Version 3 (Jan 2023)

Invasive Procedures

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1. Introduction

A universal definition for invasive procedures is currently lacking even in areas such as healthcare where use of invasive procedures is a standard practice. In 2018, the need for a definition was highlighted (Cousins et al. https://bmjopen.bmj.com/content/9/7/e028576) since an accepted definition has many benefits including improvement in the accuracy of categorisation and tracking of research activity.

Reference Definition:

- "An invasive procedure is one where purposeful/deliberate access to the body is gained via an incision, percutaneous puncture, where instrumentation is used in addition to the puncture needle, or instrumentation via a natural orifice. It begins when entry to the body is gained and ends when the instrument is removed, and/or the skin is closed. Invasive procedures are performed by trained healthcare professionals using instruments, which include, but are not limited to, endoscopes, catheters, scalpels, scissors, devices and tubes.

- Where invasive procedures also involve the administration of a medicinal product, these could be categorised as being part of an 'invasive procedure' when operator skill is required for its administration within the body, that is, when an internal action is performed to administer the product or the product is administered to a targeted anatomical area, for example, (Zhu et al). There are also procedures which involve operator skill to target something inside the body (eg, electromagnetic radiation in the eye) without an incision, percutaneous puncture or instrumentation via a natural orifice. These types of procedures do not fall within the definition of an invasive procedure."

Within the areas of sport science and sport medicine the use of moderately invasive procedures is typically required, so clinical and biological samples can be acquired to address specific research questions. In our university, invasive procedures are classified as:

- **moderately invasive**
- **invasive** and
- **more invasive** that are not routinely undertaken and can cause harm

The procedures that would fall under the definition of invasive procedures above and are widely adopted within the Carnegie School of Sport include:

1) Fingertip Blood Sampling (moderately invasive)
2) Phlebotomy and Cannulation (invasive)
3) Muscle Biopsy (more invasive)
4) Oral or venous/arterial administration of ^{13}C Stable Mass Isotopes (Invasive)
5) Using rectal thermometer and/or core temperature pills to measure core temperature (Invasive)

Each of these invasive procedures will be commented on in detail below, with regards best practice and any ethical implications. However, it is worth noting that collection and storage of clinical and biological samples falls within the scope of the Human Tissue Act (The Human Tissue Act 2004, https://www.hta.gov.uk/policies/human-tissue-act-2004) which needs to be considered alongside the use of invasive procedures.

2. Human Tissue Act

All practice that involves human tissue sampling is subject to the jurisdiction of the Human Tissue Act, 2004. Thus, the identification of what constitutes "Relevant material" is germane to any assessments on proposals made to the Carnegie School of Sport Research Ethics Advisory Group (and the University Research Ethics Committee). Current guidance would indicate that certain samples typically collected during sport and exercise research trials, (but not exclusively so) are "Not Relevant material" whilst

others are. This is of importance in the processing and storage of such samples due to the time and condition imposition within the Human Tissue Act. The following is a simple guide to "Relevant" and "Not-Relevant" material. "Relevant material" is that deemed to contain human cells.

Relevant Material includes:

Stem Cells

Bone Marrow

Blood

Faeces

Urine

Sweat

Muscle Tissue

Saliva

Not Relevant Material includes:

Hair (living person)

Nails

Plasma

Serum

It follows that samples that are "Not Relevant" may be stored on University premises (subject to compliance with standard ethical clearance for trials in which such samples are collected). Whilst this is a clear factual demarcation, this does not necessarily exclude the collection and storage of samples that are relevant. For example, if samples undergo procedures (e.g., centrifugation to separate cells from plasma/serum) that render it acellular then it need not be considered "Relevant material". In this case proposals for ethical clearance should state fully the collection and procedures which render a "Relevant" sample "Not Relevant". This is sufficient to enable storage on University premises.

The issue for our School (and University) would be the approval of proposals that include "Relevant" samples and the way in which such samples are to be analysed and stored. Thus, samples which we consider to primarily be "Relevant" could be made, by procedure "Not Relevant" (e.g., urine after centrifugation or filtration). If storage is an issue, then under the Human Tissue Act such storage must be licensed by the Human Tissue Act. At present the School and University does not have such license. Nevertheless, storage may be possible for a specific research project provided favourable opinion has been granted

by a designated ethics committee. In this instance this would be by a designated National Research Ethics Committee. Although the details of the Human Tissue Act are published (https://www.legislation.gov.uk/ukpga/2004/30/contents), several "grey" areas remain, for example what constitutes "storage", this could be interpreted as batching of a sample set over a time period or otherwise. Clearly, collection of samples over several hours and subsequent analysis or dispatch to a laboratory for which a license has been granted may be deemed acceptable by a specific interpretation of the Human Tissue Act. After previous consultation (by Professor Rod King) with Dr Andrew Rawnsley (Research Governance and Training Manager, Teeside University) some of these points had been resolved (see below), but if the extent and nature of research in the University changes then we should consider an application for a license under the Human Tissue Act to facilitate the authorisation of research in which relevant samples are an issue. The inclusion or exclusion of samples from the Human Tissue Act is of course also dependent on qualifying consent and assurance about processing of tissue with the participant of any trial.

Storage of Samples

1) *Standard Conditions pertaining to ordinary University ethical consideration (no site license in force)*

Samples that are "Relevant material" should be collected and analysed as soon as possible but not more than 24 hours after collection. Samples should then be discarded.

2) *Permitted Conditions pertaining to extraordinary University ethical consideration*

   a. *Joint Ethical Proposal*

Samples that are "Relevant material" should be collected and dispatched to a licensed laboratory as soon as possible but not more than 48 hours after collection. Such would apply for example when there is a joint protocol with another establishment at which a site license is in force at their premises. School (University) ethical consideration would have been made on such an understanding.

   b. National Research Ethics Committee Favourable Opinion

Samples that are "Relevant material" should be collected and stored in suitable University premises. Such would apply for example when special favourable opinion has been given to a specific proposal and project by an external National Research Ethics Committee. Such may be granted where the proposal and project are purely for scientific research purposes. It is unlikely that more than two such favourable opinions would be granted at any one time for the University. School (University) ethical consideration would also be made on such an understanding.

   c. *Standard Conditions pertaining to ordinary University ethical consideration (site license in force)*

Samples that are "Relevant material" should be collected and stored in suitable university premises.

Notes

The following descriptors have relevance to the Human Tissue Act and should be considered if appropriate, as associated guidelines and legislation may apply to the sampling and storage of samples.

i) Mental Health/Mental Capacity
ii) Tissue
iii) Dangerous Materials
iv) Radiation
v) Child Protection
vi) Insurance
vii) Clinical Trials (Regulations 2006, Medicine for Human Use)
viii) Consent form inclusion

3. Invasive Procedures Blood Sampling

Fingertip Blood Sampling (moderately invasive procedures)

Obtaining fingertip blood samples, when conducted by a trained and competent person and in accordance with the guidelines of our professional association (BASES), is a low-risk activity. Under the conditions stipulated below this should be approved as part of a research ethics application at a local level. **NOTE**: Similarly to question 22 (i.e. incidental health findings), applicants will need to answer "yes" to question 20 about use of intrusive or invasive procedures however the project will be treated as Risk Category 2 and NOT Risk Category 3; the only requirement will be that the applicants communicate to the relevant LREC or SLREC at the start of the main ethics application why the project was classified as Category 3.

The applicant (if an undergraduate or post-graduate student) must demonstrate experience in using this procedure during taught modules, as well as undergoing a physiology laboratory induction and the specific training for fingertip blood sampling in preparation for their research project. This training is delivered at various times throughout the year by the Learning Support Officers.

As part of that process applicants will need to be assessed by the Learning Support Officer delivering the training. They need to be signed off as competent by the Learning Support Officer and for this specific skill and have that evidence attached to their ethics application. Data collection cannot commence until the individuals engaging with data collection have been signed off as competent.

Phlebotomy and Cannulation (invasive procedures, category 3 projects)

Phlebotomy procedures are regularly used within Carnegie School of Sport's research, however, they are invasive and of higher risk. Phlebotomy (venous blood sampling) is a technique used when blood is required to be drawn on a single occasion. This is where a small needle is inserted into an appropriate vein, which remains *in situ* until the blood have been drawn and then it is immediately removed. Cannulation is a technique used when blood is required at regular intervals over a set period of time. This is where a catheter is inserted in an appropriate vein. This procedure requires a small needle to be inserted into the selected vein, once the needle is in the vein a small plastic tube is

gently pushed into the lumen of the vein. The needle is then withdrawn, and the remaining part of the catheter is secured in place for the set time period. Both techniques should only be undertaken by a trained and competent person, which is usually an academic, a learning support officer, or a post-graduate research student.

Under certain circumstances an ethics application could be signed off by the Local Research Ethics Coordinator, as long as the following criteria are met, even though this is an invasive procedure:

1) The researcher has been deemed competent and can provide the relevant supporting evidence (i.e., signed assessment log).
2) The lead researcher has previously received School Level Ethical Favourable Opinion to use these techniques on more than two research studies (this acts as a way of confirming their experience).

If criteria 1 can be satisfied, but criteria 2 cannot be met, then any ethics applications should be referred to the School of Sport Research Ethics Advisory Group for consideration using the published timetable. It is important to note that other elements of the ethics application may need to be approved by the School of Sport Research Ethics Advisory Group.

Muscle Biopsy (more invasive procedures, category 3 projects)

Taking a muscle biopsy enables a range of biological analyses to be performed to inform specific research questions. The muscle biopsy procedure involves the removal of a small piece of muscle tissue (typically 50-100 mg) typically taken from the *vastus lateralis* using a small sterile hollow needle. Prior to the taking the biopsy, and following skin cleaning, a small amount of local freezing (anaesthetic) should be injected into and under the skin. There is an extremely low risk of allergic reaction to the local injection (1 in 1 million). The chance of a local skin infection in less than 1 in 1000. Participants are likely to experience some soreness in the muscle and some local bruising following each biopsy.

Using muscle biopsy procedures in research is a high-risk activity, but under the conditions stipulated below should be approved as part of a research ethics application at School level:

Muscle biopsies should ONLY be taken by a competent and trainer professional. Presently, a range of qualified medics are supporting the School with regards this procedure. Their medical qualifications, curriculum vitae's, and where relevant confirmation of competency should be logged in the School's ethics repository for access by our Insurers. All medical consultants and clinicians are covered by the Universities Public Liability for taking muscle biopsies on a voluntary basis on behalf of the University. It will also cover all University staff (qualified medical practitioners) who conduct them as part of an approved project subject to the usual risk assessments and SOP documents.

Lastly, prior to participation all volunteers should be screened to diagnose any underlying pathology, or any medication, that could increase the risk of excessive bleeding, allergic reaction, infection or any other medical condition associated with the procedure.

Administration of isotope tracers

^{13}C Stable Mass Isotopes (invasive, category 3 project)

^{13}Carbon stable mass isotope tracer techniques are used in research that needs to quantify exogenous and endogenous (e.g., liver, muscle) carbohydrate and fat oxidation rates, following the ingestion of carbohydrate-based beverage. ^{13}C is naturally occurring in the diet (~1%) and is less abundant than the naturally occurring ^{12}C in the diet (~99%). It is a non-radioactive isotope. A trace amount is used to enrich typically carbohydrate beverages (~>1.5%), which is a safe increase.

This technique allows researchers to evaluate the ratio of ^{13}C/^{12}C in expired air and plasma glucose typically during exercise, to ascertain the rates at which the exogenous source of carbohydrate is being used as a fuel and the rate at which pre-existing stores of glycogen (liver and muscle) are being used.

Approved suppliers should always be used, and products should be stored and used in a safe and secure manner. Trained and experienced lead researchers should oversee the use and administration of ^{13}C stable mass isotopes.
This technique is low risk and there is no reason why this cannot be signed off at a local level, by the Local Research Ethics Coordinator.

Dual X-Ray Absorptiometry

Please see separate guidelines