undergo the test battery prior to starting the prescribed medication. The participants will then be permitted to start their study treatment. Two weeks post treatment with an effective dose (based on treating specialist clinical response assessment), the tests will be repeated at a similar time of day as the pre-tests. The start dates and end dates of the study will be different for each individual subject as their entry into the programme will depend on the referral date. A physical activity readiness and cardiac health risk screening questionnaire as well as a physical activity questionnaire (Appendix E) will be completed

before testing takes place and at the 4week re-evaluation. During the two weeks no guidance or interference in physical activity levels will take place, and the participants and controls will be allowed to continue physical activities as they would have. They will be asked to keep an activity log (appendix F). Similarly, diets and eating habits will not be altered.

Randomisation and substance crossover

The Department of Pharmacy and Pharmacology will label two envelopes for each of the children and each of the adult participants. These will be randomly assigned and filled with either active drug or placebo into each one and a record kept of what is in envelope 1 and what is in envelope 2, that will be handed over to the researcher at the end of the study to be decoded for data analysis. The researcher will be given two envelopes for each participant, labelled e.g. patient 1, envelope 1; patient 1, envelope 2, that will be administered in that sequence.

Biographical and medical details

Participant details will be recorded (Appendix G).

Anthropometric and Physiological parameters

Anthropometry: With the participants barefoot and wearing shorts and t-shirts, body height will be measured using a Seca GmbH stadiometer (Hamburg, Germany) and body mass with a Seca scale GmbH (Hamburg, Germany). These measurements will be used to calculate BMI ($\frac{m}{h^2}$). Waist circumference (cm) will be measured using a tailor's tape measure to the nearest cm. This will be performed with participant I standing position with tape placed horizontally near umbilicus at widest anterior extension of the abdomen (American College of Sports Medicine, 2017). In the children, particularly for the older children who may be approaching puberty at the start of the study, "maturity offset" will be calculated so that if the onset of peak height velocity happens to coincide with the study period, there may be differences in the pre-post measurements which cannot be accounted for. Maturity onset can be predicted by measuring standing height and sitting height. (Mirwald, baxter-Jines, Bailey, & Beunen, 2002)

Physiological parameters will be measured as follows: heart rate – after 5 minutes rest and

taken from the electrocardiogram (ECG). Blood pressure measured manually on non-dominant arm, in a seated position using an aneroid sphygmomanometer (C.Baum and Co, Corague, New York, USA) and stethoscope (3M™Littman® Cardiology, St Paul, Minnesota, USA).

Using a Wattbike® (Woodway, Waujesha, Wisconsin, USA), a Wattbike® ramp test protocol will be used for adults and will be used to determine the following parameters: maximum minute power (MMP), maximum heart rate (MHR), power to weight ratio, VO_2max estimate, METs (metabolic) equivalents representing the intensity of the test) (Appendix H).

A graded treadmill exercise test will be used for children using the British Columbia Children's Hospital protocol for children (Duff et al, 2017). Extrapolation of data will determine similar parameters as those from the Wattbike® test.

The tests will be terminated if participants reach ≥85% HRmax (220-age) or 70% of heart rate reserve (Heart Rate Reserve = Maximum Heart Rate – Resting Heart Rate) or if signs and symptoms are present during the graded test. No verbal encouragement will be provided throughout the test to ensure standardisation. Whilst doing the graded exercise tests, electrocardiogram tracings will be recorded. These will be pre-exercise (rest), continuous during the test and post-test up to 5 minutes (and longer if any abnormalities are noted). The electrocardiogram (QRS-Card™ Stress PC Digital ECG system, Let Medical Systems Corp., Florida, USA) will be performed using a standard 12-lead approach with chest and limb electrodes. The ECG tracings will be screened by the researcher, and if any show abnormalities, will be reviewed by a specialist cardiologist, In addition the cardiologist will do random checks on all ECG tracings.

Postural balance will be measured using the Biodex Balance system on which four tests will be administered using a mCTSIB. This tests visual, vestibular and somatosensory feedback systems under four sensory conditions.

Four situations in which the Biodex Balance System tests using the mCTSIB

Eyes Open, Firm Surface	Provides a baseline. Information available by all three sensory inputs: Somatosensory, visual and vestibular
Eyes Closed, Firm Surface	Visual not available; somatosensory and vestibular are available. If the athlete performs poorly, the vestibular or somatosensory may be compromised, with an increase in visual dependency.
Eyes Open, Unstable Surface	Somatosensory compromised; visual and vestibular are available. If the athlete performed poorly, visual or vestibular may be compromised, with an increase in somatosensory dependency.
Eyes Closed, Unstable Surface	Visual not available; somatosensory compromised, only vestibular available. Concussed athletes are most likely to present problems in this condition. If performance is reduced beyond normal or baseline readings, the vestibular system may be disrupted.

Physical parameters: Muscle strength will be determined by handgrip strength (kg) on the dominant side using (Grip-D grip strength dynamometer, Takei Scientific Instruments Company, Japan). Lower extremity power will be measured using Vertical counter movement jump, and will be recorded to the nearest millimetre using a flight-time based jump mat (Fusion Sport Smart Jump mat, Fusion Sport, 2 Henley ST, Coopers Plains, QLD, 4108, Australia) and Smart Jump PDA (HP IPAQ 112, Hewlett Packard Company, Palo Alto, CA 94304)). This has been used in adults and in children with reliability (Alricsson et al, 2001; Markovic et al, 2004).

Psychometric tests: ImPACT® is a computer-administered neuropsychological test battery that uses seven individual test modules that assess attention, verbal visual memory and learning, numerical sequencings, process speed and reaction time, therefore analysing six neurocognitive areas (Khurana & Kaye, 2012). ImPACT® was developed and has been used in concussion testing, and yields a post-concussion symptom scale (PCSS) that consists of twenty-two symptoms that are linked with concussion, grading these symptoms from zero (asymptomatic) to six (severely symptomatic). Athletes are required to self-report on these symptoms. When performing an ImPACT® test an individual who has a faster reaction time and a lower symptom score (as in concussion) suggests a better response and higher scores for verbal and visual memory and visual motor processing speed indicates better performance (Majerske, Mihalik, Ren, Collins, Reddy, & Wagner, 2008) (Majerske et al., 2008). Iverson et al., (2004) showed that athletes who sustained multiple concussions showed increased symptoms and lower memory scores. Therefore use of the ImPACT® can determine the extent of the concussion on the relevant brain areas (Majerske et al., 2008). The use of the ImPACT® in this study will be used to measure

changes in neurocognitive function that MPH may have. In addition the Stroop test will be used as an online tool (Stroop, 1935). This test has been used and validated in general and sport for general cognitive function (Chang, et al., 2015) (Gapin, Labban, Bohali, Wooten, & Chang, 2015), including preadolescents (Buck, Hillman, & Castelli, 2008). The Stroop test utilises 5 conditions (congruent, Stroop word, Stroop square, Stroop neutral, and Stroop incongruent) using words and colours.

Academic and sport performances: In order to assess changes in vivo changes before the use of and whilst on treatment, and compare to controls, academic and sporting performance records (as previously used by the South African Institute for Drug Free Sport and modified for the research by excluding superfluous information) will be kept by the participants and/or their parents/.guardians to be completed at start of study, midpoint and endpoint by the treating doctor (appendix I) and participants (appendix J).

Data analysis:

Data (Appendix K) will be captured on an Excel spreadsheet, with coding to prevent identification of individual participants. Data will be analysed using the STATISTICA V13 software package (INC StatSoft - Tulsa, USA, 2001). Statistical significance will be set at $P < 0.05$. Descriptive data will be presented as mean (95 CIs) for categorical data, and mean (SD) for normally distributed data or median (inter-quartile range) for non-parametric data.

The normality of continuous variables will be analysed using Kolmogorov-Smirnov test. The chi-square test or the Fisher's exact test will be used for the comparison of dichotomous variables between the groups; Student's t test will be used for the comparison of normally distributed continuous variables, and Mann-Whitney U test for the variables with non-normal distribution. For intragroup comparisons of continuous variables, paired t-test will be used for normally distributed variables and Wilcoxon's test for variables with non-normal distribution to measure the difference in the mean between baseline and post data. The difference between baseline and post-study period will be presented as effect sizes and the differences between study groups and controls will be determined using ANOVA. Magnitude based inferences will be used for changes (batterham & Hopkins, 2006). Typical error of measurements will be calculated for outcome variables (Mann, Lamberts, & Lambert, 2014).

Ethical considerations

Ethical clearance for this study will be obtained from the HREC (Human Research Ethics Committee-Medical, of the University of Witwatersrand) before the start of the study. Each participant will be requested to sign an informed consent form or assent + parent/guardian consent prior to the commencement of the study. Participants will also be informed that they can withdraw from the study at any stage. The study will be conducted following standard ethical guidelines such as confidentiality, privacy and anonymity. Participants will be assigned a code, and outcome measures will record the code and not identifiable information. Codes will be kept separate in a secure location.

Data will be stored safely in a secure environment by the researcher for a period of five years after which all information will be destroyed.

Budget:

Funding is available from a grant from the National Lottery Distribution Trust Fund.

Description	**Units**	**Balance**	**Total**
Printing (information sheets, consent forms, posters, data capturing sheets)	• 45c per page x ±250 • Posters R10 x 5	R170	R170
ECG electrodes	70 x2 x 10 = 1400 x 70c	R980.00	R1150
ECG printouts	70 x2 = 140 x 45c	R63.00	R1213
Biodex balance printouts	70 x2 = 140 x 45c	R63.00	R1276
Ink cartridges (Biodex printing)	2 x R400	R800	R2076
ImPACT® psychometric testing (cost of online test)	70 X 2 X R200	R28 000	R30 076
Methylphenidate and placebo	70 x R200	R14 000	R44 076
Miscellaneous		R2000	R46 076.00
TOTAL			**R46 076.00**

Timeframes:

	2017			2018										2019
	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Finalising Protocol															
Ethics Application															
Protocol Assessment															
Collecting Data															
Data Analysis															
Writing-up Thesis															
Submission															

References

Abramovitch, A., Goldsweig, G., & Schweiger, A. (2013). Correlates of Pphysical activitywith intrusive thoughts,worry and impulsivityin adults with attention deficit/hyperactivity disorder: a cross sectional pilot study. *Isr J PsychiatryRealt Sci, 50*(1), 47-54.

Alricsson, M., Harms-Ringdahl, K., & Werner, S. (2001). Reliability of sports related functional tests with emphasis on speed and agility in young athletes. *Scand J Med Sci Sports*(11), 229-232.

American College of Sports Medicine. (2017). *Complete Guide to Fitness & Health* (Second ed.). (B. Bushman, Ed.) CHampaigne, Ill, USA: ACSM.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

Andersen, S., & Navalta, C. (2004). Altering the course of neurodevelopment: a framework for understanding the enduring effects of psychotropic drugs. *Int J Devl Neuroscience, 22*, 423-440.

Arcien, R., Germinario, E., Bonati, M., Masi, G., Zudda, A., Vella, S., et al. (2012). Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. *J Child Adolesc Psychopharmacol*(6), 423-431.

Associated Press. (2009, January 10). *kwese.espn news*. Retrieved Feb 2, 2018, from kwese.espn: http://kwese.espn.com/mlb/news/story?id=3822193

Bar-Or, O., & Rowland, T. (2004). *Pediatric Exercise Medicine: From Physiologic Principles to Health Care Application.* Champaign, Ill: Human Kinetics.

Batterham, A., & Hopkins, W. (2006). Making meaningful inferences about magnitudes. *Int J Sports Phys Performance, 1*(1), 50-57.

Biederman, J. (2005). Attention-Deficit/Hyperactivity Disorder: A Selective. *Biol Psychiatry*(57), 1215-1220.

Biederman, J., Mick, E., Fried , R., Wilner, N., Spencer, T., & Faraone, S. (2011). Are stimulants effective in the treatment of executive function deficits? Results from a randomized double blind study of OROS-methylphenidate in adults with ADHD. *Eur Neuropsychopharm, 21*, 508-515.

BoxRec. (2017). *BoxRec /Mikhail_Aloyan*. Retrieved 2018, from BoxRec: http://boxrec.com/media/index.php/Mikhail_Aloyan

Bradley, C. (1937). The behavior of children receiving benzadrine. *Am J Psychiatry, 94*, 577-584.

Brossard-Racine , M., Shevell , M., Snider, S., Belanger , S., & Majnemer, A. (2012). Motor skills of children newly diagnosed with Attention Deficit. *Res Dev Disabil* (33), 2080-2087.

Bucci, M., Seassau, M., Larger, S., Bui-Quoc, E., & Gerard, C.-L. (2014). Effect of visual attention on postural control in children with attention-deficit/hyperactivity disorder. *Res Dev Disabil* (35), 1292-1300.

Buck, S., Hillman, C., & Castelli, D. (2008). The relation of aerobic fitness to Stroop task performance in preadolescent children. *Med Sci Sports Exerc, 40*(1), 166-172.

Caci, H., Doepfner, M., Asherson, P., Donfrancesco, R., Faraone, S., Hervas, A., et al. (2014). Daily life impairments associated with self-reported childhood/adolescent attention-deficit/hyperactivity disorder and experiences of diagnosis and treatment: Results from the European Lifetime Impairment Survey. *Eur Psychiatr*(29), 316-323.

Castellanos, F., & Lee, P. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Med Assoc, 288*, 1740-1748.

Center for Substance Abuse Research: Ritalin. (2015). Retrieved September 2017, from University of Maryland: http://www.cesar.umd.edu/cesar/drugs/ritalin.asp

Centers for Disease Control and Prevention. (2016). *Attention Deficit/Hyperactivity Disorder (ADHD)*. Retrieved July 14, 2017, from Centers for Disease Control and Prevention: https://www.cdc.gov/ncbddd/adhd/diagnosis.html

Chang, E.-H., Chu, C.-H., Karageorghis, C., Wang, C.-C., Tsai, J.-C., Wang, Y.-S., et al. (2015). Relationship between mode of sport training and general cognitive function. *J Sport Health Sci, 6*(1), 89-95.

Cubillo, A., Halari, R., Smith, A., Taylor, E., & Rubia, K. (2012). A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder(ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex, 48*, 194-215.

del Campo, N., Chamberlain, S., Sahakian, B., & Robbins, T. (2011). The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol Psych, 69*, 145-157.

Diamond, A. (2005). Attention-deficit disorder (attention-deficit/hyperactivity disorder without hyperactivity): A neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity). *Dev Psychopath, 17*(3), 807-825.

Duff, D., De Souza, A., Human, D., Potts, J., & Harris, K. (2017). A novel treadmill protocol for exercise testing in children: the British Columbia Children's Hospital protocol. *BMJ Open Sport Exerc Med*(3), 1-7.

Eubig, P., Aquiar, A., & Schantz, S. (2010). Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. *Envir Health Perspect, 118*(12), 1654-1667.

Fancy Bears. (2016). *Fancy Bears' Hack Team*. Retrieved 2018, from Fancy Bears' Hack Team: https://fancybear.net/

Faraone, S., Biederman, J., Spencer, T., Wilens , T., Seidman , L., Mick, E., et al. (2000). Attention-Deficit/Hyperactivity Disorder in Adults: An Overview. *Biol Psychiatry*(48), 9-20.

Faraone, S., & Antshel, A. (2008). Diagnosing and treating Attention Deficit/Hyperactivity Disorder in adults. *World Psychiatry*(7), 131-136.

Faraone, S., & Biederman, J. (2005). What Is the Prevalence of Adult ADHD? Results of a Population Screen of 966 Adults. *J Attention Dis, 9*(2), 384-391.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods, 39*(2), 175-191.

Gapin, J., Labban, J., Bohali, S., Wooten, J., & Chang, Y. (2015). Acute exercise is associated with specific executive functions in college students with ADHD: a preliminary study. *J Sport Health, 4*, 89-96.

Green, J., Olenick, A., Eastep, C., & Winchester, L. (2017). Caffeine influences cadence at lower but not higher intensity RPE-regulated cycling. *Phys and Behav*(169), 46-51.

Guskiewicz, K. (2011). Balance Assessment in the Management of Sport-Related Concussion. *Clinic of Sports Med*(30), 89-102.

Gymnastics Canada. (2015). *Gymcan National Teams*. Retrieved 2018, from Gyamnastics Canada.

Hammerness, P., Fried, R., Petty, C., Meller, B., & Biederman, J. (2014). Assessment of cognitive domains during treatment with OROS methylphenidate in adolescents with ADHD. *Child Neuropsychol, 20*(3), 319-327.

Hammerrness, P., Wilens, T., Mick, E., Spencer, T., Doyle, R., McCreary, M., et al. (2009). Cardiovascular effects of longer-term, high dose OROS Methylphenidate in adolescents with attention deficit hyperactivity disorder. *J Pediatr, 155*, 84-89.

Hay, E., Shklovski, V., Blaer, Y., Shlakhover, V., & Katz, A. (2015). Intravenous methylphenidate: an unusual way to provoke ST-elevation myocardial infarction. *Am J Em Med*(33), 313a1-313a3.

Heinonen, K., Raikonen, K., Pesonen, A.-K., Andersson, S., Kajantie, E., Eriksson, J., et al. (2010). Behavioural symptoms of attention deficit/hyperactivity disorder in preterm and term children born small and appropriate for gestational age: A longitudinal study. *BMC Pediatrics, 10*(91), 1-8.

Hellwig-Brida, S., Daseking, M., Keller, F., Petermann, F., & Goldbeck, L. (2011). Effects of methylphenidate on intelligence and attention components in boys with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol, 21*(3), 245-253.

Huang, S., Hu, H., Sanchez, B., Peterson, K., Ettinger, A., Lamadrid-Figueroa, H., et al. (2016). Childhood Blood Lead Levels and Symptoms of Attention Deficit hyperactivity. *Environ Health Perspect, 124*(6), 868-874.

Huang, Y.-S., Chao, C.-C., Wu, Y.-Y., Chen, Y.-Y., & Chen, C.-H. (2007). Acute effects of methylphenidate on performance during the Test of Variables of Attention in children with attention deficit/hyperactivity disorder. *Psych and Neurosci, 61*(3), 219-225.

Huang, Y.-S., Wang, L.-J., & Chen, C.-K. (2012). Long-term neurocognitive effects of methylphenidate in patients with attention deficit hyperactivity disorder, even at drug-free status. *BMC Psychiatry, 12*(194), 1-7.

Jacobi-Polishook, T., Shorer, Z., & Melzer, I. (2009). The effect of methylphenidate on postural stability under single and dual task conditions in childen with attention deficit hyperactivity disorder- a double blind randomized control trial. *J Neurol Sci*(280), 15-21.

Janssen Products . (2013). Retrieved 2017, from Concerta: http://www.janssen.com/southafrica/sites/www_janssen_com_southafrica/files/product/pdf/concerta_pi_april_2013_0.pdf

Johnson, S., Hollis C, Kochhar, P., Wolke , D., & Marlow, N. (2010). Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. *J Am Acad Adolesc Psychiatry, 49*(5), 453-463.

Karpuz, D., Hallioglu, O., Toros, F., & Tasdelen, B. (in press). The effect of methylphenidate, risperidone and combination therapy on ECG in children with attention-deficit hyperactivity disorder. *J Electrocard*.

Khurana, V., & Kaye, A. (2012). An overview of concussion in sport. *J Clin Neurosci*(19), 1-11.

Khurana, V., & kaye, A. (2012). Concussion in Sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J Clin Neurosci*(19), 1-11.

Kim, H., Heo, H.-I., Kim, D.-H., Ko, I.-G., Lee, S.-S., Kim, S.-E., et al. (2011). Treadmill exercise and methylphenidate ameliorate symptoms of attention deficit/hyperactivity disorder through enhancing dopamine synthesis and brain-derived neurotrophic factor expression in spontaneous hypertensive rats . *Neuroscience letters*(504), 35-39.

Klorman, R., Brumaghin, J., Fitzpatrick, P., Borgstedt, A., & Strauss, J. (1994). Clinical and cognitive effects of methylphenidate on children with attention deficit disorder as a function of aggression/oppositionality and age. *J Abnorm Psychol, 103*, 216-219.

Koblan, K., Hopkins , S., Sarma, K., Gallina, N., Jin, F., Levy-Cooperman, N., et al. (2016). Assessment of human abuse potential of dasotraline compared to methylphenidate and placebo in recreational stimulant users. *Drug and Alc Dep*(159), 26-34.

Krusch, D., Klorman, R., Brumaghim, J., Fitzpatrick, P., Borgstedt, A., & Strauss, J. (1996). Methylphenidate slows reactons of children with Attention Deficit Disorder during and after an error. *J Abnorm Child Psychol, 24*, 633-650.

Lee, S.-H., Song, D.-H., Kim, B.-N., Joung, Y., Ha, E., Cheon, K.-A., et al. (2009). Variability of Response Time as a Predictor of Methylphenidate Treatment Response in Korean Children with Attention Deficit Hyperactivity Disorder. *Yonsei Med J , 50*(5), 650-655.

Lepping, P., & Huber, M. (2010). Role of zinc in the pathogenesis of attention-deficit hyperactivity disorder: implications for research and treatment. *CNS Drugs, 24*(9), 721-728.

Majerske, C., Mihalik, J., Ren, D., Collins, M., Reddy, C., & Wagner, M. (2008). Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. . *J Athl Training*, 265-274.

Mann, T. N., Lamberts, R. P., & Lambert, M. I. (2014). Day-to-day variation in heart rate recovery post-exercise oxygen consumption after a submaximal treadmill protocol. *Int J Sportsmed, 15*(4), 352-364.

Markovic, G., Dizdar, D., Jukic, I., & Cardinale, M. (2004). Reliability and factorial validity of squat and countermovement jump tests. *J Strnegth and Conditioning Res, 18*(3), 551-555.

Martinez-Raqa, J., Knecht, C., Szerman, N., & Martinez, M. (2013). Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. *CNS Drugs*(1), 15-30.

McCarthy, S., Cranswick, N., Potts, L., Taylor, E., & Wong, I. (2009). Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the general practice research database. *Drug Safety, 32*(11), 1089-1096.

Mirwald, R., baxter-Jines, A., bailey, D., & Beunen, G. (2002). An onset of maturity from anthropometric measurements. *Med Sci Sports Ex, 34*(4), 689-694.

Olfson, M., Huang, C., Gerhard, T., Winterstein, A., Crystal, S., Allison, P., et al. (2012). Stimulants and cardiovascular events in youth with Attention Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiat, 51*(2), 147-156.

Olympics. (2017). *Olympics.org/michael-phelps*. Retrieved 2018, from Olympics.org: https://www.olympic.org/michael-phelps

Paratz, E., Cunningham, N., & MacIsaac, A. (2016). The cardiac complications of methamphetamines. *Heart, Lung Circ*(25), 325-332.

Peloquin, L., & Klorman, R. (1986). Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. *J Abn Psychol, 95*, 88-98.

PGA Tour Players. (2018). Retrieved 2018, from PGA Tour: https://www.pgatour.com/players/player.34360.patrick-reed.html

Potočnjak, I., Degoricija, V., Vukicevic Baudoin, D., Culig, J., & Jakovljevic, M. (2016). Cardiovascular side effects of psychopharmacologic therapy. *Int J Cardiol*(219), 367-372.

Rapoport, J., Buchsbaum, M., Weingartner, H., Zahn, T., & Ludlow, C. (1980). Dextroamphetamine : Cognitive and behavioral effects in normal and hyperactive boys and normal men. *Arch Gen Psychiatry, 37*, 933.

Robbins, T., & Sahakian, B. (1979). Paradoxical effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behvavioural pharmacology. *Neuropharmacol, 18*, 931-950.

Rubia, K., Halari, R., Cubillo, A., Mohammad, A.-M., Brammer, M., & Taylor, E. (2009). Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task. *Neuropharmacol, 57*, 640-952.

Rubia, K., Halari, R., Mohammed, A.-M., Taylor, E., & Brammer, M. (2011). Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder. *Biol Psych, 70*, 255-262.

Satterfield, J., Swanson, j., Schell, A., & Lee, F. (1994). Prediction of Antisocial Behavior in Attention-Deficit Hyperactivity Disorder Boys from Aggression/Defiance Scores. *Psychiatry, 33*(2), 185-190.

Scheel-Kruger, J. (1971). Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. *Eur J Pharmacol, 14*, 47-59.

Shorer, Z., Bachner, Y., Guy, T., & Melzer, I. (2013). Effect of single dose methylphenidate on walking and postural stability under single and dual task conditions in older adults - a double-blind randomized control trial. *J Gerontol A Biol Sci Med Sci, 68*(10), 1271-1280.

Shuster, J., & Olfson, M. (2012). Cardiovascular safety of central nervous system stimulants in children and adolescents : population based cohort study. *BMJ*(345), e4627.

Sobanski, E., Retz, W., Fischer, R., Ose, C., Alm, B., Hennig, O., et al. (2014). Treatment adherence and persistence in adult ADHD: Results from a twenty-four week controlled clinical trial with extended release methylphenidate. *Eur Psych*(29), 324-330.

Sokunbi, M., Fung, W., Sawlani, V., Choppin, S., Linden, D., & Thome, J. (2013). Resting state fMRI entropy probes complexity of brain activity in adults with ADHD. *Psych Res: Neuroimaging*(214), 341–348.

Solanto, M. (1998). Neuropharmacological mechanisms of stimulant drug action in attention deficit hyperactivity disorder: a review and integration. *Behav Brain Res, 94*, 127-152.

Speech, T., Rao, S., Osmon, D., & Sperry, L. (1992). A double-blind controlled study of methylphenidate treatment in closed head injury. *Brain Inj*(4), 333-358.

Stiefel, G., & Besag, M. (2010). Cardiovascular Effects of Methylphenidate, Amphetamines and Atomoxetine in the Treatment of Attention-Deficit Hyperactivity Disorder. *Drug Safety, 33*(10), 821-842.

Stroop, J. (1935). Studies of interference in serial verbal reactions. *J Exp Psychol, 18*, 643-662.

Surman, C., Hammerness, P., Pion, K., & Faraone, S. (2013). Do stimulants improve functioning in adults with ADHD? A review of the literature. *Europ Neuropsychopharmacology*(23), 528-533.

Swart, J., Lamberts, R., Lambert, M., St Clair Gibson, A., Lambert, E., Skowno, J., et al. (2009). Exercising with reserve: Evidence that the CNS regulates prolonged exercise performance. *B J Sports Med*(43), 782-788.

SwimSwam. (2018). *SwimSwam bio jack-conger*. Retrieved 2018, from SwimSwam: https://swimswam.com/bio/jack-conger/

Team USA. (2018). *Team USA fiedl-hockey/athletes*. Retrieved 2018, from Team USA: https://www.teamusa.org/usa-field-hockey/athletes/kelsey-kolojejchick

Team USA. (2018). *Team USA -gymnastics/athletes/Simone-Biles*. Retrieved 2018, from Team USA: https://www.teamusa.org/usa-gymnastics/athletes/Simone-Biles

Team USA. (2018). *Team USA-diving/athletes/Sam-Dorman*. Retrieved 2018, from Team USA: https://www.teamusa.org/usa-diving/athletes/Sam-Dorman

Team USA. (2018). *Team USA-water-polo/athletes/McQuin-Baron*. Retrieved 2018, from Team USA: https://www.teamusa.org/usa-water-polo/athletes/McQuin-Baron

Truter, I. (2009). Prescribing of methylphenidate to children. *Family Practice, 51*(5), 413-417.

U.S . Department of Justice. (1995). *Drug Enforcement Administration Report on Methylphenidate (Ritalin).* Drug and Chemical Evaluation Section. U.S . Department of Justice.

Westover, A., Nakonezny, P., Barlow, C., Vongpatanasin, W., Adinoff, B., Brown, E., et al. (2015). Exercise outcomes in prevalent users of stimulant medications. *J Psych Res*(64), 32-39.

White, R., Harris, G., & Gibson, M. (2013). Attention deficit hyperactivity disorder and athletes. *Sports Health, 6*(2), 149-156.

Winterstein, A., Gerhard, T., Kubilis, P., SaidiA, Linden, S., Crystal, S., et al. (2012). Cardiovascular safety of central nervous system stimulants in children and adolescents: population based cohort study. *BMJ*(345), 1-12.

WNBA. (2018). *WNBA/player/brittney-griner*. Retrieved 2018, from WNBA: http://www.wnba.com/player/brittney-griner/#/bio

WNBA. (2018). *WNBA/player/elena-delle-donne*. Retrieved 2018, from WNBA/player: http://www.wnba.com/player/elena-delle-donne/#/bio

World Anti Doping Agency. (2006). *2006 Adverse Analytical Findings Reported by Accredited Laboratories.* Montreal: WADA.

World Anti Doping Agency. (2016). *2015 Anti-Doping Testing Figures Samples Analyzed and Reported by Accredited Laboratories in ADAMS.* Montreal: World Anti Doping Agency.

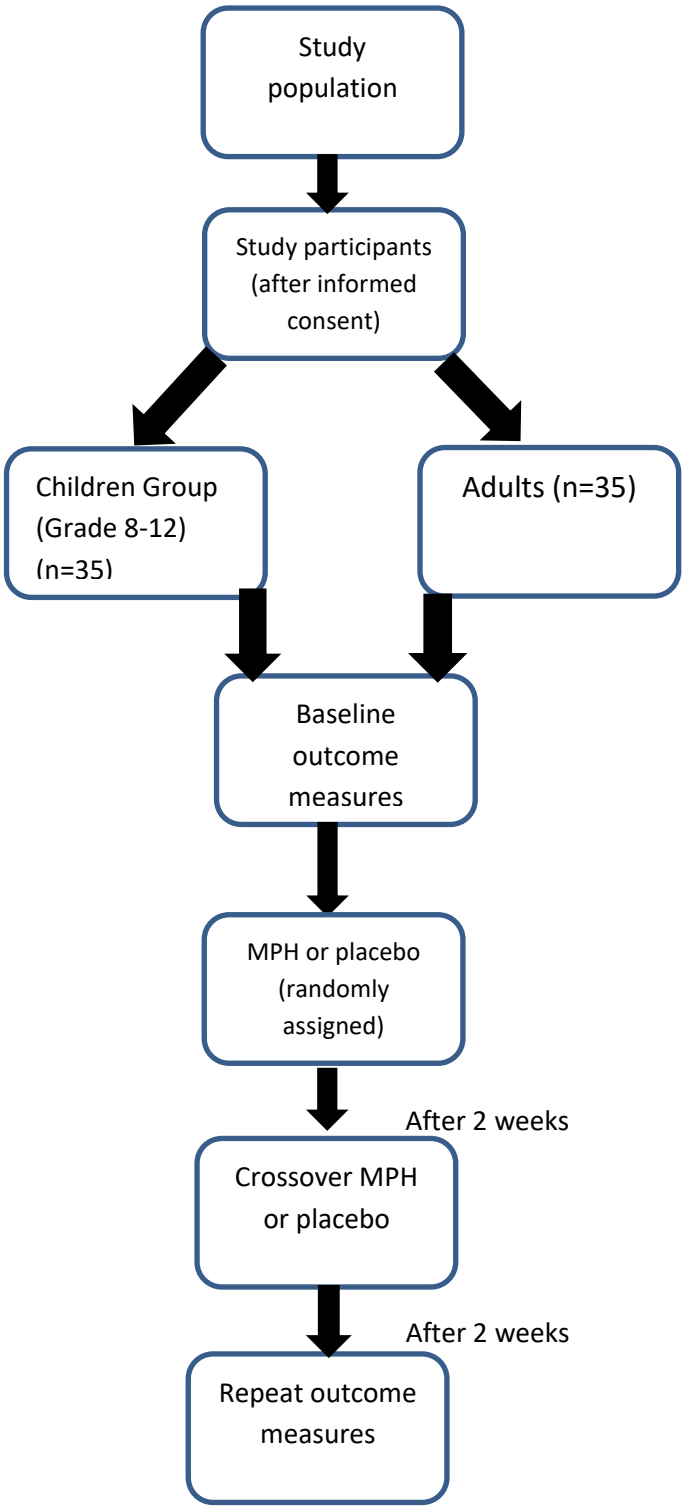
World Anti-Doping Agency. (2017). *The Prohibited List*. Retrieved September 5, 2017, from World Anti-Doping Agency: https://www.wada-ama.org/en/what-we-do/the-prohibited-list

World Anti-Doping Agency. (2017). *Therapeutic Use Exemption*. Retrieved September 10, 2017, from World Anti-Doping Agency: https://www.wada-ama.org/en/resources/search?k=TUE&search-category=resources&op=Search&f%5B0%5D=field_topic%3A161

World Health Organisation. (1992). International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Geneva: World Health Organisation.

Zheng, J., Zhao, W., Xu, K., Chen, Q., Chen, Y., Shen, Y., et al. (2017). Interaction among hERG channel blockers is a potential mechanism of death in caffeine overdose. *Europ J Pharmacol, 800*, 23-33.

Appendix A: Study flow



Appendix B: Information Document for adult participants and parents/guardians

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Study title: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

Good day. My name is Demitri Constantinou, and I am doing a PhD at the University of the Witwatersrand.

In this study we will be answering questions about the effects of methylphenidate on aspects of human function. These will include the control of the heart, muscle strength and aerobic fitness, balance, and conscious mental processes.

Invitation to participate: We are inviting you to take part in this research study (or asking for your permission to include your child in a research study).

What is involved in the study

The study will involve several tests to be conducted on you / your child before treatment by the specialist has started. The participants will be randomly divided into two groups –children age group (grades 8-12, ages 14-18 years) and adults (over 18 years). Each group will be randomly divided and given medication to take for 2 weeks. The medication will either be active methylphenidate (medication prescribed for attention deficit/hyperactivity) or placebo. A placebo is inactive medication. Neither the researcher nor the participant will know which medication will be provided so that tests are not influenced. The test will be repeated 2 weeks later. Then there will be a 3 day period of no medication and then the medication (either methylphenidate or placebo) will be swopped around so the same people will now take the other treatment for a further 2 weeks. A four week period is not a significant time to delay treatment of this chronic condition, but long enough for purposes of the study. The dosage should not be changed during the period of the study. The information derived may have a significant contribution to science. The results will be analysed to measure any changes.

The measurements will be performed at the Centre for Exercise Science and Sports Medicine on the Wits Education Campus in Parktown, Johannesburg. Unfortunately we will not be able to provide transport and request you make arrangements for this. The procedures will take approximately an hour to complete. You / your child will be one of approximately 70 people from the greater Johannesburg area participating in the study.

A questionnaire will be completed that includes medical and physical activity details, followed by the tests being performed.

The outcome measures are:

Anthropometric and Physiological parameters

Anthropometry: Height (m) and weight (kg). These will take less than 2 minutes to complete

Physiological parameters (about 20 minutes) Electrocardiogram (ECG) and heart rate – after 5 minutes rest and taken from the electrocardiogram (ECG). Blood pressure (mmHg)

The maximum minute power (MMP), maximum heart rate (MHR), power to weight ratio, VO_2max estimate, METs (metabolic equivalents) will be determined using a Wattbike® for adults and a graded treadmill exercise test will be used for children using the British Columbia Children's Hospital protocol for children (Duff et al, 2017). These tests start at slow speeds and intensities and are gradually increased

Postural balance (5 minutes) will be measured using the Biodex Balance system which involves standing on a platform which measures the balance with eyes open and with eyes closed.

Physical parameters (10 minutes) : Muscle strength will be determined by handgrip strength (kg) on the dominant side using. Leg power will be measured using a jumping test .

Psychometric tests (20 minutes) : ImPACT® is a computer-administered test that assesses attention, verbal visual memory and learning, numerical sequencings, process speed and reaction time, therefore analysing six neurocognitive areas (Khurana & Kaye, 2012. In this study the ImPACT® test will be used to measure changes in neurocognitive function that MPH may have. In addition the Stroop test will be used as an online tool using numbers and colours lso used for similar measures .

Academic and sport performances: In order to assess changes in academic and sporting performance records will be kept by the participants and/or their parents/guardians and the treating doctors to be completed at start of study, halfway and at the end.

Risks: All the tests are non-invasive. There are minimal risks, and no more than would be found in everyday activities. The most body stress activity will be walking and running for a short period of time on a treadmill or cycling. All precautions will be taken to ensure this is done safely. The researcher who will be conducting the testing is a qualified medical doctor. Should there be any injury, this will be assessed and managed by him. The placebo group would have a delay in their treatment for approximately 12

weeks, but this is not limb or life threatening and similar studies on many medications have been conducted in this way.

Benefits: There are no direct benefits being in the study; however there will be information on strength, aerobic fitness, electrocardiogram and health screening that may be provided to the individual (or parent/guardian). The participant will be given pertinent information on the study while involved in the project and after the results are available.

Participation is voluntary: Refusal to participate will involve no penalty and the subject may discontinue participation at any time without penalty.

Confidentiality: Every effort will be made to keep personal information confidential. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee and the South African Health Products Regulatory Authority (SAHPRA) (where appropriate).

Contact details of researcher/s: (for further information / reporting of study related adverse events) Demitri Constantinou. Tel. 011 717-3372 Fax. 086 63 63173. Email. demitri.constantinou@wits.ac.za

Contact details of supervisors: Prof Alan Rothberg, alan.rothberg@wits.ac.za and Prof Mike Lambert, mike.lambert@uct.ac.za

Contact details of Human Research Ethics Committee administrator and chair: (for reporting of complaints / problems). If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Professor Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC)(0114883820, clement.penny@wits.ac.za), or Ms Z Ndlovu / Mr Rhulani Mkansi – administrative officers. Telephone number; 011 717 2700/2656/1234/1252. Zanele.ndlovu@wits.ac.za; Rhulani.mkansi@wits.ac.za;
The ethics committee is an independent committee established to help protect the rights of research participants.

Appendix C: Informed Consent

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Research: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

INFORMED CONSENT

- I hereby confirm that I have been informed by the study primary investigator, Demitri Constantinou, about the nature, conduct, benefits and risks of the clinical study: *Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects*. I have also received, read and understood the above written information (Participant Information Leaflet) regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the primary researcher Demitri Constantinou
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT:

Printed Name Signature Date and Time

I, Demitri Constantinou, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

RESEARCHER:

Printed Name Signature Date and Time

Appendix D: Informed assent (Adult participants)

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Research Title: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

- I am volunteering on my own accord
- I confirm that the study details have been explained to me by the researcher
- I know that at any stage I can stop participating in the study
- I am aware that the results of the research study will be kept confidential and safe.
- I am aware that the results of the research study will be put into a study report and may be written up into academic reports
- I have had a chance to ask questions and (of my own free will) confirm that I am prepared to participate in the study

PARTICIPANT:

Printed Name Signature Date and Time

RESEARCHER:

Printed Name Signature Date and Time

Appendix E: PAR Q and Physical activity questionnaire



Physical Activity Readiness Questionnaire (PAR-Q)

PATIENT'S NAME: _____ **DOB:** _____

DATE: _____

HEALTHCARE PROVIDER'S NAME: _____

Please read the questions below carefully, and answer each one . Please check YES or NO.

☐ Yes	☐ No	Has your healthcare provider ever said that you have a heart condition and that you should only do physical activity recommended by a healthcare provider?
☐ Yes	☐ No	Do you feel pain in your chest when you do physical activity?
☐ Yes	☐ No	In the past month, have you had chest pain when you were not doing physical activity?
☐ Yes	☐ No	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐ Yes	☐ No	Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?

Excerpted from the Physical Activity Readiness Questionnaire (PAR-Q) © 2002. Used with permission from the Canadian Society for Exercise Physiology.

ACSM Risk Stratification Screening Questionnaire

Assess your health by marking all true statements.

You have had:

___ a heart attack
___ heart failure
___ cardiac arrhythmia
___ known heart murmur
___ congenital heart disease
___ any heart surgery
___ coronary angioplasty
___ heart palpitations

You have:

___ experienced chest pain with mild exertion
___ experienced dizziness, fainting, or blackouts with mild exertion
___ experienced unusual fatigue or shortness of breath during usual activities
___ been prescribed heart medications (please indicate):

Check all that apply:

___ you are a man older than 45 years
___ you smoke
___ your blood pressure is greater than 140/90
___ you take blood pressure medication
___ you are completely physically inactive
___ you currently have bone/joint problems
___ you have had a recent injury/surgery
___ you are a diabetic or take medicine to control your blood sugar
___ you have been diagnosed with high cholesterol >200 (or HDL is less than 35 mg/dL or LDL is greater than 169 mg/dL)
___ you have a close blood relative who had a heart attack before age 55 (father/brother) or age 65 (mother/sister)

___ Other (specify) _____

Use the following risk stratification scoring table (page) to sum the total number of risk factors present in your patient in determining their current level of cardiovascular disease risk.

Risk Stratification Scoring

Positive Risk Factors	Defining Criteria	Points
Age	Men ≥ 45 years, Women ≥ 55 years	+1
Family History	Myocardial infarction, coronary revascularization, or sudden death before 55 years of age in father of other 1st degree male relative or before 65 years of age in mother or other 1st degree female relative	+1
Cigarette Smoking	Current cigarette smoker or those who quit within the previous six months, or exposure to environmental tobacco smoke (i.e., secondhand smoke)	+1
Sedentary Lifestyle	Not participating in at least 30 minutes of moderate-intensity physical activity on at least three days/week for at least three months	+1
Obesity	Body mass index ≥30 kg/m^2 or waist girth >102 cm (40 inches) for men >88 cm (35 inches) for men	+1
Dyslipidemia	Low-density lipoprotein (LDL) cholesterol ≥ 130mg/dL (3.37 mmol/L) or high-density lipoprotein (HDL) cholesterol <40mg/dL (1.04mmol/L) or currently on lipid-lowering medication; If total serum cholesterol is all that is available, use serum cholesterol >200 mg/dL (5.18mmol/L)	+1
Prediabetes	Fasting plasma glucose ≥100 mg/dL (5.50 mmmol/L) but <126 mg/dL (6.93 mmol/L) or impaired glucoe tolerance (IGT) where a two-hour oral glucose tolerance test (OGTT) value is ≥140 mg/dL (7.70 mmol/L), but <200 mg/dL (11.00mmol/L)	+1
Negative Risk Factors	**Defining Criteria**	**Points**
High HDL Cholesterol	≥60 mg/dL (1.55 mmol/L)	-1

Total CVD Risk Score: _____

* See Appendix E for Risk Categories and related recommendations for Screening, Clinical Testing, and Exercise Recommendations.

Exercise Stages of Change Questionnaire

Goal: To do physical activity or exercise regularly, such as accumulating:

- 150 minutes of moderate physical activity per week, or
- 75 minutes of vigorous physical activity per week, or
- a combination of moderate and vigorous physical activity each week, such as
    - 75 minutes of moderate and 40 minutes of vigorous physical activity, or 90 minutes of moderate and 25 minutes of vigorous physical activity

Examples of Moderate-Intensity Activity

- Brisk walking
- Biking<10 mph (16kph)
- Ballroom dancing
- General gardening, such as weeding
- Golfing (no cart)
- Any other physical activity where the exertion is similar to these

Examples of Vigorous-Intensity Activity

- Jogging, running
- Tennis
- Biking>10 mph (16kph)
- Aerobic dancing
- Heavy gardening, such as digging
- Any other physical activity where the exertion is similar to these

Regular physical activity means meeting or exceeding the physical activity goal described above.

For each statement, please mark yes or no.

1.	I am currently physically active (at least 30 minutes per week).	☐ Yes	☐ No
2.	I intend to become more physically active in the next 6 months.	☐ Yes	☐ No
3.	I currently engage in **regular** physical activity.	☐ Yes	☐ No
4.	I have been **regularly** physically active for the past 6 months.	☐ Yes	☐ No

Exercise Stages of Change - Scoring Key

- *No* to 1, 2, 3, and 4 = Pre-contemplation stage
- *No* to 1, 3, and 4, Yes to 2 = Contemplation stage
- *Yes* to 1 and 2, No to 3 and 4 = Preparation stage
- *Yes* to 1 and 3, Yes or No to 2, No to 4 = Action stage
- *Yes* to 1, 3, and 4, Yes or No to 2 = Maintenance stage

Appendix F: Physical activity log

Date	Type of activity	Intensity: Low, Moderate, High	Minutes of activity or number of steps	Notes
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				

Weekly total: Low…… Moderate:……High:……

Appendix G: Administrative Information

Study ID	
Date of Interview	
Time of Interview	

Specialists details:

Name: _____ Phone: _____

Email:_____

Medication:

List any prescription medications you are now taking: _____

_____

List any self-prescribed medications, dietary supplements, or vitamins you are now taking: _____

_____

_____

List any other medical or diagnostic test you have had in the past two years: _____

_____

_____

List hospitalizations, including dates of and reasons for hospitalization:_____

_____

_____

List any drug allergies:_____

_____

CHILDREN	ADULTS
Current grade:	Occupation:
Class description (e.g A/B/C/remedial):	Married / single:
Participate in what sports?:	Participate in what sports?:
Level of sports or which team:	Level of sports / which team performance:

Appendix H: Wattbike test

THE SUBMAXIMAL RAMP TEST

WHY COMPLETE THIS TEST

The submaximal ramp will calculate your Maximum Minute Power (MMP) and Maximum Heart Rate (MHR), you can use this information to set personalised training zones and give structure to your training

WHEN TO USE THE SUBMAXIMAL RAMP TEST

Use the submaximal ramp test at the start of a training plan or block of training to set your baseline performance figures.

WHAT IS THE SUBMAXIMAL RAMP TEST

During this test you will ride in 15 watt increments until you experience a perceived rate of exertion (RPE) of 7 out of 10 (where 1= easy, 10= extremely hard), you'll no longer be able to maintain a conversation when you reach an RPE of 7.

HOW TO COMPLETE THE SUBMAXIMAL RAMP TEST

The Model B Performance Monitor has a pre-programmed submax ramp test. Simply follow the instructions below to get started:

Set your air resistance to level 8 on the Wattbike Trainer or 3 on the Wattbike Pro.

1. From the main menu select workouts/tests
2. On the test screen, select Submax Ramp
3. Input your age, weight in kg's and gender
4. Input your starting Watts (we recommend 55W if you're unfit or 100W if you're regularly exercising) then press enter
5. The live display will show your current interval and target watts
6. **The test will include a warmup phase**
7. Once you have reached 7/10 on the Borg scale of exertion, press escape to end the test

HOW TO INTERPRET YOUR RESULTS

Following the test, a 'test' screen will automatically appear which displays:

- MMP
- MHR
- Power to weight ratio
- VO2max estimate
- METs (represents the intensity of the test)

You can press the right arrow to switch between tabs for more information. For advice on how to read an interpret this data, read Wattbike Data 101 - An Ultimate Guide To Wattbike Data For Beginners.

Appendix I: Treating doctor assessments

Participant name:……

Physician full name:…… Qualifications:……..

Tel number:……

Email address:…….

Specialty:

Endocrinologist Yes / No Specialist Physician Yes / No General practitioner Yes / No

Postgraduate qualification : Yes / No if yes, which field? .....

Other:…….

HPCSA registration number:…….

I confirm that the contents of this statement are true to the best of my knowledge and belief.

Full name: ……Signature:……..Date:……

Witness name: ……..Signature:……..Date:……

Diagnosis:……Diagnosis: ICD 10 code/s:……..

Has treatment started? If so on what date……..

1.	**Medical History**

1.1 Are you the physician that made the diagnosis of ADD/ADHD? Yes / No

Date of diagnosis…….

1.2 Symptoms include:

1.2.1 **Inattentive presentation:**	**before treatment**	**on treatment**
• Fails to give close attention to details or makes careless mistakes.	Yes / No	Yes / No
• Has difficulty sustaining attention.	Yes / No	Yes / No
• Does not appear to listen.	Yes / No	Yes / No
• Struggles to follow through on instructions.	Yes / No	Yes / No
• Has difficulty with organization.	Yes / No	Yes / No
• Avoids or dislikes tasks requiring a lot of thinking.	Yes / No	Yes / No
▪ Loses things.	Yes / No	Yes / No
• Is easily distracted.	Yes / No	Yes / No
• Is forgetful in daily activities.	Yes / No	Yes / No

1.2.2 **Hyperactive-impulsive presentation:**	**before treatment**	**on treatment**
• Fidgets with hands or feet or squirms in chair.	Yes / No	Yes / No
• Has difficulty remaining seated.	Yes / No	Yes / No

- Runs about or climbs excessively in children /extreme restlessness in adults. Yes / No Yes / No
- Difficulty engaging in activities quietly. Yes / No Yes / No
- Acts as if driven by a motor; adults will often feel inside like they were driven by a motor. Yes / No Yes / No
- Talks excessively. Yes / No Yes / No
- Blurts out answers before questions have been completed. Yes / No Yes / No
- Difficulty waiting or taking turns. Yes / No Yes / No
- Interrupts or intrudes upon others. Yes / No Yes / No

1.2.3 **Combined inattentive & hyperactive-impulsive presentation:**

	before treatment	**on treatment**
• Has symptoms from both of the above presentations.	Yes / No	Yes / No

1.3 The presence of symptoms has been confirmed by:

1	Self (athlete)	Yes / No	
2	Parent/s	Yes / No	
3	Family members	Yes / No	Who?.....
4	Teacher/s	Yes / No	Name/s……
5	Work colleagues	Yes / No	Name/s……
6	Other	Yes / No	Name/s……

1.4 Have the symptoms been present since before the age of 12 years? Yes / No

1.5 Have the symptoms led to dysfunction in any of the following life areas?

1.5.1 Home Yes / No
1.5.2 School Yes / No
1.5.3 Work Yes / No
1.5.4 Sport Yes / No

1.6 Rate the current level of sport performance

1.6.1 High level of competition e.g. first team, top 10 in school/age/other category, national level, international level Yes / No
1.6.2 Intermediate level of competition e.g. provincial, top 50 category Yes / No
1.6.3 Recreational/social /non-competitive level Yes / No
1.6.4 Other (provide detail)…….

1.7 Following treatment, has there been an improvement in:

1.7.1 Sports performance as defined by:

1.7.1.1 Improved time (e.g. running, swimming) Yes / No
1.7.1.2 Having been promoted in a team e.g. position, second to first team, national to international level etc. Yes / No

1.7.1.3 Other (please specify)……

Appendix J: Self assessment

Participant code:……

I confirm that the contents of this statement are true to the best of my knowledge and belief.
Full name: ……Signature:……..Date:……
Witness name: ……..Signature:……..Date:……

Please complete the following before the start of the study, at the midpoint (you will be reminded) and at the end.
Thank you for your cooperation.

1.8 Symptoms include:

1.8.1 **Inattentive presentation:**	**before treatment**	**on treatment**
• Fail to give close attention to details or makes careless mistakes.	Yes / No	Yes / No
• Have difficulty sustaining attention.	Yes / No	Yes / No
• Struggle to follow through on instructions.	Yes / No	Yes / No
• Have difficulty with organization.	Yes / No	Yes / No
• Avoid or dislike tasks requiring a lot of thinking.	Yes / No	Yes / No
▪ Lose things.	Yes / No	Yes / No
• Easily distracted.	Yes / No	Yes / No
• Forgetful in daily activities.	Yes / No	Yes / No

Hyperactive-impulsive presentation:	**before treatment**	**on treatment**
• Fidget with hands or feet or squirms in chair.	Yes / No	Yes / No
• Have difficulty remaining seated.	Yes / No	Yes / No
• Run about or climbs excessively(if a child) /extreme restlessness (if an adult).	Yes / No	Yes / No
• Difficulty engaging in activities quietly.	Yes / No	Yes / No
• Talk excessively.	Yes / No	Yes / No
• Blurt out answers before questions have been completed.	Yes / No	Yes / No
• Difficulty waiting or taking turns.	Yes / No	Yes / No
• Interrupt or intrude upon others.	Yes / No	Yes / No

1.9 Have the symptoms led to dysfunction in any of the following life areas?

1.9.1	Home	Yes / No
1.9.2	School	Yes / No
1.9.3	Work	Yes / No
1.9.4	Sport	Yes / No

1.10 Is there a diagnosis of:

1.10.1	Mood disorder	Yes / No
1.10.2	Anxiety disorder	Yes / No
1.10.3	Dissociative disorder	Yes / No
1.10.4	Personality disorder	Yes / No
1.10.5	Substance intoxication or withdrawal	Yes / No

1.11 Rate your current level of sport performance

1.11.1 High level of competition e.g. first team, top 10 in school/age/other category, national level, international level Yes / No

1.11.2 Intermediate level of competition e.g. provincial, top 50 category Yes / No

1.11.3 Recreational/social /non-competitive level Yes / No

1.11.4 Other (provide detail)…….

1.12 Following treatment, has there been an improvement in:

1.12.1 Sports performance as defined by:

1.12.1.1 Improved time (e.g. running, swimming) Yes / No

1.12.1.2 Having been promoted in a team e.g. position, second to first team, national to international level etc. Yes / No

1.12.1.3 Other (please specify)……

1.13 Following treatment, has there been an improvement in:

1.13.1 School/academic performance as defined by:

1.13.1.1 Improved grades/marks Yes / No

1.13.1.2 Having received commendation/prizes for academic achievement Yes / No

1.13.1.3 Having received positive feedback from school/teacher/lecturer Yes / No

Appendix K: Outcome Measurements

Study ID: _____

Date of measures:_____

Resting Measurement	
Resting Blood Pressure (Right arm)	
Resting Blood Pressure (left arm)	
Resting Heart Rate	
Height (m)	
Weight (Kg)	
BMI	
Waist Circumference	
Hip Circumference	
Waist to hip Ratio	
Maturity offset (children)	

EXERCISE STRESS TEST

Adults (Wattbike)

Exercise Stress Test				
Power (watts)	**Time**	**Heart Rate**	**Blood Pressure**	**RPE**
60	1 min			
90	2 min			
120	3 min			
150	4 min			

180	5 min			
210	6 min			

Recovery (Time)	Heart rate	Blood Pressure	RPE
0 min			
1 min			
2 min			
3 min			
6 min			
9 min			
12 min			

maximum minute power (MMP)	maximum heart rate (MHR)	power to weight ratio	VO2max estimate	METs

Grip strength (kg)				

Sports cardiac screening

Name:…….

ID number:…….Ethnicity……..

Date of assessment:……..

Heart rate: ……..bpm repeat after 5 minutes rest PRN…… bpm

Heart rhythm: normal □ abnormal □
Arrhythmia……

Pulses: peripheral palpable □ absent □
radio-femoral delay □ left □ right □ both □
bruits present □ site…….

Blood pressure: ……mmHg left arm

……mmHg right arm

……mmHg ankle (if indicated)

Heart sounds: normal □ abnormal □

Split □
Paradoxically split □
3rd heart sound □
4th heart sound □

Murmur/s: absent □ present □
Systolic □ ……/6 Site……
Diastolic □……/6 Site……
Clicks □
Valslava **increases** □ decreases □
Squatting increases □ **decreases** □

12 lead electrocardiogram:

Heart rate:……bpm

Rhythm/conduction: normal □ abnormal □

- Premature ventricular complexes □
- Premature supraventricular □
- Supraventricular tachycardia □
- Ventricular arrhythmia □
- Atrial fibrillation / flutter □
- Delta wave □
- AV block
  - first degree □
  - second degree type I □
  - second degree type II □
  - third degree □

PR……ms QRS……ms QTc……..ms **highlight** □

Atrial enlargement: no □ yes □

Left □ negative portion of p wave in V_1 ≥0.1mV deep and ≥0.04 secs

Right □ peaked p-wave in II and III or V_1 ≥0.25mV in amplitude

QRS complex (depolarisation) :

Axis normal□ abnormal □ >+120° □ -30° to -90° □

Voltage normal□ abnormal □

Left ventricular hypertrophy no □ yes □

Q waves normal□ abnormal □

>0.04s or >25% of height of ensuing R wave or QS pattern in 2 or more leads

Bundle Branch block no □ yes □ right □ left □

- Complete >0.12s left □
- Complete>0.12s right □
- Incomplete left posterior □
- Incomplete right □

R wave normal□ pathologic □ R or R wave lead V1 (≥ 0.5mV +R/S ratio≥1)

Repolarisation: (ST segment, T waves, QT interval)

Early repolarisation present no □ yes □

Normal □ Abnormal □

	I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6
ST depression	□	□	□	□	□	□	□	□	□	□	□	□
ST elevation	□	□	□	□	□	□	□	□	□	□	□	□
T-flattening	□	□	□	□	□	□	□	□	□	□	□	□
T – inversion	□	□	□	□	□	□	□	□	□	□	□	□

Assessment: ECG normal □ abnormal □

Athlete fit to compete / train - unrestricted		**Athlete temporarily unfit**		**Athlete unfit**	
Athlete fit to compete with restrictions		**Other decision**			

Children (Treadmill)

Exercise Stress Test					
Speed	**Elevation**	**Time**	**Heart Rate**	**Blood Pressure**	**RPE**
		1 min			
		2 min			
		3 min			
		4 min			
		5 min			
		6 min			

Recovery (Time)	**Heart rate**	**Blood Pressure**	**RPE**
0 min			
1 min			
2 min			
3 min			
6 min			
9 min			
12 min			

maximum minute power (MMP)	maximum heart rate (MHR)	power to weight ratio	VO2max estimate	METs

Grip strength (kg)				

Cognitive performance tests

1. ImPACT scores

Composite Scores	Pre 1	Post 1	Pre 2	Post 2
Memory composite (verbal)				
Memory composite (visual)				
Visual motor speed composite				
Reaction time composite				
Impulse control composite				
Total Symptom Score				
Cognitive Efficiency Index:				

2. Stroop results

Interference change	Pre 1	Post 1	Pre 2	Post 2

Pre- and post exercise test scores are calculated for interference using the equations:

(C x W) ÷ (C+W) = CW' (Expected score)

CW – CW' = Interference

Where C is the score of correctly articulated colors of the color block test, W is the score of correctly articulated words of the black text test, and CW is the score of correctly articulated colors of the Stroop test. The interference is the difference between the actual performance score on the Stroop test and the expected score.

Appendix L: Information Document for treating physicians

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Study title: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

Good day. My name is Demitri Constantinou, and I am doing a PhD at the University of the Witwatersrand.

In this study we will be answering questions about the effects of methylphenidate on aspects of human function. These will include the control of the heart, muscle strength and aerobic fitness, balance, and conscious mental processes.

Invitation to participate: We will be inviting participants that you may be treating – children and /or adults.

This document is to inform you of the details and nature of the study and to request your permission to facilitate and participate as treating physician.]

What is involved in the study

The study will involve several tests to be conducted on the participants before treatment you have prescribed has started.. The participants will be randomly divided into two groups – children age group (grades 8-12, ages 14-18 years) and adults (over 18 years). The study will be a double blind crossover study Each group will be randomly divided and given medication to take for 4 weeks. The medication will either be active methylphenidate or placebo. Neither the researcher nor the participant will know which medication will be provided so that tests are not influenced. The test will be repeated 2 weeks later. Then there will be a 3 day period of no medication and then the medication (either methylphenidate or placebo) will be swopped around so the same people will now take the other treatment for a further 4 weeks. A four week period is not a significant time to delay treatment of this chronic condition, but long enough for purposes of the study. The dosage should not be changed during the period of the study.The information derived may have a significant contribution to science. The results will be analysed to measure any changes.

The measurements will be performed at the Centre for Exercise Science and Sports Medicine on the Wits Education Campus in Parktown, Johannesburg. Unfortunately we will not be able to

provide transport and request you make arrangements for this. The procedures will take approximately an hour to complete. The total number of participants will be approximately 70 people (35 children and 35 adults) from the greater Johannesburg area participating in the study.

A questionnaire will be completed that includes medical and physical activity details, followed by the above tests being performed.

The outcome measures are:

The outcome measures are:

Anthropometric and Physiological parameters

Anthropometry: Height (m) and weight (kg). These will take less than 2 minutes to complete

Physiological parameters (about 20 minutes) will be measured as follows: heart rate – after 5 minutes rest and taken from the electrocardiogram (ECG). Blood pressure (mmHg)

Using a Wattbike® (Woodway, Waujesha, Wisconsin, USA), a Wattbike® ramp test protocol will be used for adults and will be used to determine: maximum minute power (MMP), maximum heart rate (MHR), power to weight ratio, VO_2max estimate, METs (metabolic equivalents) representing the intensity of the test.

A graded treadmill exercise test will be used for children using the British Columbia Children's Hospital protocol for children (Duff et al, 2017). Extrapolation of data will determine similar parameters as those from the Wattbike® test.

Postural balance (5 minutes) will be measured using the Biodex Balance system on which four tests will be administered using a mCTSIB. This tests visual, vestibular and somatosensory feedback systems under four sensory conditions.

Physical parameters (10 minutes) : Muscle strength will be determined by handgrip strength (kg) on the dominant side using (Grip-D grip strength dynamometer, Takei Scientific Instruments Company, Japan). Lower extremity power will be measured using Vertical counter movement jump, and will be recorded to the nearest millimetre using a flight-time based jump mat (Fusion Sport Smart Jump mat, Fusion Sport, 2 Henley ST, Coopers Plains, QLD, 4108, Australia) and Smart Jump PDA (Hewlett Packard Company, Palo Alto, CA 94304)).

Psychometric tests (20 minutes) : ImPACT® is a computer-administered neuropsychological test battery that uses seven individual test modules that assess attention, verbal visual memory and learning, numerical sequencings, process speed and reaction time, therefore analysing six neurocognitive areas (Khurana & Kaye, 2012. When performing an ImPACT® test an individual who has a faster reaction time and a lower symptom score (as in concussion) suggests a better response and higher scores for verbal and visual memory and visual motor processing speed indicates better performance (Majerske, Mihalik, Ren, Collins, Reddy, & Wagner, 2008) (Majerske et al., 2008). Iverson et al., (2004) showed that athletes who sustained multiple concussions showed increased symptoms and lower memory scores. Therefore use of the ImPACT® can determine the extent of the concussion on the relevant brain areas (Majerske et al., 2008). The use of the ImPACT® in this study the ImPACT® test will be used to measure changes in neurocognitive function that MPH may have. In addition the Stroop test will be used as an online tool (Stroop, 1935). This test has been used and validated in general and sport for general cognitive function (Chang, et al., 2015) (Gapin, Labban, Bohali, Wooten, & Chang, 2015), including preadolescents (Buck, Hillman, & Castelli, 2008). The Stroop test utilises 5 conditions (congruent, Stroop word, Stroop square, Stroop neutral, and Stroop incongruent) using words and colours.

Academic and sport performances: In order to assess changes in vivo changes before the use of and whilst on treatment, and compare to controls, academic and sporting performance records (as previously used by the South African Institute for Drug Free Sport and modified for the

research by excluding superfluous information) will be kept by the participants and/or their parents/.guardians to be completed at start of study, midpoint and endpoint by the you, the treating doctor (attached) and participants.

Risks: All the tests are non-invasive. There are minimal risks, and no more than would be found in everyday activities. The most body stress activity will be walking and running for a short period of time on a treadmill or cycling. All precautions will be taken to ensure this is done safely. The researcher who will be conducting the testing is a qualified medical doctor. Should there be any injury, this will be assessed and managed by him. The placebo group would have a delay in their treatment for approximately 12 weeks, but this is not limb or life threatening and similar studies on many medications have been conducted in this way.

Benefits: There are no direct benefits being in the study; however there will be information on strength, aerobic fitness, electrocardiogram and health screening that may be provided to the individual (or parent/guardian). The participant will be given pertinent information on the study while involved in the project and after the results are available.

Participation is voluntary: Refusal to participate will involve no penalty and the subject may discontinue participation at any time without penalty.

Confidentiality: Every effort will be made to keep personal information confidential. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee and the South African Health Products Regulatory Authority (SAHPRA) (where appropriate).

Contact details of researcher/s: (for further information / reporting of study related adverse events) Demitri Constantinou. Tel. 011 717-3372 Fax. 086 63 63173. Email. demitri.constantinou@wits.ac.za

Contact details of supervisors: Prof Alan Rothberg, alan.rothberg@wits.ac.za and Prof Mike Lambert, mike.lambert@uct.ac.za

Contact details of Human Research Ethics Committee administrator and chair: (for reporting of complaints / problems). If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Professor Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC)(0114883820, clement.penny@wits.ac.za), or Ms Z Ndlovu / Mr Rhulani Mkansi administrative officers. Telephone number; 011 717 2700/2656/1234/1252. Zanele.ndlovu@wits.ac.za; Rhulani.mkansi@wits.ac.za. The ethics committee is an independent committee established to help protect the rights of research participants.

Appendix J: Information Document for child participants

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Study title: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

Good day. My name is Demitri Constantinou, and I am doing research at the University of the Witwatersrand.

In this study we will be answering questions about the effects of methylphenidate, which is medication you have been prescribed to assist with school and concentration. These will include the control of the heart, muscle strength and fitness, balance, and some brain processes.

Invitation to participate: We are inviting you to take part in this research study.

What is involved in the study

The study will involve several tests to be conducted on you before treatment by the specialist has started. You will be randomly divided into two groups and given medication to take for 4 weeks. The medication will either be active methylphenidate or placebo. A placebo is inactive medication. Neither you or I will know which medication will be provided so that tests are not influenced. The tests will be repeated 2 weeks later. Then there will be a 3 day period of no medication and then the other medication (either methylphenidate or placebo) will be swopped around so the same people will now take the other treatment for a 4 weeks. A four week period is not a significant time to delay treatment of this chronic condition, but long enough for purposes of the study. The dosage should not be changed during the period of the study.The information derived may have a significant contribution to science. The results will be analysed to measure any changes.

The measurements will be performed at the Centre for Exercise Science and Sports Medicine on the Wits Education Campus in Parktown, Johannesburg. Unfortunately we will not be able to provide transport and request you make arrangements for this. The procedures will take approximately an hour to complete. You will be one of approximately 70 people from Johannesburg participating in the study.

A questionnaire will be completed that includes medical and physical activity details, followed by the tests being performed.

The things we will measures are:

Anthropometric and Physiological parameters

Anthropometry: Height (m) and weight (kg). These will take less than 2 minutes to complete

Physiological parameters (about 20 minutes) Electrocardiogram (ECG) and heart rate to measure the electrics of the heart by applying electrodes (stickers) on the chest– after 5 minutes rest and taken from the electrocardiogram (ECG). Blood pressure (mmHg)

You will do a treadmill test. This test starts at slow speeds and gradually increases. You will stop when you are tired or all if I decide at any stage to stop the test.

Postural balance (5 minutes) will be measured using the Biodex Balance system which involves standing on a machine which measures the balance with eyes open and with eyes closed.

Physical parameters (10 minutes) : Muscle strength will be done by squeezing a device as hard as you can. Leg power will be measured using a jumping test .

Psychometric tests (20 minutes) : ImPACT® is a computer test that uses shapes, colours and numbers to measure attention, memory, learning and reaction time. Another computer test is the Stroop test using numbers and colours.

Risks: There are minimal risks, and similar to doing everyday activities. The most body stress activity will be walking and running for a short period of time on a treadmill. All precautions will be taken to ensure this is done safely. The researcher who will be conducting the testing is a qualified medical doctor. Should there be any injury, this will be assessed and managed by him.

Benefits: There are no direct benefits being in the study; however there will be information on strength, fitness, the heart and health that you may be given.

Participation is voluntary: You do not have to do all the tests if at any stage you do not want to**.** There is no penalty or punishment if you decide to stop and not be in the study any more.

Confidentiality: Every effort will be made to keep personal information confidential, and only your parents/guardians may know the results if it is necessary.

Contact details of researcher/s: Demitri Constantinou. Tel. 011 717-3372 Fax. 086 63 63173. Email. demitri.constantinou@wits.ac.za

Contact details of supervisors: Prof Alan Rothberg, alan.rothberg@wits.ac.za and Prof Mike Lambert, mike.lambert@uct.ac.za

Contact details of Human Research Ethics Committee administrator and chair: (for reporting of complaints / problems). If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Professor Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC)(0114883820, clement.penny@wits.ac.za), or Ms Z Ndlovu / Mr Rhulani Mkansi – administrative officers. Telephone number; 011 717 2700/2656/1234/1252. Zanele.ndlovu@wits.ac.za; Rhulani.mkansi@wits.ac.za; The ethics committee is an independent committee established to help protect the rights of research participants.

Appendix K: Informed Consent (treating physician)

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Research: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

INFORMED CONSENT

- I hereby confirm that I have been informed by the study primary investigator, Demitri Constantinou, about the nature, conduct, benefits and risks of the clinical study: *Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects*. I have also received, read and understood the above written information (Participant Information Leaflet) regarding the study.
- I am aware that the results of the study, including personal details regarding participant sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the primary researcher Demitri Constantinou
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study in completing the required questionnaires on the participants/patients being treated.

PHYSICIAN:

Printed Name Signature Date and Time

I, Demitri Constantinou, herewith confirm that the above physician has been fully informed about the nature, conduct and risks of the above study.

RESEARCHER:

Printed Name Signature Date and Time

Appendix L: Informed Consent (parent/guardian)

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Research: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

INFORMED CONSENT

- I hereby confirm that I have been informed by the study primary investigator, Demitri Constantinou, about the nature, conduct, benefits and risks of the clinical study: *Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects*. I have also received, read and understood the above written information (Participant Information Leaflet) regarding the study.
- I am aware that the results of the study, including personal details regarding participant sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the primary researcher Demitri Constantinou
- I may, at any stage, without prejudice, withdraw my consent for participation of my child in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to allow participation of my child in the study. treated.

PARENT/GUARDIAN:

Printed Name Signature Date and Time

I, Demitri Constantinou, herewith confirm that the above physician has been fully informed about the nature, conduct and risks of the above study.

RESEARCHER:

Printed Name Signature Date and Time

Appendix M: Informed assent (Child participants)

The University of the Witwatersrand Centre for Exercise Science and Sports Medicine

Research Title: Methylphenidate: Physiological, neurocognitive, balance, and physical performance effects

- I am volunteering on my own accord
- I confirm that the study details have been explained to me by the researcher
- I know that at any stage I can stop participating in the study
- I am aware that the results of the research study will be kept confidential and safe.
- I am aware that the results of the research study will be put into a study report and may be written up into academic reports
- I have had a chance to ask questions and (of my own free will) confirm that I am prepared to participate in the study
- My parent/s/guardian have agreed to my participation

PARTICIPANT:

Printed Name	Signature	Date and Time

RESEARCHER:

Printed Name	Signature	Date and Time