I. INTRODUCTION

Modality reviews, defined as central direct review (from various material sources) of information pertaining to the delivery of a treatment component (surgery, radiation therapy, systemic therapy including chemotherapy and hormones, biologics, targeted agents, etc.) remain a staple of NRG Oncology clinical trial conduct. These reviews serve multiple purposes, from confirmation of delivery quality and fidelity for assigned treatment to assurance that newly introduced treatment regimens and their constituent components can be delivered safely and effectively across institutional settings in a multicenter trial. Reviews are part of the NRG Oncology quality assurance program and have historically also provided measures of institutional performance, supplementing information from audits and other oversight processes.

To ensure support for this time-intensive activity across all NRG trials, the following guidance is provided for specification of the review plan. For a specific clinical trial, a broad outline of the specification is as follows:

1) The investigators identify the appropriate level of review according to the categories defined. Note that there is flexibility in review options, provided that justification is provided, as well as commitment to complete the reviews.
2) In conjunction with protocol development, develop the modality review plan for the trial. The protocol statistician and others will contribute to the design of any sampling plan to be implemented. In the protocol, only high-level information will be provided, with reference to the modality review document for details.
3) Establish the review schedule and participating investigator personnel. Note that during the review process, the plan may be adaptably revised to reflect findings or meet other review needs that may arise.

II. MANAGEMENT & ENFORCEMENT

This policy describes for each treatment modality, the levels of review required to assure proper oversight of study conduct. The levels include none, a sampling of cases, or all cases. The number of cases to review and the frequency of these reviews will be based on the number of patients to be accrued to the study, study complexity and number of reviewers. The Therapy Modality Review Plan is a fillable form and is provided with this policy for determining the level(s) for quality assurance reviews.

It is important that quality reviews are consistently done in a timely fashion. It is the responsibility of the assigned modality chair(s) to perform the reviews and not delegate them to someone else, unless approved by NRG Oncology.

Failure to complete quality reviews as defined in the therapy modality review plan will result in warnings, potential transfer of responsibilities, delay the publication of the study results and will result in loss of authorship privileges for the study publications.

Radiation Therapy Review

All studies utilizing radiation therapy will require a Radiation Oncologist Principal Investigator (PI), as a Co-PI of the trial. For trials undergoing radiation therapy review, it is the responsibility of these investigators to review the radiation therapy treatment on their trials in a **timely** fashion with particular attention to contouring and dose compliance so that pro-active interventions for the trial can be enacted, if necessary. Delinquency in completing reviews will result in warnings and potential transfer of PI/co-PI responsibilities to alternative investigators with loss of authorship.

Radiation oncology reviews will be conducted online utilizing a secure system. It is anticipated and appropriate that artificial intelligence (AI) tools may be used in radiation oncology reviews.

Level 0 – No Radiation Therapy in Trial:

- Radiation oncology reviews are not applicable.

Level 1 – All Radiation Therapy that utilizes only standard of care radiation delivery

- Radiation oncology reviews are not required but may be undertaken. Justification for and goals of the review should be documented
    - For example, standard treatment approaches such as 3D-CRT or standard IMRT may not warrant review.
    - For more recent radiation techniques, such as robustly planned proton treatments, reviews may still be warranted. Reviews may also be required at the direction of the National Cancer Institute.
- When radiation oncology reviews are to be conducted, review of all cases is not generally required, and a sampling plan will be devised to select cases for review. The specifics of the sampling plan will be devised during protocol development but not included in the protocol to allow for flexibility, as the number of cases that need to be sampled may be adapted based on review findings.

Level 2 – Phase II, II/III, and III Trials Where at Least One Component of Radiation Therapy is Not Standard of Care:

- Radiation oncology reviews will be conducted. AI-based tools and/or case sampling may be used in the review process. The review and sampling plan will be devised prior to trial initiation.
    - The specifics of the sampling will be developed during protocol development but not included in the protocol to allow for flexibility, as the number of cases that need to be sampled may decrease or increase based on the review results.
- If the trial is FDA registration-intent, consideration may be given to review of all cases, or may be required.
- Trials using novel approaches of radiation therapy delivery/modality may require pre-treatment reviews by the radiation oncologist PI.

Level 3 – Phase I and Any Safety Lead-in Portion of Trials with Radiation Therapy:

- Radiation oncology reviews will be conducted on all cases.
- Trials using novel approaches of radiation therapy delivery/modality may require pre-treatment reviews by the radiation oncologist PI.

Systemic Therapy Review

All studies utilizing systemic agents will require a medical oncology PI or co-PI. For trials undergoing systemic therapy review, it is the responsibility of these investigators to conduct planned reviews in a **timely** fashion, with particular attention to toxicity evaluation and management, so that pro-active interventions can be enacted if necessary. Delinquency will result in warnings and potential transfer of PI responsibilities to alternative investigators with loss of authorship. Reviews will be conducted online utilizing a secure system.

Level 0 – No Systemic Therapy in Trial:

- Systemic therapy reviews not applicable

Level 1 – All Systemic Therapy is Standard of Care Treatment:

- Systemic therapy reviews will not be required but may be undertaken. Justification for and goals of the review should be documented.
- If systemic therapy reviews will be conducted, the review does not need to be comprehensive (i.e., on all cases).
    - A sampling method may be used to select cases for review. Sampling should account for temporal, institutional, and other factors to meet review goals.
    - The sampling plan will be developed during protocol development, but not included in the protocol to allow for flexibility, as the number of cases that need to be sampled may decrease or increase based on the review results.

Level 2 – Phase II, II/III, and III Trials Where at Least One Component of Systemic Therapy is Not Standard of Care:

- Systemic therapy reviews will be conducted, but are not required to be comprehensive. A sampling method may be used to select cases for review. Sampling should account for temporal, institutional, and other factors to meet review goals.
- For FDA registration-intent trials, consideration may be given to comprehensive review. Details of the sampling will be developed during protocol development, but not included in the protocol to allow for flexibility, as the number of cases that need to be sampled may decrease or increase based on the review results.

Level 3 – Phase I and Any Safety Lead-in Portion of Trials with Systemic Therapy:

- Systemic therapy reviews will be conducted on all cases.

Surgery Review

All studies utilizing surgery as part of protocol therapy will require a surgical oncology PI or co-PI. For trials undergoing surgical therapy review, it is the responsibility of these investigators to conduct planned reviews in a **timely** fashion, with particular attention to adverse event evaluation and management so that pro-active interventions can be enacted if necessary. Delinquency of reviews will result in warnings and potential transfer of study PI responsibilities to alternative investigators with loss of authorship. Reviews will be conducted online utilizing a secure system.

Level 0 – Trials without surgical therapy

- Surgical reviews are not applicable.

Level 1 – Trials where surgery is not a focus of the primary or secondary treatment question

- Surgical reviews will not be required but may be undertaken. Justification for and goals of the review should be documented.
- If surgical reviews will be conducted, the review does not need to be comprehensive (i.e., on all cases). However, if determination of specific surgical variable information is required for analysis, review of all cases may be required to obtain this information. Additional considerations:
    - A sampling method may be used to select cases for review. Sampling should account for temporal, institutional, and other factors to meet review goals.
    - The sampling plan will be developed during protocol development, but not included in the protocol to allow for flexibility, as the number of cases that need to be sampled may decrease or increase based on the review results.
    - If the trial is FDA registration-intent, consideration may be given to reviewing all cases.
- Surgical reviews may be required for pre-study entry surgical procedures when certain requirements must be met (e.g., margin status, nodal status, size of tumor and/or gross tumor status at end of procedure), as these may have impact on trial endpoints.

Level 2 – Phase II, II/III and III trials where surgery is a focus of the primary or secondary treatment question

- Detailed surgical reviews generally will be performed on all cases. However, there are some additional considerations that may apply:
    - Sampling may still be adopted for surgical procedures that are considered standard of care.
    - As indicated above, if key variables related to outcomes are obtained via review of surgical outcome, then comprehensive review will be required.

Level 3- Phase I trials and any safety lead-in that includes surgery

- Surgical reviews will be conducted on all cases

NRG Oncology Therapy Modality Review Plan

Protocol: _____

Reviewer Name: _____

All Phases for NRG protocols will be subjected to standard quality assurance and quality control measures such as CRF edits, DMC review and site visit audits. The additional therapy modality reviews specified below will be implemented as part of the central quality assurance reviews:

Modality	Level 0	Level I	Level II	Level III	Comments
Systemic Therapy	No Systemic Review ☐	Choose an item. ☐	Choose an item. ☐	Choose an item. ☐	
Surgery	No Surgical Review ☐	Choose an item. ☐	Choose an item. ☐	Choose an item. ☐	
Radiation Therapy (RT)	No RT on Trial ☐	Choose an item. ☐	Choose an item. ☐	Choose an item. ☐	

If you select other, please specify:

Signatures: _____ Date: Click here to enter a date.
Choose an item. Signatures: _____ Date: Click here to enter a date.
Choose an item. Signatures: _____ Date: Click here to enter a date.

The plan must have sign-off approval by the Protocol Chair, Protocol Statistician, and Director of Quality Assurance.

Systemic Therapy Review (omit if Level 0)

Justification for Review Level

(Brief, or more extensive as needed)

Review Elements/Details

(Sketch out scope here. Could be boilerplate text for many trials)

Review Case Sampling Plan

(Would either describe plan or indicate comprehensive review)

Review Participants and Timeline

Surgical Therapy Review (omit if Level 0)

Justification for Review Level

Review Elements/Details

Review Case Sampling Plan

Review Participants and Timeline

Radiation Therapy Review (omit if Level 0)

Justification for Review Level

Review Elements/Details

Review Case Sampling Plan

Review Participants and Timeline