Guidelines for Ethics Approval of Research Protocols Involving Human Exposure to Magnetic Resonance Imaging

A. Introduction:

The Health Sciences Research Ethics Board at the University of Western Ontario frequently receives research applications that involve the use of (1) healthy volunteers as imaging subjects, or (2) patients volunteering for imaging studies beyond what would be considered medically necessary. Since the potential benefits of this diagnostic tool are not directly applicable to either group of participants, the potential risks need to be considered carefully.

B. MRI Background:

MRI is a widely used imaging modality for both clinical diagnosis and investigational research in human subjects because of its extreme flexibility, the capability to evaluate anatomic, physiologic and functional information and because it is non-invasive and does not use ionizing radiation. Three different electromagnetic fields are employed to create tissue specific information based on magnetic resonance: (i) a strong static magnetic field, (ii) a radiofrequency field, and (iii) time varying magnetic field gradients. There is a vast field of literature investigating the bio-effects of these electromagnetic fields produced by MRI systems and the subsequent effect on the human body. These findings indicate that in the absence of ferromagnetic foreign bodies, implants and other biomedical devices, there is no evidence of hazard to human subjects within an MR environment. Field strengths up to 8 Tesla have been used for human research since the late 1990's and field strengths up to 3 Tesla have been used clinically since the mid 1990s. Currently, human MRI systems in London operate at field strengths ranging from 1.5 T up to 7.0 T (T = Tesla, the basic unit reflecting the strength of the magnetic field. For reference, 1 Tesla is 20,000 times the earth's magnetic field).

C. The Human Effects of MRI Static Magnetic Field

There exists a broad spectrum of mechanisms between static magnetic fields and biological tissue. Included in this list are: magnetic forces from tissue susceptibility differences, magnetic torques from anisotropic susceptibilities, motion-induced currents causing nerve or muscle stimulation, changes in chemical reaction rates, magneto hydrodynamic forces, and magnetic excitation leading to sensations such as nausea, vertigo and magnetophosphenes. Despite this, and in the absence of ferromagnetic foreign bodies, there exists no replicated scientific study to suggest any health hazard with exposure (acute or cumulative) to static magnetic fields up to and including 8 Tesla. It is relevant to note that the strength of the magnetic field surrounding the magnet (fringe field)

decreases rapidly with increasing distance from the magnet centre. The nature of the fringe field is dependent on the strength, size and design of the magnet. This information is of particular interest to MRI technical personnel working in and around the magnet and for the design of surveillance and exclusion zones for metallic objects and the public.

Gradient Fields Rate of Change (dB/dt)

The lower intensity 'switched' magnetic field however, induces electric fields within the body that, if of sufficient strength, can cause peripheral nerve stimulation and therefore sensory or motor effects. If the switching rate or intensity of magnetic field is increased by a substantial factor above the peripheral nerve excitation threshold, stimulation of cardiac tissue is theoretically possible and this represents the greatest concern. For this reason, current international guidelines require that magnetic fields be kept at or below the peripheral nerve excitation thresholds. These levels are well below (approximately by a factor of 10) the cardiac stimulation thresholds. In part, this x10 safety threshold is maintained because the excitation characteristics of cardiac impaired subjects are not known, hence it is advisable to have a physician present when scanning such subjects.

Specific Absorption Rate (SAR) and Radio Frequency (RF)

Another component of the MR environment utilizes a **radio frequency (RF)** field to elicit signals from tissue. These RF pulses can increase local tissue temperature as well as body core temperature. While complex in its biological interaction there is widespread agreement that local increases of temperature, known as the **specific absorption rate (SAR)**, by one degree Celsius in a healthy individual is free of risk. The rationale for this comes from the fact that core body temperatures can rise many times this amount during normal exercise, and therefore the body clearly has mechanisms to be able to cope with this type of increase. Specific guidelines are mandated on all clinical systems to keep tissue heating below the 1 degree Celsius limit. With regard to biologically foreign objects, RF pulses can induce electrical currents in conductive devices such surgical implants, skin patches or even body piercings. Also, when using conductive patient leads during MRI scanning, such as ECG, it is especially critical that no loops are formed by the leads. To further reduce the possibility of burns, it is recommended to thermally insulate electrically conductive material in the bore of the magnet from the patient using blankets or sheets.

D. High Risk Groups

Exposure risk is highest in individuals with metallic objects, implants or biomedical devices. The MR environment can be unsafe due to the potential of dislodgement of ferromagnetic objects such as vascular clips, which may translate or torque in the magnetic field causing trauma to surrounding tissue. There is also the risk of heating or induction of electrical currents within conductive implants or devices such as skin patches, body piercing or tattoos containing metallic inks causing burns to adjacent tissue. Of special concern are individuals with cardiac pacemakers. The electromagnetic disturbance of a pacemaker's electronic program may lead to heart dysrhythmias. An international database of MRI compatible objects is maintained, but unless it can be ascertained that the object in question is safe at the magnetic field of the study, the subject should not be scanned.

In summary, from human studies of static magnetic field exposure up to 10 T and from clinical evidence involving well over 250 million clinical MRI scans, with the exception of those individuals carrying ferromagnetic implants or electronic implants, there appears to be a substantial margin of safety with human exposure up to 8 Tesla. However, there may be, as yet, unidentified risks.

E. Current US and EU Guidelines for Human MRI Exposure:

The US FDA first provided guidelines for MRI patient exposure in 1982 setting the 'safe' static magnetic threshold at 2 T adding further guidelines in 1988 to limit tissue heat induction and acoustic exposure. Harmonized guidelines were established by the EEC member states in 1994 incorporating the FDA recommendations. In July 2003, the USFDA released a new document – "Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices" - superseding the previous document – "Guidance for Magnetic Resonance Diagnostic Devices – Criteria for Significant Risk Investigations", issued in September 1997 recommending the main static magnetic field strength, increase from 4 Tesla to 8 Tesla for most populations. The FDA deems magnetic resonance diagnostic devices do not pose a significant risk when used under any of the operating conditions described below.

a) **Main static magnetic field:**

8.0 Tesla and lower – has been determined to be safe for adults, children and infants greater than 1 month old

4.0 Tesla and lower – has been determined to be safe for infants aged less than 1 month

b) **Specific Absorption Rate (SAR) of heat**:

4.0 watts / Kg /15 min whole body exposure
3.0 watts / Kg / 10 min head exposure
8.0 watts / kg / 5 min per gram of tissue in head or torso
12.0 watts / kg / 5 min per gram of tissue in extremities

c) Gradient Fields Rate of Change:

Case by case limit of change of gradient field (dB/dt) to avoid severe discomfort or painful nerve stimulation

d) Sound Pressure Level (SPL):

140 decibels (dB) peak
99 dB A-weighted root mean squared with hearing protection

F. Current Canadian Guidelines:

The Health Protection Branch of the then Department of National Health and Welfare of Canada published 'Guidelines on Exposure to Electromagnetic Fields from Magnetic Resonance Clinical Systems' in 1987. It was stated that their exposure guidelines reflected 'minimal, if any, health hazard', --- and that 'exceeding the limits specified are not necessarily hazardous, but a careful individual evaluation should be done as the presently available scientific data are not sufficient for providing general recommendations.' These guidelines are now considered to be severely outdated. Health Canada has allowed the import of over 25 Human 3T clinical MRI scanners, and research scanners from 3 to 7 T, falling back on the expertise of the FDA.

1. Under the **'Patient'** category, exposure limits are:
   a) static magnetic field: 2 T.
   b) time-varying magnetic fields: 3T/sec
   c) RF magnetic field: which does not cause an increase of body temperature (core or rectal) of more than 0.5C and of any part of the body of more than 1C.

2. Under the **'Operator'** category:
'Operators of MRI devices should not be continuously exposed to a magnetic flux density exceeding 0.01 T during the working day. Exposures to higher flux densities are permitted for short-time durations (about 10 min per hour); their number and duration should be minimized.'

3. **Special considerations:**
Individual assessment of suitability for MRI and precautionary measures should be employed for women who are pregnant or attempting to become pregnant, those wearing cardiac pacemakers and those bearing metallic implants (tooth fillings are not considered a hazard).

G. REB Considerations:

Until more current guidelines are provided by Health Canada the UWO REB will consider the following items when reviewing applications involving MRI research protocols:

1. Assurance must be provided that upper limits for operating conditions for magnetic resonance diagnostic devices, as defined in the 2003 USFDA Guidelines noted above (or most current at the time), are recognized and not exceeded by the applicants.

2. Any individual who may be subjected to magnetic resonance operating conditions which exceed the limits specified above should be specifically informed through a signed consent. While there is no replicated evidence to suggest the strength of the static magnetic field produces harmful effects there remains the potential for unknown adverse biological harm to levels of SAR, dB/dt and SPLs which are below or exceed the USFDA guidelines.

3. Precautions should be taken to ensure there are no overt or tacit inducements to specifically recruit trainees or technical staff working in the MRI laboratory under the supervision of professional staff as 'control' participants beyond their voluntary response to a general advertisement. All participants including control MRI participants should be fully informed about the principles of MR technology, its known effects on human tissue, its potential to cause harm, and have access to the current guidelines for human MRI exposure.

4. External ferromagnetic objects, implants and other biomedical devices pose the greatest potential risk to subjects in an MRI. Special precautions should be taken to ensure that study and control participants are rigorously screened prior to entering the MRI environment for contraindications to study participation.

5. Exposure to static magnetic fields up to 8 Tesla have not shown chronic biological effects.

6. Precautions should be taken to ensure participants are aware of the remote but potential risk for temporary reduction to hearing acuity from the loud noise inside the magnet and the potential for panic or anxiety due to the close confines of the MRI cylinder. The former can be reduced through the use of ear headphone protection. To avoid the latter, participants should be screened for claustrophobic tendencies.

7. Subject to these conditions, the HSREB will consider MRI studies for adults for delegated review, unless other criteria which may cause physical or mental anguish are also part of the study (e.g. pain studies, evocation of previous trauma etc.). Any study where the FDA mandated safety systems or limits are bypassed should also go to full review. All studies involving children will continue to be presented to the HSREB for full board review.

H. Special REB considerations when using neonates and infants:

Extensive and detailed studies of human brain development funded by the NIH. A large controlled study of human brain development (http://www.brain-child.org/home.htm) has found no anatomic, biological or behavioral effects of repeated MRI studies on neonates (babies aged less than one month) to 18 year old children. Nonetheless, an extended discussion of these risks in pediatric infant populations is presented here, but the conclusion is that these risks have been minimized to an acceptable level for infants participating in scientific research.

There are now several basic scientific research studies of MRI recording in non-sedated infants at 1.5T [Dehaene-Lambertz, Dehaene, Hertz-Pannier 2002][Evans 2006] and 3.0T [Gilmore, Zhai, Wilber, Smith, Lin, Gerig 2004][Rutherford, Malamateniou, Zeka, Counsell 2004], with much of that work being supported by the National Institutes of Health (e.g., MRI study of normal brain development [Evans 2006], Early brain development in twins (R01MY070890 [Gilmore 2005]), Early brain development in high risk children (P50MH064065 [Gilmore#2006]).

As mentioned above for adults and children, the US FDA lists four potential risks for the MRI: main static magnetic field, specific absorption rate (SAR), gradient fields rate of change, and sound pressure level [USFDA 2003]. In addition to these four, the presence of ferromagnetic materials in the scanner room poses a risk. The U.S. FDA considers MRI recording in infants to be a “non-significant” risk when used within FDA specified parameters [USFDA 2003][USFDA 2006]. This assessment is based on over 20 years of MRI recording in neonate and infants (e.g. [Barkovich, Kjos, Jackson, Norman 1988][Rivkin 2000]) with no reports of deleterious long-term effects, and on several studies showing no short-term or long-term effects from this type of recording [Schenck 2000][Kangarlu, Burgess, Zu 1999][Baker, Johnson, Harvey, Gowland, Mansfield 1994][Kok, de Vries, Heerschap, van den Berg, 2004][Clements, Duncan, Fielding, Gowland, Johnson,Baker, 2000][Myers, Duncan, Gowland, Johnson, Baker 1998]. These risks are discussed in detail in several sources [Stokowski 2005][Barkovich 2005][Dehaene-Lambertz 2001][Evans 2006][ACR 2002][ACR 2004] and the major points of those sources are reviewed here.

The first risk is the static magnetic field [Schenck 2000]. The FDA deems static magnetic fields up to 8.0 T are a non-significant risk to infants aged greater than 1.0 months and fields up to 4.0 T are acceptable non-significant risk for infants aged below 1 month. MRI scanning of normal neonates and infants is routinely done with magnetic fields at the 3 T level [Gilmore, Zhai, Wilber, Smith, Lin, Gerig 2004][Rutherford, Malamateniou, Zeka, Counsell 2004].

The second risk is the RF electromagnetic effects caused by electromagnetic coils and a transmitter that delivers RF pulses during the imaging [Shellock 2000]. This is the greatest of the four risks associated with the MRI process. The RF pulses may cause tissue heating, heating of implanted electrical devices, or heating of implanted metal. The RF "Specific Absorption Rate" (SAR) is the amount of energy per second absorbed per kilogram of body mass (Watts per kg, W/kg) from application of the RF pulses required by the MR acquisition. The US FDA sets the limits for SAR in MRIs. There are four maximum allowable SAR measures: 3 W/kg averaged over the whole head in 10 min, 4 W/kg averaged over the whole body in 15 min, or 8 W/kg per gram of head/torso tissue in 5 min or 12 W/kg per gram of extremity tissue over 5 min [USFDA 2003]. The SAR level is a major concern when performing MRI of infants, especially as magnetic strength increases. Compared to 1.5T, at 3T, more energy is required in order to flip the processing protons by the same flip angle. Due to infants' small mass, there is a larger proportion of body mass in the RF coil. This raises concern that any potential interactions may have a more significant effect on a body that is developing rapidly. As with adults the SAR of sequences needs to be carefully calculated and monitored. Nonetheless, as long as the FDA guidelines are adhered to, there should be no increased risk.

The magnetic gradients are the third FDA risk [Schaefer, Bourland, Nyenhuis 2000]. The magnetic gradients are time-varying magnetic fields (dB/dt) induced along the static magnetic field and induce electrical field changes in nuclei with magnetic moments. The magnetic gradients may induce circulating electrical currents in the conductive tissues of the body, producing change in nerve and muscle function, resulting in nerve stimulation, which potentially causes discomfort or painful nerve stimulation. The magnetic gradient effects are controlled by limiting the maximum rate of change in the magnetic gradients. The US FDA MRI standards state that significant risk will be "Any time rate of change of gradient fields (dB/dt) sufficient to produce severe discomfort or painful nerve stimulation" [USFDA 2003] but do not give a specific dB/dt limit. A suggested upper limit for non-significant risk are dB/dt of 20 T/sec [Schaefer, Bourland, Nyenhuis 2000]. The stimulation limits are determined by empirical procedures using clinical trials, and at the threshold level could result in nerve stimulation in nor more than 1% of individuals. Outcome studies of such effects show that the magnetic field or the magnetic gradients do not threaten the concurrent physiological stability of the infant during scanning [Battin, Maalouf, Counsell, Herlihy, Hall 1998][Taber, Hayman, Northrup, Maturi 1998][Stokowski 2005].

The fourth risk is the acoustic noise. The US FDA limit for sound is 140 dB (SPL, unweighted) or 99 dB (A) with hearing protection in place [USFDA 2003]. The main source of noise is the generation of the magnetic gradient, which can be about 100 dBA SPL for a Siemens 3 T Trio scanner. The magnet tunnel has internal acoustic insulation for noise protection which reduces noise and vibrations in the tunnel (~ -10 dbA). The sound level is reduced for the infant by placing sponge foam or wax ear plugs in the external ear canals, a foam pad

over the ears, and head phones or ear muffs (e.g., Avotec, Inc., Jensen Beach, FL) over the ears. The rise time of the gradient can also be modified to further reduce the noise levels for neonates and infants.

The fifth risk is from external ferromagnetic materials. These include biomedical implanted electrical devices (e.g., heart pacemaker, defibrillator, neurostimulator) or implanted metal (e.g., aneurysm clips, skull plate, metal pins, dental brace, bullet or bullet fragments, metal slivers, non-removable piercing), external ferromagnetic material brought into the room by the participant or parent (belts, shoes, diaper pins), and other ferromagnetic material in the scanner room. There are two risks to such ferromagnetic materials. First, the RF effects may cause heating of other materials, i.e., ferromagnetic or metal implanted materials, monitor cables or wires used for physiological monitoring, heating of diaper pins, or other materials in the scanner. Magnetic materials internal to the patient may undergo severe heating in the high magnetic fields and from the RF electromagnetic effects. Second, the ferromagnetic materials may become projectile missiles in the static magnetic field.

Another potential risk associated with conducting MRI with children is sedation. Often neonates and infants are sedated during MRI studies to reduce movement which can cause artifact or distortion in the MRI images.

Reference Sources:

1. *Criteria for significant risk investigations of magnetic resonance diagnostic devices*. www.fda.gov/cdrh/ode/guidance/793.pdf, FDA (2003).

2. Guidelines on exposure to electromagnetic fields from magnetic resonance clinical systems - Safety Code 26. www.hc-sc.gc.ca/ewh-semt/pubs/radiation/87ehd-dhm127/index_e.html, Environmental Health Directorate, Health Protection Branch, Department of National Health and Welfare Canada, (1987).

3. Schenck JF. Safety of strong, static magnetic fields. *JMRI* **12**:2-19 (2000).

4. Formica D and Silvestri S. Biological effects of exposure to magnetic resonance imaging: an overview. *Biomedical Engineering Online*, **3**:11 (2004).

5. Silva AKA, Silva EL, Egito EST, Carrico AS. Safety concerns related to magnetic field exposure. *Radiat Environ Biophys* **45**:245-252 (2006).

I. Informed consent documentation:

Wording required when the research participant is a child and the MRI is be done for research purposes only.

International controlled studies of human brain development on relatively small sample sizes (546 subjects) have shown no untoward effects of repeated MRIs between the ages of 0 and 18. Approximately 25 million clinical MRI procedures have also been performed on children, with no obvious effects. There is however, a small chance that an as yet unknown problem or side effect may be discovered.

In an effort to ensure consistency between all investigators and to streamline the review process by the HSREB, **the following wording is required to be included in the Letter of Information and Consent documentation for all studies involving use of MRI.**

Part of your participation in this study will involve a research test with Magnetic Resonance Imaging (MRI) system, a common medical diagnostic tool that uses a strong magnetic field, a low frequency magnetic field, and a radio frequency field. No X-rays are used. As with any technology there is a risk of death or injury. For MRI the risk of death is less than 1 in 10 million and the risk of injury is less than 1 in 100,000. These risks do not arise from the MRI process itself, but from a failure to disclose or detect MRI incompatible objects in or around the body of the subject or the scanner room. It is therefore very important that you answer all the questions honestly and fully on the MRI screening questionnaire.

Almost all the deaths and injuries related to MRI scans have occurred because the MRI operator did not know that surgically implanted metal hardware (such as a cardiac pacemaker) was present inside the subject during the MRI scan. Other remote risks involve temporary hearing loss from the loud noise inside the magnet. This can be avoided with ear headphone protection that also allows continuous communication between the subject and staff during the scan.

For comparison, the risk of death in an MRI is similar to travelling 10 miles by car, while the risk of injury during an MRI is much less than the risks associated with normal daily activities for 1 hour.

You may not be allowed to continue in this research study if you are unable to have a MRI scan because, for example, you have some MRI incompatible metal in your body, you may be pregnant or attempting to become pregnant, or you may have a drug patch on your skin that contains a metal foil. Should you require a medically necessary MRI scan in the future, the final decision as to whether you can be scanned will be made by a qualified physician considering all the risks and benefits.

MRI exclusion criteria
If you have any history of head or eye injury involving metal fragments, if you have some type of implanted electrical device (such as a cardiac pacemaker), if you have severe heart disease (including susceptibility to heart rhythm abnormalities), you should not have an MRI scan unless supervised by a physician. Additionally you should not have a MRI scan if you have conductive implants or devices such as skin patches, body piercing or tattoos containing metallic inks because there is a risk of heating or induction of electrical currents within the metal element causing burns to adjacent tissue.

In addition to the required wording noted above, the following paragraphs provide language you may wish to use in the Patient Information and Consent documentation to ensure participant understanding of MRI procedures. It is further suggested that subjects be provided with a link to one of a number of excellent online resources that explain the MRI process with audio-visual aids to further enhance their scanning experience.

This MRI machine uses a strong magnet and radio waves to make images of the body interior. You will be asked to lie on a long narrow couch for a certain amount of time *[state how long]* while the machine gathers data. During this time you will be exposed to magnetic fields and radio waves. You will not feel either. You will, however, hear repetitive tapping noises that arise from the magnets that surround you. You will be provided with earplugs or headphones that you will be required to wear to minimize the sound and protect your hearing. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling. There are no known significant risks with this procedure at this time because the radio waves and magnetic fields, at the strengths used, are thought to be without harm. The exception is if you have a cardiac pacemaker, or a metallic clip in your body (e.g., an aneurysm clip in your brain), have severe heart disease, body piercings, tattoos containing metallic ink or slow release pharmaceutical skin patches.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. However, you can stop the exam at anytime. The magnetism and radio waves do not cause harmful effects at the levels used in the MRI machine. However, because the MR scanner uses a very strong magnet that will attract metal, all metallic objects must be removed from your person before you approach the scanner. In addition, watches and credit cards should also be removed as these could be damaged. (These items will be watched for you).

NOTE: If any of the safety monitoring systems on the scanner is bypassed (e.g. gradient field rate of change or SAR), then this must be stated in the consent form and should require Full Board Review.