Advanced MR Imaging Manual

Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy versus Conventional Photon Irradiation with Concomitant and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma

Protocol: NRG BN001

SPONSOR:
National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP)
NRG Oncology

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Table of Contents

Letter of Introduction

Dear BN001 Imaging Staff:

Thank you for your interest in participating in the advanced imaging component of the NRG BN001 clinical trial.

To successfully meet the study objectives for advanced imaging and ensure study success, it is critical that perfusion datasets and DWI image datasets are acquired in accordance with the steps setout in the imaging protocol, (detailed in this manual) and that these datasets are promptly submitted using TRIAD software.

Quality Control (QC) review of the images will be overseen by the Imaging and Radiation Oncology Core Laboratory at the Philadelphia based ACR Clinical Research Center.

To participate in this study, an institution must first submit test imaging as described in the manual. Obtaining test imaging is straightforward and designed to ensure quality control.

Following successful approval of your test imaging submission your parent institution will be eligible for participation and you will be able to consent subjects for the advanced imaging protocol.

Please note that approval of test imaging by QC is mandatory and approval must be obtained prior to registration of any study subjects on the advanced imaging component of the protocol.

Please do not hesitate to contact us if you have any questions regarding qualification and imaging acquisition and submission.

We look forward to working with you.

Best Regards,

Lisa Cimino-lcimino@acr.org
Jim Gimpel-jgimpel@acr.org

IROC Diagnostic Imaging Core Laboratory
American College of Radiology, Philadelphia, PA
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History of Revisions

Version	Version Date	Author	Section	Change
1.0	02JUN2015	L. Cimino J. Gimpel	N/A	Final version of document
2.0	05JAN2016	L.Cimno	3.0/4.0	DWI protocol, qualification submission

Abbreviations and Acronyms

IROC	Imaging and Radiation Oncology Core Group
MRI	Magnetic Resonance Imaging
DWI	Diffusion Weighted Imaging
DSC	Dynamic Susceptibility Contrast
aMR	Advanced Magnetic Resonance
MR	Magnetic Resonance
ITW	Imaging Transmittal Worksheet
ACR	American College of Radiology
QUIC	Quality Utility for Imaging Core Laboratory

Imaging Timeline Study Schema

Imaging Timepoints (timepoints in red include advanced imaging):
(See Figure 1 below)

1. **Diagnosis**
2. **<72 hr post surgery**
3. ***Prior to start of chemo-RT****
4. ***Wk.3 mid-point during Chemo-RT* - (Additional timepoint)***
5. ***Pre-Cycle 1 adjuvant therapy***
6. ***Pre-Cycle 4 adjuvant therapy***

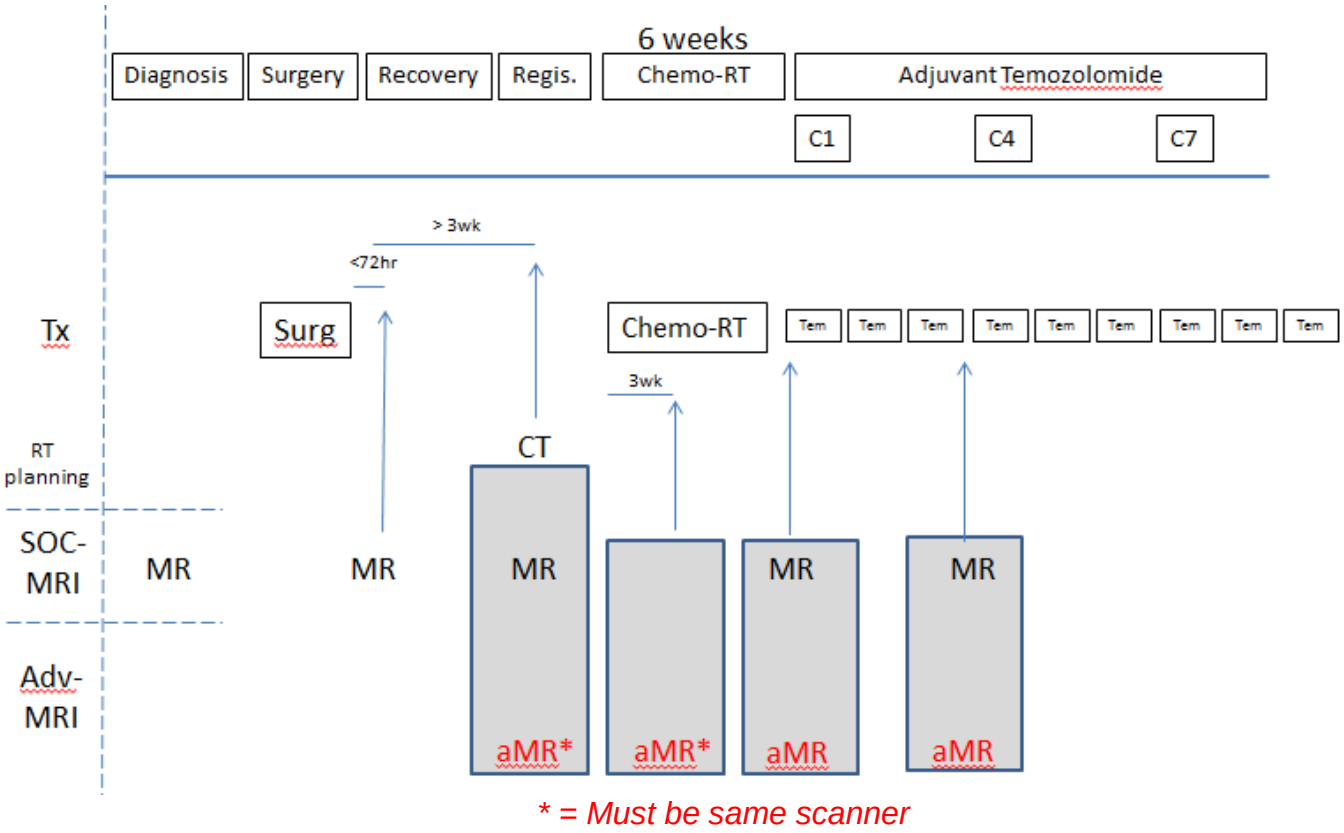

Figure 1

aMR= Advanced MR imaging to include protocol specific DWI, DSC perfusion series on the qualified scanner

- Advanced MR scans **obtained prior to the start of chemo-RT and Wk**.3 during chemo-radiation are to be performed on the *same magnet*.

- The remaining advanced MR scans obtained following chemo-radiation should be performed at the same magnet strength and vendor machine if at all possible.

Overview of Imaging Requirements

DSC-MRI and DWI Qualification	Submit prior to site activation (for each scanner): • Submission of DSC-MRI dataset, and • Phantom-based DWI and in vivo DWI datasets (Both acquired per the BN001 Advanced Imaging protocol, Appendix VIII of the BN001 Protocol and latest version of this manual) **If your site is unable to submit in vivo DWI &DSC, please contact the Imaging Core lab in section 8 of this Imaging Manual.
TRIAD version 4.x Installation	Installed prior to enrollment (https://cr-triad4.acr.org/TRIADWeb)
Time Points for Trial Examinations	DSC perfusion MRI and DWI per protocol as shown in this imaging manual: 1. **Prior to start of chemo-RT** 2. **Wk. 3 midpoint during chemo**/RT 3. Pre Cycle 1 of adjuvant Temozolomide 4. Pre Cycle 4 of adjuvant Temozolomide See Imaging Timeline Schema in Figure 1
Image Submission	BN001 advanced MR imaging timepoints should be submitted electronically to the ACR Imaging Core Lab via TRIAD **within 48 hours** after acquisition and should include an Image Transmittal Worksheet (ITW).
Data Queries	ACRIN will issue queries, as needed, based on QC review of imaging.
Rescanning With Phantom for Maintenance	The qualification DWI phantom must be rescanned and images uploaded via TRIAD every six months. In addition, the DWI phantom must be rescanned prior to any subsequent participant scan if there are any substantive changes in scanner hardware or software during the trial.

1.0 SCANNER QUALIFICATION

Approval of the test imaging submission is mandatory prior to enrolling subjects onto the BN001 advanced imaging sub-study.

Following successful completion of the qualification requirements, participating sites will receive official notification confirming that the test imaging submission on their MRI scanner has been approved by the IROC diagnostic imaging core lab.

Sites intending to use multiple scanners must have each scanner qualified prior enrollment.

Note, it is imperative that all subjects are imaged on the same scanner for the *initial two* time points (prior to start of chemo-RT and the Wk. 3 mid-point chemo-RT scan). It is preferable but not mandatory that subsequent scans be obtained on the same scanner.

For further information regarding qualification requirements and to obtain the required DWI phantom, please contact Lisa Cimino at lcimino@acr.org.

QUALIFICATION REQUIREMENTS:

For *each* scanner to be used for advanced imaging, sites are to submit the following series for qualification review:

- ❑ DWI imaging per protocol using DWI phantom) (Appendix I of this Manual)
- ❑ DWI imaging per protocol in vivo (Appendix I of this manual)
- ❑ First "preload" DSC perfusion series using ¼ standard dose contrast agent (approx. 3 minutes, per protocol)
- ❑ Second DSC perfusion series using ¾ standard dose contrast agent (approx. 3 minutes, per protocol)

See Appendix I of the Imaging Manual for detailed phantom instructions

DWI series performed on one representative in vivo case and the DWI phantom shall be submitted for qualification review with the associated ADC maps as described in Appendix I of this manual. DSC imaging performed on one representative case shall also be submitted for qualification review.

**If for any reason, in vivo imaging cannot be performed for qualification imaging, contact the imaging core laboratory staff prior to submission for further instruction (see Section 8 of this manual).

2.0 SUBJECT CONSENT AND ENROLLMENT

At time of patient enrollment, qualified imaging sites will have the ability to answer yes to the prompt “Is the patient participating in the advanced imaging sub study?” on the A0 registration mechanism.

Patients consented to participate in the advanced imaging sub study will obtain an additional MR imaging scan at Wk. 3 mid-point during chemo-RT. This will post an additional submission form in iMedidata Rave.

3.0 Advanced MR IMAGING PROTOCOL

Advanced MR imaging scans will be obtained prior to the start of chemo-RT and at subsequent follow-up time points at designated, pre-approved sites on subjects identified and enrolled into the advanced imaging substudy.

Advanced MR imaging scans obtained at (1) prior to the start of chemo-RT treatment and (2) Wk 3 mid-point during chemo-RT MRI scans will be performed on the same magnet.

Advanced MR scans obtained following chemo-radiation should be performed on the same scanner or at the same magnet strength and vendor machine if at all possible.

Diffusion MRI Protocol

Recommended parameter ranges:

Pulse Sequence	Single-Shot Spin-Echo EPI
Plane	Axial
FOV	240mm
TR	>5000
TE	min
Slice thickness	<4mm
Gap	0
Acquisition Matrix	128x128-192x192
Acquired In-plane resolution	<1.87mm
NSA	>1
Parallel Acceleration Factor	2
b value factors	0,500,1000sec/mm on 3 orthogonal axes

Some scanners automatically apply (“in-line”) spatial registration of DW images for improved quality. Typically, registered DWI are stored in a separate series from the original non registered image series. If your system performs in-line image registration, please upload both the original and registered image series via TRIAD.

Dynamic Susceptibility Contrast (DSC) MRI Protocol

Description

Leakage of Gd contrast into the interstitial space alters DSC signals and adversely affects perfusion values. A “pre-load” (first DSC scan) of at least 5cc of Gd contrast delivered approximately three minutes before the second DSC scan will greatly mitigate this effect.

This pre-load followed by DSC can be accomplished by acquisition of two identical DSC-MRI scans where one-quarter (¼) standard dose of Gd contrast agent is delivered for the first DSC scan followed by the remaining three-quarter (¾) standard dose of Gd contrast agent administered for the second DSC scan, and the start of the two DSC scans are approximately three minutes apart.

Total Gd contrast dose is calculated by body weight. For example, a FULL body-weight dose of 0.1mmol/kg = 0.2cc/kg is 20cc of contrast for a 100kg patient, where 5cc of Gd contrast is administered for the first DSC scan followed by 15cc of Gd contrast for the second DSCscan.

General technique

The single shot EPI sequence should be set up to collect 80 or more time points with a TR between 1.3 and 1.7 seconds. A multiphase single shot GRE-EPI is recommended with echo time (TE) between 30 to 40 milliseconds to achieve adequate sensitivity to susceptibility contrast.

Specific DSC-MRI acquisition

- Start the first DSC-MRI sequence to obtain near full-brain coverage at least encompassing the full tumor volume.

- After collecting 20 baseline points, inject the bolus of contrast agent using one-fourthof the standard dose of 0.1 mmol/kg (up to 10cc) at a rate of $\geq$2 cc/sec rate followed by 15cc flush

- Continue collecting the data so that at least 60 more time-points are collected per slice.

- At the conclusion of the first DSC series, repeat the series using with the remaining three-fourths of the standard dose of gadolinium agent.

Recommended Perfusion-Weighted Imaging Parameters

Pulse Sequence	2D EPI
Plane	Axial
TR	1.3 – 1.7 sec
TE(ms)	30-40
Repetitions	80-120
Flip Angle	60°
FOV	220-240mm
PFOV	100%
Sl. Thickness	4-6mm
Gap	0 to 2.5mm
Matrix	128x128
Phase Direction:	A-P

4.0 IMAGING SUBMISSION AND QUALITY CONTROL

Scanner Qualification Images must be submitted to the imaging core lab via QUIC (Qualification Utility for Imaging Core Laboratory). QUIC is a web based tool that provides an efficient means for submitting and managing MR/CT/PET scanner qualification process and communicating with core lab staff.

After completing the registration for access to the QUIC website (https://quic.acr.org/), site personnel can complete the online MR application, upload images track and review progress, and receive timely updates. Information about a MR scanner's qualification expiration is also available to help site plan ahead for requalification.

To download the QUIC User Guide visit:
https://quic.acr.org/Pages/UserGuide.aspx

Clinical Trial Submission via TRIAD v.4

- . Complete information regarding installation and account generation for TRIAD is available at http://triadhelp.acr.org/Home.aspx.

Clinical trial subjects will be submitted using the submission type of "Clinical Trial". In addition to the imaging submission, an Imaging Transmittal Worksheet (ITW) is to be completed in iMedidata Rave at the time of submission.

8.0 SUPPORT

For questions related to MRI imaging and advanced imaging submission, please contact:

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For questions related to ACR TRIAD software, log on to:

http://triadhelp.acr.org/TechSupport.aspx

BN001 Advanced Imaging Manual
Appendix I

ICEWATER DWI PHANTOM PREPARATION AND SCAN INSTRUCTIONS

Objective:
Measure apparent diffusion coefficient (ADC) values of a known temperature-controlled fluid to confirm proper MRI system performance in acquisition of diffusion weighted (DW) images of the brain.

DWI Ice water Phantom Preparation Procedure:

> ***Please plan on filling the phantom with ice water well in advance of scanning. Once prepared, an icewater phantom requires approximately 1hour to reach thermal equilibrium. Once at equilibrium, the phantom will be usable for several hours. Keep the foam insulation sleeve and plastic bag shipped with the phantom for future use.***

1) The phantom consists of a 3.8 liter plastic container with a single 175ml measurement tube pre-filled with distilled water. The tube is held in place by foam rings mounted to the top and bottom of the phantom. The tube itself is not cemented in place and can be removed to add water if there is a large air bubble (>4cc) in the tube. (Refer to Figure 4 for tube re-fill instructions). For phantom preparation, temporarily remove the container from the foam insulation sleeve and plastic bag.
2) You will need a source of ice cubes or ice chips and a sink basin for phantom filling. The volume of ice cubes/chips required is approximately twice the volume of the phantom. Hold the measurement tube centered and seated in the phantom, and fill the phantom to the top with ice cubes/chips (Figure 1a). Add cold tap water and fill to the top (Figure 1b) – the colder the water, the better. Let the phantom sit for an "initial cool down period" of approximately 10 minutes.
3) Depending on how cold your tap water is, much of the ice will melt relatively quickly. After the initial 10 minute cool-down period, pack-in as much ice as possible to replace the melted ice. Fill ice to the top allowing displaced water to overflow into the sink. The objective is to have ice cubes/chips the full depth of the phantom and the interstitial space filled with water and minimal air (Figure 1c and Figure 3a). Screw cap on tightly, dry off the phantom and inspect for leaks. MAKE SURE PHANTOM IS NOT LEAKING BEFORE PLACING INTO THE SCANNER.
4) Put the phantom in the foam insulation sleeve with the container top toward the open end of the sleeve (Figure 2a), add the foam cap and put all in the plastic bag (Figure 2b). The plastic bag will keep condensate off of MRI components. **Set the phantom aside for an additional 50 minutes to allow the central tube to come to thermal equilibrium with the surrounding icewater.** As long as there is adequate ice in the phantom, temperature will be controlled to near 0^{o}C thereby holding water within the tube at a known diffusion coefficient of $1.1x10^{-3}mm^{2}/s$. The phantom should be usable for several hours (~3-4hrs) if kept within the insulation sleeve. If desired, you can store the phantom in a refrigerator (not a freezer) to extend the usable time (5-10hrs). MAKE SURE PHANTOM IS IN THE FOAM INSULATION SLEEVE AND THE PLASTIC BAG AND IS NOT LEAKING BEFORE PLACING IT INTO SCANNER!

5) After scanning, simply empty the icewater down the drain but leave the central tube filled and sealed for use at a later date by following the same procedure.

DWI Ice water Phantom Scan Procedure:
Position the DWI phantom in the head coil with measurement tube axis along superior/inferior direction and wedge in place with foam pads as shown in Figure 2c. Prop the cap end up slightly so that any air bubbles accumulate toward the cap (foot end). This phantom is primarily used for ADC quantitation and geometrical aspects of the phantom are imprecise, so exact positioning of the phantom is not crucial. Start a "New Patient/Exam" using "Head First, Supine" convention.

Overview of Series Required for DWI QC Phantom Scanning:

1) Three-plane scout/survey
2) Sagittal 3D T1wt spoiled gradient echo.
3) Axial 3-direction DWI using single-shot echo-planar-imaging (EPI) at b-values of 0, 500 and 1000 s/mm^2 using parameters detailed in Table 1.
4) "Copy-&-Paste" the DWI series and repeat the acquisition a **total of four times** in immediate succession so that four consecutive series are generated. Avoid changing scan prescription or scanner pre-scan/hardware settings between these four consecutive series.
5) Some scanners automatically apply ("in-line") spatial registration of DW images for improved quality. Typically, registered DWI are stored in a separate series from the original non registered image series. If your system performs in-line image registration, please upload both the original and registered image series into QUIC for ACR Image Core Lab analysis.

Details of Required Series:

1) Three-plane scout/survey: Use site-preferred sequence as this is only used for graphic prescription of subsequent series.
2) Sagittal 3D T1wt spoiled gradient echo, or equivalent to show "anatomy" of phantom (Figure 3a).

   FOV = 260mm (A/P phase) x 260mm (S/I frequency) at 256 x 256 matrix.

   Acquire sufficient quantity of 1-2mm thick slices to encompass full R/L width of the phantom (~170mm). TR=4-10ms, TE=min, flip angle 10^o, single average.
3) Axial 3-orthogonal direction DWI: Single spin-echo, diffusion-weighted, single-shot echo planar imaging (EPI) by parameter settings listed in Table 1. Total scan time for acquiring all four consecutive DWI data sets should be less than 15 min.

Table 1. DWI Icewater Phantom Scan Parameters				
Field Strength	1.5T or 3 T		DWI Sequence	Single-Shot SE EPI Single Echo
Receiver Coil	Head array		TR (ms)	≥6000
FOV (mm)	240RL x 240AP		TE (ms)	minimum
Acquisition Matrix	160RL x 160AP [(a)]		Half-scan, Partial-Fourier, Frac-NEX	No if avoidable [(a)]
Reconstruction Matrix	256 x 256 [(b)]		Number of Gradient Directions [(c)]	3 orthogonal axes
Orientation	Axial (Foldover Phase AP; Freq RL)		Freq Enc Bandwidth per Acq Pixel (Hz) [(d)]	1500 to 2500
Qty Slices	33		Parallel Imaging (eg. SENSE factor)	2
Slice Thickness (mm)	4		bvalues (s/mm^2) [(e)]	0, 500, 1000
Gap (mm)	0		# Signal Averages	2
Image Filtering (eg.SCIC or CLEAR)	Off		Fat Suppression [(f)]	On

a) Some systems may require “half-scan”, “partial-Fourier”, or “fractional-NEX” in DWI scans. It is preferred to acquire the full phase-encode matrix = 160 by setting half-scan/ partial-Fourier/Fractional-NEX to “No” or at least as close to 1 as possible.

b) Interpolate image matrix to 256 x 256. Some systems may do this automatically.

c) Acquire DWI along three orthogonal axes so that “isotropic” or “trace” diffusion weighted images are generated for each slice and b-value. Individual diffusion axes DW images are not required. Only the b=0 and DWI trace images at b-value of 1000 s/mm^2 are required.

d) Frequency encoding bandwidth may not be under full operator control. If possible use “maximum bandwidth”, or equivalently “minimum fat shift per pixel”, or set within 1500 to 2500 Hz/pixel range.

e) **Do not allow the system to adjust hardware settings between the 4 consecutive DWI series (i.e. hold transmit/receive gain constant).**

NOTE: THE PHANTOM PROTOCOL CALLS FOR FOUR ACQUISITIONS.

f) While the phantom does not contain a fat signal, still use site-preferred spectral fat suppression technique, such as “SPAIR”. However DO NOT USE the Inversion-Recovery fat suppression technique “STIR” for DWI Phantom scans.

ADC Map Generation:

Generate ADC maps for all slices using software tools available on the scanner for at least one of the four passes. If possible, make a “screenshot” of a region-of-interest (ROI) drawn in a

central tube region showing ROI size/location and resultant statistics (eg. Figure 3b is DWI, 3c illustrates ADC map with ROI statistics). The screenshot should be simply saved within the phantom examination as a DICOM image.

Figure 1 (a) (b) (c)

Figure 2 (a) (b) (c)

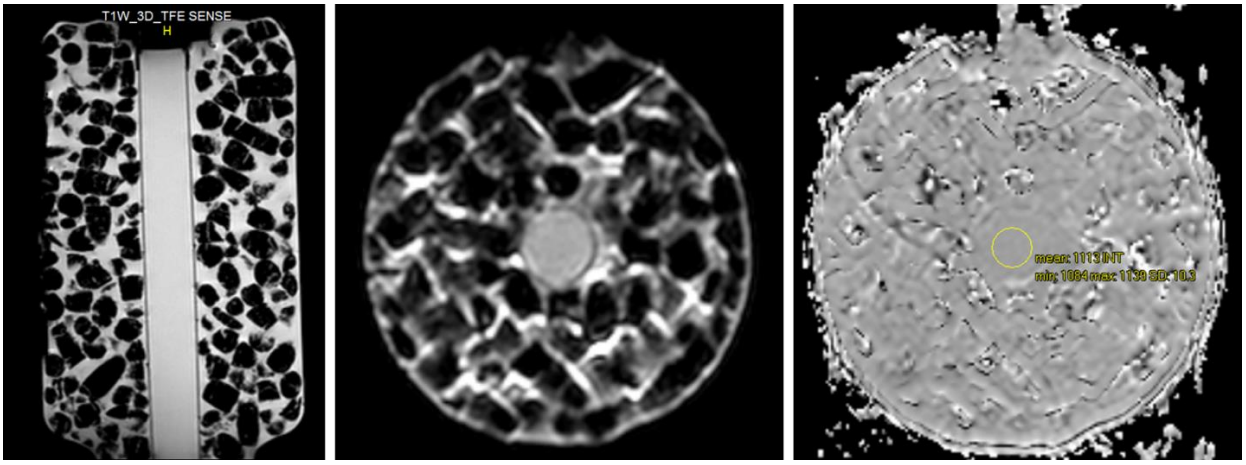

Figure 3 (a) (b) (c)

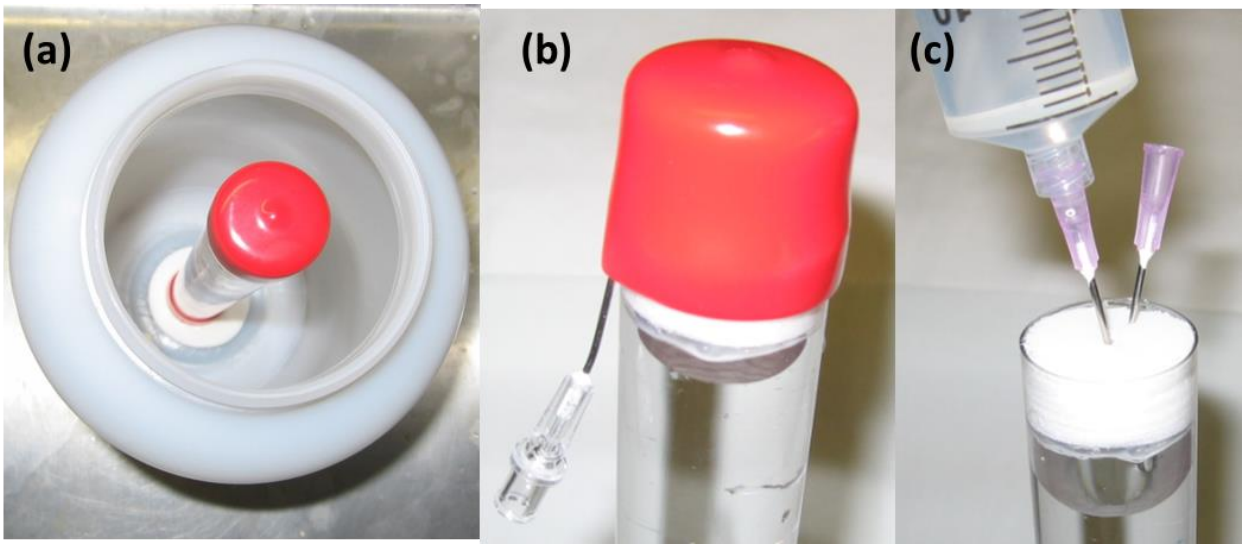

Figure 4: ***Method to replenish water in central tube only if there is a large (>4cc) air bubble***. (a) Remove tube from phantom. The tube is only held in place by friction in the foam rings. (b) Slide a needle (or toothpick) under rad cap to facilitate removing the red cap. (c) Inject water through foam plug while second needle allows air to escape. Slide a needle (or toothpick) under the rim of the red cap (as shown in (b)) as replace the red cap on the tube. Reseat tube into foam ring on the bottom of the phantom (as shown in (a)).

When finished scanning the phantom, upload the images for QC review using provided upload instructions.