

**ACRIN Protocol 6664****SUMMARY OF CHANGES**

July 7, 2006

Amendment # 2

**COVER PAGE**

Under the **Gastroenterologists** “David Ahlquist, M.D.” has been replaced by “J. Paul Limburg, M.D.” at Mayo Clinic.

The **Study Statistician** has been changed from “Alicia Y. Toledano, Sc.D” “Mei-Hsiu Chen, Ph.D.” It now reads:

**Study Statistician**

*Mei-Hsiu Chen, Ph.D.  
Center for Statistical Sciences  
Brown University, Box G-H  
Providence, RI 02912  
Phone # (401) 863-2578  
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[chenmei@stat.brown.edu](mailto:chenmei@stat.brown.edu)*

The title for Alicia Y. Toledano, Sc.D has been changed from “**Study Statistician**” to “**Co-Investigator.**” It now reads:

**Co-Investigator**

*Alicia Y. Toledano, Sc.D.  
Biostatistics Consulting, LLC.*

The **Radiologists** section of the cover page has been extensively revised to account for the inclusion of several radiologists to the study. It now states:

**Radiologists**

*Giovanna Casola, MD  
UCSD Medical Center  
Jugesh Cheema, MD  
Yale University  
Kevin Coakley, MD  
Clinical Radiologists, S.C  
Abraham Dachman, M.D.  
Univ. Chicago Hospital  
Jeff Fidler, M.D.  
Mayo Clinic  
Robert A. Halvorsen, MD  
Medical College of Virginia Hosp.  
Amy Hara, M.D  
Mayo Clinic  
Karen Horton, MD  
Johns Hopkins University  
Jay Heiken, M.D.*

*Mallinckrodt Institute of Radiology  
Revathy Iyer, MD  
MD Anderson Cancer Center  
Mark Kuo, MD  
Scottsdale Medical Imaging, LTD.  
Christine Menias, MD  
Mallinckrodt Institute of Radiology  
Martina Morrin, FFRRCSI  
Richard Obregon, M.D.  
Radiology Imaging Associates  
Ronald Summers, M.D., Ph.D.  
National Institutes of Health  
Judy Yee, M.D.  
San Francisco V.A. Medical Center  
Michael Zalis, M.D.  
Mass. General Hospital  
Peter Zimmerman, MD  
UCLA School of Medicine*

Under **Version Date** “Including Amendment 1” has been added.

Under **Activation Date** “Not yet active” has been replaced by “February 1, 2005.”

#### **SCHEMA (PAGE 5)**

Under **Required Sample Size** an additional statement has been added explaining the reason for the amendment. Furthermore, the previous statement stating “Each institution will accrue until 12 participants with proved clinically significant colorectal neoplasia have been confirmed; the total number of participants at each institution and in the trial is not predetermined. As a guideline, the expected number of participants at each institution is 152 (95th quantile: 224; i.e., 95% of institutions will require no more than 224 participants to be accrued in order to accrue 12 participants with proved clinically significant colorectal neoplasia). The expected total number of participants in the trial is 2289 (95th quantile: 2607; i.e., we are 95% certain that the total number of participants will be at most 2607)” has been deleted. It now reads:

**Required Sample Size:** 15 institutions. *Based on recommendations by the ACRIN Biostatistics Center and the ACRIN DSMC and in accordance with the trial's accrual monitoring plan, the accrual strategy has been modified such that each institution will accrue patients until either 1) the overall trial accrual reaches 2607 participants or 2) December 31, 2006, whichever occurs first. The total number of participants accrued at each institution will vary according to local institutional accrual rates and thus cannot be predetermined.*

#### **2.0 BACKGROUND AND SIGNIFICANCE (Page 14, 16)**

In section **2.4.3.2 Cost-Effectiveness** the reference to the Cost-Effectiveness Modeling Section has been changed from “14.1” to “14.0.”

In section **2.5.3.2 Cost-Effectiveness** the reference to the Cost-Effectiveness Modeling Section has been changed from “14.1” to “14.0.”

**4.0 STUDY OVERVIEW (Page 17)**

In the fourth and fifth sentences of this section information regarding the expected sample size as well as relevant sections to refer to in the protocol has been changed. It now states:

*The expected sample size is 2607 participants at 15 institutions (see Section 15.5). The CT scanning technique is described in Section 12.0 and image review methods are described in Section 12.0.*

**5.0 PARTICIPANT SELECTION (Page 18)**

The first sentence of this section was revised to account for the change in the sample size for the protocol as well as the section that is referenced in the protocol. It now states:

The sample size for this study is expected to be 2607 outpatients at 15 institutions (see Section 15.5).

**6.0 SITE SELECTION (PAGE 21-22)**

In the second sentence of the first paragraph of section **6.3.3 Accrual Goals and Monitoring** the phrase “there is approximately 95% probability that accrual will take less than 1.64 years” has been deleted. Furthermore, in this sentence the time that each institution is expected to accrue patients has been changed from “1.64” years to “1.16” years.

In the second sentence of the third paragraph of section **6.3.3 Accrual Goals and Monitoring** the word “at” has been deleted.

The fifth paragraph of section **6.3.3 Accrual Goals and Monitoring** has been extensively revised to account for the alternative accrual plan that has been added to this protocol. It now states:

*The ACRIN Data Safety and Monitoring Committee (DSMC) will monitor this protocol. At a regularly scheduled meeting of the ACRIN DSMC following trial activation, the ACRIN Biostatistics Center will provide an analysis including projections of sample size and accrual duration under the original accrual plan (12 positives per institution), and under an alternative accrual plan (limiting the trial accrual period to the shorter of December 31, 2006 and/or the time when the total accrual reaches the budgetary limit of 2607 participants). The impact of each plan on the ability of the trial to achieve its primary aim of estimating average sensitivity across radiologists with desired precision will be described. Various combinations of the average sensitivity across radiologists and the variance in sensitivity across radiologists, average prevalence across institutions and variance in prevalence across institutions, and models for accrual rates across institutions will be considered, as will methods of estimating average sensitivity other than taking a simple average of estimates across radiologists. The impact of these closure-to-accrual rules on the ability to estimate area under the ROC curve with desired precision will also be considered. As part of this report, the ACRIN Biostatistics Center will include a recommended rule for closure to accrual from a statistical perspective.*

The following paragraph has been deleted from this section. It stated:

*The ACRIN Biostatistics Center will also provide a proposal for an interim analysis at the first regularly scheduled ACRIN DSMC meeting following trial activation. The proposal for interim analysis will include guidelines, based on 9 months of accrual, for determining the feasibility of continuing with the current study design; and a proposal for switching to an alternate design if needed. Accrual will not stop at any site until after the evaluation of feasibility, even if 12 confirmed positives have been accrued. The most likely alternative to the current design would be a study design based on a pooled estimator of diagnostic accuracy, such that sites would continue to accrue independent of the number of confirmed positives accrued, with a total of no more than 2607 participants accrued on the study.*

**7.0 ONLINE REGISTRATION SYSTEM (Page 22)**

The title of this section has been revised from “ONLINE REGISTATION SYSTEM” to “ONLINE REGISTRATION SYSTEM.”

**9.0 DATA COLLECTION FORMS (PAGE 26, 29, 30)**

The following form has been deleted from this section:

**LX – Recruitment Log:** Dates and times of recruitment contact, reason for refusal if refused.

The following sentence has been deleted from the third paragraph of section **9.1 For Aim 3.3.2 (Database for Computer-Aided Diagnosis)**:

*For each type of software used, the location of the 0,0 coordinate must be noted.*

In section **9.2 For Aim 3.3.2 (Cost-Effectiveness)** the reference to the Cost-Effectiveness Modeling Section has been changed from “14.3.1” to “14.0.”

In section **9.3 Data Collection Forms** a clarification has been made under P1 Pathology Report. It now states:

Pathology Report <sup>a</sup> (P1) <i>(to be submitted for each case with polyps and sent to Pathology; regardless of size)</i>	Clinical Site	ACR	Within 4 weeks of biopsy/surgical procedure
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<sup>a</sup> Non-web reports

**12.0 IMAGING METHODOLOGY (Page 36)**

In section **12.1.1 Laxation** under **12.1 Patient Preparation** the phrase “10 mg of” has been deleted from the second sentence. Furthermore the phrase “(10 mg or current institutional standard of care)” has been added to this sentence. It now states:

All three preparations will also include the use of bisacodyl tablets (10 mg or current institutional standard of care) that will act to remove any residual fluid and stool in the colon.

In section **12.3CT Colonography** the phrase “*or current institutional standard of care*” has been added to the second sentence. It now reads:

With either preparation participants will also receive bisacodyl tablets (10 mg *or current institutional standard of care*).

In section **12.3CT Colonography** the word “ten” has been deleted from the third sentence. Furthermore, the phrase “*usually from 7 to 15*” has been added to the third sentence. It now reads:

Glucagon, 1 mg (subcutaneous, unless contraindicated), will be given usually from 7 to 15 minutes prior to the procedure unless contraindicated.

### **13.0 REFERENCE STANDARD (Page 39)**

In the first sentence of section **13.3 Lesion Matching** the word “*manually*” has been added.

At the end of section **13.3 Lesion Matching** information has been added regarding automated matching and manual matching. It states:

*An automated computer matching algorithm using the same size and location matching criteria outlined in appendix V (but without the aid of any written reports, morphology, or images) will also be compared to the consensus manual matching. Any discrepancies between the automated matching and the manual matching will be adjudicated by the first unused member of the review committee.*

### **14.0 COST-EFFECTIVENESS MODELING (Page 43-44)**

The title of section 14.3 has been changed from “**Data To Be Collected in the Proposed Study for Sse in the CEA Modeling**” to “**Data To Be Collected in the Proposed Study for Use in the CEA Modeling.**”

In the fourth sentence of the first paragraph of section **14.3.1 CTC Cost Estimation** the phrase “(3 *being test cases*)” has been added. Furthermore, the number of procedures to be performed has been changed from “45” to “54.” It now states:

Costs will be estimated using a micro-costing approach on a random sample of 18 CTC procedures (3 *being test cases*) performed at each of 3 participating study sites (54 procedures total).

In the third paragraph of section **14.4 Modeling Process** the unit of measurement has been changed in the second sentence from “cm” to “mm.” It now states:

Existing models typically dichotomize adenoma size into small (<10mm) and large (>= 10mm) states with a fixed annual probability of progressing from large to small.

### **15.0 STATISTICAL CONSIDERATIONS (Page 45, 47, 51)**

In the first sentence of section **15.1 Statistical Overview** the total sample size has been changed from “2289” to “2607.” Furthermore, the phrase “with a minimum of 12 participants with proved clinically significant colorectal neoplasia at each institution” has been deleted from this sentence.

In section **15.2.9 For Aim 3.3.2 (Cost-Effectiveness)** the reference to the Cost-Effectiveness Modeling Section has been changed from “14.4” to “14.0.”

In section **15.4.8 For Aim 3.3.2 (Cost-Effectiveness)** the reference to the Cost-Effectiveness Modeling Section has been changed from “14.4” to “14.0.”

In the second and fourth sentences of the second paragraph of section **15.5 Sample Size Considerations** the signs for measurement have been changed from “>” to “≥.”

In the second paragraph of section **15.5 Sample Size Considerations** the word “*originally*” has been added to the seventh sentence. It now states:

The trial team *originally* determined that this would require at least 10 evaluable positives per institution.

The following information has been added as the third paragraph of section **15.5 Sample Size Considerations**:

*However, based on observed accrual and following the accrual monitoring plan, the ACRIN Biostatistics Center and the ACRIN DSMC recommended the use of the alternative accrual plan limiting the trial accrual period to the shorter of December 31, 2006, and/or the time when total accrual reaches the budgetary limit of 2607 participants. Under this plan, any institutions having accrued 12 positives would remain open to accrual, and all institutions would be closed at the same time even if some institutions have not accrued 12 positives. This plan will be adopted by the trial. Based on accrual to date, it is expected that 2607 participants will be accrued before December 31, 2006.*

#### **APPENDIX I: SAMPLE CONSENT (Page 69-70)**

Under the question **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?** the amount of participants expected to enroll in the study has been changed from “2289” to “2607.”

The second sentence under the question **WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?** under **During the study** has been revised. It now states:

You will also be given *several* pills (bisacodyl tablets as *per your institution’s standard of care*) as part of the bowel preparation

The third sentence under the question **WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?** under **During the study** has been revised. It now states:

You may be given an injection of a medication (glucagon, 1 mg) to help relax your colon and prevent cramping *usually from 7 to 15 minutes* prior to the colonoscopy.

**Appendix V: Evaluation of Large Lesions (Page 80)**

The unit of measurement under lesion size at CTC has been changed from “10 cm” to “10 mm”. It now reads:

Lesion Size at CTC > 10 <i>mm</i>
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Thank you in advance for your attention and consideration.

Sincerely,

Michael Bradley  
Protocol Associate  
ACRIN Protocol Development and Regulatory Compliance

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