



ACRIN Protocol 6666
SUMMARY OF CHANGES

November 9, 2007

Amendment # 6

Due to the black box warning of nephrogenic systemic fibrosis with gadolinium-based contrast agents in patients with severe kidney disease, ACRIN 6666 has been amended as follows:

- **Cover Page**

Amendment 6 and version date November 9, 2007, have been added.

- **5.6. Exclusion Criteria for MRI of the Breast, Page 54**

The 4th criterion was added and reads:

Participant with severely impaired renal function with estimated glomerular filtration rate (GFR) < 30 mL/min/1.73m² and/or on dialysis.

Note: Sites may calculate GFR using institutional standards. A web calculator for GFR is available at: http://www.nkdep.nih.gov/professionals/gfr_calculators/

- **9.3.5 Expected Adverse Events from MRI of the Breast, Page 68**

The last 3 paragraphs were added and read:

“Precautions should be exercised for patients with severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic or cardiovascular reactions, should be considered, especially for patients with a known sensitivity to Gd or history of asthma.

Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with moderate to end-stage kidney disease (glomerular filtration rate <30mL/min/1.73m²) and in patients with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had a MRI scan with gadolinium-based MR contrast agents (GBMCA).

NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels. Reference: FDA/Center for Drug Evaluation and Research. May 23, 2007 http://www.fda.gov/cder/drug/infopage/qcca/qa_200705.htm

- **Appendix IIIA Supplemental Sample Informed Consent, Page 130**

Under “Risks of Contrast Agent/rare but serious,” the second bullet was added and reads,

Nephrogenic systemic fibrosis (NSF)/nephrogenic fibrosing dermopathy (NFD): In rare cases, some patients who have severe kidney disease developed symptoms of tightening or scarring of the skin and organ failure called nephrogenic systemic fibrosis (NSF) and nephrogenic fibrosing dermopathy (NFD) after they have had an MRI scan with gadolinium-based contrast agent.

NSF has not been seen in patients with normal working kidneys or mild problems in kidney function. If there is concern about your kidney function, you may be asked to have a blood test to determine if your kidneys are working properly before you have the MRI.

NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. It can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels. In very rare cases, it can be deadly. Reference: FDA/Center for Drug Evaluation and Research. May 23, 2007, http://www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm.

- **Eligibility Checklist, Page 137**

Question 4f was added and reads: “Impaired renal function, with estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m² and/or on dialysis?”

The following additional changes were made:

- **Table 1: Participating Sites and Principal Investigators, Page 3**

Contact information was updated for the following investigators:

Dr. Berg: “Green Spring” was corrected to “Greenspring”

Dr. Mendelson: E-mail address was updated to “emendelson@nmff.org”

Dr. Fein-Zachary: Name and e-mail address were added to replace Dr. Baum

Dr. Berns: Northwestern University was removed and e-mail address was updated to “eric.berns@gmail.com”

- **Schema, Page 7**

In the 1st text box/last line, “4 weeks” was corrected to “8 weeks.”

- **4.12.1 Timeline for Receiving MRI Component of Trial, Pages 43-4**

The last sentence of the 1st bullet was added and reads, “If the MRI examination has to be rescheduled, it must be completed within 3 full months of the 24-month US and mammography examinations.”

In the 6th bullet/last paragraph/last sentence, “uninsured patients” was changed to “patients with inadequate insurance coverage” and “up to” was added before “\$500.”

- **9.1 Data Collection Forms, Page 65**

The F2 was added as #24.

- **9.2 Data Collection Timetable, Page 66**

The F2 was added between the F1 and CC.

- **9.3.5 Expected Adverse Events from MRI of the Breast, Page 68**

Text was added before the bulleted lists of risks and reads, “Any adverse events for the MRI study with attribution of possible, probable, or definite require reporting (see section 9.3.8 below)”

Under “Contrast Agent – Gadolinium,” vomiting, hives, temporary low blood pressure, and allergic reaction were added as the last 4 bulleted risks.

- **9.3.6 Expected Adverse Events from IV Needle Place, Page 68**

The entire section was added in place of the previous 9.3.6 text and reads,

- Hemorrhage (hematoma at the injection site);
- Infection (catheter related infection) at the injection site;
- Minor discomfort;
- Bleeding;
- Infection;

- Bruising;
- Venous thrombosis.

- **9.3.10 How to Report, Pages 70-1**

Section 1: The last 2 paragraphs were rewritten and read,

Protocols involving only imaging procedures must be submitted using a paper version. Investigators following those protocols should omit the Course Information section and the Protocol Agent section, even though the template indicates those as mandatory. (Do not try to send the form via the web site; it will not accept a form without those fields filled in.)

General questions regarding completion of the AdEERS report or submission can be sent to CIPSAEReporting@tech-res.com. AdEERSMD helpline is available for any questions via phone at 301-897-7497. "

Section 2: The text was rewritten and reads, "To make an expedited telephone reports to NCI/CIP, contact TRI staff at (301) 897-1704, available 24 hours a day (recorder after hours from 7:30 PM to 7:30 AM Eastern Time)."

Section 3: The text was rewritten and reads, "An expedited adverse event report must be sent with the above-mentioned timeframe to NCI/CIP by fax at (301) 897-7402. All fatal adverse events should be reported by telephone within 24 hours of the event."

Section 4: The text was renumbered from Section 3.

Section 5: The text was added and reads,

A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215) 717-0936 and the original signed and dated report must be sent to ACRIN.

*ACRIN 6666 Adverse Event
Attn: ACRIN 6666 AE Coordinator
1818 Market Street, 16th Floor
Philadelphia, PA 19103"*

Section 6: The text was renumbered from Section 4.

- **9.4.6 Table 3. Summary of Source Documentation Required, Page 75**

The F2 was added between the F1 and BX

- **Appendix IIIA Supplemental Sample Informed Consent, Page 130**

Under "Risks Associated With Intravenous Catheter (IV) Placement," 1) "IV" was added to the heading; and 2) "venous thrombosis" was added under "less likely."

Under "Risks Associated With Biopsies," the spelling of "pneumothorax" was corrected under "less likely."