MRI Research Safety Form for IRB Approval

Please complete and e-mail to Julie Hanlon and Vera Kimbrell
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Study Name:
Contact:
Anticipated Start Date:

The MRI Safety Review process will not start until the IRB has on file a specific MR protocol and procedure including identification and detailed description of all study related pulse sequences, contrast use, and hardware. This description should be sufficiently detailed to guide full implementation of the study after approval, and will be forwarded to the MR safety sub-committee and MR technical staff upon approval of the IRB protocol. ***Without this information we cannot begin the review.***

MR Research Site:

☐ ***Plan for performance of safety reads of all anatomic images produced during the research study [0]:***

☐ ***MR Protocol: This can be hand written or sent as an attachment***

Level One MR Safety Approval

ANSWER **ALL** OF THE FOLLOWING QUESTIONS **YES** OR **NO**

NOTE: A proposed study may be eligible to obtain administrative provisional approval from staff of the Partners Human Research Committee and/or BWH MRI Safety Committee if the answers to the following questions are all **NO**:

1. Will any study related implanted device, external device or other hardware be in contact with the patient or volunteer during MRI?	☐ Yes	☐ No
2. Will any study related hardware be brought into the MRI room (Zone 4)?	☐ Yes	☐ No
3. Is any of the proposed MRI pulse sequence software different in any way from the standard FDA-approved commercial product software in use at BWH?	☐ Yes	☐ No
4. Will the consent language related to MRI risks differ in any way from the full unmodified language of the standard BWH MR related study consent template? **[1]**	☐ Yes	☐ No
5. Will the study risk statement differ in any way from the full unmodified language of the BWH MR related study risk statement template? **[2]**	☐ Yes	☐ No

The criteria are different for healthy volunteers and clinically indicated research subjects. Please check ***ALL*** box(es) that apply to your population and answer the associated questions.

☐ THE STUDY INCLUDES RESEARCH SCANS WHICH ARE NOT PART OF A CLINICALLY INDICATED MRI EXAMINATION.

1. Will contrast agents be used for MR imaging of healthy volunteers? If yes complete Level 2C page.	☐ Yes	☐ No
2. Will contrast agents be used for MR imaging of patients whose clinically indicated workup would otherwise not include contrast enhanced MRI? If yes complete Level 2C page?	☐ Yes	☐ No
3. Will anesthesia or other medications be administered during the MR exam or in the MR area?	☐ Yes	☐ No

If **YES,** full MRI Safety Committee review required.		
4. Will ***subjects who are pregnant, under 18 years old or have implanted devices, be included in MRI scanning?*** If **YES**, full MRI Safety Committee review required.	☐ Yes	☐ No

☐ THE STUDY INCLUDES RESEARCH SCANS PERFORMED AS PART OF A CLINICALLY INDICATED MRI EXAMINATION.

1. Will any part of the relevant clinical BWH MR protocol or any BWH standard MRI procedure related to ***contrast agent use*** be modified, including especially: • patient screening, • selection of contrast agent, • dose, route, injection rate or timing? If **YES**, complete Level 2C page [9].	☐ Yes	☐ No
2. Will BWH clinical MRI policy and procedure relevant to patient screening, risk-benefit assessment, protocol prescription, scanning, use of sedation or anesthesia, MRI in pregnancy, MRI in children, or MRI in patients with implanted medical devices be modified in any way? If **YES**, full MRI safety review required.	☐ Yes	☐ No
3. Will any sequence of the standard clinical BWH MR protocol for the relevant indication be eliminated or modified in any way? If **YES**, complete Level 2A page.	☐ Yes	☐ No

Level 2A – Non-conforming Software

ANSWER ALL OF THE FOLLOWING STATEMENTS **YES** OR **NO**

NOTE: A proposed study which does not conform to the above Level 1 criteria because of non-standard or modified pulse sequence software may be eligible to obtain administrative provisional approval from the appropriate staff of the BWH MRI Safety Committee if the answers to the following statements are **ALL** '**YES**':

1. The modified pulse sequences are ***ALL*** minor modifications of FDA approved pulse sequences.	☐ Yes	☐ No
2. The modified pulse sequences incorporate standard system safety checks for SAR and dB/dt that have not been altered or circumvented in any way.	☐ Yes	☐ No
3. The modified pulse sequences will run with the scanner in Normal or First Level operating mode.	☐ Yes	☐ No
4. All pulse sequence modifications are described in detail in the application.	☐ Yes	☐ No
5. All modified pulse sequences will produce images of similar diagnostic quality and utility to the analogous sequences eliminated from or replaced in the standard BWH protocol for the relevant indication.	☐ Yes	☐ No

Level 2B – Non-conforming Hardware

ANSWER ALL OF THE FOLLOWING STATEMENTS **YES** OR **NO**

NOTE: A proposed study which does not conform to the above Level 1 criteria related to non-standard or modified hardware may be eligible to obtain administrative provisional approval from the appropriate staff of the BWH MRI Safety Committee providing the answers to the following statements are **ALL** '**YES**':

1. All research hardware proposed is FDA-approved and FDA designated as MR-Safe. **[3]**	☐ Yes	☐ No
2. All research hardware has been previously approved and labeled "BWH MR Safe" by the relevant designated BWH MR Safety technologist. **[4]**	☐ Yes	☐ No
3. No research hardware will be in contact with the patient while the patient is in the scan room (zone 4).	☐ Yes	☐ No
4. The research hardware includes no laser, high intensity LED, or other significant optical emission component.	☐ Yes	☐ No
5. The research hardware emits no ionizing radiation.	☐ Yes	☐ No
6. The research hardware emits no detectable heat.	☐ Yes	☐ No
7. The research hardware includes no component that may pose a risk of tissue burns or fire and contains no explosive gas or liquid component.	☐ Yes	☐ No
8. The research hardware contains no cryogens, or other compressed gas.	☐ Yes	☐ No
9. The research hardware contains no other chemicals.	☐ Yes	☐ No
10. The research hardware does not emit noise louder than 90db.	☐ Yes	☐ No

Level 2C – Non-conforming Contrast Use

(As of 3/21/14 – Provisional until definitive revision by BWH CASC)

ANSWER ALL OF THE FOLLOWING STATEMENTS **YES** OR **NO**

NOTE: When a proposed study does not conform to Level 1 criteria related to contrast use the study may still be eligible to obtain administrative provisional approval from BWH MRI Contrast Agent Safety Committee if the answers to the following statements are **ALL**'**YES**':

I –Answer for **ALL** exams that require contrast to be administered:

1. All contrast agents are FDA-approved gadolinium based contrast agents.	☐ Yes	☐ No

II – Administration of contrast agents to patients as part of a clinically indicated contrast enhanced MRI protocol relevant to the patient's condition:

1. Patient screening, contrast agent selection and administration parameters pose no significant additional risk to research subjects compared with the parameters specified in the relevant BWH clinical MR protocol.	☐ Yes	☐ No
2. The proposed contrast agent selection and administration parameters will produce contrast enhanced images similar in diagnostic quality to the standard clinically indicated contrast enhanced images that are part of the relevant standard clinically indicated MRI protocol.	☐ Yes	☐ No
3. If contrast enhanced MRI is proposed for research purposes at time-points when MRI is not indicated clinically, fewer than 10 additional doses of contrast will be administered per year ***AND*** the number of additional contrast doses administered solely for research purposes during the study is less than 10 times the number of doses indicated clinically.	☐ Yes	☐ No

III - Administration of contrast to patients <u>for research purposes</u> as part of a clinically indicated non-contrast clinical MRI scan (i.e. proposed use of contrast agent in patient who would otherwise undergo a non-contrast MRI):

1. Subjects with any history or other evidence of kidney abnormality or increased risk of allergic or chemotoxic contrast reaction will be excluded.	☐ Yes	☐ No
2. eGFR will be checked on the day of study and subjects with eGFR < 60 will be excluded.	☐ Yes	☐ No
3. Subjects will be encouraged to drink as much fluid as tolerable over the 24 hours prior to the study, unless otherwise directed by a physician.	☐ Yes	☐ No
4. The proposed contrast agents have an identical or better safety profile than the contrast agents currently used in relevant BWH clinical imaging protocols.	☐ Yes	☐ No
5. Full unmodified language from standard BWH CASC consent template for use of intravenous contrast will be included in the informed consent. **[5]**	☐ Yes	☐ No
6. Full unmodified language from standard BWH CASC risk statement template for use of intravenous contrast will be included in the risk statement. **[6]**	☐ Yes	☐ No

IV - In regard to proposed contrast administration to healthy volunteer subjects:

1. Subjects with any history, family history or other evidence of kidney or liver abnormality or increased risk of allergic or chemotoxic contrast reaction will be excluded, ***following the exclusion criteria below***	☐ Yes	☐ No
2. eGFR will be checked on the day of study and subjects with eGFR < 60 will be excluded.	☐ Yes	☐ No
3. Subjects will be encouraged not to take NSAIDs for 72 hours prior to the exam.	☐ Yes	☐ No
4. Subjects will be encouraged to drink as much fluid as tolerable over the 24 hours prior to the study	☐ Yes	☐ No
11. Contrast agents are as safe or safer than agents in current clinical use at BWH	☐ Yes	☐ No
5. Full unmodified language from standard BWH CASC consent template for use of intravenous contrast in normal volunteers will be used in the informed consent. **[7]**	☐ Yes	☐ No
6. Full unmodified language from standard BWH CASC risk statement template for use of intravenous contrast in normal volunteers will be used in the risk statement. **[8]**	☐ Yes	☐ No

PROVISIONAL EXCLUSION CRITERIA FOR USE OF Gd BASED CONTRAST AGENTS IN HEALTHY VOLUNTEER RESEARCH STUDIES
(As of 3/21/14 – Provisional until definitive revision by BWH CASC)

1. Fetal of Newborn Exposure Risk Factors
   Woman known to be pregnant
   Woman breastfeeding a child
   Sexually active woman of reproductive age not using contraception

2. Allergic Contrast Reaction Risk Factors
   History of significant or multiple allergies or significant atopy
   History of GdBCA Contrast Reaction
   History of CT/Radiography/Angiography Contrast Reaction
   History of asthma or bronchospasm

3. Chemotoxic or Osmotic Contrast Reaction Risk Factors
   Congestive heart failure
   Congenital heart disease
   Pulmonary hypertension
   History of heart attack

4. Factors that would complicate resuscitation in case of severe contrast reaction
   Sleep Apnea
   Morbid Obesity
   History of respiratory failure requiring intubation
   History of difficult intubation for surgery
   Abnormal craniofacial anatomy that might complicate intubation
   Other severe systemic disease

5. NSF Related Risk Factors
   - Known Kidney Disease or Kidney Abnormality
     - Dialysis
     - History of renal insufficiency or failure (acute or chronic, prior or current)
     - Kidney surgery
     - Kidney tumor
     - Kidney transplant recipient or donor
     - Horseshoe Kidney
     - Single Kidney
     - Polycystic Kidney Disease
     - Any other kidney Disease
   - Conditions Predisposing to Kidney disease
     - Diabetes
     - Hypertension
     - Known cardiovascular disease (cardiac or peripheral)
     - Multiple myeloma
     - Systemic lupus
     - Collagen vascular disease
     - Autoimmune disease
     - Family history of kidney disease
     - Age >70 year old
   - Known Liver Disease

Cirrhosis
Other Liver Disease
Liver transplant
Hepato-renal syndrome

Other
Scleroderma
History of multiple prior gadolinium based contrast agents for MRI

6. Medications
Metformin
Chemotherapy (especially cisplatin or methotrexate)
Immunomodulatory or Immunosuppressive agents
Antiretroviral medications
Nephrotoxic antibiotics within 6 months
NSAIDs within 2 weeks
Any CT, Radiography, or Angiography IV contrast within 1 month
History of multiple prior gadolinium based contrast agents for MRI

REF:

1. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. AJR Am J Roentgenol. 2011 Feb;196(2):W138-43. doi: 10.2214/AJR.10.4885. PMID:21257854[PubMed - indexed for MEDLINE]
2. ACR Manual on Contrast Safety V9
3. FDA-Information on Gadolinium-Based Contrast Agents
4. The use of gadolinium in patients with contrast allergy or renal failure requiring coronary angiography, coronary intervention, or vascular procedure.
Catheter Cardiovasc Interv. 2011 Nov 1 ;78(5):747-54. doi: 10.1002/ccd.22907. Epub 2011 Jul 21 .

EXPLANATION OF PROCESS AND NOTES:

(I) Provisional Approval

If preliminary review of the submitted information reveals no unacceptable MRI related risks, the MRI Safety Committee will recommend that a research proposal undergo full review by the IRB. The MRI Safety Committee may make additional comments or recommendations to the IRB for consideration at the time of full review. This is NOT final approval for the MRI portion of the study

Eligibility for Administrative Provisional Approval The final determination of eligibility for Level 1-3 administrative provisional approval rests with the MRI Safety Committee. Sufficient information must be provided to satisfy the BWH MR Safety technologist, in consultation with relevant members of the BWH MR Safety, BWH Radiology MR Managers, BWH Contrast Agent Safety Committees and/or other relevant clinical radiology staff as needed, that the attestations above are true. Studies that do not meet Level 1-3 safety review criteria must undergo a FULL REVIEW by the MRI sub-committee to obtain Provisional Approval. Regardless of the above criteria, the BWH MR Safety Technologist may refer any study for full review by the committee at any point in the process for any reason.

(II) Final Approval

Regardless of the path to provisional approval, AFTER approval by the IRB, ALL research proposals involving MRI will undergo final MRI Safety Committee review before final approval to begin the MRI portion of the study. During final review, the BWH MR Safety Technologist, other members of the MRI Safety Committee, members of the BWH Contrast Agent Safety Committee and/or other members of the BWH radiology technical and/or professional staff designated by the MRI Safety will at minimum:

(1) Confirm that no portion of the final research proposal, procedure, hardware, software, contrast agent, or other information differs significantly from the information provided at time of provisional approval
(2) Review and, if deemed necessary, perform phantom testing of any research related MRI pulse sequence or other software,
(3) Inspect, test and, if deemed necessary, perform a dry-run of using any research related hardware
(4) Discuss with the relevant MR research site lead technologist to confirm that adequate information and/or demonstration has been

performed to ensure that no aspect of the proposed study will raise significant operational, safety or efficiency concerns
(5) Confirmation with the relevant radiology sub-specialty section chief of service or designee that any research sequences proposed to be performed as part of a clinically indicated MRI protocol will produce diagnostic image quality that is acceptable clinically and similar to the standard relevant BWH protocol.
(6) Confirm with the appropriate staff of the BWH Contrast Agent Safety Committee that the CASC committee has reviewed and approved any proposed modification to standard clinical practice related to use of contrast and/or any use of contrast that is not clinically indicated.

At the discretion of the BWH MR Safety technologist the final review may be referred to the full MRI Safety Committee and/or the full BWH MRI Managers Committee for full review for any reason. A formal presentation by the PI and/or other relevant investigators to these committees may be required, especially if new research related hardware are proposed.

Discovery during final review of information that differs from that disclosed at time of provisional IRB approval will in most cases lead to immediate provisional disapproval of the study pending a full MRI safety re-review and will be reported to the IRB.

(III) Post-Approval Changes
After final approval the principle investigator is REQUIRED to report ANY proposed modification or alteration of ANY PART of the MRI related portions of the protocol including contrast agent selection and/or administration parameters to the IRB for investigation and approval by the MRI Safety Committee and/or Contrast Agent Safety Committee PRIOR TO using such modified procedure.

ATTESTATION:

I understand that omission of relevant information or provision of inaccurate information in this form could result in serious injury or death to research subjects. I attest that I have read and completely understand the above, attest that I have obtained any assistance I need to be certain that the answers provided are complete and correct, and attest that the information provided above is complete and correct.

_____	_____	_____
PI Name & Degree	*Signature*	*Date*

Notes & Attachments:

[0] Safety Reads - A process to insure that (A) A BWH MRI Radiologist of the appropriate subspecialty will review any and all images produced in every case. (B) The radiologist will inform the principle investigator of any significant abnormality appreciated. (C) The principle investigator will inform the patient/volunteer and refers the patient/volunteer to an appropriately qualified licensed physician for appropriate further evaluation, care and/or treatment of any finding or condition uncovered. The protocol must include an explicit acknowledgment by the principle investigator that he or she understands, is qualified to meet, and willingly assumes sole professional responsibility for this process. The risk statement and consent must include standard recommended language informing the patient/volunteer of the risk of unexpected findings leading to need for additional consultation, testing and/or treatment which may entail additional discomfort, risk, and cost to the patient, the patient's family and/or the patient's insurance company.

[1] *Standard Language for MRI Research Consent*

"As part of this study, you will have one or more "Magnetic Resonance Imaging" (MRI) scans. MRI does NOT use ionizing radiation like x-rays. Instead it uses strong magnets and radio waves to make images of the inside of a person's body. The MRI scan should not cause you any pain. The MRI scan is not known to have any significant effect on health

Although MRI is not known to have any significant effect on the fetus of a pregnant woman, the effect of such strong magnetic fields and radio-waves on fetal development has not been thoroughly studied. For this reason, the technologist will ask you if you could be pregnant. If you are or could be pregnant it is recommended that you should not have the MRI scan and you may not be able to participate in this study.

Because MRI uses strong magnets and Radiofrequency certain kinds of medical devices implanted in or on your body may be damaged by the MRI scan, malfunction during or after the scan or injure you during MRI. The MRI technologist will have you complete a safety questionnaire to make sure that you don't have any implanted device or other objects such as bullets or nails in your body that would make it unsafe for you to have an MRI scan. If you have such an implants, bullet, tattoos, etc. that would cause MRI to be

hazardous to you, you may not be able to receive the MRI scan and you may not be able to participate in the study.

The MRI also produces loud beeping and hammering sounds when the scanner is operating. This is normal and you will be given earplugs and/or other ear protection to reduce the noise to safe levels.

The MRI scanner is a narrow tube and some people become uncomfortable inside the magnet. During the scan you will be able to talk with the MRI technologist through an intercom system, so that any discomfort or anxiety you are experiencing can be immediately addressed and the scanning stopped if needed."

***[2]** Standard MRI Risk Statement Language*

"As part of this study, you will have several scans using "Magnetic Resonance Imaging" (MRI). MRI does NOT use ionizing radiation like x-rays. Instead it uses strong magnets and radio waves to make images of the inside of a person's body. The MRI scan should not cause you any pain. The MRI scan is not known to have any significant effect on health. Because MRI uses strong magnets and Radiofrequency certain kinds of implants or devices in or on your body may be affected by the MRI scan or create a significant risk for you. The MRI technologist will have you complete a safety questionnaire to make sure that you don't have any such device and to see if it is safe for you to have an MRI scan. If you have certain implants, tattoos, etc. that could be a problem, you may not be able to receive the MRI scan and you may not be able to participate in the study.

The MRI also produces loud beeping and hammering sounds when the scanner is collecting measurements. This is normal and you will be given earplugs and/or other ear protection to reduce the noise.

The MRI scanner is a narrow tube and some people become uncomfortable inside the magnet. During the scan you will be able to talk with the MRI technologist through an intercom system, so that any discomfort or anxiety you are experiencing can be immediately addressed and the scanning stopped if needed.

[3] MR Safe – The term 'MRI Safe' refers to designation by the BWH MRI Safety Technologist. This designation is based on the US FDA designation of a device as 'MRI Safe'. This FDA designation is an explicit component of medical device labeling and indicated that the FDA, on the basis of data submitted by the device manufacturer, has determined that neither the entire device nor any component of the device has will pose any significant risk to any patient during any for- seeable use in any FDA approved MRI device or standard MR environment under any conceivable scan condition. The data

considered by the FDA in making this determination explicitly address risks including but not limited to attraction, deflection, torque, heating, induced current, and auditory noise.

[4] The MRI Safety technologist will confirm the FDA MRI Safe labeling with testing and/or additional consultation as she/he deems necessary before designating a device 'BWH MRI Safe'. In certain cases, an unlabelled device may be designated 'BWH MRI safe' at the discretion of the MRI committee and/or technologist. In general, devices designated unsafe for MRI by the manufacturer and/or FDA will not be designated 'BWH MRI Safe' or allowed into the MRI department at BWH.

[5] Standard Consent Language for Research Use of Gadolinium Based Contrast Agents in patients (PROVISIONAL AS OF 3/21/14 PENDING DEFINITIVE REVISION BY CASC).

During your MRI, you will be given a contrast agent/medication used to enhance the information in the images produced by the MRI. The medication will be given through a needle and small tube called an "IV catheter" placed in a vein in your arm using standard hospital techniques.

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a metal element called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms are typically not dangerous, occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium. Most reactions are mild, not dangerous and resolve with no treatment or medications including anti-histamines and steroids. In a very small number of people a severe allergic reaction occurs, which can be life threatening. These severe allergic reactions are very rare, and are estimated to occur in less than one in 300,000 people.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This is a fatal disease which causes fibrosis. Poor kidney function is a known risk factor for developing NSF/NFD. There is thought to be no significant risk of NSF/FD in people with normal renal function or mild kidney disease. In order to make sure that we do not administer gadolinium contrast to people at risk for NSF/NSD, we may require a blood sample to check your kidney function before you receive gadolinium contrast for your MRI.

[6] Standard Risk Statement Language for Research Use of Gadolinium Based Contrast Agents in patients (PROVISIONAL AS OF 3/21/14 PENDING DEFINITIVE REVISION BY CASC).

Exclusion Criteria should include:

1. ***History of Renal disease(eGFR less than 60)***
2. ***Pregnant women or nursing mothers***
3. ***History of Allergic Reaction to Gadolinium based contrast***

Gadolinium based contrast agents (GBCA) are administered as an intravenous injection and therefore pose a small risk of soft tissue infiltration, phlebitis, and infection. Standard BWH infection control policies and procedures will be followed during the administration of any contrast media.

GBCA are commonly used in MRI studies and involve minimal risk but allergic reactions can occur. These reactions range from mild or moderate (skin irritations, rash, nausea, hives, sneezing, coughing) to severe systematic reactions (anaphylactic shock, drug reaction, brain damage due to respiratory arrest or death). Estimates in the peer reviewed literature vary, but the rate of severe reaction is thought to be less than 1 per 300,000 doses. The average number of contrast related deaths reported to the FDA in recent years has been reported to be roughly 7 per year or 1 per 1,000,000 doses.

Most people experience a warm feeling when GBCA are injected, and may experience a metallic taste. This is not dangerous and resolves rapidly without treatment.

GBCA do cross the placenta in animal testing. The effects of GBCA on fetal health are unknown. GCBA is only used clinically in pregnant women under very unusual circumstances when there is a very strong indication for contrast enhanced MRI no reasonable alternative. As such, if women of childbearing potential are included in the study, the protocol must provide for a pregnancy test within a week prior to the MRI scan with contrast. If the pregnancy test is negative, then the study may proceed with appropriate consent language. If the pregnancy test is positive, the patient will not be permitted to receive GBCA except after review and explicit approval of each individual case by the IRB followed by PI discussion of the fetal exposure to GBCA with the patient and documentation of additional consent for GBCA by the patient. This additional consent must be performed personally by the PI.

Gadolinium-based contrast agents have been identified as a factor strongly associated with the development of fatal Nephrogenic systemic fibrosis (NSF) in vulnerable patient populations. To date except for very rare reports of NSF

after organ transplantation (heart and kidney) without prior GBCA exposure, the vulnerable population is thought to be patients with renal impairment who have an eGFR < 30, acute kidney impairment and/or are dependent on hemodialysis.

NSF has been reported in 5 of the FDA approved GBCAs, as well as with other GBCA in use in Europe. For the purposes of IRB policy all gadolinium based agents should be considered to confer a risk for NSF in a vulnerable subjects.

The overall incidence of NSF is quite rare. Since 2000, approximately 200 million patients worldwide have been exposed to gadolinium, but less than 500 cases of NSF have been reported. As such while this may be a slight underestimate, the risk of developing NSF per dose of GCBA in an unscreened population is estimated to be roughly 1 in 400,000.

In patients with renal failure or impairment the risk is still low, but much higher than this estimate. In populations appropriately screened to exclude patients with renal failure or insufficiency or other risk factors, the risk of NSF is much lower and recent experience suggests that it may be near zero. As such, guidelines for safe use of GBCA focus on identifying vulnerable subjects and excluding them from use of GBCA.

The following requirements for safe use of GBCA are based on US FDA and American College of Radiology guidelines:

- All subjects will have a determination of their estimated glomerular filtration rate (eGFR) within 24 hours of undergoing any study where gadolinium based contrast agents will be administered.
- Subjects should not have a known history of recent onset acute renal dysfunction.
- Subjects with a history of stable chronic renal dysfunction may participate in studies using GBCA based on their eGFR, as outlined below.
- Subjects should not have severe liver dysfunction, particularly when associated with kidney disease.
- Subjects should receive GBCAs in the perioperative period (i.e. within 4 weeks) after renal or liver transplantation.

Since the occurrence of NSF is very strongly linked to renal function, the BWH GBCA usage guidelines are stratified by the eGFR.

1) <u>eGFR > 60 ml/min/1.73 m^2 : Normal subjects or patients with stage 1 or 2 chronic kidney disease</u>

a. There is no evidence that these subjects are at an increased risk of developing NSF.
b. GBCA used should be administered within FDA dosing guidelines.

2) eGFR 30 - 59 ml/min/1.73 m^2 : Patients with stage 3 chronic kidney disease, history of renal or liver transplant beyond the perioperative period (even if eGFR > 60 ml/min/1.73 m^2)
   a. If renal function has been stable the risk of NSF is estimated to be extremely low.
   b. The protocol should not use more than a single doses of GBCA (≤ 0.1 mmol/kg)
   c. Subjects must not have received any other GBCA within 1 week of the study.

3) eGFR < 30 ml/min/1.73 m^2 : Patients with recent renal or liver transplant (within 4 weeks even if their eGFR is good)
   a. These subjects are at the highest risk of developing NSF.
   b. These subjects should not receive gadolinium based contrast agents in research studies.

[7] Standard Consent Language for Research Use of Gadolinium Based Contrast Agents in healthy volunteers (PROVISIONAL AS OF 3/21/14 PENDING DEFINITIVE REVISION BY CASC).

Same as # 5

[8] Standard Risk Statement Language for Research Use of Gadolinium Based Contrast Agents in healthy volunteers (PROVISIONAL AS OF 3/21/14 PENDING DEFINITIVE REVISION BY CASC).

Same as #6 but with the following added statement:

In this study, all pts with eGFR <60 or any other evidence of kidney or liver disease or any reason to suspect increased risk of allergic or chemotoxic reaction to GBCA will be excluded from participation according to unmodified standard IRB recommended detailed exclusion criteria.

[9] BWH policies related to screening, agent selection, and administration of contrast are updated from time to time. Note that answering 'no' to this question means that you understand and accept that the use of contrast in your study may be changed from time to time to meet current BWH policy. If this is not acceptable for your study, you answer 'yes' to this question and your proposal will need to undergo further review by the BWH Contrast Agent Safety Committee (CASC).

[10] MR Conditional- The term 'MRI Conditional' refers to designation by the US FDA as an explicit component of medical device labeling that the FDA, on the basis of data submitted by the device manufacturer, has determined that a given device may be used with reasonable safety in certain defined MR environments ONLY IF certain explicitly defined guidelines are followed AND ONLY if such use is deemed to be appropriate by a qualified physician who has considered the patient's clinical situation and the risks and benefits of MRI and of other alternative diagnostic options. BWH MRI Safety Policy, reflecting the recommendations included in the American College of Radiology 2013 Consensus Statement on MRI Safety, stipulates that to be qualified to perform such risk-benefit assessment, a physician must be a BWH clinical subspecialty radiologist in the appropriate subspecialty section currently qualified as a Level 2 MRI provider by the BWH MRI Safety Committee.