Guidelines for Documentation and Consent for Nonclinical, Nonresearch MRI in Human Subjects

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Magnetic resonance imaging (MRI) of human subjects is widely performed for clinical and research purposes. Clinical MRI requires a physician order, while research MRI typically requires an approved protocol from a local Institutional Review Board, as well as informed consent. However, there are several circumstances in which it is appropriate to perform MRI in human subjects, that constitute neither clinical nor research activities. Examples include clinical protocol development, training and teaching, and quality assurance testing. We refer to such activities as *nonclinical, nonresearch MRI*. The purpose of this document is to provide principles and guidelines for appropriate and safe use of MRI in human subjects for nonclinical, nonresearch purposes.

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Magnetic resonance imaging (MRI) is a noninvasive cross-sectional imaging technique that has revolutionized the diagnosis of disease and is commonly used around the world in clinical practice. Furthermore, there are tremendous continued research activities developing new MRI techniques as well as using established MRI methods as part of important research studies including human subjects.

If an MRI study is performed for clinical purposes, a physician order is required and informed consent from the patient is usually not necessary given the high safety protocol and low risk of MRI, relative to many medical procedures. If the activity constitutes research, standard ethical principles typically require the use of locally approved Institutional Review Board (IRB) or Ethics Board (both hereafter referred to as IRB) protocols for research studies. In particular, most prospective research protocols also involve some form of informed consent.

The appropriate use of an IRB protocol depends highly on the definition of research. Although this definition varies widely, the United States Federal Government defines research as "a systematic investigation, designed to develop or contribute to generalizable knowledge."[1] Other governments and regions of the world have related but different definitions.[1–4] It will be incumbent upon the reader of these guidelines to familiarize himself or herself with the definition of research that is relevant to their country, and consider this concept in the proposed guidelines.

There are many circumstances where MRI in human subjects (hereafter "volunteers") falls into a gray zone that constitutes neither research nor clinical imaging. This leads to tremendous uncertainty as to whether these activities should be performed as part of an IRB approved protocol, or whether any form of informed consent is even necessary. We refer to such an activity as "nonclinical, nonresearch" MRI.

Currently, the use of volunteers in MRI scanners for nonclinical, nonresearch purposes is highly variable. At

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many institutions, no formal consent is used, while at other institutions, IRB research protocols are being used. Although MRI is an exceptionally safe imaging modality, it is not free from all risk. For this reason, guidelines for the appropriate use of nonclinical, nonresearch MRI scanning and for appropriate use of informed consent are needed. A structured process is needed to ensure safe and appropriate scanning of volunteers, and also to provide the necessary information about the potential risks of MRI to volunteers undergoing nonclinical, nonresearch MRI.

The purpose of this document is to provide suggested principles and guidelines for appropriate MRI of volunteers for nonclinical, nonresearch purposes. The essence of these guidelines closely follows the general principles of research and safety pertaining to the appropriate screening of volunteers, informed written consent, and all standard safety precautions. It is essential to note that the definitions of research, authority of local IRBs, and the laws and regulations of different countries and regions of the world are highly variable. The guidelines described below may not be applicable in all regions. The intention of this document is not to dictate how such an approach should be performed but rather provide helpful guidelines, should the need for a structured process arise at a specific institution. Any implementation of the guidelines described in this document may benefit from consultation with the local IRB and must be consistent with local guidelines, laws, and customary practices. Please note that the following guidelines have been written on behalf of and approved by the International Society for Magnetic Resonance in Medicine (ISMRM) Safety Committee. A list of Safety Committee members at the time of drafting this document is found in the on-line Supporting Information.

Definition of Nonclinical, Nonresearch MRI

There are many potential uses of MRI for nonresearch, nonclinical purposes. While this varies depending on regional regulation, the most common applications of nonclinical, nonresearch MRI include the following:

Clinical Protocol Development

When developing new clinical MRI protocols or refining existing clinical MRI protocols, it is often necessary to image volunteers to ensure adequate image quality has been achieved, before using these protocols in patients for clinical purposes. These protocols are generally comprised of sequences approved by local regulatory bodies for use as defined by the supervising physician.

Training and Teaching

It is sometimes necessary to image volunteers for the purposes of teaching students and for training operators on the safe and effective use of MRI systems.

Quality Assurance / Quality Improvement

Testing of existing, repaired or new equipment occasionally requires volunteers to evaluate system performance for quality assurance and quality improvement purposes. Evaluation may include (but is not limited to) testing of signal-to-noise ratio performance, evaluation of image artifacts, and any metric related to the performance of the MRI system.

In addition to the above applications, there may be other appropriate applications for the use of nonclinical, nonresearch MRI in volunteers. These may vary by site and by region, and depend on the specific needs of a particular institution. It is important to note, however, that establishing and implementing a research MRI protocol using volunteers, before embarking on a research protocol with patients, does not constitute a nonclinical, nonresearch MRI activity. A separate IRB protocol may be required, if the overall activity is related to research.

Guidelines for Nonclinical, Nonresearch MRI

The following guidelines aim to describe the basic principles and suggested requirements for implementing a careful and orderly process for institutions that wish to implement processes for nonclinical, nonresearch MRI scanning activities. The following guidelines attempt to provide helpful suggestions to ensure safe MRI practices and to protect volunteers by following accepted principles of informed consent.

1. The use of volunteers for the purposes of clinical protocol development, training and teaching, and quality assurance testing should be minimized wherever possible. The use of phantoms is advised whenever possible. However, there are currently no phantoms that adequately mimic all the physiological processes that affect an MRI examination, including human anatomy, physiological activity, body composition, and MRI relaxation parameters, and other important features that may impact an MRI acquisition, such as ECG signals and respiratory gating. It is recognized, therefore, that in many circumstances that MRI in volunteers is ultimately necessary for testing clinical protocols, training, and teaching, and for some quality assurance applications.
2. It is recommended that sites contact their local IRB, before implementing a nonclinical, nonresearch MRI activity, to ensure that the proposed MRI activities in human subjects do not constitute human subjects research requiring IRB approval. Nonclinical, nonresearch MRI should never be used to circumvent the appropriate use of IRB approved research protocols.

   In general, MRI involving nonapproved software and/or hardware ("devices") requires regulatory and/or local IRB oversight, although this may vary from region to region. Before using nonapproved devices as part of nonclinical, nonresearch MRI, it is recommended that the

site consult with appropriate regulations and the local IRB regarding the use of nonapproved devices. For example, in the United States, the Food and Drug Administration Code of Federal Regulations (CFR) 812 may provide the necessary guidance.[5]

3. In general, all nonclinical, nonresearch MRI should be performed in healthy adults who can participate in the informed consent process without additional consent required from a parent or guardian. Nonclinical, nonresearch MRI should not, in any way, replace a medically necessary imaging study.
4. Archiving of images, as well as anonymization and/or deidentification of images should follow local institutional practices similar to those used for research studies. For some applications, such as teaching and training, there may be no need to archive images.
5. Individuals from vulnerable populations,[1] which includes children, wards of the state, prisoners, pregnant patients, persons who are mentally disabled or cognitively impaired, or are economically or educationally disadvantaged should be excluded from participation. Furthermore, individuals who are impaired and unable to provide informed consent, including those individuals unable to speak the local language adequately, or have communication impairments should also not participate in nonclinical, nonresearch MRI activities.
6. All nonclinical, nonresearch MRI should be performed under the direct supervision of an experienced and qualified (in accordance with local guidelines) MRI operator. In the case of teaching, it may be appropriate for an inexperienced MRI operator to perform the examination, but only under direct supervision of an experienced and qualified operator.
7. A major purpose of developing guidelines for nonclinical, nonresearch MRI is to ensure that all volunteers undergo appropriate MRI safety screening. MRI safety screening should be performed at a level equivalent to that used for research and/or clinical purposes. As there is no benefit to the volunteer, any concern whatsoever about scanning a volunteer with a contraindicated implant or other questionable contraindication (e.g., claustrophobia) should exclude the volunteer from participating. Furthermore, if it were necessary to perform involved procedures such as radiographs to exclude orbital metallic fragments, for example, the volunteer should not undergo nonclinical, nonresearch MRI.
8. Documentation of appropriate MRI safety screening (e.g., signed safety screening forms) is considered essential.
9. The use of contrast agents for the purpose of nonclinical, nonresearch MRI is highly discouraged. Although gadolinium based contrast agents are considered safe, they are not free from adverse events including allergic reactions and in patients with renal failure, nephrogenic systemic fibrosis (NSF). However, it is recognized that there may be rare and unforeseen circumstances where the use of a contrast agent is needed for an appropriate nonclinical, nonresearch MRI activity that is not considered research and, therefore, is inappropriate to use under an IRB approved protocol. This determination should be made in conjunction with the local IRB, if possible.

   Should contrast agents be used for nonclinical, nonresearch MRI, all standard risks of contrast agents, including allergic reactions, NSF, and other known risks, should be included in the consent form, similar to that listed in an IRB approved consent form for the use of contrast enhanced MRI for research purposes. All standard institutional procedures for the safe use of contrast, including the availability of appropriate equipment, drugs and trained individual(s) needed to treat contrast reactions should be followed. Finally, contrast agents are drugs, and like any drug, the administration of a contrast agent always requires prescription and oversight from a licensed physician.

   Recently, there have been several reports describing increased signal with T1 weighted imaging in the deep nuclei of the brain in patients receiving multiple doses of gadolinium based contrast agents.[6–9] This imaging observation has raised concern for the possibility of toxicity related to cumulative gadolinium deposition. However, no paired data demonstrating any adverse biological or clinical outcomes have been reported, despite hundreds of millions of administered doses. As there are no known risks related to gadolinium deposition, no specific recommendations regarding informed consent and gadolinium deposition can be made by the ISMRM at this time. Should any adverse biological or clinical effects related to gadolinium deposition be discovered subsequent to this publication, it may be appropriate to include these risks as part of the consent process.
10. Use of nonclinical, nonresearch scanning should never be performed for any medical purpose. It should be made clear to volunteers that this MRI activity should never be used to replace clinical imaging. Volunteers who are symptomatic or have concerns of underlying disease should consult their physician.
11. Careful consideration should be made to whether to scan employees or trainees within your institution or volunteers from outside the institution. It may be preferable to recruit volunteers who have a working knowledge of MRI safety and the local MRI environment to facilitate the safest possible scanning activity. There may also be important implications related to workers' compensation and, if needed, appropriate wavers of liability may be necessary within the consent form. Consultation with the appropriate departmental human resources team is encouraged, to ensure that nonclinical, nonresearch policies are consistent with institutional policies. If employees or trainees are recruited,

a supervisor with an authority relationship over volunteers should never be involved in the recruitment of volunteers. It is recommended that a standardized approach for approval of employee participation in nonclinical, nonresearch MRI be instituted.

Should volunteers who are not employees of the institution be recruited, standard recruiting mechanisms (e.g., billboards, emails, etc.) such as those used by the IRB may be appropriate based on local institutional practices. Any process that introduces an element of coercion, such as a status relationship or excessive compensation should be avoided. In general, it is recommended that minimal payment, if any, to compensate subjects for their time and expenses (e.g., travel, parking) should be used.

12. Oversight of nonclinical, nonresearch MRI activities by an appropriate institutional oversight committee, such as an MRI Safety Committee or a dedicated "NonClinical, NonResearch MRI Committee" is highly recommended. Similar to an IRB committee, this committee should have experts with experience and training in the principles of human subjects research. Guidance and oversight by a professional with expertise in MRI safety, perhaps as a member of the oversight committee, is also recommended. The oversight committee should appoint one or more qualified individuals who are authorized to approve nonclinical, nonresearch imaging activities. Finally, in challenging situations, escalation to broader institutional oversight such as the institutional Safety Committee or Risk Management may be necessary. It is incumbent upon the oversight committee to identify and understand the appropriate institutional pathway(s) should escalation be necessary, before implementing local nonclinical, nonresearch guidelines.

The above list of suggestions provides the basic framework for performing nonclinical, nonresearch MRI scanning in human subjects. It is recognized that institutional guidelines and regional differences in laws and other regulations supersede all of the above guidelines. If appropriate for your local institution, the above guidelines may provide helpful suggestions for providing an organized process and framework on the appropriate nonclinical, nonresearch use of MRI in human subjects. In this way, the safe and appropriately documented use of this MRI activity can be performed.

Informed Consent

Informed consent for nonclinical, nonresearch MRI should be performed to the same standards as performed for research studies. Key elements of informed consent, as listed below, should be included in the consent process. It is also highly recommended that signed informed consent, to document the consent process, is performed. Furthermore, all individuals involved in the consent procedure for nonclinical, nonresearch MRI activities should have undergone standard research training and certification. For example, standard CITI (Collaborative Institutional Training Initiative) and HIPAA (Health Insurance Portability and Accountability Act) training is recommended for those individuals performing nonclinical, nonresearch MRI in the United States

All of the basic elements of informed consent, similar to that required in research protocol should be captured in the consent form. The specific elements of informed consent may vary from region to region. One suggestion is to begin with an existing IRB approved consent form and modify it appropriately to suit the scanning activities for nonclinical, nonresearch purposes. A new MRI safety screening form and informed consent should be performed every time a volunteer enters the MRI environment for nonclinical, nonresearch MRI. In circumstances where the volunteer is an employee and an advanced MRI operator (e.g., MRI technologist / radiographer) with an existing safety screening form on file, other safety screening procedures that ensure rigorous MRI safety screening may be adopted. Note that knowledgeable operators may have pre-existing conditions that are acceptable as an MRI operator, but not as a volunteer (e.g., MR conditional device, or medication that interferes with the thermoregulatory system).

When seeking informed consent for research, there are several key elements that should be included in the consent process. Based on widely accepted principles of informed consent,[10] we advise that the following basic elements of informed consent used for research should also apply to volunteers for nonclinical, nonresearch MRI:

1. A statement that explains the purposes of the MRI activity, the expected duration of the imaging session, and a description of the procedures that will be followed.
2. A description of any foreseeable risks or discomfort to the subject should also be included. This includes physical or psychological effects, which for MRI may include: (a) claustrophobia, (b) skin burns, (c) risk of projectiles, (d) nerve stimulation, (e) heating, (f) acoustic noise, (g) risk of disclosing personal medical information to those who may see the images, (h) risk of discovery of a finding of uncertain medical significance, (i) risks of contrast agents, if used.
3. An explicit explanation that there is no direct benefit to the volunteer, although there may be benefit to future patients by establishing and improving clinical protocols, teaching of MRI operators and through quality assurance and quality improvement of the medical practice.
4. A statement regarding whether or not an expert interpreting physician will review images for incidental findings, should be included (please see next section for further details regarding incidental findings).

5. If images will undergo a formal review, the potential consequence of identifying findings of unknown clinical significance and potential psychological and health consequences, as well as potential consequences for insurability for healthcare should also be included as a potential risk.
6. A statement describing the extent, if any, to which confidentiality of images and any identifying information will be maintained.
7. A statement regarding compensation, if any, and/or medical treatments that are available should injury occur as part of this activity. All statements must follow local laws and regulations. It should be noted that the sample consent forms provided in the on-line supporting information are from the United States.
8. Information on an institutional contact for any questions that the volunteer may have related to the scanning activity. The specific choice of institutional contact listed on the consent form should be based on the same approach taken for local IRB protocols.
9. A statement that participation in this activity is voluntary and that refusal to participate will involve no penalty or other loss of benefits to which the subject would be otherwise entitled. Volunteers are permitted to withdraw at any time without penalty. A copy of the consent form should be made available to the volunteer.

Incidental Imaging Findings

Incidental findings in nonclinical research activities present an unusual challenge. There is a difficult balance weighing the potential benefits such as a life-saving diagnosis of an unsuspected abnormality versus the potential harm created by the anxiety of a finding of uncertain significance and potential implications for employment and insurability. There are no clear consensus approaches for managing incidental imaging findings in the context of research related imaging, and it is recognized that there remains a general "... lack of evidence on which to base practice ... on the balance of harm versus benefit in telling research participants about findings ...".[11] Formalized review of nonclinical, nonresearch incidental findings may also place an undue burden on sites to find an available licensed physician who is willing to perform formal image reviews.[11,12]

Despite these challenges and lack of evidence, guidance on the development of specific policies and procedures for managing incidental findings are becoming increasingly available.[11–13] For example, Thorogood et al propose that feedback polices for incidental findings should describe procedures for determining which data (if any) should warrant review, evaluating incidental findings, re-identifying subjects with findings discovered on anonymized image data, and contacting subjects with incidental findings.[13]

In general, we recommend that no formal image review be performed for nonresearch, nonclinical MRI, so long as this is disclosed in the consent form. This approach may help avoid potential abuse by volunteers seeking MRI as a surrogate for a clinically necessary MRI exam. It should be noted, however, that at some institutions, IRB protocols require review of certain research MRI studies by board-certified radiologist or other clinician. This practice varies between specific IRB protocols, institutions, and regions. The local IRB may be helpful to provide guidance on this issue, although it should be noted that oversight of the IRB applies only to human subjects research activities, and does not apply to nonclinical, nonresearch MRI activities.

As discussed above, any guidelines that choose to review images for incidental findings should include a statement in the consent form describing the process for informing the subject and/or his/her physician.

In conclusion, the principles and guidelines described in this document are aimed at providing a useful framework and process for appropriate and safe nonclinical, nonresearch MRI of human volunteers. Without a physician order and without an approved IRB protocol, many institutions do not have well developed processes including elements of informed consent that ensure that standard MRI safety practices, and the principles of beneficence and informed consent are adhered to. We believe that this document provides a reasonable approach to provide an orderly process for human scanning in the gray zone between clinical and research MRI activities.

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References

1. Department of Health and Human Services, Code of Federal Regulations, Part 46: protection of human subjects. Available at: http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html. Accessed April 3, 2016.
2. Health Canada Research Ethics Board - Ethics Review of Research Involving Humans - Administrative Policy and Procedures Manual. Available at: http://www.hc-sc.gc.ca/sr-sr/pubs/advice-avis/reb-cer/index-eng.php. Accessed April 3, 2016.
3. Australian Code for the Responsible Conduct of Research. Available at: http://www.nhmrc.gov.au/_files_nhmrc/file/research/research-integrity/r39_australian_code_responsible_conduct_research_150811.pdf. Accessed April 9, 2016.
4. Frascati Manual. Proposed standard practice for surveys on research and experimental development. Available at: http://www.keepeek.com/Digital-Asset-Management/oecd/science-and-technology/frascati-manual-2015_9789264239012-en#page1. Accessed April 9, 2016.
5. Food and Drug Administration Code of Federal Regulations Title 21 2015. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=812. Accessed April 3, 2016.
6. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients

with normal renal function, suggesting dechelation. Invest Radiol 2014;49:685–690.

7. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014;270:834–841.
8. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015;275:772–782.
9. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015;275:783–791.
10. Department of Health and Human Services, Code of Federal Regulations, Part 46.116: informed consent checklist - basic and additional elements. Available at: http://www.hhs.gov/ohrp/policy/consentckls.html. Accessed date April 3, 16.
11. A report by Representatives of Research Imaging Centers PS, Regulatory Bodies, Funding Organisations, Royal Colleges involved in research imaging and Patient Organisations, in the UK. Management of Incidental Findings Detected During Research Imaging 2011. Available at: https://www.rcr.ac.uk/management-incidental-findings-detected-during-research-imaging. Accessed date April 3, 16.
12. Wardlaw JM, Davies H, Booth TC, et al. Acting on incidental findings in research imaging. BMJ 2015;351:h5190.
13. Thorogood A, Joly Y, Knoppers BM, et al. An implementation framework for the feedback of individual research results and incidental findings in research. BMC Med Ethics 2014;15:88.