PENNSTATE

HRP-591 - Protocol for Human Subject Research

Protocol Title:

Does reduction in contrast administration dose in computed tomography arteriograms degrade image quality? A single institutional review of an ultra-low contrast dose protocol.

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Version Date: 19 July 2017

Clinicaltrials.gov Registration NCT02669784

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1.0 Objectives

1.1 Study Objectives

The purpose of the study is to determine if the dose of contrast administered for computed tomographic arteriograms (CTA) can be reduced without degradation of image quality. The hypothesis is that there is no difference in image quality using ultra-low dose contrast in CTA exams compared to routine dose exams.

1.2 Primary Study Endpoints

The objective is to prospectively evaluate image quality of CTA examinations performed with an ultra-low contrast dose protocol. The primary endpoint would be to show that there is no statistical difference in the quality of the images.

1.3 Secondary Study Endpoints

Not Applicable

2.0 Background

2.1 Scientific Background and Gaps

Currently, at our institution, routine CTA examinations are obtained with a dose of 100mL of intravenous contrast. In the setting of renal dysfunction, this dose is reduced to 75mL to minimize the risk of contrast induced nephropathy. This dose can be further adjusted giving some flexibility depending on the BMI of the patient and type of scanner used. Given the recent advancements of computed tomography hardware, the scanning speed has greatly increased allowing for reduction in contrast dose. However, at our institution, the dosage and administration rate of intravenous contrast has not yet been adjusted to take advantage of improvements in scanning hardware.

2.2 Previous Data

A small number of patients have been imaged with a decreased contrast dose (up to 60% less contrast volume). By taking advantage of scanner speed and number of detectors, a smaller overall dose can be given while still obtaining adequate diagnostic imaging. Quantitative measurements of vascular enhancement (in Hounsfield units) at select locations show no differences in vascular opacification. In addition, qualitative evaluation of these images by board certified diagnostic radiologists show no difference in image quality between examinations performed with reduced contrast dose versus examinations performed with standard contrast dose. This data suggests that the same quality of images can be obtained with a lower dose of contrast minimizing the risk of contrast induced nephropathy. No references are available at this time regarding the rate of re-imaging due to non-interpretable CTA studies. In correspondence with several CT technologists, they stated that in their experience, rarely does a CTA of the chest or chest, abdomen and pelvis have to be repeated

2.3 Study Rationale

CTA is the imaging of choice for the evaluation of the aorta. Aortic CTAs are performed for evaluation of acute aortic syndromes, vasculitidies, as well as chronic conditions such as aortic aneurysms and congenital anomalies. Examinations are performed for pre-operative evaluation and post-operative follow up in many of these patients. This patient population includes patients with many comorbidities, such as hypertension and diabetes, as well as elderly patients. All these conditions contribute to renal dysfunction. For this reason, the radiology department at this institution has a policy to evaluate renal function before a contrast enhanced CT scan in the setting of increased age (>60 years), history of renal dysfunction or diabetes. Decreasing the contrast dose is important to prevent further damage to the kidneys by contrast induced nephropathy (CIN). It is thought that reducing the contrast dose will reduce

the risk of nephropathy. Development of a low dose protocol would potentially decrease the risk of contrast induced nephropathy in this patient population.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Any adult patient scheduled for a computed tomographic arteriogram (CTA) of the chest or CTA of the abdomen or CTA of the chest and abdomen or CTA of the abdomen and pelvis or CTA of the chest, abdomen and pelvis who had undergone a prior CTA of the same region performed with the standard contrast dose (100 mL) at this institution will be included in the study.
2. The follow-up scan will be routine standard of care, no emergency imaging patient will be approached for this research.

3.2 Exclusion Criteria

1. Patients with no prior CTA imaging for comparison.
2. Any pediatric patient (age <18).
3. BMI >40
4. Inability to follow instructions.
5. Allergy to intravenous contrast.
6. GFR less than 60 mL/min/1.73 m^2 – GFR should be within normal range. This would allow a repeat study if needed and not pose an increased risk to renal dysfunction.
7. Cognitively Impaired Adults
8. non-English speaking patients
9. Pregnant Females
10. Endoleak studies – decreased contrast makes evaluation of an endoleak difficult on delayed imaging.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Patient may decline or withdraw from participation at any time after the consent is signed.

3.3.2 Follow-up for withdrawn subjects

The information required for the study is obtained at the initial time of evaluation. If a person declines to participate, no data will be acquired. There is no reason to follow up withdrawn subjects.

4.0 Recruitment Methods

4.1 Identification of subjects

Medical records of adult patients scheduled for a routine computed tomography arteriogram will be evaluated prior to CTA imaging to identify subjects meeting the inclusion/exclusion criteria.

4.2 Recruitment process

Patients scheduled for routine CTA examinations will be screened, via medical records, to find out if they have had a prior CTA of the aorta with routine dose of intravenous contrast within the past two years. Those patients within this group that meet inclusion criteria and do not have any exclusion criteria will be offered to participate in the study.

4.3 Recruitment materials

Not Applicable

4.4 Eligibility/screening of subjects

We will be entering medical records to screen for eligibility. Therefore, we are requesting a waiver of consent and a HIPAA waiver of authorization to screen for eligibility criteria prior to the consent form being signed.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Informed consent will be obtained prior to examination in the IV preparation room or scanner room.

5.1.1.2 Coercion or Undue Influence during Consent

The individual obtaining consent will explain to the patient that participation is voluntary; that they do not have to take part in this research and that they can withdraw at any time. The decision whether or not to participate will have no impact on the availability of their current and future care within PSHMC. They will also be told that there is no compensation or reward for participating in the study.

5.1.2 Waiver or alteration of the informed consent requirement

We will be requesting a waiver to enter medical records to screen for eligibility.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Informed consent will be documented through the use of the long form consent. The language used in the informed consent document will be understandable to the subject. Both the subject and the person obtaining consent will sign the document, along with the date informed consent was obtained/given. A copy of the signed and dated informed consent document will be given to the subject. A signed copy of the consent will also be included in the patient's medical record.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not Applicable

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not Applicable

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not Applicable

5.3.2.2 Adults Unable To Consent

Not Applicable

5.3.2.3 Assent of Adults Unable to Consent

Not Applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not Applicable

5.3.3.2 Assent of subjects who are not yet adults

Not Applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

As the CTA scan is part of the patient's medical care, the images, with identifiers, will remain in the patient's medical record. The study linking list will be destroyed as per study guidelines.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Given that subject eligibility is based on previous CTA imaging with standard contrast dose (100 mL), it would not be possible to identify potential subjects without access to their medical records.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Potential subjects' history of procedures completed at this institution are kept within medical records, which contain PHI. Therefore, without a partial waiver, study team members will not be able to appropriately identify potential subjects.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Any adult patient scheduled for routine CTA meeting the inclusion/exclusion criteria and providing consent will be included in the study. The patient will be administered a low dose of intravenous contrast based on the study examination as described below. The contrast agent being used is Omnipaque. The scan will be performed under the supervision of the primary investigator or the described team members to make sure that the study is of diagnostic quality.

The following dose protocols will be followed:

CTA of the chest: 40 mL of intravenous contrast at a rate of 5mL/sec. A region of interest (ROI) to trigger the scan will be placed in the aortic arch. If scan is performed using high pitch helical mode, the scan delay will be increased by 2 seconds.

CTA of the abdomen OR or CTA of the chest and abdomen or CTA of the abdomen and pelvis or CTA of the chest, abdomen and pelvis: 50 mL of intravenous contrast at a rate 5mL/sec. A region of interest (ROI) to trigger the scan will be placed in the aortic arch. If scan is performed using high pitch helical mode, the scan delay will be increased by 2 seconds.

All other imaging parameters will remain unchanged, given that the subjects enrolled will be clinical patients of the principle investigator.

Following the examination, the primary investigator (PI) or team members will evaluate the images obtained with low contrast dose and each patient's prior CTA examination performed with routine contrast dose. This will be done by quantitative and qualitative measures. For the quantitative portion, the PI or team members will place regions of interest on predetermined arterial locations to obtain measure the degree of opacification. For qualitative measurement, the images will be presented in a blind fashion to two thoracic trained board certified radiologists and a board certified interventional radiologist to determine the quality of the images based on a Likert numerical scale. Qualitative and quantitative data for the images obtained with low contrast dose and those for the prior CTA examinations performed with routine contrast dose will be compared. This data along with details of the

scan protocol (dose, dose rate, scanning parameters etc.) and demographic data (such as sex, age and BMI at the time of examination) will be recorded in Redcap.

7.2 Study Procedures

7.2.1 Clinic Visit

The process of obtaining the CTA images will be unchanged from the patient's standpoint. One difference will be that the examination will be supervised by a team member. The intravenous contrast dose administered will be decreased according to the parameters written above. If the study is deemed non-diagnostic at the time of scanning, the study will be repeated. The standard of care at this institution in the setting of a non-diagnostic study is to repeat the study with a 75mL dose of contrast, for a total of 175mL of contrast. Given that the dose of contrast that will be administered for this study (40-50mL) is below the routine amount (100mL). Performing a repeat study with 75mL of intravenous contrast will not exceed the contrast dose that would have been normally administered.

7.2.2 EXAMPLE: Visit 2 or Day 2 or Post-test, etc. (format accordingly)

Not Applicable

7.3 Duration of Participation

The individual's participation will only be for the duration of the CTA examination.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Intravenous contrast, Omnipaque, will be administered as described above. The intravenous contrast is FDA approved for use of CTAs and is a standard of care practice at PSHMC with the standard contrast dose of 100 mL.

7.4.2 Treatment Regimen

At this institution, CTAs are performed with the standard contrast dose of 100 mL. This study will administer intravenous contrast, Omnipaque, at a dosage of 40 mL at a rate of 5mL/sec or at 50 mL at a rate of 5mL/sec as described above.

7.4.3 Method for Assigning Subject to Treatment Groups

Not Applicable

7.4.4 Subject Compliance Monitoring

Not Applicable

7.4.5 Blinding of the Test Article

Not Applicable

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The intravenous contrast, Omnipaque, will be received according to standard practice of the institution

7.4.6.2 Storage

The intravenous contrast, Omnipaque, will be stored according to standard practice of the institution.

7.4.6.3 Preparation and Dispensing

The intravenous contrast, Omnipaque, will be prepared and administered as per standard of care procedures.

7.4.6.4 Return or Destruction of the Test Article

Not Applicable

7.4.6.5 Prior and Concomitant Therapy

Not Applicable

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

The number of study subjects anticipated is 180 patients.

8.2 Sample size determination

This number of patients achieves 80% power, with a 7.5% equivalence margin, at a 5% significance level using a two-sided equivalence test of correlated proportions when the actual difference of the proportions is zero.

8.3 Statistical methods

Measured data from CTAs performed with low intravenous contrast dose and from CTAs performed with routine intravenous contrast dose for each patient will be analyzed using paired t-tests. The statistical methodology will be reviewed by consultation with biostatistics.

9.0 Confidentiality, Privacy and Data Management

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

See the Research Data Plan Review Form

9.1.1.1 Use of Codes, Master List

See the Research Data Plan Review Form

9.1.2 Storage of Data and/or Specimens

See the Research Data Plan Review Form

9.1.3 Access to Data and/or Specimens

See the Research Data Plan Review Form

9.1.4 Transferring Data and/or Specimens

See the Research Data Plan Review Form

9.2 Subject Privacy

See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The PI and research study team will periodically evaluate the data and communicate regarding subject safety. Data collected for the first 20 patients will be summarized and submitted to the IRB for review to

ensure safety of subjects. This data will include information about image quality of the CTA examinations, any adverse events that occurred, and how many subjects required repeat scans.

10.2 Data that are reviewed

Data acquired during low-contrast CTA will be reviewed.

10.3 Method of collection of safety information

Data will be collected at time of screening and CTA

10.4 Frequency of data collection

Data will be collected at time of screening and CTA

10.5 Individuals reviewing the data

The PI and research study team will be responsible for reviewing data.

10.6 Frequency of review of cumulative data

Cumulative data will be reviewed on a weekly basis by the principal investigator and study team members.

10.7 Statistical tests

Statistical tests are as outlined in section 8.2 and 8.3.

10.8 Suspension of research

Not Applicable

11.0 Risks

There is a minimal risk of loss of confidentiality.

There is a risk of increased radiation if the scan needs to be repeated due to a non-diagnostic clinical exam. If the exam is non-diagnostic due to inadequate vascular enhancement, the examination will be repeated. This may lead to an increased radiation dose to the patient. It is important to note that non-diagnostic studies can, and do occur with the standard volume of contrast currently administered for these examinations. When this occurs, the examination is repeated with a second standard or reduced dose of contrast. Given the low dosage of intravenous contrast of the planned low dose protocol, a repeat examination can be performed without exceeding the standard of care contrast dose to the patient,

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There is no guaranteed benefit from participating in this study. Potential benefits to the patient include a decrease in contrast dose which inevitably reduces the risk for development of contrast induced nephropathy.

12.2 Potential Benefits to Others

Given the increasing number of contrast enhanced studies performed in the hospital each day, the risk of contrast induced nephropathy has theoretically increased. Specific populations of patients are susceptible to contrast induced nephropathy. Avoidance of this complication by low dose examinations can preserve renal function and potentially decrease hospital stay and health care costs.

13.0 Sharing Results with Subjects

Not Applicable

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not Applicable

15.0 Economic Burden to Subjects

15.1 Costs

Subjects will not be responsible for any cost for participating in the study other than their standard of care imaging. The repeat CTA scan, contrast and administration, if required, will be provided at no cost to patient.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of the research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

The research will be conducted in the department of Radiology at Penn State Hershey Medical Center 500 University Drive Hershey, PA 17033.

16.2 Feasibility of recruiting the required number of subjects

Study investigators regularly see patients for CTA scans. Therefore, the ability to recruit 180 subjects is feasible.

16.3 PI Time devoted to conducting the research

The PI has devoted time to academic endeavors.

16.4 Availability of medical or psychological resources

Hershey Medical Center's Emergency Department is available 24/7.

16.5 Process for informing Study Team

Ultra-low dose protocols will be presented to the Radiation Awareness Group (RAG) committee in the Radiology department. Following approval, the CT technologists will be made aware of the protocol changes in selected patients meeting inclusion criteria. In addition, the PI or team members will be available to oversee the examination.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not Applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of the Use of Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☒ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload the Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans
Not Applicable

18.2 Data Submission and Security Plan
Not Applicable

18.3 Subject Enrollment
Not Applicable

18.4 Reporting of Adverse Events and New Information
Not Applicable

18.5 Audit and Monitoring Plans
Not Applicable

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB
In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be

(1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

Not Applicable

21.2 Location of storage

Not Applicable

21.3 Duration of storage

Not Applicable

21.4 Access to data and/or specimens

Not Applicable

21.5 Procedures to release data or specimens

Not Applicable

21.6 Process for returning results

Not Applicable

22.0 References

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