SECTION 1

PROPOSAL RESEARCH GRANT APPLICATION

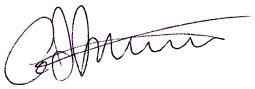
Application Detailed Instructions Link

Total Amount Requested: $ 30,000 DATE: 071718

NOTE: To undertake the project, the PI has access to additional funding to bridge the gap between the maximum value of the OTA grant ($30,000). And the total cost of the project ($33,840). The additional sum will cover the majority of the consumable costs for the project.

This request is made by the undersigned, who also agree(s) to comply with the following:

(1) Funds granted as a result of the request are to be expended for the purposes set forth herein.
(2) All reports or original investigations supported by any grant made as a result of this request shall acknowledge support provided by the Orthopaedic Trauma Association.
(3) Reports will be made as required and necessary records and accounts, including financial and property controls, will be maintained and made available to the Orthopaedic Trauma Association.

NAME	TITLE	DEPARTMENT	SIGNATURE
Principal Investigator: Alan J Johnstone	Professor	Trauma & Orthopaedics Aberdeen Royal Infirmary, and University of Aberdeen	 Phone: +441224551251 Fax: +441224552180 E-mail: alan.johnstone@abdn.ac.uk
Co-Principal Investigator: Andrew H Schmidt	Dr	Dept. of Orthopaedic Surgery, Hennepin County Medical Center, Minneapolis, MN	 Phone:+16127208231 Fax: E-mail: schmi115@umn.edu
OTHER INVESTIGATORS ASSOCIATED WITH PROJECT:			
Derek Ball	Dr	School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Scotland, UK	 Phone: +441224437456 E-mail: derek.ball@abdn.ac.uk
Institution Name and Address: University of Aberdeen, King's College, Aberdeen AB24 3FX, Scotland, UK			

SECTION 2

ABSTRACT OF RESEARCH PLAN

PROJECT TITLE:

Diagnosing acute compartment syndrome using an intramuscular pH probe: what pH level equates to impending cell death and are some muscles more susceptible than others to ischemia?

Abstract of research plan: Please provide an abstract of 250 words or less with 5 underlined phrases for a project summary. Please avoid summaries of past accomplishments and the use of the first person. The abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application.

Acute compartment syndrome (ACS) is a form of progressive ischemia that predominantly affects muscle.

Progressive muscle ischemia, irrespective of the cause, results in reduced aerobic respiration and increased anaerobic respiration, as cells attempt to survive. Although we are aware of the biochemical pathways and the key metabolites involved in progressive ischemia, and the histological changes that occur when cells progress from reversible to irreversible cell injury (death), research has not been undertaken to accurately correlate the biochemical and histological processes.

Our first aim is to assess/correlate the biochemical and histological findings using a progressive ischemic muscle model. This will enable us to identify which biochemical marker(s) are indicative of varying degrees of muscle ischemia ultimately resulting in cell death. This will form the basis for future research investigating the diagnostic potential of biochemical markers to diagnose ischemia, including ACS, that will overcome the limitations of current diagnostic methods.

Our second aim is to investigate the potential of continuous indwelling intramuscular pH (IMpH) readings as an easy to use and real-time objective assessment of aerobic and anaerobic respiration. Our earlier research confirmed a very high correlation between the concentrations of key biochemical metabolites and continuous IMpH. The proposed research will expand on these findings by refining the biochemical findings further and by incorporating the histological findings.

In summary, by combining the detailed biochemical, histological and pH findings, we hope to identify new avenues for diagnosing progressive muscle ischemia, including ACS, that will radically improve our diagnostic capabilities and speed of intervention.

SECTION 3

FACILITIES – Laboratory Space and Major Equipment

Please provide an accurate description of laboratory facilities and major equipment available at the grantee's institution that will support this project. Please recall the list of supplies and support that the grantee's institution, or grant funds other than those from the OTA, are expected to provide:
click to see the list

University of Aberdeen

Medical Test Facility (Animal Research)
The University if Aberdeen has a state-of-the-art new build small animal research facility that undertakes a full spectrum of research under the guidance of the UK Home Office.
Given that the research proposed will be using freshly euthanised large rodents, there are no ethical or UK Home Office research concerns. Having undertaken a similar but less detailed small animal experiment at the facility in the past year, we know that all of the laboratory space available is adequate, and that the equipment and other facilities are available to undertake the experiments as described in the Research Plan.

Laboratory Space
A comprehensive suite of laboratory facilities is provided in the Health Sciences Building; these include spectrophotometric and fluorescent analysis of biochemical metabolites. Light and fluorescent microscopy for histochemical and immunohistochemical analysis. Ultra-low cold storage and freeze-drying facilities for the storage of muscle samples.

Equipment

1. Specialist pH equipment:
   Softcell Medical Ltd manufactures a highly accurate real-time pH monitoring system that has been designed specifically for use with a variety of medical conditions, including acute compartment syndrome, where tissue/organ ischemia is a problem. SoftCell will provide pH probes and a dedicated pH recorder free of charge to undertake the proposed research.

2. Biochemical experiments
   Camspec Spectrophotometer, Jenway Fluorimeter, refrigerated centrifuge, glassware and consumables to conduct biochemical analyses.

3. Histological experiments
   The institute of Medical Sciences has a core imaging facility that permits state-of-the-art light and fluorescent microscopy and provides training to use the facilities. The project will utilise these facilities as costed.

Office Space
Post-graduate students are provided with a desk and computer facilities in the post-graduate office. In addition, post-graduate students receive training in research methods, health and safety, careers advice as part of the postgraduate training program at the University of Aberdeen.

SECTION 4

RESEARCH PLAN

Click for Research Plan Instructions

A. SCIENTIFIC AIMS (not exceed 400 words)

Hypotheses:

1. Key intramuscular metabolic events can be assessed by measuring the tissue concentration of important metabolites and directly relate to cell health/death, and also correlate with directly measured IMpH levels.
2. Muscles composed of different proportions of fast-twitch and slow-twitch muscle fibres may be more or less susceptible to ischemia depending upon their composition and may provide some insight as to why some muscle groups are more prone to cell death and subsequent contracture.

Aims: Using an animal muscle model of progressive ischemia ending in cell death (and not specifically a model of compartment syndrome);

1 To measure biochemically, a number of important metabolites that are recognised to directly influence cell health, over time.

Pyruvate and glucose-6-phosphate have key roles in the oxidative phosphorylation (aerobic) pathway, and lactate is produced as a by-product of the glycolytic (anaerobic) pathway. Both pathways result in the formation of the major high energy molecules, Adenosine tri-phosphate (ATP) and phosphocreatine (PCr), that are required to power all energy requiring skeletal muscle cell activities.

Adenosine di-phosphate (ADP) and especially Adenosine mono-phosphate (AMP) muscle tissue concentrations are indicative of end stage ischemia.

2 To assess the proportion and pattern of muscle cell health/death histologically, over time.

A combination of functional histology (living/dead cell dyes) combined with observed structural cellular changes (H&E staining), and both interpreted in relation to the proportion and distribution of muscle fibre type (immunohistochemistry) will provide detailed information cellular susceptibility to ischemia.

3 To directly measured muscle tissue pH using an indwelling pH probe, over time.

The potential for this objective method to assess the balance between aerobic and anaerobic respiration could provide clinicians with an easy to use diagnostic and monitoring tool that could effectively omit the need to measure the concentrations of the key metabolites listed above.

4 To compare and, where appropriate, correlate the findings of aims 1, 2 and 3.

This will be the first study of its type to define cell health/death histologically and to correlate this to the tissue concentration of key biochemical markers of metabolism that could be used to indicate tissue health/death, and ultimately to assess the potential of a new objective measure, tissue pH, to act as a real-time measure of cell health/death since it could effectively measure the balance between aerobic and anaerobic respiration.

B. BACKGROUND & SIGNIFICANCE (not to exceed 400 words)

Accurately diagnosing trauma-induced acute compartment syndrome (ACS) remains the crux to timely surgical intervention, subsequent treatments and ultimately the long-term outcome for patients[1,2]. As ever, making the diagnosis remains difficult and despite recent research into other possible diagnostic methods, the current main stays (the 'gold standards') for diagnosing ACS remain regular clinical assessment and intracompartmental pressure monitoring (ICP)[1,3-6]. Unfortunately, clinical assessment is very subjective, and clinicians' opinions vary considerably[3]. In particular, clinical assessment remains hampered by the main clinical symptom, pain, the severity of which is difficult to judge after an acute injury especially in children or in multiply injured patients, and clearly is impossible to assess in unconscious patients. By comparison, ICP is an objective measure of localized tissue swelling that results in a pressure change within a muscle compartment. However, considerable debate remains about the type of pressure monitoring equipment[1,7,8] that should be used, but more importantly, the pressure criteria that should be used to diagnose ACS[1,4,6,8-10]. Therefore, it is not surprising that many traumatologists remain skeptical about the real value of routine ICP monitoring[3]. But why, after considerable research, have we failed to accurately define the diagnostic pressure criteria? The answer is relatively straightforward if we focus upon the underlying process that gives rise to ACS; namely progressive muscle ischemia. Although pressure

changes within a muscle compartment influence ACS, pressure is only one factor contributing to ischemia. Since ICP cannot quantify the extent of the traumatic muscle injury present or compensate for differences (individual tolerances) that clearly exists between individuals and directly influence the extent of muscle ischemia present, ICP monitoring is at best a surrogate marker for ACS[1]. Therefore, ICP will never be able to give us a true picture of the extent of ischemia present.

Understandably, there has been considerable interest in new technologies to complete the 'ischemic picture' of which Near Infrared Spectroscopy (NIRS) has looked particularly promising. However, researchers have had mixed experiences with NIRS and it is clear that another method(s) are required to provide real-time information about the extent of muscle ischemia possibly leading to ACS[11,12]. Only by doing so, will it be possible to anticipate which patients are developing ACS, and, in late presentations of ACS, which patients have sufficient tissue that is potentially still salvageable without inviting an unacceptable risk of systemic complications associated with limb reperfusion in the presence of significant muscle necrosis.

C. PREVIOUS WORK DONE ON THE PROJECT **(Not to exceed 400 words)**

Research undertaken in our unit has highlighted the very real potential for continuous intramuscular pH monitoring (IMpH) to be able to resolve the ACS diagnostic conundrum, as well as other causes of ischemia[13,14]. We have already undertaken a clinical prospective cohort study comparing the current, but suboptimal, 'gold standard' diagnostic methods of regular clinical assessment and continuous ICP, with continuous IMpH measurements[13]. Although clinicians were blinded to the IMpH readings, and the IMpH findings were examined retrospectively in light of the acute clinical and ICP findings by which clinical decisions were made, our research demonstrated that IMpH would have been much better at diagnosing ACS compared with the other two methods, resulting in a significantly earlier time to diagnosis (approximately of 2.5 hours earlier). In addition, IMpH would have correctly diagnosed an additional 35% of patients who at long-term follow up (1-year post-injury) had clearly sustained an undiagnosed ACS that was not detected acutely using either of the current gold standard methods.

In addition to our clinical study, we have also undertaken a limited laboratory study using fresh animal muscle, whereby IMpH readings were correlated to the intramuscular concentrations of key metabolites including; lactate, pyruvate, glucose-6-phosphate, phosphocreatine (PCr) and adenosine triphosphate (ATP)[15]. IMpH readings correlated well with the breakdown of key energy metabolites and the production of lactate (Figure 1)[16]. Although since this study lacked histological evidence of cell survival/death, we were unable to identify the key pH or metabolite related thresholds that related to varying degrees of cell health/irreversible cell injury and ultimately cell death. Nor did our study address which cells types (Fast twitch or Slow twitch muscle fibres) deteriorated/died first and at what pH thresholds.

Therefore, further research is required to investigate the links between continuous IMpH monitoring, key metabolic events and the histological findings that confirm the presence of severe ischemia leading to cell death, or better still, anticipate the progressive development of ischemia that will ultimately result in cell death. The basic science research project proposed below will investigate these relationships in detail and will add to the pool of knowledge available to help researchers to design truly useful future clinical studies and RCTs to address the timely diagnosis of ACS, perhaps using IMpH or other biomarkers, aimed at optimizing the time of treatment, or in the case of late presentations of ACS, to decide whether or not fasciotomy is appropriate.

D. METHOD **(not to exceed 1200 words and 4 pages)**

Note: The model to be used will be a model of progressive skeletal muscle ischemia that we have experience with, and not a specific model of compartment syndrome. Since compartment syndrome is predominantly a variant of progressive muscle ischemia, we feel that the model described below is relevant given our aims, research experience, and the finance that is available to undertake this project.

Animal model:
A recently sacrificed rat muscle model will be used providing fresh gluteus maximus muscle (bilateral) specimens from 20

rats will be used, the number being based on a power calculation that assumes a pH change of 0.3 pH units, an alpha (false-positive rate) 0.01 and a Beta (false negative rate) of 0.15. Each rat will be kept moist and humidified at 37˚C using a thermostatically controlled incubator. A modern and highly accurate glass pH probe will be inserted into one gluteus muscle to give a continuous pH reading along with a highly sensitive tissue thermometer. The contralateral muscle will be the source of the biopsy specimens. Based on our previous research we have undertaken, (i) baseline biopsies, (ii) further biopsies when the continuous pH recordings decline by 0.1 of a pH unit (usually observed within the initial 15-30 minutes depending individual variation). (iii) thereafter at 30-minute intervals up to a total of 3 hours, during which pH changes occur less rapidly and ultimately plateau. At these time points, two small muscle biopsies will be removed from the contralateral limb

Biochemical analyses:
Each muscle biopsy specimen will be divided into two ,with one sample immediately SNAP frozen and stored at -80˚C prior to freeze drying. Subsequently, these biopsy specimens will be freeze dried prior to being powdered and then deproteinised in perchloric acid containing EDTA. After centrifuging, the supernatant will be analysed for Lactate, Pyruvate, Glucose-6-phosphate, Phosphocreatine, Adenosine tri-phosphate, Adenosine di-phosphate and Adenosine mono-phosphate using methods as previously described[17,18].

Advanced histology:
The remaining half of the biopsy will initially be stored fresh at 4˚C in a refrigerator in a 24-well plate containing 'Vitality dyes' for between 4 to 6 hours and then SNAP frozen immediately in isopentane before sectioning and mounting. The proportion of living and dead cells will be assessed using immunofluorescent histochemistry. In addition, representative sections will be thawed and prepared in wax for H&E staining, and others mounted in TissueTek for immunohistochemical staining to determine muscle cell type. Some of these sections of Histological specimens will be assessed for the proportion of living and dead cells present at baseline and at the pH that corresponds, and subsequent slices will be assessed by further immunohistochemical staining to identify muscle fibre type and distribution.

Analyses of data:
All timed biochemical and histological results and pH readings will be analysed using 3rd or 4th order polynomial that models the change in pH over time or metabolite as a function of pH to determine the highest and lowest rate of change. Based on the assumptions of normality of distribution and variance characteristics standard parametric statistical methods and correlations to assess the majority of the data will be applied to the data.

Summary of proposed project:
Through this animal tissue study, it should be possible to confirm the biochemical profile of muscle tissue with progressive ischaemia ultimately resulting in cell death and relate this to the proportion of living to dead cells assessed histologically and their distribution according to muscle fibre type. In addition, we will be able to assess the efficacy of the indwelling pH probe to directly measure pH comparing it to calculated pH using the aerobic-anaerobic equation first described by Sahlin, that is based upon tissue concentrations of pyruvate and lactate.
We anticipate that the results of this research will provide essential background information about likely important biochemical markers and real-time pH levels when designing future clinical studies and RCTs for acute compartment syndrome and other forms of progressive muscle ischemia.

All of this research will be undertaken at the University of Aberdeen, Scotland.

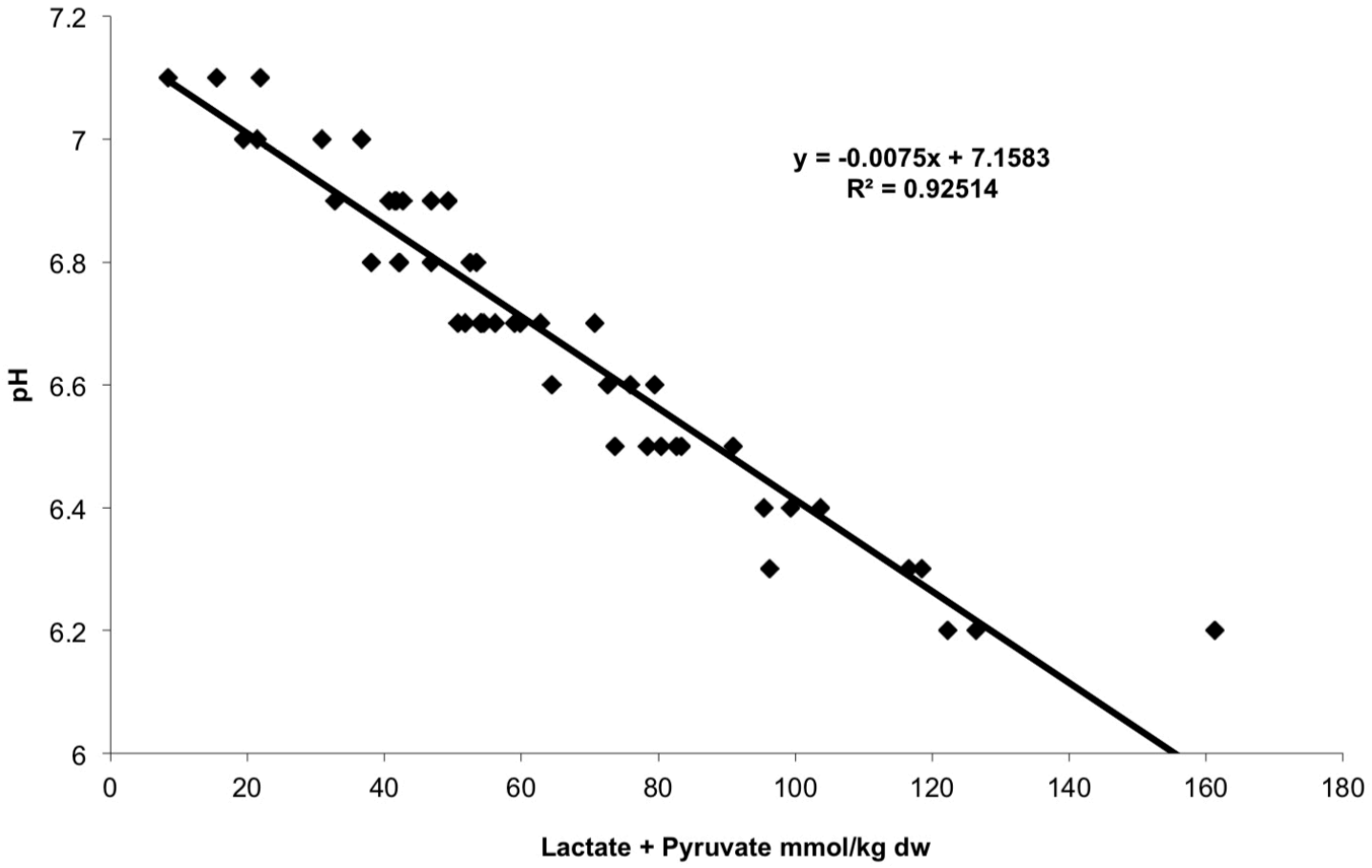
NOTE: To undertake the project, the PI has access to additional funding to bridge the gap between the maximum value of the OTA grant ($30,000). And the total cost of the project ($33,840). The additional sum will cover the majority of the consumable costs for the project.

E. REFERENCES **(not to exceed 2 pages)**

1. Elliott, KGB, Johnstone AJ. Diagnosing acute compartment syndrome. JBJS, 2003.
2. Schmidt AH. Acute compartment syndrome. Injury 2017;48(Suppl):S22-S25.
3. Collinge C, Attum B, Tornetta P III, et al. Acute compartment syndrome: An expert survey of Orthopedic Trauma Association (OTA) members. J Orthop Trauma. 2018;32(5):e181-e184.
4. McQueen, MM, Court-Brown CM. Compartment monitoring in tibial fractures: the pressure threshold for decompression. JBJS 1996.
5. McQueen MM, Duckworth AD, Aitken SA, Court-Brown CM. The estimated sensitivity and specificity of compartment pressure monitoring for acute compartment syndrome. J Bone Joint Surg Am 2013;95-A:673-677.
6. Ovre S, Hvaal K, Holm I, Stromsoe K, Nordsletten L, Skjeldal S. Compartment pressure in nailed tibial fractures: a threshold of 30mmHg for decompression gives 29% fasciotomies. Arch Orthop Traum Surg, 1998.
7. Boody AR, Wongworawat MD. Accuracy in the measurement of compartment pressures: a comparison of three commonly used devices. JBJS 2005.
8. Willy C, Gerngross H, Sterk J, Measurement of intracompartmental pressure with use of a new electronic transducer-tipped catheter. JBJS 2009.
9. Williams PR, Russell ID, Mintowt-Czyz WJ. Compartment pressure monitoring – current UK orthopaedic practice, Injury, 1998.
10. Wall CJ, Richardson MD, Lowe AJ, Brand C, Lynch J, de Steiger RN. Survey of management of acute, traumatic compartment syndrome of the leg in Australia. ANZ J Surg, 2007.
11. Hope MJ. Near-Infrared Spectroscopic Diagnosis of Acute Compartment Syndrome. MD Thesis, University of Edinburgh, 2010.
12. Schmidt AH, Bosse M, O'Toole RV, Obremskey W, Zipunnikov V, Junrui D, Frey K, MacKenzie E. Continuous near-infrared spectroscopy demonstrates limitations in monitoring the development of acute compartment syndrome in patients with leg injuries. J Bone Joint Surg Am 2018, in press.
13. Elliott KGB. Intramuscular pH as a novel diagnostic tool for acute compartment syndrome: A prospective clinical study. MD Thesis, University of Aberdeen, 2011
14. Collins PWH. Assessing the Severity of Lower Limb Ischaemia and the Thrombo-inflammatory Response to Surgery and Exercise in Peripheral Arterial Disease. MD Thesis, University of Aberdeen, 2008.
15. Patton MS. A review of the underlying biochemistry of muscle ischaemia in relation to intramuscular pH measurements. MD Thesis, University of Aberdeen, 2013 (unpublished)
16. Sahlin K. Muscle energetics during explosive activities and potential effects of nutrition and training. Sports Med. 2014;44:S167-73.
17. Maughan RJ. A rapid simple method for the determination of glucose, lactate, pyruvate, alanine, 3-hydroxybutyrate and acetoacetate on a single 20 µl blood sample. Clin Chim Acta 1982; 122:231-240.
18. Harris RC, Hultman E, Nordesjo L-O. Glycogen, Glycolytic intermediates and High-Energy Phosphates Determined in Biopsy Samples of Musculus Quadriceps Femoris of Man at Rest. Methods and Variance of Values. Scand.J.Clin.Lab Invest, 1974: 33, 109-120.

FIGURES (if figures added outside of the text pages – **not to exceed 1 page**)

Figure 1: Correlation of directly measured intramuscular pH versus calculated tissue pH using the Aerobic/Anaerobic equation in an ischemic mammalian animal model



SECTION 5

BIOGRAPHICAL SKETCH

Not to exceed two pages for each person. Copy and paste below the two Bio-Sketch pages for each additional Investigator.

NAME Alan J Johnstone	TITLE Professor	BIRTHDATE (Mo., Day, Yr.) 06/01/63
PLACE OF BIRTH (City, State. Country) Stirling, Scotland, UK	NATIONALITY (If non-US citizen indicate visa status) British – ESTA visa	SEX (right click on the check in box/properties/default value/checked Male ☒ Female ☐

EDUCATION (Begin with baccalaureate training and include postdoctoral.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Edinburgh	MB,ChB	1986	Doctor of Medicine & Surgery
Royal College of Surgeons of Edinburgh	FRCSE	1990	Surgery in General
Royal College of Physicians & Surgeons of Glasgow	FRCS(Glas)	1990	Surgery in General
Intercollegiate	FRCSE(Orth)	1995	Trauma & Orthopaedic Surgery

RELATIONSHIP TO PROPOSED PROJECT	MAJOR RESEARCH INTEREST
Principal Investigator	Trauma, Compartment syndromes, RCTs

HONORS

Visiting Professor, University of Perugia, Italy (2005 - 2015)

OTHER RESEARCH SUPPORT

RESEARCH AND/OR PROFESSIONAL EXPERIENCE (Start with present position: list ALL experience relevant to project. Include publications.)

Trauma Surgeon & Professor, Aberdeen Royal Infirmary & University of Aberdeen, Scotland UK, (1997-present)

Runner up for the prize – 'Scottish Health Innovator of the Year 2006'

Winner - 'The most promising SME in Bio-Sciences in Scotland Year 2006' (B1 Medical Ltd.)

SoftCell Medical Limited – Inventor, Clinical Director (2010 - present)

Director of Research, Orthopaedic Trauma Unit, Aberdeen (2011- present)

Board Member, International Society for Fracture Repair (2012 – present)

Winner - 'The SHIL award for the Best Innovation originating in NHS Scotland, Year 2012

Member of the British Orthopaedic Association Research Committee (2013 – 2017)

Highlight Paper Award, Orthopaedic Trauma Association, (2015)

Chairman, Data & Safety Monitoring, World Hip Trauma Evaluation RCTs 4, 5 & 7 (2016 – 2020)

Chair of the Research Committee, Orthopaedic Trauma Society, United Kingdom (2016 - present)

Winner – 'The Innovation Award', Elevator awards, 2018 (Softcell Medical Ltd)

Recent or relevant publications:

Johnstone AJ, Ball D. Determining ischemic thresholds through our understanding of cellular metabolism. Compartment syndrome: a guide to diagnosis and management. Eds: Mauffrey C, Hah DJ, Martin MP. Springer,2018 (in press).

Nherera LM, Trueman P, Horner A, **Johnstone AJ**, Watson TJ, Fatoye FA. Comparing the costs and outcomes of an integrated twin compression screw nail (ITCS) with standard of care using a single lag screw or a single helical blade cephalomedullary nail in patients with intertrochanteric hip fractures. J Orthop Surg Res 2018 (in press).

Rehman H, Gardner WT, Rankin I, **Johnstone AJ**. The Implants used for Intramedullary Fixation of Distal Fibula Fractures: A Review of Literature. Int J Surg. 2018 [Epub ahead of print].

Medlock G, Smith M, **Johnstone AJ**. Combined Volar and Dorsal Approach for Fixation of Comminuted Intra-Articular Distal Radial Fractures. J Wrist Surg. 2018;7:219-26.

Nherera L, Trueman P, Horner A, Watson T, **Johnstone AJ**. Comparison of a twin interlocking derotation and compression screw cephalomedullary nail (InterTAN) with a single screw derotation cephalomedullary nail (proximal femoral nail antirotation): a systematic review and meta-analysis for intertrochanteric fractures. J Orthop Surg Res. 2018;13:46.

McMillan TE, **Johnstone AJ**. Primary screw perforation or subsequent screw cut-out following proximal humerus fracture fixation using locking plates: a review of causative factors and proposed solutions. Int Orthop 2018;42:1935-42.

McMillan TE, **Johnstone AJ**. Technical considerations to avoid delayed and non-union. Injury 2017;48:S64-68.

Smith M, Medlock G, **Johnstone AJ**. Percutaneous screw fixation of unstable ankle fractures in patients with poor soft tissues and significant co-morbidities. Foot Ankle Surg. 2017;23:16-20.

Medlock G, Wohlgemut JM, Stevenson IM, **Johnstone AJ**. Magnetic resonance imaging investigation of radio-lunate relations: use in assessing distal radial fracture reduction. J Hand Surg Eur Vol. 2017;42:271-4.

Handoll HH, Brealey SD, Jefferson L, Keding A, Brooksbank AJ, **Johnstone AJ**, Candal-Couto JJ, Rangan A. Defining the fracture population in a pragmatic multicentre randomised controlled trial: PROFHER and the Neer classification of proximal humeral fractures. Bone Joint Res. 2016;5:481-9.

Barker SL, Rehman H, McCullough AL, Fielding S, **Johnstone AJ**. Assessment Following Distal Radius Fractures: A Comparison of 4 Scoring Systems, Visual Numerical Scales, and Objective Measurements. J Hand Surg Am. 2016;41:219-24.

Morrisey BE, Delaney RA, **Johnstone AJ**, Petrovick L, Smith RM. Do trauma systems work? A comparison of major trauma outcomes between Aberdeen Royal Infirmary and Massachusetts General Hospital. Injury. 2015;46:150-5.

Elliott KG, **Johnstone AJ**. Diagnosing acute compartment syndrome. J Bone Joint Surg Br. 2003;85:625-32.

Elliott KGB, **Johnstone AJ**. Acute Compartment Syndrome: resolving the diagnostic challenges using intramuscular pH. Highlight Paper, OTA Specialty Day, New Orleans, USA, 2014. (Paper)

Elliott KGB, **Johnstone AJ**. Diagnosing Acute Compartment Syndrome: Clarity at last! AAOS, Chicago, USA, 2013. (Paper)

Elliott KGB, **Johnstone AJ**. Acute Compartment Syndrome: resolving the diagnostic challenges using intramuscular pH. OTA, Phoenix, USA, 2013. (Paper)

Johnstone AJ, Elliott KGB. Acute compartment syndrome: intramuscular pH supersedes pressure in making the diagnosis. 13th International Society for Fracture Repair Meeting, Kyoto, Japan, 2012. (Paper)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Andrew H. Schmidt	Professor	12/06/1960
PLACE OF BIRTH (City, State. Country) Denver, CO, USA	NATIONALITY (If non-US citizen indicate visa status) USA	SEX (right click on the check in box/properties/default value/checked Male ☒ Female ☐

EDUCATION (Begin with baccalaureate training and include postdoctoral.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Colorado, Boulder, CO	BSEE	1984	Electrical Engineering
University of California, San Diego, CA	MD	1988	Medicine
Oregon Health & Science University, Portland, OR	Internship	1989	General Surgery
Oregon Health & Science University, Portland, OR	Residency	1993	Orthopaedic Surgery
Hennepin County Medical Center, Minneapolis, MN	Fellowship	1994	Trauma, Total Joint, Shoulder surgery

RELATIONSHIP TO PROPOSED PROJECT	MAJOR RESEARCH INTEREST
Co-Principal Investigator	Trauma, Compartment syndromes, RCTs

HONORS

Visiting Professor, University of California, San Francisco, April 2018

OTHER RESEARCH SUPPORT

1. CDMRP Log Number: JW160020 Grants.gov ID Number: GRANT12126684
   Project Duration: 48 months Total Budget Requested: $5,061,721 Direct Costs: $3,824,265 Indirect Costs: $1,237,455
   Title: Development and Dissemination of Clinical Practice Guidelines and Appropriate Use Criteria for Treatment of Major Extremity Trauma
   Principal Investigator: Ellen Mackenzie, Co-PIs Andrew Schmidt, MD, AE Johnson MD
   Contracting Organization: Johns Hopkins University

2. "Major Extremity Trauma Research Consortium, CORE site PI". Department of Defense. $844,242, 9/1/10 – 8/31/15. Seven METRC studies being done at my institution

RESEARCH AND/OR PROFESSIONAL EXPERIENCE (Start with present position: list ALL experience relevant to project. Include publications.)

Chief of Orthopaedic Surgery, Hennepin County Medical Center, Minneapolis, 2014-present

Professor, University of Minnesota, (2009-present)

President, Orthopaedic Trauma Association, 2013-2014

Fellow, American Orthopaedic Association

Relevant publications:

Schmidt AH, Bosse MJ, Obremskey WT, et al. Is continuous near-infrared spectroscopy a reliable method to monitor development of acute compartment syndrome in patients with leg injuries? J Bone Joint Surg Am, 2018, in press.

Collinge C, Attum B, Tornetta P III, Obremskey W, Ahn J, Mirick G, **Schmidt** A, et al. Acute compartment syndrome: An expert survey of Orthopedic Trauma Association (OTA) members. J Orthop Trauma 2018;epub.

Schmidt AH, Bosse MJ, Frey K, et al. Predicting Acute Compartment Syndrome (PACS): The Role of Continuous Monitoring. J Orthop Trauma 2017;31 Suppl 1:S40-S47.

Schmidt AH. Acute Compartment Syndrome. Injury 2017;48 Suppl 1:S22-S25.

Schmidt AH. Acute Compartment Syndrome. Orthop Clin N Am 2016;47(3):517-525.

Harvey EJ, Sanders DW, Shuler MS, Lawendy A-R, Cole AL, AlQahtani SM, **Schmidt AH**. What's new in acute compartment syndrome? J Orthop Trauma 2012;26:699-702.

Schmidt AH. Invited Commentary: The reliability of measurement of tissue pressure in compartment syndrome. J Orthop Trauma 2012;26:e166.

Odland RM, **Schmidt AH**. Compartment syndrome ultrafiltration catheters: report of a clinical pilot study of a novel method for managing patients at risk of compartment syndrome. J Orthop Trauma. 2011;24:358-365.

Schmidt AH. The impact of compartment syndrome on hospital length-of-stay and charges among adult patients admitted with a fracture of the tibia. J Orthop Trauma. 2011;25:355-357.

Weinlein J, **Schmidt AH**. Compartment syndrome in tibial plateau fractures. Beware! J Knee Surg 2010;23:9-16.

Odland R, **Schmidt AH**, Hunter B, Kidder L, Bechtold JE, Linzie BM, Hargens AR. Use of tissue ultrafiltration for treatment of compartment syndrome: A pilot study using porcine hindlimbs. J Orthop Trauma, 2005;19:267-75.

Other recent publications:

Sprague S, Schemitsch EH, Swiontkowski M, et al. Factors Associated with Revision Surgery Following Internal Fixation of Hip Fractures. J Orthop Trauma [Accepted February 2018]

Sprague S, Bhandari M, Heetveld MJ, et al. Factors Associated with Health-Related Quality of Life, Hip Function, and Health Utility after Operative Management of Femoral Neck Fractures. Bone Joint J [Accepted September 2017]

Kyle RF, Duwelius PJ, Haidukewych GJ, **Schmidt AH**. Arthroplasty for Unreconstructable Acute Fractures and Failed Fracture Fixation About the Hip and Knee in the Active Elderly: A New Paradigm. Instr Course Lect. 2017;66:181-192.

Sprague S, Slobogean GP, Bogoch E, et al. Vitamin D Use and Health Outcomes After Surgery for Hip Fracture. Orthopedics. 2017 Oct 1;40(5):e868-e875.

Stinner DJ, Wenke JC, Ficke JR, et al. Military and civilian collaboration: The power of numbers. Mil Med 2017;182:(3/4 Suppl):10.

Wegener S, Carroll E, Gary J, et al. Trauma collaborative care intervention: effect on surgeon confidence in managing psychosocial complications following orthopaedic trauma. J Orthop Trauma, 2017;31(8):427-433.

Obremskey WT, **Schmidt AH**, O'Toole RV, et al. A Prospective Randomized Trial to Assess Oral Versus Intravenous Antibiot the Treatment of Postoperative Wound Infection After Extremity Fractures (POvIV Study). J Orthop Trauma 2017;31:S S38.

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Manson T, **Schmidt AH**. Acetabular Fractures in the Elderly: A Critical Analysis Review. JBJS Reviews 2016;4(10);e1.

SECTION 5

BIOGRAPHICAL SKETCH

Not to exceed two pages for each person. Copy and paste below the two Bio-Sketch pages for each additional Investigator.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Derek Ball	Dr	12/14/60
PLACE OF BIRTH (City, State. Country) Bolton, Lancashire, UK	NATIONALITY (If non-US citizen indicate visa status) British – ESTA visa	SEX (right click on the check in box/properties/default value/checked Male ☒ Female ☐

EDUCATION (Begin with baccalaureate training and include postdoctoral.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Royal College of Nursing	RGN	1985	General Nursing
Manchester Metropolitan University	BSc (Hons)	1989	Sport Science
University of Aberdeen	PhD	1993	Medical Sciences

RELATIONSHIP TO PROPOSED PROJECT	MAJOR RESEARCH INTEREST
Co-Investigator	Muscle metabolism, exercise physiology and biochemistry

HONORS

Fellow of Royal Society of Biology (elected in 2015)

OTHER RESEARCH SUPPORT

RESEARCH AND/OR PROFESSIONAL EXPERIENCE (Start with present position: list ALL experience relevant to project. Include publications.)

Head of Sport Science, University of Aberdeen, Scotland UK, (2017-present)

Director of Program in Human Health and Disease, Heriot-Watt University, Edinburgh, UK, (2006-2017)

Finalist - Converge Challenge (Scotland's company creation program) 2012

Recent or relevant publications:

Relevant publications

Johnstone AJ, **Ball D**. Determining ischemic thresholds through our understanding of cellular metabolism. Compartment syndrome: a guide to diagnosis and management. Eds: Mauffrey C, Hah DJ, Martin MP. Springer,2018 (in press).

Ball D. Metabolic and endocrine response to exercise: sympathoadrenal integration with skeletal muscle. J Endocrinol 2015; 224: R79-R95

Ferguson RA, Krustrup P, Kjaer M, Mohr M, **Ball D**, Bangsbo J. Effect of temperature on skeletal muscle energy turnover during dynamic knee-extensor exercise in humans. J Appl Physiol. 2006; 101:47-52.

Collins P, Ford I, **Ball D**, Macauley E, Greaves M, Brittenden J. A preliminary study on the effects of exercising to maximum walking distance on platelet and endothelial function in patients with intermittent claudication. Eur J Vasc and Endovasc Surg 2006; 31:266-73.

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Sakkas GK, **Ball D**, Sargeant AJ, Mercer TH, Koufaki P, Naish PF. Skeletal muscle morphology and capillarization of renal failure patients receiving different dialysis therapies. Clin Sci (Lond). 2004;107:617-23.

Sakkas GK, **Ball D**, Mercer TH, Naish PF. An alternative histochemical method to simultaneously demonstrate muscle nuclei and muscle fibre type. Eur J Appl Physiol. 2003;89:503-5

Rajab P, Fox J, Riaz S, Tomlinson D, **Ball D,** Greenhaff PL. Skeletal muscle myosin heavy chain isoforms and energy metabolism after clenbuterol treatment in the rat. Am J Physiol (Regulatory Integrative Comp Physiol). 2000;279:R1076-81

Ferguson RA, **Ball D,** Krustrup P, Aagaard P, Kjaer M, Sargeant AJ, Hellsten Y, Bangsbo J. Muscle oxygen uptake and energy turnover during dynamic exercise at different contraction frequencies in humans. J Physiol, 2001;536:261-71

SECTION 6

RESEARCH SUPPORT, SUBMISSIONS

Please combine the information on this page for PI and Co-PI. Add additional lines and pages as needed, there is no word limit in this section.

Prior OTA Funding to Principal Investigator or Co-P.I.:			
SOURCE OF SUPPORT	TITLE OF PROJECT	AMOUNT	PERIOD OF
OTA	Intramedullary Nails versus Plate Fixation Re-Evaluation Study in Proximal Tibia Fractures: A Multicenter Randomized Trial Comparing IM Nails and Plate Fixation (IMPRESS)	$80,000	1/1/08 – 12/31/09
OTA	Effect of OP-1 on Gene Expression in Chronically Infected Femoral Segmental Defect in the Rat	$25,000	1/1/05 – 12/31/05
OTA	Role of Bone Morphogenetic Protein-2 in Bone Formation in the Presence of an Infection. A Titanium Bone Chamber Model in Rabbits	$18,263	1/1/00 – 12/31/00
OTA	Therapeutic Role of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) in Infected Fractures of Rabbit	$19,892	1/1/97 – 12/31/97.

Research Support to Principal Investigator or Co-PI Relevant to THIS Project Past 5 Years (Include That From Own Institution):			
SOURCE OF SUPPORT	TITLE OF PROJECT	AMOUNT	PERIOD OF
Softcell Medical limited	Pilot experiment comparing new medical pH recording equipment to current devices	£15,110	03/01/18 – 05/01/18

Support To Principal Investigator or Co-PI for OTHER Research Projects:			
SOURCE OF SUPPORT	TITLE OF PROJECT	AMOUNT	PERIOD OF

Previous Research:			
SOURCE OF SUPPORT	TITLE OF PROJECT	AMOUNT	PERIOD OF
Smith & Nephew Inc	Semi-extended v 90˚ flexion of the knee – IM nailing of the tibia	£32,000	10/01/10-11/01/14
National Institute for Health Research (UK)	FixDT (Distal Tibial Fracture study	£24,000	01/01/14-05/01/16
	UKSTAR trial (Achilles tendon rupture)	£19,200	10/01/16-06/01/18

Current Research:			
SOURCE OF SUPPORT	TITLE OF PROJECT	AMOUNT	PERIOD OF
INSURT group (Canada)	INSURT (Suprapatellar v infrapatellar nailing	CD$750/patient	Due to

	of the tibial)	recruited	commence Autumn 2018
Johns Hopkins Bloomberg School of Public Health (Co-PI)	Development and Dissemination of Clinical Practice Guidelines and Appropriate Use Criteria for Treatment of Major Extremity Trauma	$45,735.00 (paid to Minneapolis Medical Research Foundation)	10/1/16 – 9/30/17

Submissions Of This Or Similar Project To Other Agencies:

SUBMITTED: None

PLANNED: None