

*ACRIN 6652 Summary of Changes
Digital vs. Screen-Film Mammography*

10-27-03

#9

We have noted three errata in the 1-24-03 amendment (places where the summary of changes and the protocol did not match), and we have corrected them here.

Index

We have added a new Appendix (VI), and deleted the former Appendix VI. The Acceptance Tests and QC Procedures will now be provided to the sites as a separate document.

(In the amendment of 1-24-03, we mistakenly stated that we had added “12.0 Audit Source Documentation” to the index; instead, we added “12.0 Adverse Event Reporting.” This was correct in the 1-24-03 protocol, but wrong in the summary of changes.)

1.0

The number of participating sites has been changed from “at least 29” to “at least 35.”

2.9

The number of participating sites has been changed from 29 to 35. (In the 1-24-03 amendment, we stated in the summary of changes that the number of sites had been changed from 19 to “at least 29,” but it was not actually changed in the protocol.)

4.3

The parenthetical comment has been changed from “(see Section 4.4).” to “(See Section 4.4.)” The fourteenth sentence of the first paragraph has been changed; it previously read, “During those two weeks, if a woman refuses study entry, minimal information regarding her age and race will be collected,” but it now reads, “During those two weeks, minimal information regarding age and race will be collected for all patients not enrolled in the study.”

4.4.4

In the fourth sentence, the phrase “Although the registration screens will not review the entire eligibility checklist” has been deleted.

4.4.7

At the end of the first bullet, a colon has been deleted; a colon and a comma have been added to the second bullet. In the second sentence of the third paragraph, “through: Please” has been changed to “through, please”.

5.2.3

After the first sentence, a new sentence has been added: “(Staff at institutions are not allowed to share passwords; all individuals should have their own.)”

5.2.5

The phone number for the DMC has been added: (215-574-3245).

5.2.6

#1—The description for this form now reads as follows: “The Eligibility Checklist (Appendix III). This form is to be completed by the RA at the clinical site before registration to confirm participant eligibility for the clinical trial. It must be kept in the participant’s file.”

#6—The description for this form now reads as follows: “IM Form: The Additional Work-Up/Prior Films Form. This form is to be completed by the radiologist who completes additional imaging work-up of enrolled participants based on findings seen on the initial study screen-film or digital mammogram. This form is also used to report any reinterpretation of initial study images that occur once prior films have been received. It includes recommendations for follow-up and additional imaging studies.”

#11—The description for this form now reads as follows: “F1 form. This form is required for all participants except those who have been diagnosed with bilateral breast cancer within the first 12 months after enrollment. It is used to record the findings from a mammogram taken 10-15 months from the date of enrollment. This form is also used to record the findings of short term interval follow-up, if any, recommended on the basis of the initial screening images or on the basis of the 1-year follow-up exam (3, 6, 9, 15, 18, or 21 months from enrollment).”

#12—The following has been added to the end of the form description: “It may also be required for an additional 50 cases during the second year of the study.”

#17—11 months has been changed to 10 months. An extra period has been deleted at the end. (In the 1-24-03 amendment, the summary of changes stated that the first sentence read, “if there are changes since a prior study”; however, that should have matched the protocol, which correctly reads, “if there are *clinically significant* changes since a prior study.”)

#19—The Patient Nonparticipation Form is now called the “PR Form (Patient Nonparticipation).”

#20 and 21—These forms have been added:

E2 (Breast Cancer Status Summary) Form: This form is used to document the best source of information about a participant’s breast cancer. It is to be completed in the following circumstances: Participant does not return for one-year mammogram; participant does not provide your institution with mammograms taken at an outside facility; and you are unable to obtain a mammography report of a mammogram taken at least 10 months after the date of enrollment. This form will be added to the participant calendar for all participants who are reported as lost/unknown on their 1 year F1 form. It may

also be requested for participants known to be alive and reported as such on the F1 form, but for whom no screening mammography data is available.

DE (Documentation of Effort) Form: This form is to be completed for all participants who do not respond to initial requests to return for their 1 year follow-up mammogram. It is used to document all attempts to contact participants to schedule 1 year follow-up examinations. Refer to Appendix VI for more detailed information regarding the protocol for contacting participants for follow-up. For most cases for which it is required, the DE form will be kept as part of the participant’s study record, but it will not be submitted to ACRIN. The DE form may be requested by Data Management for cases where the F1 form reports the case as lost or the E2 form reports breast cancer status as unknown. For other cases without follow-up mammography, the DE form will be part of the participant’s study record, and will be subject to audit.

5.2.7

In the chart, the following has been added to the due date of the IA and ID forms: “(if prior images are referenced, can be submitted within 30 days of imaging, per MQSA guidelines)”.

The collection of both the F1 and IE Forms has been changed from 6 and 9 months to 3, 6, and 9 months.

In the row for “Confidential Patient Contact Form,” the final sentence in the second column (beginning “Faxed to UNC...”) has been deleted.

The Patient Nonparticipation Form is now called the “PR Form (Patient Nonparticipation).”

Two final rows have been added to the chart:

E2 Form – Breast Cancer Status Summary	After 18 months of enrollment (if the participant has not provided a screening mammogram and does not have one scheduled and the site is not able to obtain a mammography report taken at least 10 months after the date of enrollment into DMIST)
DE Form – Documentation of Effort	At the request of DMC

5.3.4

At the end of the 5th sentence, the words “(recorded on form PO)” have been added. At the end of the 11th sentence, “as well as the PL and P4 forms” has been added. In the last sentence, a space has been added between “identifiers” and “replaced” to correct a typo.

5.3.5

At the end of the first sentence, the words “(form PO)” have been added.

5.4.1

At the end of the sixth sentence, “and the more thorough checks” has been deleted.

5.7.1-5.7.2

These sections have been extensively revised and now read as follows:

5.7.1 After the first 100 participants have been accrued at a participating site, the site may be contacted by an ACRIN auditor by telephone for an assessment interview, and the site will be eligible for an audit. Auditors will follow procedures established by the Clinical Trials Monitoring Branch and the Cancer Imaging Program of the NCI. Auditors will review on-site records against the submitted data forms, and they will record their findings on specially prepared questionnaires. IRB procedures, approvals, and consent forms will also be reviewed during the audit.

Major deficiencies will be forwarded to the appropriate oversight body within ACRIN.

In advance of the audit date, ACRIN will provide institutions with detailed instructions for preparing for audit, along with a list of up to 45 of the case numbers that have been selected. Five cases from the selection list will be reserved as surprise cases.

Cases to be audited will be randomly selected from three groups of participants:

- 1. Those diagnosed normal or definitely benign;*
- 2. Those referred for additional imaging, but not for biopsy; and*
- 3. Those referred for biopsy.*

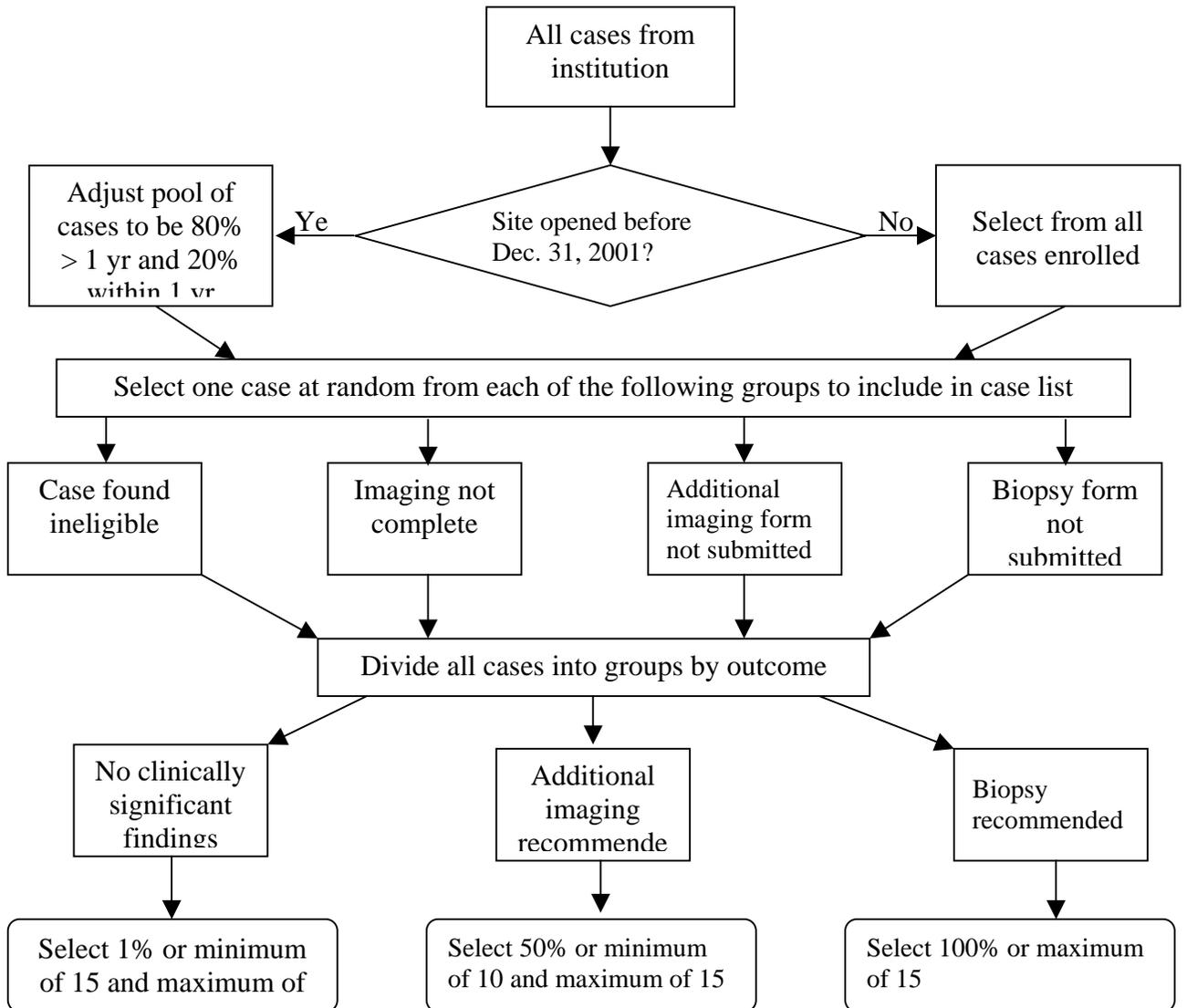
Because the vast majority of cases fall into the first category and very few fall in the last, DMIST has chosen to select from these categories at different rates to ensure adequate representation from each. ACRIN will select 1% of cases from group 1, but no more than 20 and no fewer than 15; 50% of cases from group 2, but no more than 15 and no fewer than 10; and 100% of cases from group 3, but no more than 15.

For the first audit for institutions opened by December 31, 2001, 80% of the cases selected will be from those enrolled a year or more before the audit, and 20% will be selected from cases enrolled within one year. This ensures that the auditors review follow-up data forms, as well as the forms required from the baseline visit. It also ensures that data from each year of the study will be audited over the course of the study.

In addition to these selections, at least one case fitting each of the following descriptions will be included among cases audited (these are not mutually exclusive of the groups above): participants who were found to be ineligible, those who did not receive both a digital and a screen-film mammogram at study entry, those who were referred for additional imaging but who did not comply with this recommendation, and those who were referred for biopsy but who either did not comply or whose data regarding the biopsy have not yet been received. The schema below illustrates the audit case selection.

DMIST Audit Selections

Strata from Which Initial Audit Cases Selected



If the initial audit is acceptable, subsequent audits will be scheduled for 12 and 24 months after the initial audit date. If any of the audits are unacceptable, follow-up audits will be scheduled as per the ACRIN Audit Manual guidelines.

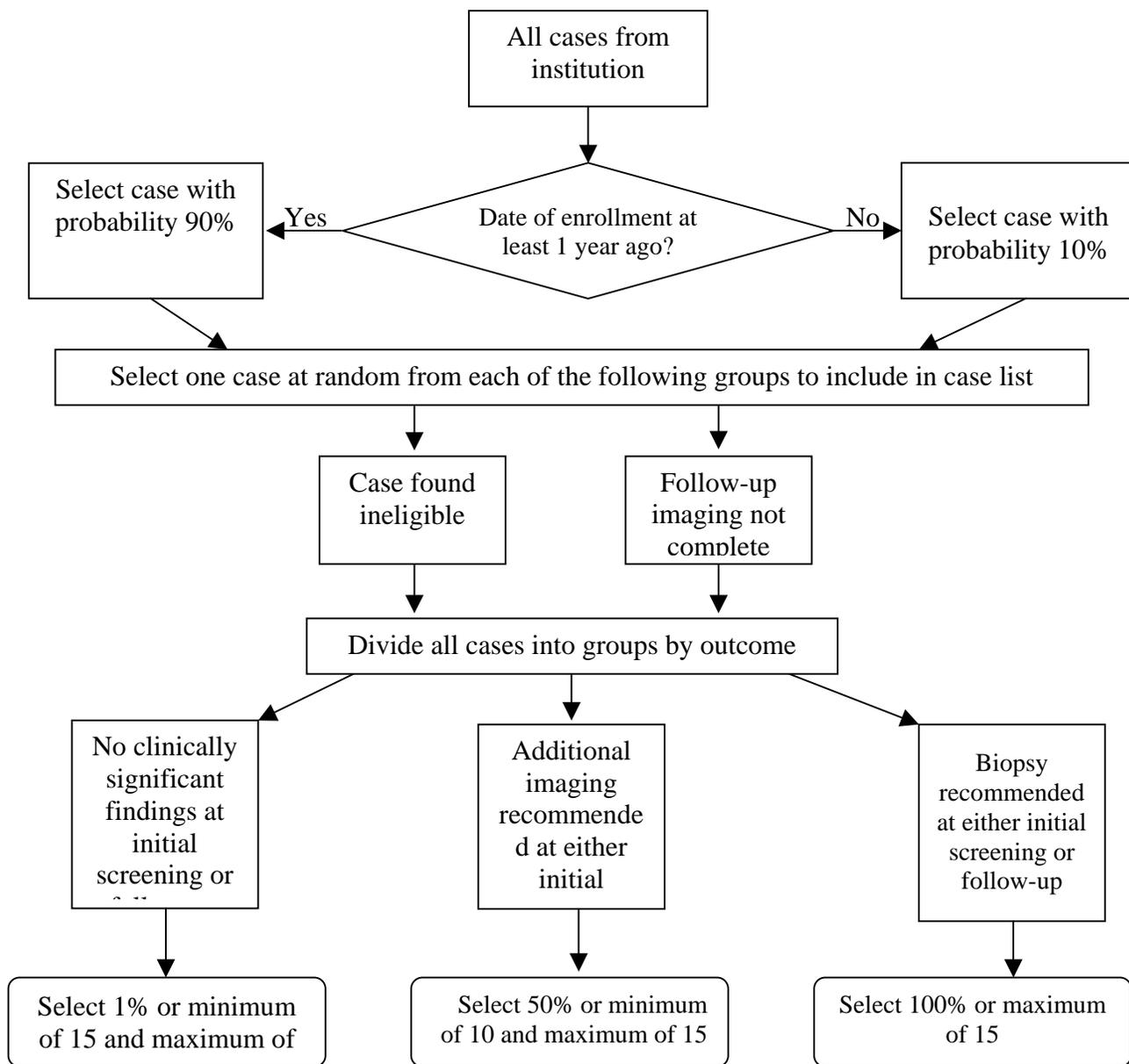
Selection of cases for follow-up audits

Selection of cases for follow-up audits will be completed according to the criteria outlined above for initial audits with the following exceptions:

- *Cases previously audited and found acceptable will not be re-audited.*
- *Cases previously audited which required corrective action may be included in subsequent audits.*
- *90% or more of the cases will be selected from among those who were enrolled 1 year or more from the date the list is generated so that forms for follow-up can be reviewed.*
- *At least 1 case for whom follow-up data has not been submitted on time, if any exist, will be included.*

Documentation of Effort forms (DE) detailing steps taken to obtain the breast cancer status of the participant will be required for all cases for which 1-year follow-up information has not been collected by 18 months from enrollment. If one has been requested, a Breast Cancer Status form (E2) will also be required. The schema below illustrates the case selection for follow-up audits.

Strata from Which Follow-Up Audit Cases Selected



5.2.7 *To aid sites in preparing for ACRIN audits and to assure the clinical RA maintains records accurately, the ACR Audit Department will offer regional audit educational training. The training sessions will cover all aspects of data collection as related to protocol-specific audit requirements, i.e. acceptable source documentation necessary to verify the accuracy of submitted data for audit purposes. ACRIN held training sessions at the October 2002 and the 2003 fall meetings.*

6.0

The following has been added after the third sentence of the second paragraph: “Both film screen and digital images should be acquired on the same day unless equipment failure precludes same day imaging. In the case of digital equipment failure, digital images may still be acquired up to a maximum of 30 days after film screen imaging. Should this occur, interpretation of the film screen mammogram must be postponed to insure that the interpretations are completed within the required 7 day limit of each other.”

7.1

In the third sentence of the second paragraph, “Old films” has been changed to “Prior films.” At the end of that paragraph, a new sentence has been added: “If prior films are referenced, they must be available for both digital and screen-film interpretations; in that case, the IA and ID forms may be submitted within 30 days of imaging, per MQSA guidelines.”

In the third sentence of the third paragraph, “Old films” has been changed to “Prior films.”

The following sentence has been added at the end of the fifth paragraph of this section: “Hologic study mammogram initial reads may be done in either hard copy or soft copy.”

In the fourth sentence of the sixth paragraph, the typo “it” has been deleted.

8.1

In the second sentence of the third paragraph of this section, the FI form has been changed to the F1. The end of this paragraph has been changed. It previously read, “If additional imaging is necessary on follow-up exams, forms F1 and IE should be completed after additional imaging has been completed. Mammograms taken up to 15 months following original study screening mammograms will be accepted as the one-year follow-up mammogram.” It now reads, “If additional imaging is necessary on follow-up exams, forms F1 and IE should not be submitted until after the additional imaging has been completed. If, after additional imaging has been completed, the BI-RADS classification is 3, 4, or 5, forms F1 and IE should be completed. If the BI-RADS classification is 1 or 2, only the F1 form should be completed. Mammograms taken 10 to

15 months from the date of enrollment will be accepted as the one-year follow-up mammogram.”

In the first sentence of the following paragraph, “presence of malignancy of 6 and 9 months” has been changed to “presence of malignancy at 3, 6, and 9 months”. After that sentence, the following has been added: “Study personnel will encourage participants to have a follow-up mammogram, even if the participant is unable to be imaged within the 10-15 month window. They will also obtain pathology specimens and results from any biopsies performed as a result of initial or follow-up imaging.” At the end of that paragraph, the following has been added: “Data from participant contacts will be recorded on the Breast Cancer Status Form (E2). For women who do not respond to these contacts, a search of their medical chart, state tumor registries, and/or the National Death Index (NDI) will be conducted. An E2 Form will be used to record these data as well.”

8.2

In the first sentence, “as Appendix III” has been changed to “to the sites as a separate document.”

11.9.1

In the first sentence, “at least 29 institutions” has been changed to “at least 35 institutions.” The average expected accrual per institution has been deleted.

12.3

CTC has been changed to CTCAE 3.0.

12.4

Under expected adverse events for mammography, “skin tear” has been added.

Appendix I

Under the heading, “What are the risks of this study?”, we have added a sentence: “This compression can cause bruising, discomfort, or tearing of the skin.”

Under the heading “What about confidentiality?”, in the second paragraph the word “questions” has been deleted.

Appendix IV

The address for the UVA medical center has been corrected from NC to VA. The spelling of Massachusetts General Hospital has been corrected. The spelling of Johns Hopkins has also been corrected.

The following sites have been added:

Allegheny Cancer Center
320 E. North Avenue

Pittsburgh, PA 15212

The Elizabeth Wende Breast Clinic
170 Sawgrass Drive
Rochester, NY 14620

H. Lee Moffitt Cancer Center
12902 Magnolia Drive
Tampa, FL 33612

Brown University
Rhode Island Hospital
Diagnostic Imaging Research
593 Eddy Street
Providence, RI 02903

Lahey Clinic
41 Mall Road
Burlington, MA 01805

Appendix V

Under “Registration,” in both bullets “violation” has been changed to “deficiency.” In the second bullet, the word “registration” has been added.

Under the heading about regulatory binders, “for approval from the ACRIN Regulatory Department” has been changed to “to be kept on file by the ACRIN Regulatory Department.”

Under the “Consent Form” heading, the second bullet now reads as follows: “If the site consent form requires the PI’s signature, a letter from the IRB must state a time frame within which the PI must sign. If no time frame is specified, all consents should be signed by the PI within two weeks of the participant’s signature.”

Under the “Randomization Sequence” heading, the bullet now reads, “Randomization sequence will be verified by documentation containing the technologist’s printed name, signature, and the date.”

In the “Source Documentation” column for the A0 form, the final bullet has been changed from “Signed and dated by the Research Associate” to “Randomization form signed and dated by the Technologist.”

In the “Source Documentation” column for the I1 form, the following white bullet has been added: “I1 Form (completed by participant), Signed and dated by the participant.”

In the “Source Documentation” column for the IA form, the word “OR” has been added before the final black bullet. The final black bullet under “Source Documentation” for

the IA form now reads, “Clinical mammography report, clearly stating the reader of the film screen, the date of the film screen, the date of the interpretation, and the BI-RADS score.” In the asterisk below it, “UNC” has been deleted, and the following has been added: “(if prior images are referenced, form can be signed and submitted within 30 days of imaging, per MQSA guidelines).”

In the “Source Documentation” column for the ID form, in the third black bullet “IA” has been changed to “ID.” An “OR” has been added, followed by a third white bullet: “Printed ID Form—signed and dated by the Radiologist*.” The word “OR” has also been added before the final black bullet. The final black bullet under “Source Documentation” for the ID form now reads, “Clinical mammography report, clearly stating the reader of the digital imaging, the date of digital imaging, the date of the interpretation, and the BI-RADS score.” In the asterisk below it, “UNC” has been deleted, and the following has been added: “(if prior images are referenced, form can be signed and submitted within 30 days of imaging, per MQSA guidelines).”

Under “Source Documentation” for the IM form, the third black bullet has “OR” added before a new white bullet, which reads, “Printed IM Form—signed and dated by the Radiologist*.” In the asterisk below it, “UNC” has been deleted.

The F1 form now says, “(3, 6, and 9 months, if recommended, and at 12 months for **all** participants).” Under “Source Documentation” for the F1 form, “Printed F1 form signed and dated by RA” has been changed to “F1 form, printed, verified for accuracy, signed by RA, and dated day form is printed.” A parenthetical comment has been added: “(One year follow-up mammography to be completed within 10-15 months of the initial imaging.)”

This IE form is now due “(at 3, 6, and 9 months, if recommended; at 1 year only if participant has BI-RADS 3, 4, or 5 at 1-year follow-up).” Under “Source Documentation” for the IE form, under the third black bullet the word OR has been added, followed by a white bullet, which reads, “Printed IE form—signed and dated by the Radiologist*.” It is followed by and “AND.” In the asterisk below, “UNC” has been deleted.

The PR form is now identified as the “PR (Patient Non-Participation) Form.” In the first bullet under “Source Documentation,” “Copy” has been changed to “Copy of PR form,” and “Research Associate” has been changed to “RA.”

The following forms have been added:

DE Form: Documentation of Effort	<ul style="list-style-type: none"> • Completed, signed, and dated by the RA
E2 Form: Breast Cancer Status Summary	<ul style="list-style-type: none"> • Completed, signed, and dated by the RA <li style="text-align: center;">AND • Clinical reports, imaging reports, pathology reports, surgical reports, progress notes, etc., as applicable

The QP, QL, QF, and Quality of Life forms have been deleted from the audit source document table because they will not be audited. They were originally included in error. This does not appear as a tracked change on the highlighted document.

The footnote at the end of the table has been deleted.

Appendix VI

The following appendix has been added:

DMIST Annual Follow-up

These guidelines are based on follow-up procedures at UNC. All follow-up strategies must follow the guidelines of the local IRB.

Forms must be submitted for each participant enrolled in the DMIST approximately 1 year after the date of the enrollment. The purpose of these forms is to determine if the participant has been diagnosed with breast cancer since the prior mammogram or has had any breast health problems since her enrollment in DMIST. Each participant, except those diagnosed with bilateral breast cancer within 15 months of enrollment, must have an F1 form completed. The RA will complete the F1 form. Any participant who is a BI-RADS 3, 4, or 5 requires that an IE form be completed by a DMIST radiologist in addition to an F1 being completed.

Procedure

Prior to calling the participant, check to see if a radiology report for an annual mammogram is present. If it is present, print out the report, complete an F1, and, if necessary, have reading radiologist complete an IE. Submit forms and file all forms in participant case file. Enter participant into DMIST follow-up database. A participant call record does NOT need to be completed.

If no radiology report is present, check to determine if participant is scheduled to return for annual mammogram. Make note of appointment date on a participant call record and file in follow-up log book. Follow above procedures once report is available.

If no appointment is scheduled the participant must be contacted.

Participant Contact Schedule

The participant must be contacted 12 months after her enrollment in DMIST. Please note the date the participant was enrolled in DMIST on the call record and the DE form. An attempt to contact the participant must be made at least once every 2 weeks for up to three months. If no contact is made during the three consecutive months, a final attempt to reach the participant must be made 18 months after her enrollment in DMIST. If the participant's phone is not working,

the participant's doctor and/or contact person must be contacted in order to obtain accurate contact information. A busy number does not qualify as a contact, and another attempt to contact the participant must be made that month. Please follow the participant's instructions as noted on the Confidential Contact Form when contacting the participant at work or leaving a message. Do NOT leave a message for participants who do not specifically express permission to do so. All calls must be noted on a call record.

If the participant schedules an appointment, note the date of the appointment on the participant call record. When the appointment passes and a clinical report is available, complete the above procedures.

If the participant has had a mammogram at another facility, an attempt must be made to obtain the films and/or the clinical report from this mammogram.

If a participant is contacted, but she refuses to return for an annual mammogram, please obtain necessary information.

If contact is made with the participant but no appointment has been scheduled at 18 months past participant enrollment in DMIST, the RA may obtain information from the participant. If the participant is not willing to schedule a mammogram at that time, the RA should request that DMIST be notified of the results the next time she does have a mammogram. This information must be documented on the record and the DE form. However, the participant should be encouraged to return at that time, even though her imaging would occur outside the 10-15 month window.

If no contact is made with the participant after six months (18 months after enrollment in DMIST), submit the F1. Contact date is the last date your institution had contact with the participant (at screening/additional work-up/or if any other phone calls made in the interim). The RA must check with the State Tumor Board Registry to determine participant has not been diagnosed with breast cancer.

Attempts must be made to collect information about the participant's breast cancer status. E2 and DE forms are used for this purpose for women with no follow-up mammogram. The Documentation of Effort (DE) form is used to record all attempts to contact the participant to schedule her follow-up mammogram, as well as steps taken to determine her breast cancer status. E2 and DE forms are not required for any participants for whom you have a BI-RADS score from a mammogram taken 10 months or more from enrollment.

The E2 form will be submitted on paper to Data Management where the data will be entered into the main database. Data Management will add E2 forms to participants' calendars for every participant whose F1 form reports her as lost. Documentation of Effort (DE) forms will be required for all of these cases, but

will only be submitted to Data Management if requested. The DE form should be kept as part of the participant's study record and is subject to audit.

*** 6652 DE and E2 forms are posted on the ACRIN web site (www.acrin.org).*

Appendix VI

The QC manual, formerly Appendix VI, has been deleted and will now be distributed to the sites separately from the protocol.

*ACRIN 6652 Summary of Changes
Digital vs. Screen-Film Mammography*

1-24-03

#8

(In earlier versions, this amendment was mistakenly labeled #7.)

Throughout the Protocol

The word “patient” has been replaced by “participant.”

Title Page

Dr. Masood’s phone number has been corrected to (904) 244-4387 and her fax number to (904) 549-4060. Dr. Masood’s e-mail address has been corrected to Shahla.masood@jax.ufl.edu.

Index

“12.0 Audit Source Documentation” and “Appendix V: DMIST Source Documentation” have been added. Page numbers have been corrected for this new version of the protocol.

1.0

The number of participating centers has been changed from 19 to “at least 29.”

2.9

The number of participating centers has been changed from 19 to “at least 29.”

4.4.1

In the second sentence, “Appendix IV” has been changed to “Appendix III.”

5.2.6

In Item 1, “Appendix IV” has been changed to “Appendix III.”

In Item 7, “any time during the 1 year after” has been changed to “any time during the 15 months after.”

In Item 8, “Part of” has been added to the first sentence, and “by one of the two pathology consultants” has been changed to “by the local RA, and then it is sent to the pathology consultant who will”.

In Item 9, “Part of” has been added to the first sentence, and “one of the two pathology consultants, who will record his or her interpretation” has been changed to “by the local RA, and then it is sent to the pathology consultant to record her own interpretation”.

Item 17 formerly read, “IE Form: This form will record the study radiologist’s interpretation of screen-film mammograms at interim time points post study enrollment based on initial imaging recommendations. An IE form will be submitted in conjunction with an F1 form at 6, 12, and 15 months post enrollment.” It has been changed to read, “IE Form: This form is completed by the site radiologist who interprets the participant’s

short-term interim follow-up screen-film or digital mammogram, or if there are changes since a prior study. This form will also be completed for BIRADS 3, 4, or 5 follow-up mammograms obtained 11 months or more after study entry. The completed form is submitted to the ACR.”

5.2.7

In the chart, the due date for the IM form has changed from “Within 1 month of imaging” to “Within 12 weeks of recommendation for additional work-up.” The due date for the BX form has been changed from “Within 2 weeks of biopsy” to “Within 8 weeks of biopsy recommendation.” In the row for the IE form, the phrase “for BI-RADS 3, 4, or 5” has been added. In the row for the TA form, the phrase “and as needed thereafter” has been added. For Confidential Patient Contact Form, “Reproduced and mailed to UNC within two days of the patient’s random selection to undergo QOL or CE surveys” has been changed to “Faxed to UNC the same day that the participant is notified of the need for additional work-up.”

5.3.1

In the address, a line has been added: “Philadelphia, PA 19107.”

5.3.4

Dr. Masood’s phone number has been corrected to (904) 244-4387. Dr. Masood’s e-mail address has been corrected to Shahla.masood@jax.ufl.edu. After the address, a sentence has been added: “If regulations at your institution will not allow you to send the entire tissue block, two unstained slides will be accepted in its place.” In the final paragraph, “identify” has been replaced with “identifiers.”

5.7.1-5.7.2

The original sections 5.7.1 and 5.7.2 have been replaced by the following:

- 5.7.1 Institutional on-site audits take place after the first 100 participants have been accrued at a participating site, and as needed thereafter. Contingencies have been made for sites that have accrued over 100 participants. Auditors will follow procedures established by the Clinical Trials Monitoring Branch and the Biomedical Imaging Program of the NCI. Instructions for audit preparation will be sent to the sites in advance of the audit date. The instructions will specify the case records to be scrutinized during the audit. Auditors will review on-site records against the submitted data forms, and they will record their findings on specially prepared questionnaires. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will be also reviewed during the audit.*
- 5.7.2 To aid sites in preparing for ACRIN audits and to assure the clinical RA maintains records accurately, the ACR Audit Department will offer regional audit educational training. The training sessions will cover all aspects of data collection as related to protocol-specific audit requirements, i.e. acceptable source documentation necessary to verify the accuracy of submitted data for audit purposes.*

5.7.4

This section has been deleted and replaced by the later adverse event reporting section.

7.1

The second paragraph originally read, “For this study, the screen film mammograms for all participating women will be interpreted by one radiologist, the one assigned to the clinical service as per the usual practice at that hospital. Patients will be called back for additional work-up for any lesions that are seen that suggest the need for further workup. Old films on the patient will be available for comparison.”

It has been changed to read: “For this study, two different radiologists will interpret the mammograms, one for the study screen-film and the other for the digital mammograms of all participating women. Participants will be called back for additional work-up for any lesions that are seen that suggest the need for further work-up. Old films on the participant can be used for comparison for the interpretation of both sets of images, unless they are not available.”

In the fourth paragraph, the spelling of “FUJI” has been corrected.

8.1

The following paragraph has been changed. It formerly read, “All women will be encouraged through the study newsletter to undergo mammography one year after their entry mammogram at the site where they were enrolled. The follow-up mammography will be either a screen film or digital mammogram as per usual clinical protocols at the involved sites. At that time, they will be asked about prior breast biopsies. In addition, follow-up for these screen film or digital mammograms will be obtained and interpreted by study radiologists. This interpretation will be recorded on Form IE. If that exam leads to a biopsy, that information will be included in the record on that patient through completion of another BX form. Mammograms taken up to 15 months following original study screening mammograms will be accepted as the one-year follow up mammogram.” It has been changed to two paragraphs, which read:

All women will be encouraged through the study newsletter to undergo mammography one year after their entry mammogram at the site where they were enrolled. The follow-up mammography will be either a screen film or digital mammogram as per usual clinical protocols at the involved sites. At that time, information will be obtained about prior breast biopsies that have occurred since the previously recorded visit.

Breast cancer status will be recorded on form F1 for all study participants each time there is a short-term interim or one year follow-up screen film or digital mammogram, or if there are changes since a prior study. In addition to form F1, form IE will be completed for all participants returning for short-term interim follow-up mammograms. Form IE will also be completed for all one-year follow-up mammograms with a BIRADS classification of 3, 4, or 5. Form IE will NOT be completed for negative one-year follow-up mammograms. BIRADS classification 0 — needs additional imaging will not be allowed on follow-up

mammography exam forms. If additional imaging is necessary on follow-up exams, forms F1 and IE should be completed after additional imaging has been completed. Mammograms taken up to 15 months following original study screening mammograms will be accepted as the one-year follow-up mammogram.

11.9.1

In the first sentence, “twenty sites” has been changed to “at least twenty-nine sites.”

12.0

This section has been added to assist in the reporting of adverse events:

12.0 ADVERSE EVENT REPORTING

12.1 Definition of Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

12.2 Definition of Serious Adverse Effect

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- *Results in death or is life-threatening (at the time of the event) or*
- *Requires inpatient hospitalization or prolongation of an existing hospitalization or*
- *Results in persistent or significant disability or incapacity*

12.3 Adverse Event Grading

Grade is used to denote the severity of the adverse event. An AE is graded using the following categories (provided the term does NOT appear in the current version of the Common Toxicity Criteria [CTC]):

0 – Within normal limits

1 – Mild

2 – Moderate

3 – Severe

4 – Life-threatening or disabling

5 – Fatal

(For terms listed in the CTC, the grade is still recorded as 1, 2, 3, 4, or 5; however, the definition of the various grades will be specific to the term being used.)

12.4 Expected Adverse Events from Mammography

Bruising

Discomfort

12.5 Expected Adverse Events from Contrast Agent (gadolinium)

Nausea

Headache
Hives
Temporary low blood pressure
Allergic reaction

12.6 Expected Adverse Events from Biopsy

Minor discomfort
Bleeding
Infection
Bruising
Collection of air or gas in the chest cavity (pneumothorax)
Anesthesia-related problems

12.7 Reporting of Adverse Events

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research. Please refer to the ACRIN Adverse Event Reporting Manual for specific details about what to report and when. Anyone uncertain about whether a particular adverse event should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance. Any event that is judged to be NOT related to the treatment or procedure should NOT be reported as an adverse event. However, an adverse event report should be submitted if there is a reasonable suspicion of the medical treatment or imaging procedure effect.

12.8 When to Report

12.8.1 You must use expedited event reporting to within 10 working days for all Grade 5 events occurring within 30 days of the study intervention, regardless of attribution and regardless of whether the event was expected or unexpected. You must use expedited event reporting within 10 working days for Grade 4 unexpected events occurring within 30 days of the study intervention, regardless of attribution. These reports should be sent to ACRIN, NCI's Biomedical Imaging Program (BIP), and the local Institutional Review Board (IRB).

12.8.2 All fatal (Grade 5) adverse events should also be reported by telephone to NCI and ACRIN within 24 hours of the event.

12.8.3 Expedited adverse event reporting is NOT required for expected events of grades 1-4 or unexpected-indirect adverse events of any grade.

12.8.4 All expedited reports should be reported within ten (10) working days of knowledge of the event. All fatal adverse events should also be reported by telephone to the NCI and to ACRIN within 24 hours of knowledge of the event.

12.9 How to Report

12.9.1 An expedited adverse event report requires submission to the NCI-BIP and ACRIN using the paper templates "Adverse Event Expedited Report—Single Agent" or "Adverse Event Expedited Report—Multiple Agents," available on the CTEP home page, <http://ctep.info.nih.gov>. 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.)

12.9.2 *Completed expedited reports should be sent to:*

NCI

Barbara A. Galen, MSN, CRNP, Program Director

Re: Adverse Event Report

Biomedical Imaging Program

6130 Executive Blvd., MSC 7412

Bethesda, MD 20892-7412

To make a telephone report, contact NCI at (301) 496-9531, available 24 hours a day (recorder after hours from 5 PM to 9 AM ET).

12.9.3 *A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215)-717-0936. All fatal adverse events should be reported by telephone within 24-hours of the event. To make a telephone report to ACRIN, call (215)-717-2763, available 24 hours a day (recorder after hours from 5 PM to 8 AM ET).*

12.9.4 *All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events not requiring expedited reporting are normally reported to your local IRB in an annual report.*

Appendix III

In Item 9 of the eligibility checklist, the words “and radiation therapy” have been deleted.

Appendix IV

New sites have been added and some addresses have been corrected. The list now reads:

APPENDIX IV

Participating Institutions

*Beth Israel Deaconess Medical Center
Department of Radiology
330 Brookline Avenue
Boston, MA 02215*

*Shore Memorial Hospital
1 E. New York Avenue
Somers Point, NJ 08244*

*Memorial Sloan-Kettering
Guttman Diagnostic Center
55 Fifth Avenue, 12th Floor
New York, NY 10003*

*University of Cincinnati Hospital
234 Goodman St.
Cincinnati, OH 45219*

*LaGrange Memorial Hospital
5101 S. Willow Springs Road
LaGrange, IL 60525*

*University of Iowa
Department of Radiology
200 Hawkins Dr.*

*University of North Carolina
Department of Radiology
Campus Box 7510
Chapel Hill, NC 27599-7510*

*University of California Davis
Department of Radiology
4860 Y Street, Suite 3100
Sacramento, CA 95817*

*University of California Los Angeles
Department of Radiological Sciences
200 UCLA Medical Plaza, Rm 165-47
Los Angeles, CA 90095-6952*

*University of Washington
Roosevelt Clinic
4245 Roosevelt Way NE
Seattle, WA 98195*

*Northwestern University
Department of Radiology
Lynn Sage Breast Screening Center
676 N. St. Clair, Suite 1950
Chicago, IL 60611*

*Washington Radiology Associates, PC
2141 K Street, NW
Suite 900
Washington, DC 20037*

*University of Colorado Hospital
Campus Box F724
1635 N. Ursula
Denver, CO 80010*

*The Emory Clinic
1365-B Clifton Road NE, Suite 1300
Atlanta, GA 30322*

*University of Pennsylvania
Department of Radiology
3400 Spruce Street
Philadelphia, PA 19104-4283*

Iowa City, IA 52242

*University of Texas Southwestern
Medical Center at Dallas
Breast Imaging Center
2201 Inwood Road
Dallas, TX 75390*

*Washington University in St. Louis
School of Medicine
Barnes-Jewish Hospital
Breast Health Center
Ct.r for Advanced Medicine, 5th floor
4921 Parkview Place
St. Louis, MO 63110*

*Mt. Sinai Medical Center
One Gustave L. Levy Place
New York, NY 10029-6374*

*Monmouth Medical Center
The Jacqueline M. Wilentz
Comprehensive Breast Center
300 2nd Ave.
Long Branch, NJ 07740*

*University of Virginia Medical Ctr.
Department of Radiology
1215 Lee st.
Charlottesville, NC*

*William Beaumont Hospital
3577 W. 13 Mile Rd.
Royal Oak, MI 48073*

*Massachusetts General Hospital
Department of Radiology
55 Fruit St.
Boston, MA 02114*

*Sunnybrook & Women's College HSC
2075 Bayview Avenue
Toronto, Ontario, Canada M4N 3M5*

*Columbia Presbyterian Medical Center
Breast Imaging Center
Herbert Irving Pavilion, 10th Floor
161 Fort Washington Avenue
New York, NY 10032*

*Thomas Jefferson University
Mammography Screening Center
909 Walnut St.
Philadelphia, PA 19107*

*Johns Hopkins University
Mammography and Breast Imaging, Rm. 4155
Johns Hopkins Outpatient Center
601 North Caroline Avenue
Baltimore, MD 21287*

Appendix V (new)

The following appendix has been added:

<i>DMIST Source Documentation</i>
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Registration

- *On line immediate registration up to 24 hours from the time of consent is not a violation.*
- *Off line over two business days is considered a major violation.*

Regulatory binders must have:

- *All source documentation for initial IRB approval*
- *All annual re-approval letters from IRB within 365 days from the last approval*
- *All Protocol Amendments, checked for IRB approval, verifying version date, and amendments*
- *310 Form, IRB letter or IRB meeting minutes approving Protocol participation*
- *Current version of the informed consent*

Approved IRB consent form must be sent to ACRIN Headquarters for approval from ACRIN Regulatory Department.

- *If the incorrect IRB approval is sent to headquarters, a regulatory staff member will notify site that an incorrect approval was obtained (i.e., expedited instead of full) and inform the site to resubmit to their IRB. A general list of regulations will not be sent to the sites.*

Consent Form

- *This form must be signed and dated by participants and contain all other signatures requested by the local IRB.*
- *If the site consent form requires PI signature, a letter from the IRB must state a timeline for date of the PI's signature. If no timeline is specified, all consents should be signed within two weeks of the participant's signature.*
- *Informed consent will be checked to verify that the witness and participant have signed on the same date.*
- *Twenty year consent form if agreed to and signed/dated by participant.*

Randomization Sequence

- *Documentation of Randomization sequence will be verified from the A0.*

Supplemental instructions for audit documentation.

Sites will maintain electronic copies of submitted data and any supporting source documentation within the participant's research file. The site Research Associate will print the documents required by the auditor's upon notification of the audit date.

Superscript detail descriptions for the following source documentation:

- 1 Print selected pages of the forms.*
- 2 Good Clinical Practice (GCP) standards should be followed when recording data. All data documentation provided by the participant is expected to be reviewed by the Research Associate and the participant. In the event a discrepancy is noted upon review of documents completed by the participant, the initials of the participant and the RA in addition to the date must be noted next to the revised item.*
- 3 The utility for digitized signatures will be available at all sites for use when data is entered directly into the web application.*

ACRIN will provide the RAs at the institutions the capability to store verifiable signatures that are entered by the participants in a digital format. This capability can be accomplished by means of software application developed by the HQ. These digital signatures will be associated with specific forms completed by an RA and can then be saved into the local machine. The document with the digital signature is viewable and can be printed at a later stage. The digital signature can be captured via the web by various input devices such as Mouse, Pen Pad, etc. This technique of capturing signature is designed to improve the functionality of the Web by providing more flexible and adaptable information identification.

<u>Form</u>	<u>Source Documentation</u>
<p align="center"><u>A0 Form</u> Registration/ Eligibility and Randomization</p> <p>Registration Confirmation¹ i.e. Randomization sequence confirmation screen</p>	<ul style="list-style-type: none"> • Eligibility Checklist signed and dated by Research Associate (printed copy of Appendix III) <p>OR</p> <ul style="list-style-type: none"> • If information is entered directly on-line, the confirmation email must be printed, signed and dated by the RA <p align="center">OR</p> <ul style="list-style-type: none"> • A printed copy of the A0 signed and dated by the RA with verification of information origination, i.e. participant interview, mailed in form. • Patient registration confirmation¹. • Signed and dated by the Research Associate
<p>II Form – Initial Evaluation</p>	<ul style="list-style-type: none"> • UNC Worksheet² (completed by participant) <ul style="list-style-type: none"> ○ Signed and dated by the participant <p>OR</p> <ul style="list-style-type: none"> • Site specific worksheet² (completed by participant) <ul style="list-style-type: none"> ○ Signed and dated by the participant <p>OR</p> <ul style="list-style-type: none"> • II Form¹ <ul style="list-style-type: none"> ○ Direct entry of information obtained directly from participant through interview <ul style="list-style-type: none"> ▪ Participant's digitized signature³ and date ▪ Documented notation stating the source of information and the method, e.g., participant interview ▪ RA's digitized signature³ and date <p align="center">OR</p> <ul style="list-style-type: none"> • Mammography Department Questionnaire² in addition to any of the above <u>OR</u> in place of the above <u>if ALL</u> pertinent information is collected on the questionnaire. (completed and signed by participant)

<u>Form</u>	<u>Source Documentation</u>
<p><i>IA Form – Study Mammography Interpretation Film-Screen</i></p>	<ul style="list-style-type: none"> • <i>UNC Worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> • <i>Site-specific worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> • <i>IA Form¹</i> <ul style="list-style-type: none"> ○ <i>Direct entry of information obtained directly from the study images,</i> ○ <i>Radiologist’s digitized signature³ and date*</i> <p style="text-align: center;"><i>OR</i></p> <ul style="list-style-type: none"> ○ <i>Printed IA Form - signed and dated by the Radiologist*</i> <p style="text-align: center;">• <i>Clinical Mammography Report is required in addition to the IA Form, worksheet and site specific worksheet</i></p> <p><i>*Date of the signature on UNC worksheet or IA form is within 2 weeks of study interpretation.</i></p>

<i>Form</i>	<i>Source Documentation</i>
<p><i>ID Form</i> <i>Digital Interpretation</i></p>	<ul style="list-style-type: none"> • <i>UNC Worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> • <i>Site-specific worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> • <i>IA Form¹</i> <ul style="list-style-type: none"> ○ <i>Direct entry of information obtained directly from the study images</i> ○ Radiologist's <i>digitized signature³ and date*</i> • <i>Clinical mammography report if dictated on the digital imaging.</i> <p><i>*Date of the signature on UNC worksheet or ID form is within 2 weeks of study interpretation.</i></p>
<p><i>IM Form –</i> <i>Additional Work-up/ Prior Films</i></p>	<ul style="list-style-type: none"> • <i>UNC Worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> • <i>Site-specific worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> • <i>IM Form¹</i> <ul style="list-style-type: none"> ○ <i>Direct entry of information obtained directly from the study images</i> ○ Radiologist's <i>digitized signature² and date</i> <p style="text-align: center;"><i>AND</i></p> • <i>All applicable clinical reports, e.g., Biopsy, surgical, imaging reports.</i> <p><i>*Date of the signature on UNC worksheet or IM form is within 2 weeks of study interpretation.</i></p>
<p><i>BX Form –Biopsy Procedure</i></p>	<ul style="list-style-type: none"> • <i>Copy of Biopsy procedure report in Participant Research file.</i>
<p><i>PI Pathology Report</i></p>	<ul style="list-style-type: none"> • <i>Copy of pathology report in Participant Research file.</i>

<i>Form</i>	<i>Source Documentation</i>
<p><i>F1 Form</i> <i>Breast Cancer Status Follow-up</i></p>	<ul style="list-style-type: none"> • <i>Site-specific Worksheet</i> <ul style="list-style-type: none"> ○ <i>Signed and dated</i> by the RA <p style="text-align: center;"><i>OR</i></p> <ul style="list-style-type: none"> • <i>F1 Form¹</i> <ul style="list-style-type: none"> ○ <i>Direct entry of information obtained directly from participant through interview</i> <ul style="list-style-type: none"> ▪ <i>RA's digitized signature² and date</i> ▪ <i>Documented notation stating the source of information and the method, e.g., participant interview</i> <p style="text-align: center;"><i>OR</i></p> <ul style="list-style-type: none"> ○ <i>Printed F1 form signed and dated by RA</i> <p style="text-align: center;"><i>AND</i></p> <ul style="list-style-type: none"> • <i>Imaging reports, pathology reports, operative reports and progress notes as applicable.</i>
<p><i>IE Form – Follow-up</i> <i>Mammography Interpretation (at 3 months and 6 months; 1 year only if participant has BI-RADS 3, 4, or 5 at 1-year follow-up)</i></p>	<ul style="list-style-type: none"> • <i>UNC Worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> <ul style="list-style-type: none"> • <i>Site-specific worksheet (completed by Radiologist)</i> <ul style="list-style-type: none"> ○ <i>Signed and dated*</i> by the Radiologist <p style="text-align: center;"><i>OR</i></p> <ul style="list-style-type: none"> • <i>IE Form</i> <ul style="list-style-type: none"> ○ <i>Direct entry of information obtained directly from the study images</i> ○ <i>Radiologist's digitized signature² and date</i> <ul style="list-style-type: none"> • <i>Prose Report is required in addition to the IE Form, worksheet and site-specific worksheet.</i> <p style="text-align: center;"><i>*Date of the signature on UNC worksheet or IE form is within 2 weeks of study interpretation.</i></p> <p style="text-align: center;"><i>Prose Report</i></p>
<p><i>QP Form-EQ-5D and STAI Y-6</i> <i>(participant self administered)</i></p>	<ul style="list-style-type: none"> • <i>Copy in Participant study Research file signed and dated by the participant for the first 42 cases at each site.</i>

<i>Form</i>	<i>Source Documentation</i>
<i>QL Form (EQ-5D and STAI Y-6) telephone base</i>	<ul style="list-style-type: none"> • <i>Maintained on file at UNC</i>
<i>QF Form (EQ-5D, STAI Y-6 and PQ) 12 month telephone contact</i>	<ul style="list-style-type: none"> • <i>Maintained on file at UNC</i>
<i>Quality of Life Selection Screen</i>	<ul style="list-style-type: none"> • <i>Faxed UNC Contact form for positive and control participants</i> • <i>File copy in participant’s study file</i>
<i>Patient Non-Participation Form</i>	<ul style="list-style-type: none"> • <i>Copy in Participant Research file, signed and dated, by Research Associate. All applicable notes in and/or e-mails should be filed in the participant’s study chart.</i> • <i>RA must clearly document the reason a participant refuses to continue in the study e.g., technical difficulties, scheduling conflicts, withdrawn consent, etc.</i>

- i. *Prior to the enrollment of any participant onto the trial at a participating site, each site will be visited by a site trainer, a Headquarters Imaging Staff, and a physicist to determine that the site is in compliance with all protocol requirements. A participating site may not enroll participants to the D-MIST until the site has been visited and approved by the initiation visitors.*

Appendix VI

An address has been added:

DMIST QC Core:

DMISTQC@sten.sunnybrook.utoronto.ca

Fax: 416-480-6719

B. Joseph has been added to the committee.

Appendix VI, Table I

A footnote has been added to Table 1 in the Phantom Image Quality row after the word “daily.” The footnote at the bottom of the chart reads, “*This test is to be performed daily, but only one phantom image each week, normally acquired on the same day each week, is to be submitted to the ACRIN DMIST QC ftp site for each digital mammography system used in DMIST.”