**Appendix D**

**Toronto Neuroimaging Facility Protocol**

**Policies Concerning Human Research at the**

**Brain Imaging Research Facility at University of Toronto**

This document describes policies and procedures for human participant safety along with data management at the Brain Imaging Facility.

**MRI Background**

MRI is a widely used imaging modality for investigational research in human participants 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. There is a vast field of literature investigating the bio-effects of the 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. The MRI system at the Brain Imaging Facility operates at field strength of 3.0 T. 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 for clinical and research purposes since the mid 1990s and are thought to be less hazardous than a comparable x-ray computed tomography (CT) examination.

**MRI Specific Risks**

Despite being considered as having minimal, if any, health hazards, there are some important safety considerations associated with MRI scanning.

**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.’ The exposure limits for ‘Patients’ are as follows:

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.

These guidelines are now considered to be severely outdated, particularly with respect to the static field strength. Health Canada has allowed the import of dozens of 3T MRI scanners, falling back on the expertise of the US FDA.

**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 US FDA 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 US FDA deems magnetic resonance diagnostic devices do not pose a significant risk when used under any of the operating conditions described below.

The US FDA classified risks of MRI scanning into four categories:

a) Acoustic Noise Levels,

b) Gradient or Time-varying Magnetic Fields,

c) Radiofrequency (RF) Magnetic Fields, and

d) Static Magnetic Fields.

a) Acoustic Noise

The acoustic noise associated with MRI imaging is related to the mechanical movement of the gradient coils during the scanning process.

FDA Guidelines: "The acoustic noise levels associated with the device must be shown to be below the level of concern established by pertinent Federal Regulatory or other recognized standards setting organizations. If the acoustic noise is not below the level of concern, the sponsor must recommend steps to reduce or alleviate the noise perceived by the human subject." Current FDA guidelines follow the regulations of the International Electrotechnical Commission (IEC) Standard 601-2-33, which stipulate that for MR equipment used in medicine, hearing protection is required when the system can produce acoustic sound levels above 99 dB and that the protection should be able to reduce noise levels to below 99 dB. The FDA has approved systems for which noise levels have been quantified, ranging up to 105 dB RMS for scanners operating at field strengths of 1.5 Tesla. It is important to note that the static magnetic field strength is only one factor, and not necessarily the most important one, in determining acoustic noise. Among the factors listed above, the design and construction of the gradient coils plays a major role in the noise level that MRI scanning produces. Therefore, noise levels are not necessarily greater when scanning at 3.0 T compared with 1.5 T field strengths. It is nevertheless possible that, in some circumstances, our system could produce noise levels higher than 99 dB, as do many systems operating at lower field strengths. The acoustic noise levels perceived by human subjects when undergoing MRI examination in our 3.0 Tesla magnet constitutes a non-significant risk; specifically, our system will not be operated in a way that will present more noise to human subjects than is approved or recommended by the FDA.

*Ensuring Safety From Acoustic Noise:* As suggested by the FDA, we will take steps to reduce or alleviate the noise levels experienced by human subjects in this protocol. This will be accomplished by one of two commomethods:

i. Use of disposable earplugs

ii. Use of acoustically shielded headsets

b) Peripheral Nerve Stimulation

The time-varying magnetic fields used in MRI can, in some instances, induce stimulation of peripheral nerves, thereby producing sensations such as 'twitching' or 'tingling'. In very rare instances, this nerve stimulation can be painful. Nerve stimulation is particularly likely when human subjects are physically positioned in a way that increases the likelihood of inducing stimulation, such as with hands clasped or arms folded. It should be noted that the parameter of interest here, dB/dt (the rate of change in the magnetic field per unit time), is not a function of the strength of the static magnetic field, so evaluating risk in a 3T MRI scanner involves the same considerations as evaluating other MRI systems operating at lower magnetic field strengths (i.e., the same issues apply to all the commercially available, FDA approved scanning systems). Thus, it is the gradient system only that needs to be evaluated to determine the risk of producing nerve stimulation.

FDA Guidelines: The FDA Guidance of 1995 was developed specifically to consider the fact that many clinical systems were capable of exceeding levels of dB/dt that could produce nerve stimulation. It was originally considered that a warning level should be implemented to guard against peripheral nerve stimulation, but the FDA finally concluded that: '... this warning level is not considered critical since there are no harmful effects associated with mild peripheral nerve stimulation’. The current guidelines therefore include monitoring procedures to help avoid painful peripheral nerve stimulation, and without specific dB/dt limitations. Summary of Risks: The gradients used in our 3.0 Tesla MRI system will typically be operated at levels below those considered to be negligible according to FDA guidelines. Our system, like most commercially available, FDA-approved systems, does have the capacity to exceed this level, but it will include the same safeguards that are included in other FDA-approved clinical systems. Furthermore, policies and procedures will be implemented according to FDA guidelines to avoid the possibility of painful peripheral nerve stimulation. Therefore, in all circumstances the system will be operated in a way that poses non significant risk to the participant.

*Ensuring Safety from Peripheral Nerve Stimulation*

i. The gradient switching times and strengths is automatically monitored by software on the system.

ii. All MR operators will receive special training to prevent peripheral nerve stimulation.

iiii. Before any scanning procedure that might stimulate peripheral nerves, an operator will

- Inform the participant that peripheral nerve stimulation may occur

- Describe the nature of the sensation to the participant

- Instruct participants not to clasp their hands, since this may create a conductive loop which will increase the possibility of stimulation

- Maintain constant verbal contact with the participant

- Instruct participants to inform the MR operator if they experience discomfort or pain

- Terminate the scan if the participant complains of discomfort or pain

- Complete a report of any incidents involving severe discomfort or pain, including a description of the associated circumstances (imaging parameters, dB/dt value, level of pain, etc.), and submit this report immediately both to the REB and to the MRI Safety Committee

c) Tissue Heating

MRI scanning induces some heating of body tissues. This specific absorption rate (SAR) that determines heating is the amount of radiofrequency (RF) energy deposited (typically by a coil or “helmet”-like apparatus placed over the human subject’s head) per unit volume of tissue per unit time. RF energy in MRI examinations is not a function of the strength of the static magnetic field. Rather, the Specific Absorption Rate (SAR) for RF radiation is related to the amplitude of RF power, the duration of the RF pulse, the type of RF coil used, the frequency of RF radiation, the resistivity of the tissue, the configuration of the anatomical region being examined, and several other parameters

FDA Guidelines: "The following are levels of concern at which the reviewer shall exercise appropriate actions to ensure that the safety of the device is substantially equivalent to a predicate device: A) If SAR 0.4 watts per kilogram (W/kg) whole body; and if SAR 8.0 W/kg spatial peak in any 1 gram of tissue; and if SAR 3.2 W/kg averaged over the head: below level of concern. Or B) If exposure to radiofrequency magnetic fields is insufficient to produce a core temperature increase in excess of 1°C and localized heating to greater than 38°C in the head, 39°C in the trunk and 40°C in the extremities: below level of concern. The parameter SAR cited above must be shown to fall below either of the two levels of concern by presentation of valid scientific measurement or calculation evidence sufficient to demonstrate that SAR is of no concern." It should be noted that this guideline is based on the calculation of a system that has no thermoregulatory response, and thus it is a very conservative estimate compared with the temperature change that would be experienced in any living human subject. Normal diurnal temperature variations in humans, for example, are about +/-1°C from the normal set point 37°C, and healthy people with normal thermoregulatory responses can easily dissipate any excess (or, in this instance, deposited) heat by increasing their peripheral blood flow or sweat rate. Thus, the heating effect of MRI with the SARs used in accord with these guidelines is extraordinarily unlikely to cause any acute effects in healthy human subjects. Summary of Risks: Because all experiments performed on the 3.0 Tesla system will comply with FDA guidelines with regard to SAR, and because appropriate RF power safety checks are in place, the criterion for classification of NSR is satisfied.

*Ensuring Safety from Tissue Heating Risks*

The magnitude of temperature increase during MRI scanning is minimal. Increases are always within FDA guidelines, which include core temperature increases less than 1°C, as well as localized heating to less than 38°C in the head, 39°C in the trunk, and 40 °C in the extremities. Our 3.0 Tesla system has in place a means to monitor RF power levels and ensure that energy deposition is sufficiently low to stay well within these guidelines for temperature increases. First, a "system security" unit is employed to integrate the output of the RF amplifiers. This integration takes into account the amplitudes and duty cycle of the transmitter. If system security detects an output that might exceed the guidelines noted above, it automatically shuts down the entire RF power system. Secondly, all pulse sequences are evaluated, based on calculations and sound scientific measurements, to ensure that SAR remains within FDA-approved guidelines, prior to their use in humans. Any experiment performed on our 3.0 Tesla system will comply with all FDA guidelines with regard to RF power deposition. Proper and routine monitoring of all RF electronics (e.g., coils, transmitters, system security, etc.) will be performed on a regular basis. All pulse sequences will be evaluated (by calculation and by valid scientific measurement) prior to use in humans.

d) Static Magnetic Fields

The possible risks of static magnetic fields have received much attention in the lay press, but scientific consensus on these risks has yet to be fully reached. The FDA has deemed that systems operating at 8.0 Tesla or less do not pose a significant risk. Moreover, experience with tens of thousands of studies over the past decade, and with multiple human investigations carried out at higher field strengths over this period, have not revealed risks of exposure to higher static magnetic fields. The most significant risk associated with static magnetic fields is that ferromagnetic objects, such as aneurysm clips or heart valves, can interact with the magnetic field of an MRI scanner, causing the device to malfunction or to move, and injuring the human subject. For some human subjects, rapid head movement while in the magnetic field may cause dizziness, vertigo, or a metallic taste in their mouth.

FDA Guidelines: “Studies conducted at 8T or less are not considered significant risk" (FDA Center for Devices and Radiological Health, memorandum 7-14-03).

*Summary of Risks:* This category of risk applies to work conducted around superconducting magnets of any kind (including standard clinical diagnostic MRI units). It is not unique to our 3.0 Tesla facility. The MRI facility will maintain a safety policy to safeguard human subjects and staff members from these incidental risks. Systems with static magnetic field less than 8 Tesla have been considered to represent a non-significant risk (NSR) by the FDA. The static magnetic field of our system (3.0 Tesla) is therefore to be classified as posing NSR to human subjects.

*Ensuring Safety from Static Magnetic Field Risks*

The minimization of risks associated with the static magnetic field of 3.0 Tesla is mainly related to incidental risks (see below). These risks are the same as in other commercially available systems, and like other MRI centers, our facility will incorporate a complete range of procedures, including:

i Assure the security of the restricted access area.

ii Entrance doors to the MRI department will be kept closed at all times.

Access to the MRI suite will be tightly controlled, allowing access for only personnel and human subjects who have legitimate reason to be there. Doors to the MRI suite will be securely locked.

* Entryways to the MRI suite will be labeled with clear visible signs warning of the presence of the magnetic field and the exclusion from entry by individuals with implanted metal objects such as prostheses, pins, clips, IUD’s, pacemakers, etc.
* The MRI operator will conduct careful screening of potential participants before they enter the magnet room (appended at the end of this document).

e) Incidental Risks

The physical confinement and isolation produced by the scanner could cause mild to moderate emotional distress, although in our extensive past experience, participants generally tolerated the procedures remarkably well. All participants will be able to communicate directly with the operators to inform them of any emotional or physical distress during the scanning procedure. If they wish, the scan will be terminated immediately and the participant will be removed from the scanner.

f) Ensuring Data Safety

All MRI data will be stored behind firewalls at facility.

g) Scanning of Children

We will develop additional procedures for scanning children once the initial set of policies are approved. These policies will go through REB approval and be amended to these documents.

**Incidental findings**

The Brain Imaging Facility is a research facility at University of Toronto. The Brain Imaging Facility is part of the College of Arts & Sciences, and is not affiliated with the medical school or the University Health Network hospital. MRI scans are undertaken for research purposes only and not for diagnostic or therapeutic purposes. The Brain Imaging Facility does not have medical or radiological staff that interprets MRI scans, thus no information regarding normal or abnormal findings will be routinely provided to research participants or their physicians. Variations from expected brain morphology can be seen in many research participants undergoing MRI scans. In light of such variations, and given the rapidly increasing number of research MRIs conducted, significant ethical questions about responsibilities and procedures for detecting and disclosing incidental findings have been raised. Variations may or may not have medical implications.

There is no national requirement to have every research scan read by an outside neuroradiologist. However, in recognition of the fact that, on occasion, potential incidental findings may need to be investigated medically, research participants will be informed of that possibility in a best-faith effort. Specifically, if a potential anomaly is detected, data will be sent to a neuroradiologist for screening. The neuroradiologist will determine if the observed abnormality merits further investigation. If the neuroradiologist determines that further investigation is warranted the PI or a designated member of the facility staff will contact the participant and inform him or her of the finding.

All investigators conducting human research who plan to use the Brain Imaging Facility must obtain REB approval for their research protocol. Under no circumstances will such an investigator be allowed to use the facility without submitting proof of REB approval and approved REB application and research protocol. The REB application include an explicit description the tasks that the participant will complete, as well as the procedures for handling all findings, including incidental findings. The informed consent document shall contain an explicit description of the limits of communication with the participant with respect to scan findings and follow up responsibilities. All participants have the right to be informed of the strengths and limitations of the research team in identifying, interpreting, or communicating findings.

Mandatory Language for Informed Consents:

“The magnetic resonance imaging (MRI) scan you will receive during the course of this study is for research purposes only. It is not a clinical scan intended for diagnostic or therapeutic purposes. The Brain Imaging Facility is a research center. It is NOT a clinical MRI facility in a hospital. There are no neuroradiologists at the Brain Imaging Facility, therefore the staff are unable to make any medical comments about your scan. Should you want to know if your scan is normal or abnormal, the staff will not be able to tell you. In the rare event someone on the research team suspects an anomaly, data will be sent to a neuroradiologist for examination. You have the right to decline this evaluation.”