

## **GUIDANCE ON GADOLINIUM ADMINISTRATION IN HUMAN SUBJECTS RESEARCH AT THE NIH INTRAMURAL RESEARCH PROGRAM**

### **Background**

On December 19, 2017, the US Food and Drug Administration (FDA) issued a MEDWATCH Safety Alert for all gadolinium-based contrast agents (GBCA) concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these agents. <https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm> To date, gadolinium retention has not been directly linked to adverse effects in patients with normal kidney function, and the FDA concluded that the benefit of all approved GBCAs continues to outweigh any potential risks in the clinical setting. The FDA recommended considering retention characteristics of each GBCA for patients who may be at higher risk for gadolinium retention, and to minimize repeated GBCA exposure when possible. A review of scientific publications and adverse events by the FDA shows that linear GBCAs lead to retention of more gadolinium in the brain than macrocyclic GBCAs.

Following the December 2017 MedWatch Safety Alert, the potential risks of gadolinium retention were discussed at the March 8, 2018 NIH Human Subjects Research Advisory Committee (HSRAC) meeting, specifically in relation to the use of GBCAs in NIH research studies. There was particular concern for healthy volunteer subjects who may undergo many MRI scans with GBCA administration across multiple ICs. An ad hoc Committee was established to solicit input from Principal Investigators who perform MRI research in preparation for development of a policy for HSRAC and NIH leadership review.

The FDA issued a Drug Safety Communication update on May 16, 2018 announcing approval of updated prescribing information for gadolinium, including distribution of Medication Guides for each GBCA as they become available. The Communication included the statement "All MRI centers should provide a Medication Guide the first time an outpatient receives a GBCA injection or when the information is substantially changed. In general, hospital inpatients are not required to receive a Medication Guide unless the patient or caregiver requests it. A health care professional who determines that it is not in a patient's best interest to receive a Medication Guide because of significant concerns about its effects may direct that it not be provided to that patient; however, the Medication Guide should be provided to any patient who requests the information." Given the research mission of the NIH, it is appropriate that all NIH research participants be given FDA approved Medication Guides for any GBCAs they receive, if such a guide is available for the agent to be administered.

At the NIH Clinical Center, MRIs with GBCA may be performed solely for research purposes in both healthy subjects and patient volunteers, such as in studies exploring technical development of new imaging devices or processing. They may also be used for medical purposes within a research protocol, e.g., to diagnose a condition or measure response to treatment or disease progression. Finally, MRIs with GBCA may be used solely for medical purposes outside the context of a research protocol, consistent with community practice. An example of such scans at the Clinical Center are those performed on patients who experience an untoward change in health status during the course of research participation. This guidance document addresses all scenarios stated above, with human subjects protection emphasis on MRIs with GBCA in research protocols in which there is no prospect of direct benefit.

Many questions remain regarding the accumulation of GBCAs in humans. Studies are currently underway to evaluate these questions, including some protocols at the NIH Clinical Center. Some unknowns include: the exact nature of the difference between accumulations of linear vs. macrocyclic preparations; the difference, if any, in the accumulation of GBCA in healthy volunteers and patients; and the significance, if any, of GBCA accumulation in various organ systems. It is expected that research will soon yield information regarding these questions

In the absence of hard data on GBCA dosing thresholds and adverse effects of gadolinium retention, if any, this guidance document presents a framework which the IRB can apply in evaluating protocols in which gadolinium is administered to human subjects. Specific annual exposure limits are suggested, but the IRB has the discretion to allow the limit to be exceeded if justified by the strength of the scientific question after consideration of a favorable risk/benefit ratio.

Given the current paucity of data, the limits were chosen out of prudence, based on exposures typical of current research employing GBCAs. Accordingly, doses at or below the guidance limits in this policy should not be interpreted to be “safe,” nor doses above the limits be considered “unsafe.”

This guidance addresses the use of GBCAs for research purposes. It does not address the use of GBCAs as part of the clinical care of the patient. The IRB considers all scans that are required by the protocol to be part of the research, even if the scan might also be done outside of the research context.

It is anticipated that this guidance will require revision over time, including the possibility that it will no longer be necessary if no risks are identified.

### **Guidance on the use of Gadolinium in human subjects research**

1. The use of GBCA solely for research purposes in which there is no prospect of direct benefit, whether for healthy subjects or patient volunteers, should be limited to macrocyclic GBCAs such as gadobutrol. However, the use of a linear agent may be justifiable in a protocol for scientific reasons, OR if in the judgment of the responsible physician, a linear agent is necessary for participant safety. For example, an IRB may approve the use of a linear GBCA in participants who have had an allergic response to prior administration of macrocyclic agents.
2. When the administration of a GBCA provides the prospect of direct benefit to the research subject, the use of macrocyclic GBCAs are strongly encouraged. However, linear agents may be used if the responsible physician considers it preferable for specific imaging considerations (such as the use of gadoxetate disodium [Eovist] for liver lesions) or for safety purposes (such as a history of allergic reaction to macrocyclic agents).
  - There is no limit on the amount of GBCA administered per year if there is the prospect of direct benefit, however, as with all procedures, prudence should be exercised to minimize exposure to the least necessary.

3. When the administration of a GBCA provides no prospect of direct benefit to the research subject, whether for healthy subjects or patient volunteers, the exposure to the GBCA should not exceed 0.6 mmol/kg of gadobutrol (or equivalent for other GBCAs) per 12-month period in any individual participant. This translates to approximately three cardiovascular scans or five to six non-cardiovascular scans with GBCA administration. In select circumstances, it may be acceptable to exceed the annual limit after a risk-benefit analysis by the IRB which takes into consideration the scientific merit.
4. Serial scans using GBCAs within a research protocol, regardless of the prospect of direct benefit, should be spaced to provide sufficient time for clearance of the GBCA from circulation. Short-term dosing is limited to 0.2 mmol/kg per five half-lives. This translates to approximately one cardiovascular scan or two non-cardiovascular scans with GBCA administration per 12 hours (for gadobutrol). In select circumstances, it may be acceptable to allow a shorter interval between scans using GBCAs, after a risk-benefit analysis by the IRB which takes into consideration the scientific merit.
5. Participants who undergo an MRI scan that utilizes a GBCA will be provided the FDA-approved Medication Guide for the GBCA they are to receive, if one exists for the agent to be used. An exception is in those instances where GBCA is administered in an urgent medically indicated situation. In these cases, the Medication Guide may be provided afterwards at an appropriate time.
6. There is not agreement as to whether the use of GBCAs for research purposes in children with a disorder or condition presents a significant increment over minimal risk or merely a minor increment over minimal risk. The risk determination should be made by the reviewing IRB in the context of each research protocol. Accordingly:
  - a. GBCAs cannot be approved by the NIH IRB for use in healthy children for research purposes because GBCAs are associated with greater than minimal risk and would not offer the prospect of direct benefit. (45.CFR.46 subpart D). Administration in healthy children requires approval by the Secretary of DHHS under §45.CFR.46.407/§21.CFR 50.54
  - b. GBCAs may be used in children with a disorder or condition for research purposes if the reviewing IRB finds that either:
    - i. The use of GBCAs in the context of the protocol is greater than minimal risk but presents the prospect of direct benefit to the individual child, that the risk is justified by the anticipated benefit, and that the anticipated benefit is at least as favorable as available alternatives (§45.CFR.46.405/§21 CFR 50.52). With this risk determination, research is not permissible if there is no prospect of direct benefit to the individual child. OR
    - ii. The use of GBCAs in the context of the protocol presents no more than a minor increment over minimal risk, the intervention presents an experience reasonably

commensurate with those inherent in their actual or expected experience, and the intervention is expected to yield generalizable knowledge about the subject's disorder or condition, and that it is important for the understanding or amelioration of their condition. (§45CFR46.406/§21 CFR 50.53)

7. Participants who have GBCA exposure, will be provided, upon request, information about gadolinium retention noted in the organ systems during their imaging exams.
8. GBCA orders will be entered via CRIS to allow investigators to determine a participant's GBCA administration history.
9. GBCA administration data will be placed in a BTRIS registry, once available. Historical data will also be entered for subjects whose IC investigators did not originally enter GBCA orders through CRIS. These data may be used for research purposes with IRB approval.

### **Suggested Protocol Language**

*This language should be used **in addition to existing gadolinium language that describes its administration and other risks.***

#### **Procedures:**

MRI scans may include intravenous administration of an FDA-approved, macrocyclic, gadolinium-based MRI contrast agent (*if applicable add*: including in healthy volunteers) for research purposes. Unless otherwise specified in the protocol, contrast agents will be used at FDA-approved doses. (*If linear GBCAs may be used add*: Under certain circumstances, participants in this study may receive a linear chelate. Examples of situations in which this may occur include the following: (1) prior sensitivity to all macrocyclic agents; OR (2) participation in a longitudinal study in which a linear chelate was previously approved and there is a clear advantage to maintaining the same gadolinium protocol. In accordance with the FDA Drug Safety Communication of 05/16/2018, the FDA Approved Medication Guide for the applicable GBCA will be given to all subjects who receive them. Upon request, participants will be provided individual information about gadolinium retention noted in their exams.

#### **Risks:**

Most of the gadolinium contrast is eliminated in the urine. However, recent studies have found very small amounts of residual gadolinium in the body, including the brain and bone, by imaging and at autopsy. Macrocyclic gadolinium-containing contrast agents are substantially less likely to leave gadolinium behind than linear agents. (*If linear GBCAs may be used add*: The use of macrocyclic vs. linear agents in this study is delineated in the procedures section above.) There is presently no evidence that the retained gadolinium is associated with any adverse effects or other health risks.

**Please refer to the “consent library” posted on the OHSRP website for consent language.**