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MRI Research Proposals Involving Child Subjects: Concerns Hindering Research Ethics Boards from Approving Them and A Checklist to Help Evaluate Them

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Introduction

The process of research is often lengthy and can be extremely arduous. It may take many years to proceed from the initial development of an idea through to the comparison of the new modalities against a current Gold-Standard practice. Each step along the way involves rigorous scientific review where protocols are scrutinized by multiple scientists not only in the specific field at hand but related fields as well. In addition to scientific review, most countries require a further review by a panel that will specifically address the ethics of the proposed research. In Canada, those panels are referred to as Research Ethics Boards (REB), with the United States counterparts known as Institutional Review Boards (IRB).

In general, while REBs are responsible to ensure ethical treatment of research subjects, they also scrutinize broader ethical, social and/or political aspects of research in order to protect the safety of both research subjects and the population in general [1,2]. Of particular concern to REBs are protocols involving research with children [3]. The reasons for the concern are far ranging and include a full spectrum of questions that arise from if children should be included in research studies to when and if assent can be given by a child to participate in research investigations, parental motivations to allow participation of their children in research to considerations of when children can participate in research that carries risks of any level [4, 5]. Although debates continue regarding the many issues relating to inclusion of children in research, REBs function by applying the existing, pertinent regulatory policies to protocols that have children as their focus. In Canada, all social, scientific and medical research involving human subjects is bound by the guidelines set forth in the Tri-Council Policy Statement (TCPS):

Ethical Conduct for Research Involving Humans with other countries implementing similar but not identical regulatory policies [6, 7, 8].

Even though regulations regarding human subject research exist, they are often outdated as newer technologies, with limited track records and rapid evolution bring to the forefront many questions not previously addressed by REBs. Additionally, it can be very difficult for REB members to comprehend the science behind the rapidly emerging technologies which in turn, may hamper their evaluation of research protocols involving such technology. Magnetic Resonance (MR) technology [which includes Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), and Functional Magnetic Resonance Imaging (fMRI)] is a prime example of leading edge research falling into that category [9, 10]. In particular, evaluating research protocols when they involve both children and MR technology have posed many difficulties for REBs when it comes to approving such research protocols [11, 12].

Additionally, MR researchers who have their protocols refused by REBs can find the whole process of ethical review both puzzling and frustrating. While MR researchers understand all of the technological details within their field, they frequently have a limited understanding of the ethics review process and all of the factors considered when REBs make their decisions. Resultant to those differences between MR researchers and REBs is an inadequate understanding of the specific nuances which govern each group's decision-making.

This paper will bridge the gap between MR researchers attempting to further knowledge of children's medical needs and concerns and REBs that evaluate their research protocols. The main focus of this paper will be to present the ethical concerns

that tend to be of major concern for REBs when children are research subjects for MRI protocols. It will then offer a pragmatic solution, a checklist, which may benefit both MR researchers in their planning of research protocols and REBs in their evaluation of such research from more common ground.

Guidelines for Research Ethics Review

It is well accepted that The Nuremberg Code (1948), the Declaration of Helsinki (1964), and The Belmont Report (1979) represent the initial historical guideposts for research involving human subjects following World War II [13, 14]. By nature of their mandates, however, none of these important guidelines specifically elaborated on research conducted on socially vulnerable or incompetent populations, including children. Although consisting of first order principles, the United Nations' Universal Declaration of Human Rights (1948) emerged with general guidelines for decision making when it came to assessing viability of any research investigation [15]. In general interpretation, the declaration put forth the notion that no matter how important a research investigation may be, if it violates the rights of just one person, then the research is not justifiable.

Currently, many countries have or are adopting ethical guidelines for evaluation of research protocols for medical/scientific research including child subjects [16, 17, 18, 19, 20, 21, 22]. In Canada, social, scientific and medical research involving human subjects that is conducted within institutions that receive funding from the tri-agencies or researchers who are otherwise ethically tethered, for example, the Alberta College of Physicians and Surgeons, are bound by the guidelines set forth in the Tri-Council Policy Statement (TCPS): Ethical Conduct for Research Involving Humans [23]. Article 5.1 addresses the

necessary inclusion of children in research, Article 5.3 states that children, as members of groups incapable to give consent, cannot be automatically excluded from research. Article 2.5 mandates that research with children must not expose them to more than minimal risk unless the research offers potential for individual benefit.

In the United States, federally funded research involving children is regulated by the Code of Federal Regulations for the United States Department of Health and Human Services (DHHS) [24]. Title 45, Part 46, Subpart D sets forth guidelines for the inclusion of children as research subjects both above and under acceptable "minimal risk". Subpart A, known as the "Common Rule", defines minimal risk as the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Concerns to Consider When REBs Review Research Proposals Involving MR Technology under Current Guidelines

The process of ethical review and approval of protocols involving children in scientific/medical research clearly has a number of issues that have been delineated within the literature [25, 26, 27, 28, 29, 30, 31, 32, 33].

Regardless of those issues, it is agreed upon that children must be studied as their own group because of the uniqueness of their biochemistry and physiology. What remains unresolved are important parameters under which research can proceed. One of the main stumbling blocks for REBs and a subsequent approval of research protocols involving children for all protocols including MR is the vague definition of minimal risk as written in the regulating guidelines of ethics. Presently, many in research use the daily risk criteria to designate minimal risk as its standard for enrolling people, both adults

and children, into scientific studies with most defining minimal risk using the United States definition as presented above [34].

When it comes to documenting and delineating the combination of minimal risk, involvement of children and MR technology, the concern becomes multi-fold when REBs scrutinize research protocols. Firstly, the term 'minimal risk' applies to both the MR technology and risk/harm of the research protocol pertaining to the participation of a child subject. Secondly, the definition of minimal risk conflates the risk and harm which are separate and not necessarily related concepts. Lastly, to assure that the protocol has scientific validity and that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation must be compared to the risks and benefits of alternative devices or procedures. So when it comes to applying the regulated daily risk standard to participation of human subjects in research, let alone children, it is difficult for researchers and/or REBs to agree what actually constitutes the risks inherent in daily life for both populations and individuals within a given research protocol. Resultant to that may also be the use of invalid comparisons, paternalistic and protectionistic thinking that often contains more bias than objectivity. For all these reasons, proposed research may or may not proceed on the basis of what might be considered subjective determinations of minimal risk by REBs. The literature clearly substantiates difficulties with the use of a nebulous standard for minimal risk and although other standards have been proposed for use, they have yet to be adopted [35, 36, 37, 38, 39, 40, 41, 42, 43, 44].

In an attempt to bring forth positive change and help resolve some issues of involving children in research, the American Food and Drug Administration (FDA)

incorporated the 2002 federal Better Pharmaceuticals for Children Act into their 1997 Modernization Act. This Act radically shifted public policy to test new or patented drugs in children [45, 46]. However, the controversial changes in that Act met with major criticisms. In particular, Sharav stated that "the current gate keeping system raises serious doubts about the sustainability of IRBs as protectors of human research subjects", and called for an immediate and radical overhaul of the current research review system in order to provide children with the legal protections that they deserve while participating in research [47]. Similarly, Frost and Levine have asserted that the current regulatory system is "increasingly dysfunctional" [48]. Additionally, they expressed "concerns that the system is overregulated, with more time and expense devoted to activities of marginal utility in protecting human research participants." They further suggested that the system only served to further obfuscate forth coming solutions for problems of approving research involving children in addition to the stifling of research productivity, the discouragement of investigators, and reluctance of senior scientists to become members of REBs because of the perception that the work done by REBs is primarily focused on bureaucratic matters and unimportant minutiae.

Another concern when research protocols are reviewed under current guidelines and/or acts of government is that there is no one regulating body for REBs that would oversee the process of protocol approvals or rejections. REBs are constituted according to the policies of their own institutions and/or regulatory bodies and generally consist of individuals who represent many different fields or interests and include lay people as well as experts in research design, medicine, law, ethics, and faith. Given such broad membership, which also can be quite variable across REBs, it is not surprising that

REBs do not immediately evaluate issues similarly. Willison et al determined that large variations existed when comparing REB notions of consent for access to medical records and suggested the need for training for REB members [49]. A recent review of enforcement letters issued to IRBs by their oversight committee and a review of a mock research protocol involving fMRI by Canadian REBs also revealed similar findings [50, 51].

REBs are as vulnerable to group dynamics as any other large group. Schuppli et al have investigated the functioning of REBs and have proposed some factors which can influence their effectiveness:

- Committee composition that may potentially lead to research/institutional preference versus those of the research subjects or community.
- The dynamic of the committee may prevent full participation of all members. This is an especially noteworthy point for under this topic lies the very reasons that some people are chosen for particular roles and others are not. For example, an overbearing chairperson may not solicit or want diversified opinions so one or more members of the committee may feel isolated or intimidated to either go along with or go against a decision that they would in other environments not do.
- Recruitment for positions on an REB may create bias from many different perspectives but mainly those of a particular institution and its research interests versus interests of research subject and the community.
- The motivation for any one member for joining the REB may be to pursue an agenda other that the prescribed agenda of the REB.
- The workload for individual REB member may be excessive.

- There may be inadequate participation by REB members which in turn would not provide for an adequate review of protocols.
- The length of time REB members can serve on a committee is not often limited or renewed without reassessment of their contributions to the process. This is turn may limit new ideas and risk the indoctrination of “group think” [52].

REBs must be made aware of the factors which might limit their effectiveness. This could be achieved in many ways from having a handout that outlines not only their responsibilities in reviewing research proposals to having an orientation session where open and honest discussion occurs serving to bring forth the potential areas where subjectivism can enter in their decision making process as an individual as well as a group. In addition, while still maintaining an appropriate level of confidentiality, REBs need to have a transparent decision-making processes open to all involved in the review process. This would serve to promote accountability for the decisions made as well as other components of due process of the REB in addition to assisting researchers whose protocols require revision or total re-write.

Emerging MR Technology and Risk

Issues surrounding children's involvement in research involving emerging technologies, such as MR, add further complexity to the review process. This is because, as new technologies progress, current understanding can be challenged as knowledge is in flux, and can leave even seasoned researchers in a state of theoretical ignorance. Considering this, it would be no surprise that REBs, with their diverse memberships, may also have difficulty understanding research proposals involving

emerging technology as well as judging their potential benefit and risk. While differences in opinions might arise from this within individual REBs, differences in opinion also can occur between REBs examining similar protocols. A recent study where multiple REBs were asked to evaluate a mock neuroimaging research protocol, revealed marked inconsistencies in REB decisions [53].

A recent publication by Marshall et al has summarized the current legal and ethical standard for disclosure of risk for those participating in research within Canada as well as broadly presenting the risks know to be associated with MR technologies, including physiological, psychological, and result-related risks [54]. However, often times, there is confusion between the risks associated with the MR technology itself, the associated risks of the MR technologies and involvement of children in research considering the known risks.

With respect to MR technology itself, concerns arise for children that are involved in research with this technology regarding the level of heating they are exposed to and whether or not the level is safe for them. It has been determined that from a physiological standpoint involving MR technology, there are 4 major concerns that should be considered when determining the risk level of research participants: the main static magnetic field, the specific absorption rate (SAR), the gradient field rate of change, and the sound pressure level. With respect to those concerns, the current standards that pose no significant risk for MRI and fMRI devices as outlined by Canadian and United States guidelines are as follows:

- For adults and children and infants greater than one month, a main static magnetic field of 8 T or less; for neonates (infants under one month of age), a field strength of 4T or less.
- Although varying with site in the body, the specific absorption rate (SAR) ranges from 4 watts per kilogram (W/kg) for a whole body dose over 15 or more minutes to 8 W/kg for the head or torso dose per gram of tissue over 5 or more minutes.
- For the switching rate or intensity of the lower 'switched' magnetic field, fields kept at or below the peripheral nerve excitation thresholds and well below cardiac stimulation thresholds are a required operating parameter.
- For a peak un-weighted sound pressure level of 140 dB or less or a weighted root mean square (rms) sound pressure level of 99 dB or less with hearing protection in place and not exceeding the Occupational Health and Safety Association guidelines for length of exposure to such noise levels.

Canadian regulations, first published in 1987, state that MR exposure reflects "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" [55].

It is now generally considered that the above mentioned guidelines are outdated**.** Due to that unfortunate disconnect, it is generally accepted that Canadian Guidelines follow the United States FDA criteria for MRI patient exposures [56, 57, 58].

Overall, such information serves to confuse even the most seasoned professional. For REB members who do not have the scientific background, their concerns about the technology safety may lead to err on the side of caution. For MR devices, it must be understood that they carry a designation of non-significant risk to 8T under current government guidelines of operation [59]. In addition and beyond risks relating to exposure to magnetic and radio-frequency fields, both researchers and REBs must also be aware that there are risks which relate to the general safety around strong magnets. For reference, these are well summarized by organizations specializing in the safety of MR technologies [60, 61].

In addition to the primary risks associated with MR technologies, there are secondary risks of note. Firstly, psychological risk associated with MR scanning includes claustrophobia or isolation within the small scanner space as well as pre- and post- anxiety about the imaging or its results. As such, MR researchers have developed pragmatic approaches to lessen imaging-related anxiety or distress for adults, including talking to subjects between scans to lessen the feeling of isolation, warning them when scanner noise is about to start, and giving reminders to stretch so as to avoid muscle fatigue. For children, in addition to these similar basic inclusions for comfort and relaxation, small pillows can be placed around a child`s head to aid restraint (rather than use a forehead strap as with adults), weighted blankets can guard against body motion, special toys can be kept by children while in the magnet, etc.

Additionally, a consideration of pre- and post-anxiety experienced by children undergoing MR imaging has lead REBs to question the use of children with this technology. Current investigations by the authors' research group include measuring

and reducing fear and unwanted motion in children during MR scanning. Recent work by Malisza et al, has determined the proportion of children between the ages of 3 and 7 who successfully approach and enter an MR scanner without fear, as well as the points in an approach sequence where some children become most fearful and want to leave the MR environment [62]. Subsequent work by Martin et al demonstrated that graduated exposure to a mock MR scanner can successfully reduce anxiety in children who had previously been apprehensive around an MR scanner [63]. Martin et al also have successfully used a mock scanner environment to train children to remain still for a period of time that would be necessary to complete an imaging series by using praise and contingent display of a preferred video as reinforcement (Martin et al, personal communication).

It has recently been suggested that post-scanning anxiety can be significant for individuals awaiting diagnostic or prognostic results. In a research setting, the subject must be made aware that research scans generally are not designed to reveal diagnostic information. However, just as with clinical scans, there is the possibility that a research scan will identify a previously unexpected incidental finding. As such, the issue of incidental findings should be a major concern and research protocols should have a protocol to have potentially concerning findings reviewed by a radiologist.

There has been some discussion in the literature that attributes incidental or unexpected findings of symptomatic (un)treatable abnormalities and the risks of life long implications such as profiling, stigmatization, discrimination and diminished expectations and opportunities as psychological risks of MRI [64]. With respect to these types of issues, any resultant profiling, stigmatization and discrimination can only come from breeches

of confidentiality by people involved in the research study or the patient themselves divulging their own confidential information to other people by choice. In regard to children where parents/legal guardians are consenting for the child, the parents/legal guardians are considered to be people involved in the research and therefore would also be expected to maintain confidentiality. Where disclosure of confidential information is by choice i.e. for such things as employment or insurance purposes, the individual then chooses to share the information thereby also choosing to open themselves up to the potential problems of profiling, stigmatization and discrimination. If and when those problems occur, since the actions of profiling, stigmatization and discrimination can be attributed to occur as a result of other peoples', companies' or governments' behavior directed at the patient, a means to protect confidentiality must be paramount for all involved in the research with enforced penalties imposed where breeches are determined to have occurred up to and including legal prosecutions where appropriate.

While the risk from breeches of confidentiality exists for all human-subject research and is not particular to MR research, it does remain a significant issue particularly in light of incidental findings with potential for lifelong impact.

Lastly, in addition to the psychological risks, there are some physiological risks that can be associated with secondary procedures that are used when undergoing MRI. Those secondary procedures involve the use of sedation and contrast agents. They are both a concern within the clinical and research environment. Details with respect to the individual risks of sedation and contrast agents should also be consideration of REBs within the research environment should some protocols require their usage.

A Checklist for Pediatric MR Research Ethics Review - Rationale

As stated, MR scanning has been regulated for technical and physiological risk. MR researchers are aware that they must take specific steps to actively promote a safe environment for all but especially when vulnerable subjects like children are involved in their work. In addition, risks known to arise from secondary materials including sedation and contrast materials, their procedures, psychological factors, and incidental findings, must also receive attention in research protocols with special concerns being addressed, where necessary, when children are involved. When all is assessed, it becomes clear that many factors remain in the hands of REBs in their determination of whether an MR protocol exceeds minimal risk.

In that regard, the question arises as to whether REBs are sufficiently knowledgeable, not only within the field of ethics, but also with respect to MR research so as to make informed decisions regarding research proposals [65, 66]. Several publications are now not only questioning the knowledge component of an REB member but many varied aspects pertaining to the functioning and accountability of the REB members and boards with some of those even questioning the potential for fully regulating REBs in both Canada and the United States [67, 68, 69, 70, 71, 72, 73, 74].

On the other side of the equation is that there are researchers who are sufficiently aware of ethical standards and regulations that develop research proposals minimizing risks while at the same time presenting the best chance of forwarding knowledge in their field of study. In that regard, Intemann and de Melo-Martin tackled the larger question of whether or not scientists should be left alone to decide what research to do and how to perform the work [75]. As a generalized result, they

determined that researchers do understand the notion that there should be some ethical constraints on their work. In and of itself, the arguments surrounding such a question has resulted in a more complete debate over what are the necessary regulations governing research. However, as pointed out by Borenstein,

> "It is not possible to evaluate and monitor every form of research involving human participants thoroughly given current constraints. The IRB review needs to be appropriately limited. Even with other review mechanisms being put into place to complement the IRB system, there has to be a point where trust prevails. The integrity of researchers is an essential and irreplaceable component of a thriving research enterprise." [76]

However those assertions may be, to assist both researchers and REBs, we have developed a checklist (Appendix A) that concentrates on MR research involving children and meets current technological and research ethics criteria. It is also suggested that with minor adaptations it could also be used for MR research with adults, or even adapted for other fields of enquiry.

The rationale behind this is that checklists are known to be powerful tools for reducing errors and aiding individual judgment in health care and other contexts [77]. A recent study by Luijin et al determined that a majority of surveyed REB members would like to receive additional information and/or education to effectively assess the risk/benefit ratio of research protocols [78]. Checklists were requested specifically by some respondents as a helpful form of training. Although responses were made in the context of evaluating clinical cancer trial protocols, generality across medical procedures and technologies seems likely. Researchers too can benefit from a checklist

that summarizes relevant ethical issues and standards. During a two-year deployment at a regional university, 90% of faculty and students surveyed indicated that a set of general REB protocol preparation checklists were helpful for critically reviewing and improving their proposals [79].

With respect to our checklist, we intend that it offer assistance to both MR researchers and REBs. With respect to the researchers, they can test the ethical concerns within their protocol designs against the checklist to see if they have forgotten to address any specific issues prior to submission to an REB. For REBs, using the checklist will help them address the issues we have outlined that seem to challenge REBs when determining the acceptability of research protocols involving MR technologies. In that regard, with particular respect to research involving children, some separate issues need to be considered in addition to those we have already mentioned. Work done by Mahoney has identified concerns that arise when REB members evaluate protocols involving children [80]. Incorporating those concerns with others that have been brought forth in current literature, the following provides a formidable list of concerns that must be addressed when children are to be involved in scientific research:

- Underlying issues of informed consent and assent including:
    a. parental consent and child assent
    b. therapeutic misconception
    c. legal guardianship
    d. socioeconomic status and parental consent
    e. passive consent by legal guardians
    f. developmental disability and other vulnerable populations

- A risk/harms/benefit analysis of the proposed research including identification of:
    a. direct benefit to children (therapeutic research)
    b. no direct benefit to children (non-therapeutic research)
    c. minimal risk research
    d. more than minimal risk research
    e. protections offered to volunteers when risk/benefit ratio is high
- Liability. Children must not be resigned to exclusion in research because of convenience, difficulty and cost or which may provide an avenue for litigation now and in the future.
- Legislation/ethical guidelines/regulations, locally, nationally and internationally.

  Legislation varies within and amongst the many levels of governments in all countries. Compliance issues must be resolved for all participating parties.
- Validity of the proposed research
- Ethnicity and cultural concerns

  In order to demonstrate respect for certain ethnic groups and their culture, a different level of perspective as well as scrutiny by researchers and REBs may be required.
- Justification for exclusion.

  Previous to NIH revised guidelines, researchers were resigned to exclusion of children from research for numerous reasons. It is no longer acceptable and children must be included in research.

Conclusions

Although there is much ongoing debate and concern about the processes of scientific/medical research and ethical guidelines that currently govern their acceptance within our societal confine especially when they involve any vulnerable populations, like children, such should be the case. Although fraught with trials and tribulations for all concerned in the processes, what exists in many countries does provide the best set of check and balances under which scientific research is performed.

It is quite clear that when it comes to involving human beings in scientific/medical research, all who are involved in such work should and do consider safety and protection against harm as their primary, common and realistic goals. Concurrently, those same persons must also work in consort to facilitate and not hinder unnecessarily, the pursuit of advances in or solutions to scientific and/or medicine issues. With some scientific/medical techniques and procedures, in order to do that, detailed regulations/guidelines may need to be present or if necessary, need be developed to aid in attaining those goals.

Public policies may at times be very blunt instruments. Researchers and REBs everywhere need to understand the existing regulatory requirements and ethical guidelines while concurrently understanding the need for medical research at all levels of risk in all populations. By working together, involving continuing research, debate, discussion and revisions as needed through advancing time, it is believed that a working balance between ever changing ethical concerns and often times outdated regulatory requirements along with the preservation and integrity of research design can

be achieved and made realistically practical while ensuring the protection of research participants whether they be capable adults, or children any other vulnerable population.

Appendix A

Checklist for Protocols Involving Children and Magnetic Resonance Imaging Studies

This checklist is intended for use by both research scientists when designing research protocols as well as scientific review and REB members to aid them in the evaluation of research protocols involving children and Magnetic Resonance imaging studies under the current TCPS guidelines. Under each category, please select **ALL** that apply to a specific protocol.

Age Group & Medical Considerations:

Age Group	
Newborn (1 day to 3.9 months)	☐
Infant (4 to 11.9 months)	☐
Toddler (1 to 3.9 years)	☐
Pre-school (4 to 6.9 years)	☐
School-age (7 to 12.9 years)	☐
Adolescent (> 12 years)	☐

Medical Considerations		Please Describe
Specified Medical Condition	☐	
Normal Development	☐	
Abnormal Development	☐	

Is the use of children for this research adequately justified? YES ☐ NO ☐

Study Design:

Is the study achievable given its current design? YES ☐ NO ☐
Is the study likely manageable in the suggested time-frame? YES ☐ NO ☐
Are the recruitment statistics justifiable? YES ☐ NO ☐
Is the recruitment/advertising process appropriate? YES ☐ NO ☐
Are Inclusion and Exclusion Criteria adequate? YES ☐ NO ☐

Risk Considerations:

Minimal Risk pertaining to human subject participation in research in the TCPS is being no greater than the risks of daily living. Research which might surpass the minimal risk standard cannot be undertaken with children who cannot consent unless it has the potential for direct benefit to them.

Minimal Risk pertaining to MRI technology for adults and children and infants greater than one month, a main static magnetic field of 8 T or less; for neonates (infants under one month of age), a field strength of 4T or less.

Risks to Consider:

MRI Technology risks to be addressed in Protocols:

Magnet strength under 8 T	YES ☐	NO ☐
SAR < 8 W/Kg	YES ☐	NO ☐
Switching Rates below nerve & cardiac excitation thresholds	YES ☐	NO ☐
Sound protection to < 99 Db	YES ☐	NO ☐
Will sedation be used?	YES ☐	NO ☐
Is sedation appropriate for the research?	YES ☐	NO ☐
Assurance of safety during sedation?	YES ☐	NO ☐
Will contrast be used?	YES ☐	NO ☐
Is contrast appropriate for the research?	YES ☐	NO ☐
Assurance of safety for contrast procedure?	YES ☐	NO ☐
Will anxiety be appropriately managed?	YES ☐	NO ☐
Will excessive movement be appropriately managed?	YES ☐	NO ☐
Will unexpected Incidental Findings be appropriately managed?	YES ☐	NO ☐
Does the protocol adequately address Minimal Risk?	YES ☐	NO ☐
Might there be a Direct Benefit to the participants?	YES ☐	NO ☐

Technical Issues:

Is there appropriate technical expertise for this study?	YES ☐	NO ☐
Is there appropriate safety expertise for this study?	YES ☐	NO ☐
Is there appropriate technical equipment for this study?	YES ☐	NO ☐
Is there appropriate safety equipment for this study?	YES ☐	NO ☐

Additional Ethics Concerns:

Is the Informed Consent Process adequate?	YES ☐	NO ☐
Has the concept of Assent been adequately addressed?	YES ☐	NO ☐
Is the Information for Guardians adequately simple?	YES ☐	NO ☐
Will honourarai been ethically managed?	YES ☐	NO ☐
Will motivations for participation be adequately explored?	YES ☐	NO ☐
Has Therapeutic Misconception been adequately avoided?	YES ☐	NO ☐
If present, have cross-cultural issues been adequately explored?	YES ☐	NO ☐

Have all the following TCPS Standards been met? YES ☐ NO ☐

- ☐ Respect for Human Dignity
- ☐ Respect for Free and Informed Consent
- ☐ Respect for Vulnerable Persons
- ☐ Respect for Privacy and Confidentiality
- ☐ Respect for Justice and Inclusiveness
- ☐ Balance of Harms and Benefits

For REBs ONLY:

I have sufficient understanding of all elements of this study? YES ☐ NO ☐

- ☐ Age & Medical Considerations
- ☐ Study Design
- ☐ Risk Considerations
- ☐ Technical Issues
- ☐ Additional Ethics Concerns

For any reason, might I be more predisposed to accept or deny studies of this sort? YES ☐ NO ☐

(e.g. involving children or other populations, MR research, personal experience, etc.)

Final Decision:

☐ I recommend acceptance of the study as presented

☐ This study must be adapted to address the following:
(attached additional sheets if required)

_____
_____
_____
_____
_____
_____
_____
_____
_____

Signature: _____ Date: _____

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