

**CT Scan With IV Contrast Alone (CT IV): The  
Role of Intra-abdominal Fat (IAF) on the  
Sensitivity of CT IV to Visualize the Normal  
Appendix  
(IAF Appendix)  
PECARN Protocol Number 23**

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Pediatric Emergency Care Applied Research Network  
Maternal and Child Health, Emergency Medical Services  
for Children (EMSC) Program

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This protocol is PECARN Protocol Number 23, and the lead PECARN investigator for this protocol is Madelyn Garcia, M.D., MPH, University of Rochester Medical Center.

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PROTOCOL TITLE:

CT Scan With IV Contrast Alone (CT IV): The Role of Intra-abdominal Fat (IAF) on the Sensitivity of CT IV to Visualize the Normal Appendix

Short Title: IAF Appendix  
PECARN Protocol Number: 23

Lead Investigator and Author:  
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Protocol Version: 1.00  
Version Date: March 20, 2009

*I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I have read and understood the contents of the Package Insert for metoclopramide, and the information sheets on the nutritional supplements. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.*

Principal Investigator Name: \_\_\_\_\_

Principal Investigator Signature: \_\_\_\_\_

Date: \_\_\_\_\_

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## 1 Introduction and Purpose

Appendicitis, which affects 80,000 children annually in the US, is the most common surgical condition of the abdomen and often requires diagnostic imaging during ED evaluation.<sup>1, 2</sup> Despite the increasing use of Computed tomography (CT) scan to diagnose appendicitis,<sup>3</sup> the choice of CT protocol utilized varies by institution. CT protocols for appendicitis differ based on the type of contrast used (different combinations of oral, rectal and intravenous (IV) contrast).<sup>4-6</sup> Oral contrast is utilized because it is believed to help radiologists by highlighting bowel, improving appendix visualization. Bowel opacification with oral contrast is believed helpful because children may lack the intra-abdominal fat (IAF) of adults that serves as a natural contrast for inflammation. While oral contrast protocols are sensitive and specific,<sup>7, 8</sup> oral contrast poses several problems: (1) contrast administration prolongs Emergency Department (ED) length of stay,<sup>9</sup> (2) use of "delayed" CT images (if contrast fails to reach the area of the appendix) exposes children to the risks of additional radiation, and (3) drinking contrast is uncomfortable for children with abdominal pain and a challenge for families and providers.

Given the recent focus on improving patient satisfaction and streamlining ED evaluation times to address overcrowding concerns,<sup>10</sup> we should seek an evidence based approach<sup>11</sup> to improve and standardize the ED imaging of patients with suspected appendicitis. While increasing awareness about the risks of radiation exposure is leading more sites to use ultrasound rather than CT, ultrasound use depends on (a) available radiologists who feel comfortable with this technique and (b) suitability of patient body-habitus (i.e. ultrasound is only useful in the non-obese patient.) A survey of pediatric EDs participating in the Pediatric Emergency Care Research Network (PECARN) found that 94% (16/17 sites) used CT to evaluate appendicitis. **This study will try to define which subset of patients is suitable for CT imaging without oral contrast.**

Our **long term goal** is to foster the use of CT IV (eliminating oral contrast) for appropriate patients with possible appendicitis, streamlining ED evaluation times, limiting unnecessary radiation exposure and alleviating patient discomfort. We hypothesize that if CT IV has the sensitivity to visualize the un-inflamed appendix, then it should be adequate for ruling out appendicitis (where inflammation and other findings should facilitate visualization). Rather than study the performance of CT IV for appendicitis, however, this study takes a step back to focus on the technical aspects of imaging. Specifically, we will examine the role of a patient's intra-abdominal

fat (IAF) on test performance. We believe that CT protocols are not "one-size-fits-all" and should be tailored to each patient using clinically available variables. CT IV, for instance, may not be appropriate for thin patients who lack IAF. Thus, **the purpose of this study** is to examine whether IAF plays a role in visualization of a normal appendix and whether we can predict which patients will have adequate IAF, and thus forgo oral contrast.

## 2 Study Summary

### 2.1 Hypothesis

The purpose of this study is to examine whether IAF plays a role in visualization of a normal appendix and whether we can predict which patients will have adequate IAF, and thus forgo oral contrast. We will build upon previous studies of CT IV with the following aims:

#### 2.2 Aim 1

To evaluate the effect of IAF on CT IV sensitivity to detect a normal appendix. Hypothesis: CT IV will be more sensitive in children with adequate IAF (IAF+) than in those with inadequate IAF (IAF-).

#### 2.3 Aim 2

To determine the association between IAF adequacy and clinically available patient characteristics (age and weight) so that a practical heuristic can be developed allowing us to identify children that would be suitable candidates for CT IV in lieu of oral contrast. Hypothesis: Patient age and weight are associated with adequacy or inadequacy of IAF.

#### 2.4 Aim 3

To assess inter-reader reliability for IAF adequacy determination. Hypothesis: IAF characterization will be reproducible between radiologists.

We will use the database of CTs already completed from the IRB-approved PECARN Intra-abdominal Injury (IAI) study to obtain our sample of patients. The IAI study is a retrospective study collecting information about children less than 18 years who undergo ED evaluation following blunt abdominal trauma. The aim of the IAI study is to develop imaging guidelines for abdominal trauma (i.e. determine which patients need CT scan after trauma). The PECARN IAI study is an currently ongoing national



study being conducted with waiver of informed consent. Our study design utilizing CT scans obtained for alternate purposes is common in studies of appendicitis imaging,<sup>12-14</sup> with the rationale that it avoids the patient risks and challenges of a prospective study and allows evaluation of the technical aspects of diagnostic testing. The ongoing PECARN IAI study is a perfect opportunity as it provides a large repository of CT scans of children imaged using CT IV.

Given the relatively low incidence of appendicitis in younger children, and the desired age distribution for our study sample (i.e. half the patients younger than 10 years old) it might prove challenging to find younger patients who have had an appendectomy by the time of their IAI CT sScan. The incidence of appendicitis varies greatly in the literature: appendicitis occurs in 1 to 8 percent of children evaluated in urgent care settings for abdominal pain<sup>15, 16</sup> with fewer than 5% of patients diagnosed under age five.<sup>17</sup> Nevertheless, while our cohort may have few patients without an appendix, these patients are not crucial for our specific aims 1-3. In fact, previous studies have studied the role of IAF on appendix visualization by completely excluding patients with prior appendectomies.<sup>18</sup>

### 3 Background and Rationale

In today's medical evaluation of suspected appendicitis in the ED setting, several CT scan protocols are frequently utilized; these vary by the route of contrast administration utilized. CT IV is a valid diagnostic modality for evaluating abdominal pain in children. Kaiser, et al. in 2004 demonstrated the added benefit of using IV contrast over un-enhanced CT to evaluate appendicitis in children, with the addition of IV contrast improving the sensitivity of un-enhanced CT scan from 0.66 to 0.90.<sup>19</sup>

Prior studies also suggest that CT IV has comparable performance to protocols utilizing enteric contrast, whose sensitivity is 0.92 and specificity is 0.87.<sup>20</sup> Further, Taylor and colleagues at Boston Children's Hospital showed that omitting enteric contrast did not lead to worse outcomes: the rate of incorrectly interpreted scans remained 4%, regardless of contrast protocol.<sup>21</sup> At our institution, Garcia, et al. showed that CT IV for appendicitis also produced promising results (sensitivity = 87%, specificity = 96%)<sup>22</sup> similar to others.<sup>20-23</sup> Despite such evidence, however, CT IV has not been widely adopted. This is potentially because of the limitations of prior studies: (1) small sample sizes (2) single institution designs (3) over-reliance on radiologists experienced with using CT IV and (4) focus on the diagnostic perfor-

mance of CT scan rather than focusing on the technical aspects important to radiologists. Results, therefore, have not been generalizable.<sup>3, 24, 25</sup>

Radiologists are reluctant to eliminate oral contrast for CT in children, citing a child's lack of IAF as a limitation that makes CT interpretation difficult.<sup>26-28</sup> IAF, a radiologic patient characteristic, highlights inflammation (fat stranding) and allows radiologists to rule-out appendicitis even in cases when the appendix isn't seen.<sup>29-32</sup> A small pediatric study found a significant difference in appendix visualization rates between patients with low and medium amounts of fat and showed that appendix visualization improved in older patients.<sup>33</sup> This finding was confirmed by others who showed a trend towards more IAF and better appendix visualization in children older than 10 years.<sup>13-18</sup> Conversely, a lack of IAF may contribute to more indeterminate CT interpretations<sup>34, 35</sup> and more diagnostic errors.<sup>21, 24, 36</sup> Levine showed that 96% of patients with incorrect CT interpretations had little IAF.<sup>37</sup> The practical problem for the ordering clinician is that a patient's IAF (which is determined during CT interpretation) is unknown at the time the CT scan is ordered: thus, how can one decide which CT protocol to choose for a given patient?

If CT imaging for pediatric appendicitis is to move away from using oral contrast, we must move beyond the single-institution design, illustrating adequate CT sensitivity and specificity. Studies to change practice patterns need be multi-centered and address the factors cited by radiologists as barriers: such as the role of IAF. Lastly, an effective study should bridge the gap between the perspective of the radiologist and that of the emergency clinician: specifically, studies should answer the question of whether clinicians can predict which patients will have adequate IAF to safely forgo drinking oral contrast for their CT. *The proposed study represents the first multi-center work to examine the technical aspects CT imaging for evaluation of the appendix in children.*

### 3.1 Patient Eligibility

#### 3.1.1 Inclusion Criteria

- Ages 3-17 years as recorded in existing IAI database; AND
- Patient weight available in the existing database; AND
- Patient had an ED abdomen/pelvis CT scan with IV contrast only (CT IV); AND

- CT scan has no intra-abdominal injury (defined per the PECARN IAI study); AND
- Patient surgical history available (to allow determination of prior appendectomy).

### 3.1.2 Exclusion Criteria

- Age less than 3 years as recorded in existing IAI database; OR
- Weight unavailable; OR
- CT performed with enteric (oral or rectal) contrast; OR
- CT scan shows IAI or other confounding finding which could impact appendix visualization (e.g. right lower quadrant surgical staples or congenital intestinal malrotation); OR
- Surgical history unavailable.

## 4 Methods

This is a **multi-center retrospective observational study** using a subset of 280 patients previously enrolled in the ongoing PECARN Intra-abdominal Injury (IAI) study who have had abdominal/pelvic CT IV scans for trauma evaluation which showed no intra-abdominal injury.

**Two equal groups (n=140) will be enrolled: children with adequate IAF (IAF+) and children with inadequate IAF (IAF-).** Since patient IAF adequacy will be unknown as the study groups are initially being compiled, age will be used as a surrogate for IAF during initial patient selection. This is based on the work of Grayson, et al,<sup>18</sup> showing that children greater than age 10 years had more abdominal fat on CT scan than younger children. This study will be conducted in **Four Phases**, seen in Figure 1:

### 4.1 Phase 1: Patient Identification at the CDMCC Level

Following study approval from each site's IRB, patient identification will begin. The CDMCC will query the PECARN IAI study database (Trial DB) using some of the pre-determined inclusion/exclusion criteria to generate a list of potentially eligible patients for each participating site.

<b>Phase</b>	<b>Description</b>
1. Patient Identification (CDMCC Level)	Generates list of patients from TrialDB query using study Inclusion criteria: + Age 3-17 yrs + Had CT IV + CT IV showed no IAI + Pt has weight available
2. Patient Identification (Site Level)	Reviews CDMCC list to generate site list of patients, determined by retrospective chart/medical record/CIS review for + appendectomy history available + confirmation that CT did not use enteric contrast + confirmation that pt weight was accurate
3. Radiologist CT Interpretation	Site radiologists review patient CT scans to (1) ensure patient eligibility (2) answer study questions: (1) Did you see the appendix? And (2) Please characterize pt IAF.
4. Data Processing	Data from each site will be entered to CDMCC database

Figure 1: Study Phases

#### 4.1.1 Inclusion criteria for the CDMCC query

Inclusion criteria for the CDMCC query are:

1. patient age 3-17 years
2. who have a recorded patient weight (actual weight used preferentially) and
3. who have had a CT of the abdomen/pelvis without enteric contrast
4. which did not reveal any IAI (defined per IAI study protocol).

Patients with only free fluid on CT scan will be eligible for this study, as this finding alone does not constitute an IAI and free fluid can be encountered in patients with abdominal pain.

To improve study accuracy, the CDMCC will attempt to create our study patient list using patients who have actual weights available in the database. If we are unable to meet our sample size using patients with actual weights, then we will expand our list to include patients with weights obtained by other means. The order of weights selected will be: actual, then Broselow, then parental estimate, then clinician estimate. This rank order was based on prior work showing that in lieu of actual weights, parental estimates are superior to clinician weight estimations.<sup>38-41</sup>

#### 4.1.2 Exclusion criteria for the CDMCC query

Exclusion Criteria for the CDMCC query are:

1. Age less than 3 years
2. Patient weight unavailable/unknown
3. CT Scan was done with enteric contrast or
4. CT shows an IAI injury

IAI injury is defined in the PECARN IAI study as follows: any injury that occurs within the abdominal cavity that includes any of the following injuries:

- Spleen (Splenic) injury
- Liver (Hepatic) injury
- Gallbladder injury
- Kidney (renal) injury
- Urinary bladder injury
- Adrenal injury
- Pancreatic injury
- Fascial injury
- Gastrointestinal injury: includes
  - Mesentery (Mesenteric injury)
  - Intestine (Intestinal or Bowel injury): including injuries to the small intestine (duodenum, jejunum, ileum) and colon (ascending colon, descending colon, transverse colon, sigmoid colon, rectum)
- Omental injury: the omentum is the fatty tissue covering the intestines.
- Abdominal vasculature injury: any injury to the abdominal vasculature structures: aorta, inferior vena cava (IVC), superior mesenteric artery, inferior mesenteric artery, renal artery, etc.

For this study, however, we will include patients with either thoracic injuries or pelvic fractures, because these conditions should not confound appendix visualization.

At the end of this study phase, the CDMCC will produce a list of patients for each site. The overall study goal is to enroll 280 children with an equal distribution of patients by IAF. The total number of patients to be enrolled at each site may vary but will be less than 40 children given at least 7 participating sites. If, for example, 10 sites participate in this study, then each site should be responsible for enrolling approximately 28 children. If 15 sites participate, each site should enroll approx 19 patients. To allow for some attrition during subsequent Study Phases (below), the CDMCC will provide each participating site with a list of potential patients that will have double the number of children they would need to enroll.

## 4.2 Phase 2: Patient Identification at the Site Level

The goal of this phase is to create a list of patients with as close to an equal distribution of patients as possible by age (the two age groups would be: children less than and greater than 10 years old). Again, age is serving as a surrogate marker of IAF. Thus, using the CDMCC provided list, the site research coordinator (RC) (with site PI support as needed) will screen patients using the following inclusion criteria:

1. A surgical history is available that notes whether patient did or did not have an appendectomy performed before their CT,
2. The CT in the IAI study used only IV contrast and
3. That the weight provided by the CDMCC was accurate.

Results of this phase will be recorded on a RC Data Collection Form and data will be entered into a study database created and maintained by the CDMCC.

### 4.2.1 Site selection steps

1. **Surgical / appendectomy history** will be determined by review of these sources in the following order:
  - (a) ED charts (from date of IAI study enrollment) will be reviewed for evidence that the patient was asked about surgical history. If the ED chart contains a section/checkbox for Past Surgical

History (PSHx) the site RC will note if this box was checked, or if "none" or "N/A" are written in for surgical history. If either of these is found, this would indicate that the patient had been asked about prior surgeries and has not had any. This patient would be enrolled. This is distinctly different from a lack of any recorded history.

- (b) If the check box on the ED chart is left blank or if no other written documentation is found in the ED chart, then this patient would go on to be screened for surgical history using the following two sources:
- i. computerized information system (CIS) records and
  - ii. inpatient or outpatient medical records.

Using CIS records, both pathology and operative reports will be reviewed for procedure and diagnostic codes classified according to the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9, CM). ICD.9 codes to be used are:

- appendectomy (47.0)
- laparoscopic appendectomy (47.01)
- other appendectomy (47.09)
- incidental appendectomy/laparoscopic (47.11)
- incidental appendectomy/other (47.19)
- Ladd operation (54.95)

The CIS search should capture patients who have had surgery at the participating site. If surgical history cannot be found in CIS, then two inpatient or outpatient visits in the medical record (preceding their date of enrollment in IAI) will be reviewed for evidence of a surgical history. This information is frequently found in admission notes or discharge summaries.

Note: Given that the **reference standard for this study** will be the presence or absence of an appendix, the study cohort must have an available surgical history. If all sources are reviewed and documentation of surgical history is unavailable, this patient would not be eligible for this study. Thus, while both patients with and without appendectomy will be eligible for this study, those in whom surgical history is unknown will be excluded.

2. Next, the RC will **ensure that the patient's CT scan does not have any enteric (oral or rectal) contrast**. Site RCs will provide

their PI with final (attending) dictated radiology reports for each patient's CT scan. The PI will review these reports to ensure that the CT scan was done with IV contrast alone, excluding any patients that had enteral contrast.

3. Lastly, in this phase, the RC will screen the patient medical record as a double-check that the **weight provided by the CDMCC was accurate**. Sources to be reviewed must be from the same visit/date as the date of IAI enrollment and CT scan and include these sources: ED chart, nursing triage notes, medication order sheets, admission or discharge summaries and trauma flow-sheets. If a weight is found and recorded in kilograms to one decimal point, that will be assumed to be an "actual" weight and should be used preferentially to any estimated weights provided by the CDMCC.

### 4.3 Phase 3: CT Interpretation by Radiologists

Once the final patient list has been compiled at each site, this list will be provided to the participating radiologist(s) so they may perform CT interpretation. This list will contain as many patients as possible following Phases 1 and 2, to allow for more attrition following verification of eligibility criteria by radiologists. Patients on this list will be identified by medical record number/IAI study number, DOB and date of trauma CT scan to ensure data accuracy (i.e. that the correct CT scan is being interpreted). Radiologists will retrospectively review each patient's CT scan and complete a radiology data collection form blinded to appendectomy history.

Blinding of radiologists will take place as follows:

1. Radiologists will not be provided with surgical history and
2. Will be asked not to refer to the previous CT report performed for trauma purposes (which might comment on the appendix).

Further, to test the association of patient weight and IAF adequacy, radiologists will not be provided with patient weights. Given access to imaging software at each site, however, blinding to age will not be possible, as most CT scans have a patient's DOB on the CT.

Radiologists will perform the final verification of patients for study eligibility as they interpret each CT scan. They will exclude patients if they see either **exclusion criteria for radiologists**:

1. Enteric contrast used on the CT. This serves as a quality control, as this was already screened at the site level.



2. Unexpected CT findings that could influence appendix visualization such as: intestinal malrotation (no cecum in the expected location of the appendix) or surgical staples in the area of the appendix implying prior undiscovered appendectomy (this could occur if a child had their surgery performed at another institution and or if misinformation was collected in the chart ).

Once a patient has met these screening criteria, the radiologist will interpret the CT scan to answer the study questions:

1. Did you see the appendix? and
2. Characterize this patient's IAF.

#### 4.3.1 Appendix visualization.

Radiologists will record whether or not the appendix was seen (yes, no, uncertain) and the CT images or cuts on which the appendix was seen. We expect that most study patients will have a normal appendix on CT scan. In order to decrease spectrum bias (i.e. over-reporting of a normal appendix being "seen") radiologists will be blinded to patient surgical history.

Further, at sites with more than one participating radiologist, a kappa DCF will be completed on a subset of patients (to be determined based on radiologist commitment). This will assess whether radiologists agree on appendix visualization. Image overlap (defined as a cut overlap of more than 3 CT cuts) will be used as a concordance measure for appendix visualization. This is based on expert radiologist author (George Taylor) experience and was chosen over direct appendix measurements as it is less work for participating radiologists yet still gives an objective assessment of appendix visualization. (Note: This is not a study specific aim, but should provide some additional information about CT IV sensitivity.)

#### 4.3.2 IAF characterization.

Radiologists will characterize the patient's IAF as either "adequate" or "inadequate", using definitions provided on the DCF. IAF adequacy will be defined based on the work of Basak (2002)<sup>27</sup> as follows:

**Adequate IAF (IAF+)** will be defined as any amount of fat that completely surrounds the cecum.

**Inadequate IAF (IAF-)** will be defined as fat that *does not* completely surround the cecum.

We chose to make IAF characterization dichotomous to minimize subjectivity and facilitate study reproducibility.

Further, at sites with more than one participating radiologist, a kappa DCF will be completed on a subset of patients (to be determined based on radiologist commitment) to assess the **inter-observer reliability of IAF characterization** (Specific Aim 3).

Because this is a retrospective multi-centered study, we will be unable to "standardize" CT scan cuts (cuts refers to CT slice thickness measured in millimeters) used at all sites. This is because it is not possible to alter stored CT scan images that are more than a few months old since limited storage capacity only allows radiology departments to store a few months worth of raw digital CT data. Given that slice thickness is important for the determination of the sensitivity of CT IV, the radiologist's DCF also collects information on CT collimation cuts used. This allows us to account for variation in CT protocols by slice thickness used at different sites. Since most CT protocols used to evaluate appendicitis use 5 mm cuts, however, we feel that the 3-5mm cuts used at our participating sites for trauma CT protocols should be adequate to visualize the appendix in this study.

#### 4.4 Phase 4: Data Processing

On an ongoing basis, site RC will enter data into the CDMCC database. The CDMCC will provide oversight to ensure patient confidentiality and that data security is maintained. (see Section 8 for more on Human Subjects)

## 5 Study Outcomes

### 5.1 Specific Aim 1

To evaluate the effect of IAF on CT IV sensitivity to detect a normal appendix. **Outcome:** The sensitivity of CT IV to visualize a normal appendix will be determined with 95% CI around these point estimates for each group (IAF+ and IAF-). In cases where the radiologist states they are "unsure" whether the appendix was visualized, these patients will be analyzed as having been interpreted as "appendix not seen". This will allow a more conservative data analysis for CT sensitivity.

## 5.2 Specific Aim 2

To determine the association between IAF adequacy and clinically available patient characteristics (age and weight) so that a practical heuristic can be developed allowing us to identify children that would be suitable candidates for CT IV in lieu of oral contrast. **Outcomes:**

- *IAF Adequacy* will be determined by interpreting radiologists using definitions established in this protocol.
- *Patient age* at the time of the study CT scan will be defined as: Patient DOB - date of CT scan. Patient age will be measured in years and months to one decimal point.
- *Patient weight* at the time of the CT scan will be obtained from the query of the IAI database and accuracy of this weight ensured during Study Phase 2. Patient weight will be measured in kilograms to one decimal point.

## 5.3 Specific Aim 3

To assess inter-reader reliability for IAF adequacy determination. **Outcome:** In a subset of patients, kappa DCF will be completed by radiologists to assess their agreement on a patient's amount of IAF (adequate or inadequate).

## 6 Data Management

**Data Security/HIPAA:** Subject anonymity will be kept as follows: a password-protected database with IAI study numbers and patient DOB but no other patient identifiers will be maintained. The CDMCC will supply the unique study ID number. Each site will have the patient medical record number (MRN) and patient name and can supply this to their participating radiologist. The RC will then load the completed radiologist data into a database de-identifying the information with no MRN or patient name. Each site will be expected to maintain data security in accordance to institutional standards and abide by local privacy guidelines.

## 7 Data Analysis and Sample Size

### 7.1 Specific Aim 1

To compare the sensitivity of CT IV for each group (IAF+ vs. IAF-) the lower bound of the 95% CI for CT sensitivity in each group will be compared. This lower bound represents the minimally acceptable test performance and is most important in deciding whether or not to adopt any imaging test. If our pre-study assumption is true (that CT IV sensitivity will be 0.95 for IAF+ patients and 0.85 for IAF- patients), then our sample size (N=280) allows us to report narrow confidence intervals around the CT sensitivity: 3.6 to 5.7.

In cases where the radiologist reports appendix visualization as 'indeterminate', those subjects will be analyzed in the "appendix not visualized" group for sensitivity determination.

For those sites at which a second radiologist performs an independent CT interpretation (kappa DCF), this will provide us with IAF characterization as well as the image cuts on which the appendix was visualized (if visualized). We will assess raw agreement between the radiologists. As determined by our expert radiologist (Dr. Taylor) agreement on appendix visualization will be defined as an overlap of more than 3 cuts.

### 7.2 Specific Aim 2

In order to determine the association between IAF adequacy and clinically available patient characteristics (age and weight) we will perform single variable logistic regression using the outcome of IAF adequacy (dependent variable) against both patient age and weight (independent variables) individually. Age and weight will be analyzed in two ways: as continuous and categorical variables to determine which manner produces the most clinically useful information. Further, an interaction term (of weight + age) will be analyzed, as this should allow us to determine whether one should adjust for changes in weight based on a patient's age (i.e. is a 10 kg difference more important in a 5 year old than in an adolescent?) Receiver operator characteristic (ROC) curves will be used to determine if adequate IAF can be predicted by specific cutoffs for age and weight.

Further, to examine the role of patient characteristics on IAF adequacy, classification and regression trees will also potentially be explored during data analysis. Recursive partitioning may allow us to examine possible interactions that could prove clinically useful (e.g. the effect of gender and age on IAF adequacy).

### 7.3 Specific Aim 3

To assess inter-reader reliability for IAF adequacy determination. Since the characterization of patients into the IAF+ and IAF- groups depends solely on the interpretation of the radiologist, we will look at the reproducibility of these results. The inter-reader reliability for IAF characterization will be measured on a cohort of patients using the kappa statistic. The plan is to do this for 20% of our study (n=56), but more may be possible, if more radiologists participate.

### 7.4 Sample Size

Our study sample size is 280 patients. Study sample size was derived based on specific aim 1 which seeks to compare the sensitivity of CT IV among patients with IAF+ and IAF- . A sample size of **280 patients** will have **80% power to detect a 10% difference in CT sensitivity for appendix visualization** ( $\alpha = 0.05$ , 2 tailed test) if a difference exists between the groups (140 IAF+ patients and 140 IAF-). A 10% difference was chosen as a minimum threshold for this initial study, as this represents a clinically important difference in performance that might influence a provider's decision to utilize a given CT protocol or not.

The following assumptions were made in sample size determination:

1. CT IV sensitivity in patients with adequate IAF will be 0.95 vs. 0.85 in patients with inadequate IAF and
2. We can create a study population with an even distribution of patients with and without adequate IAF by using age as a reasonable surrogate for IAF, based on the work of Grayson, et al.<sup>18</sup>

Any deviation from an equal number of patients in the IAF+ and IAF - groups (if they are not balanced in terms of size), will decrease the power of this study.

The **number of patients needed at each site** will be calculated based on the number of sites/radiologists participating.

## 8 Human Subjects

### 8.1 Potential Risks and Benefits

There are no major risks associated with participating in this study, as this is an observational study and no therapeutic intervention is being tested. There is a **minor risk of loss of confidentiality**, as the subject's medical record number will be written on a data collection form. All patient identifiers, however, will be removed from the analytical database after study completion (see below).

Additionally, the **inadvertent discovery of unknown medical condition** is another potential risk of this study. It is possible that during the limited review of a patient's CT, an unknown condition might be discovered (e.g. mass, concerning lymph nodes, renal stone). This will be handled at the institutional level. First, the interpreting radiologist will review the original CT interpretation for evidence that these findings were not noted earlier. If not, efforts will be made, as medically deemed necessary or appropriate, for the radiologist or study PI to contact the patient's physician to make them aware of such findings. This is the standard of care whenever a CT is over-read or when a final "attending" interpretation discovers a new finding. These new findings are uncommon and unlikely given that in this study, radiologists are performing a very limited CT interpretation, focusing only on the area of the appendix. Further, as this is a retrospective study, in some cases, radiologists will review CT scans that can be several months to years old, making timely notification of families less likely to be clinically important.

The **benefit from this study** is that we will gain substantial evidence on which to base decisions about abdominal CT scan use in the future. If more children are scanned without oral contrast, this will hopefully lead to shorter ED lengths of stay and more streamlined evaluations for abdominal pain/suspected appendicitis. Radiation exposure to future children with abdominal pain will possibly be reduced and lives will be spared from radiation-induced malignancies, as potentially less "repeat" abdominal CT scans are needed. We anticipate that this pilot work will lead to subsequent studies that will standardize, in an evidence-based manner, the imaging of children with suspected appendicitis.

### 8.2 Protection Against Risks

Patient names will not be sent to the data coordinating center at The University of Utah. To prepare the analytical database, the data coordinating

center will encrypt patient and institution identifiers so that the analytical database will be free of patient identifiers, and will be a de-identified data set in accordance with definitions of the Health Insurance Portability and Accountability Act (HIPAA). This analytical database will be the only one available for the analysis of the current and future derivative studies.

### 8.3 Data Security

The data coordinating center at the University of Utah has a dedicated, locked server room within its offices, and the building has 24 hour on-site security guards. The data coordinating center has a state-of-the-art computer infrastructure and coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the data coordinating center with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. TrialDB is the clinical trials software used at the data coordinating center in Utah, and eRoom<sup>TM</sup> is used for communications about the study. TrialDB, eRoom<sup>TM</sup> and other web applications use the SSL protocol to transmit data securely over the Internet.

Direct access to data coordinating center computers is only available while physically located inside the data coordinating center offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

The investigators and staff of the data coordinating center are fully committed to the security and confidentiality of all data collected for PECARN studies. All personnel at the data coordinating center at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from

employment at the University of Utah. In addition, all personnel involved with data coordinating center data systems have received Human Subjects Protection and HIPAA education.

## 8.4 IRB Review/Waiver of Consent

This protocol will be submitted to the IRB at each site and approval documented prior to start of this study. No collection or submission of data will occur at any specific HEDA until IRB approval is obtained at that site. This is a retrospective review for which we will request waiver of written informed consent and waiver of HIPAA authorization to collect protected health information. Data collected in this project do not include names, but do include sufficient identifying information (such as date of birth, gender) that project investigators must protect the confidentiality of the research data in accordance with privacy regulations such as the Health Insurance Portability and Accountability Act (HIPAA). This will be accomplished by the following actions:

- All data (paper or electronic) will be maintained in secure locations in locked offices, locked filing cabinets, and password protected computers that will shut-down after 15 minutes of non-use.
- Subsequent to chart abstraction onto paper data collection form, unique patient identifiers and patient medical record will be stored in separate secure locations.
- All data transmission will be encrypted.
- All analyses and reports will be presented in aggregate fashion.
- No identifiable data will be released by study investigators or CDMCC at any time.

## 9 Study Site Monitoring and Quality Assurance

### 9.1 Data Quality

The accuracy of data will be ensured in the following manner:

1. CDMCC will track missing data fields in the database to ensure accuracy. This will be conducted on an ongoing basis (to be determined by CDMCC standards).



2. CDMCC will conduct Logic Check to look at accuracy of data elements entered. This will capture errors such as weights incorrectly entered as pounds rather than kilograms. There will be no on-site data monitoring by the CDMCC.
3. Site RCs will verify the accuracy of patient weights by reviewing patient ED charts and medical records for the dates of IAI enrollment. The most accurate weight will be used in the study.
4. Radiologists will serve as a second level of screening at the site level of the study population for study eligibility, as they will verify patient eligibility before CT interpretation by excluding patients with
  - (a) oral contrast used on the CT scan or
  - (b) with unexpected abnormal findings on CT which could impact the appendiceal region.

## 9.2 Record Retention Requirements

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for **at least 3 years** after completion of the research. Completion of the research generally includes planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of research also entails completion of all publications relating to the research.

## 10 Appendix

**Table of Participating Sites**  
**Radiologists and Number of CT Scans Meeting CDMCC Inclusion Criteria (Study Phase 1)**  
**as of January 15, 2009**

	<b>Institution</b>	<b>Site PI</b>	<b>Radiologist 1</b>	<b>Radiologist 2</b>	<b>CT Scans</b>
1	Bellevue	Mike Tunik	Fefferman, Nancy		14
2	Boston Children's	Lise Nigrovic	Taylor, George	Callahan, Michael	40
3	Buffalo Children's	Kathy Lillis	Iqbal, Vaseem		193
4	Children's Hospital of Michigan	Prashant Mahajan	Joshi, Aparna		28
5	Children's Hospital of NY (Columbia)	Maria Kwok	Susie Su-chi Cehm	Ruzal-Shapiro, Carrie	15
6	Children's National of D.C.	Shireen Atabaki	Vyas, Pranav		101
7	Children's Hospital of Philadelphia	Elizabeth Alpern	Anupindi, Sudha		72
8	Cincinnati Children's Hospital	Rich Ruddy	Strouse, Peter J		115
9	DeVos/Michigan	John Hoyle	Junewick, Joe		157
10	Howard County General (Hopkins)	David Monroe	Yang, Shirley	Morton, Andrew	32
11	Hurley Medical Center	Dominic Borgialli	Veeramani	Kotia, Raj	58
12	Jacobi Hospital	Stephen Blumberg	Blumfield, Einat		22
13	Primary Children's (Utah)	Kathleen Adalgais	Dansie, David	Hoeg, Karin	112
14	St. Louis Children's - Washington U.	Dave Jaffe	Sonavane, Sushil Kumar	Siegel, Marilyn	167
15	UC Davis	Leah Tzimenatos	Gorges, Sandra W.		426
16	University of Michigan	Alexander Rogers	Strouse, Peter J		71
17	University of Rochester	Madelyn Garcia	Klionsky, Nina	Vyas, Rajashree	96
<b>Total</b>					1719

Figure 2: Participating Sites

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