A Novel Pilot Study of Online Proton Adaptive RadioTherapY (PARTy) Utilizing Computed Tomography On Rails

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Protocol Revision History

Initial Approval Version	**19 March 2024**
Amendment #1 Version	**06 January 2025**
Amendment #2 Version	**10 July 2025**
Amendment #3 Version	**12 September 2025**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following ethical guidelines and regulations:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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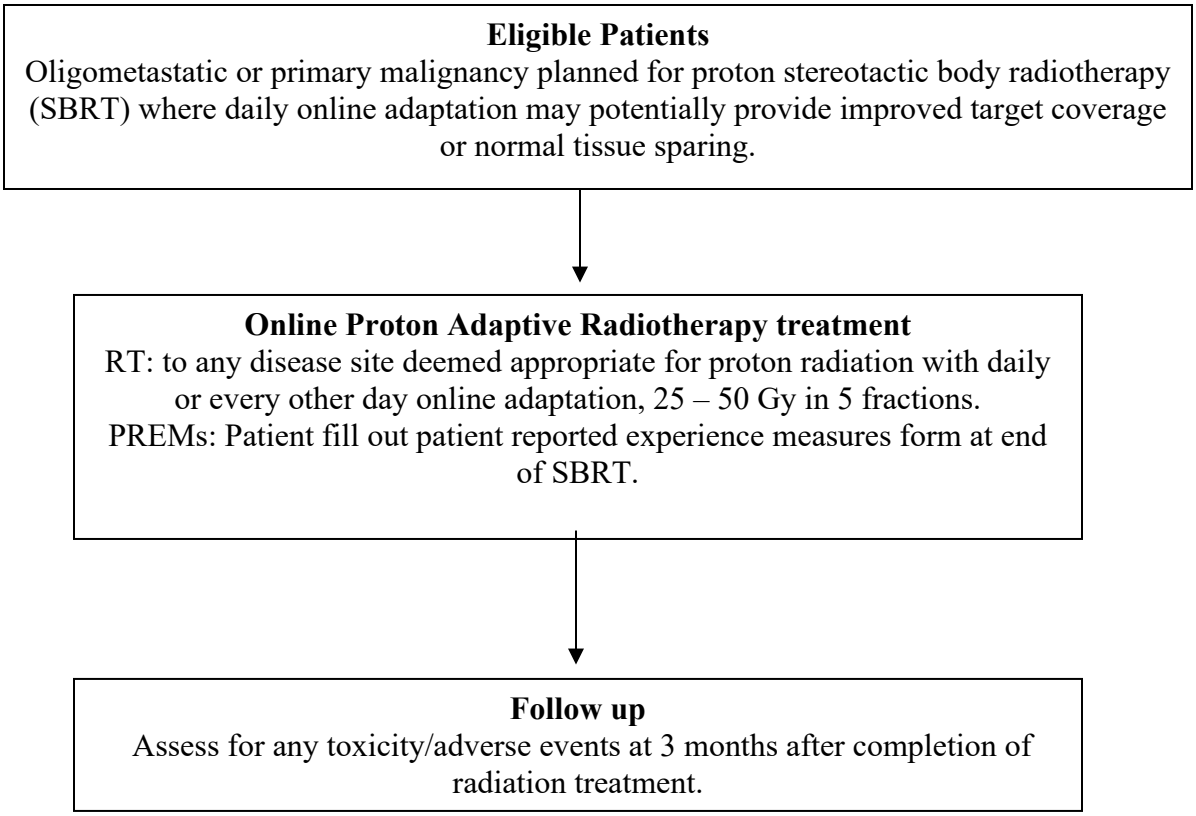
PROTOCOL SUMMARY

Title:	A Novel Pilot Study of Online Proton Adaptive RadioTherapY (PARTy) Utilizing Computed Tomography On Rails
Study Description:	This pilot study aims to evaluate the feasibility of daily online adaptive planning for patients undergoing proton radiation therapy.
Objectives:	Primary Objective: To assess the feasibility of online proton adaptive radiotherapy based on successful deliver of more than 70% of attempted fractions where treatment adaptation is indicated. Secondary Objective: 1. To assess the safety of online proton adaptive radiotherapy. Exploratory Objectives: 1. To assess patient tolerability and satisfaction with online proton adaptive radiotherapy process. 2. To assess dosimetric differences for target coverage and organ at risk (OAR) sparing between adaptive and non-adaptive proton therapy.
Endpoints:	Primary Endpoint: Successful completion of online adaptive proton radiotherapy workflow through treatment delivery in at least 70% of planned adaptive fractions. Success will be defined as PARTy plan creation and delivery of the fraction using the study workflow in one on-table attempt. Unsuccessful planning and workflow delivery will be defined as multiple attempts of the PARTy workflow for one treatment fraction without treatment delivery such that the study workflow is abandoned. Secondary Endpoint: 1. Grade 2+ radiation-related toxicity at 3 months as measured by CTCAE v5.0 Exploratory Endpoints: 1. Patient reported experience measures (PREMs). 2. Dosimetry evaluation and comparison to non-adapted proton pre-plan.
Study Population:	The study plans to enroll 10 evaluable adult patients with any solid tumor (excluding small cell histology).

Phase:	Not Applicable
Description of Sites / Facilities Enrolling:	Patients will be treated at a single facility, at the S. Lee Kling Proton Therapy Center, as the technology required for this study is confined to this center.
Description of Study Intervention:	Patients planning to receive standard of care proton therapy will be consented to the study. After study enrollment, at time of each daily or every other day fraction, patients will undergo online evaluation for proton replanning based on prespecified dosimetric objectives of improving tumor coverage and/or normal organ at risk sparing.
Study Duration:	12 months accrual + 3.5 months for patient treatment and follow-up + 3 months analysis = 18.5 months
Participant Duration:	1 to 2 weeks of treatment + 3 months follow-up = 3.5 months

SCHEMA


Eligible Patients
Oligometastatic or primary malignancy planned for proton stereotactic body radiotherapy (SBRT) where daily online adaptation may potentially provide improved target coverage or normal tissue sparing.
Online Proton Adaptive Radiotherapy treatment
RT: to any disease site deemed appropriate for proton radiation with daily or every other day online adaptation, 25 – 50 Gy in 5 fractions.
PREMs: Patient fill out patient reported experience measures form at end of SBRT.
Follow up
Assess for any toxicity/adverse events at 3 months after completion of radiation treatment.

SCHEDULE OF ACTIVITIES

Screening assessments should occur within 4 weeks prior to the start of SBRT unless otherwise noted. The window for the 3 mos post-Tx visit is +/-4 weeks.

Daily SBRT Schedule							
	Screening	**D1**	**D2**	**D3**	**D4**	**D5**	**3 mos post-Tx**
Informed consent	X						
Medical history	X						
H&P	X						X
Volumetric imaging[1]	X						
Pregnancy test[2]	X						
Diagnostic scan based preplan[3]	X						
Adaptive proton SBRT		X	X	X	X	X	
Patient Reported Experience Measures						X[4]	
Adverse events assessment		X----------					----------X

[1] CT, MRI, or PET are acceptable as per routine clinical evaluation at the discretion of the treating physician.
[2] Women of childbearing potential only; within 14 days prior to the start of treatment.
[3] Initial radiation treatment plan based on standard CT simulation.
[4] Questionnaire of patients' experience with adaptive workflow, given at the end of the last treatment (window +7 days).

Every Other Day SBRT Schedule[5]							
	Screening	**D1**	**D3**	**D5**	**D7**	**D9**	**3 mos post-Tx**
Informed consent	X						
Medical history	X						
H&P	X						X
Volumetric imaging[1]	X						
Pregnancy test[2]	X						
Diagnostic scan based preplan[3]	X						
Adaptive proton SBRT		X	X	X	X	X	
Patient Reported Experience Measures						X[4]	
Adverse events assessment		X----------					----------X

[1] CT, MRI, or PET are acceptable as per routine clinical evaluation at the discretion of the treating physician.
[2] Women of childbearing potential only; within 14 days prior to the start of treatment.
[3] Initial radiation treatment plan based on standard CT simulation.
[4] Questionnaire of patients' experience with adaptive workflow, given at the end of the last treatment.
[5] RT will not be administered on a weekend; a 2 day break in between fractions due to scheduling is acceptable (window +7 days).

1.0 BACKGROUND AND RATIONALE

1.1 Rationale for Proton Radiotherapy

While photon-based linear accelerators remain the primary method for modern radiation therapy, proton radiotherapy has emerged as an alternative approach with unique dose delivery characteristics.

Conventional photon radiotherapy is delivered using a linear accelerator (LINAC) that generate high energy X-rays or photons. A photon radiation beam deposits most of its energy as it enters the body and continues to release energy as it passes through tissue resulting in both entrance and exit radiation doses. The introduction of intensity modulation and inverse treatment planning has further minimized radiation exposure to surrounding healthy tissues by enabling modulation of the beam into separate beamlets to improve conformality.[1] Nonetheless, in most instances, there remains a residual low-dose radiation exposure to normal tissues.

Compared to photon radiation, proton therapy offers an advantage of minimizing radiation exposure to critical Organs at Risk (OARs). This is primarily attributed to the unique dose distribution of protons, allowing the dose to deposit most of their energy within the targeted volume and subsequently stop, limiting further radiation dose to healthy tissues beyond the target. As a result, proton therapy may offer superior sparing of OARs, reducing the potential for unnecessary radiation dosing to surrounding healthy organs.

This feature makes proton therapy particularly advantageous for cancer cases where minimizing radiation to critical OARs or lowering total integrated dose is paramount, such as in pediatric cancers and in reirradiation cases. As planning and access to proton therapy have become more widespread, its clinical benefit has been demonstrated to more diverse cancer sites, including cancers of the head and neck, esophagus, breast, and lung.[2–5]

1.2 Online Adaptive Radiation Therapy

Another potential method for further minimizing unnecessary radiation dose is through adaptive radiotherapy. Adaption in radiation therapy is the process of modifying a patient's treatment plan during the course of fractionated radiotherapy treatment to account for changes in patient anatomy, tumor size, or changes in setup in order to ensure the treatment plan remains effective and safe for the patient.

Adaptation for radiotherapy can occur either offline or online. Offline adaptive radiation therapy is a common practice for various cancer types, both in proton and photon therapy.[6] Typically, offline adaptation involves re-evaluation of treatment plans based on imaging and clinical factors during treatment. Offline adaptation is typically completed between treatment sessions with a revised treatment plan used for future sessions. Internally, we have been using offline adaptation in patients treated with proton therapy.[7]

Conversely, online adaptation occurs just before each treatment fraction is delivered, allowing for more immediate adjustments. Online adaptation is particularly advantageous

for abdominal malignancies as it enables precise alignment of the radiation plan with the target and allows for plan modifications based on daily bowel motion, which offers significant dosimetric benefits for patients with cancerous lesions in the abdominal region. This is achieved through daily high quality MRI or cone beam CT scan just before their daily treatment session. The original treatment plan contours, created during simulation, are then superimposed onto the most recent scans of the day. If any necessary adjustments to the target and organs at risk (OARs) are identified, they are incorporated into a modified plan, which is subsequently administered.

There have been numerous studies that affirm the effectiveness of online adaptive radiotherapy using CT and MRI guidance.[7–9] These studies have demonstrated good disease control with acceptable or improved toxicity profiles. These studies included patients treated for malignancies in the abdominal region for which adaptive radiation is particularly attractive due to the substantial changes in position between treatments for luminal gastrointestinal (GI) structures.[10,11] The integration of CT and MRI guidance for online adaptation has enabled the delivery of ablative radiation doses to abdominal malignancies by accounting for daily positional changes of target and nearby critical OARS. Online adaptation has also proven effective in the treatment of thoracic malignancies and breast cancers, allowing for tailored and precise radiation therapy to optimize treatment outcomes.

1.3 Limitations of Proton Dosimetry and Rationale for Online Adaptive Proton SBRT

Although proton therapy offers dosimetric advantage of highly conformal radiation and finite proton beam range, accounting for uncertainties in treatment delivery remains a significant challenge. Plan robustness for protons accounts for range uncertainty from poor CT calculation and insufficient heterogeneity correction, changes in patient anatomy, proton energy variations and relative biological effectiveness dose assumptions.[12] The result of these uncertainties can compound and lead to overdosing healthy tissue and under-treating the intended target.

In the context of treatment planning, margins are a common approach to account for uncertainties and increase the likelihood of adequately covering the target volume. However, applying margins in proton therapy presents challenges, primarily due to site-specific range uncertainties and range uncertainty variations across specific beam angles.

Another strategy to address uncertainties in proton dosimetry is robust optimization, which integrates uncertainty models into the treatment plan optimization process. This approach aims to strike a balance between ensuring target volume coverage while sparing OARs. However, establishing a precise and reliable uncertainty model to predict anatomical variations in proton treatment planning can be particularly challenging. Consequently, robust optimization alone may not always be sufficient to consistently deliver a dependable and accurate treatment plan.

Due to such challenges, there is an unmet need to explore online adaptation methods in proton radiotherapy. Even minor daily uncertainties can lead to significant dose deviations due to dose conformality and finite range of proton beams potentially resulting in inadequate target volume coverage and overdosing OARs.

The implementation of daily online adaptation and delivery of daily optimized treatment plans provides a means to combine the specific dosimetric advantages of proton therapy with adaptive radiotherapy. This approach enables a more precise and effective radiation dose to the tumor while effectively accommodating daily uncertainties. Consequently, it minimizes radiation exposure to healthy tissues, optimizing the therapeutic impact while concurrently reducing the potential for radiation-induced toxicity to nearby OARs.

1.4 Preliminary Studies

The following is a proposed workflow for online adaptive proton therapy. This workflow draws upon our institutional expertise in MR-guided and CT-guided online adaptive radiotherapy.

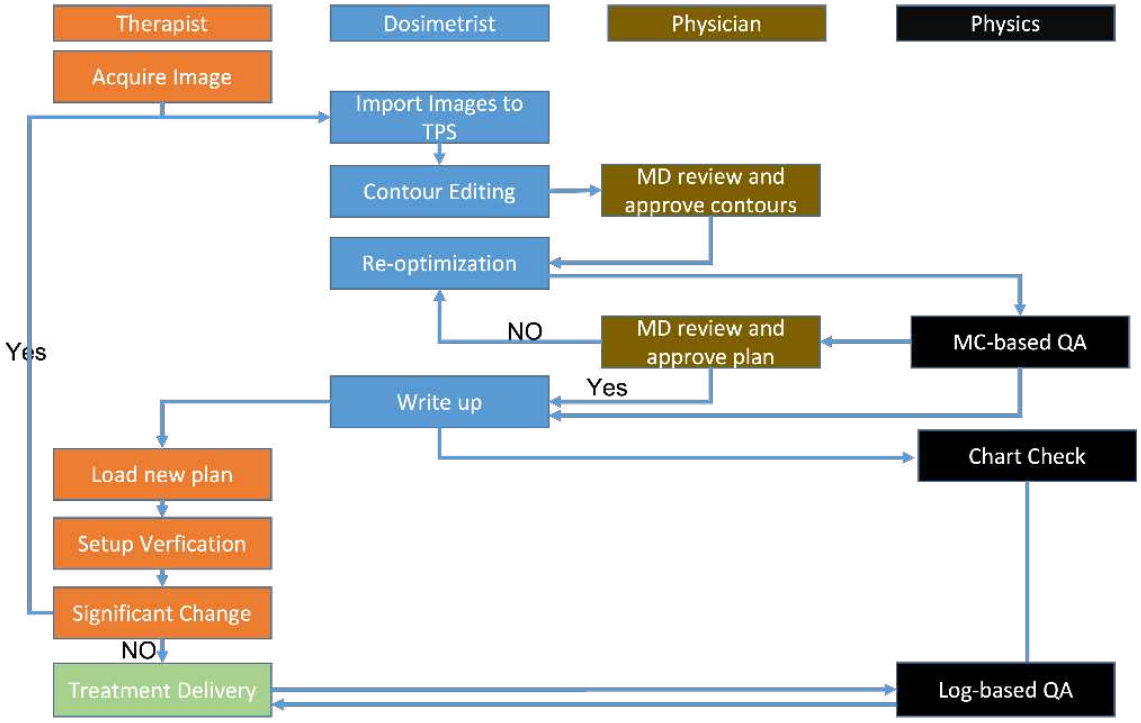


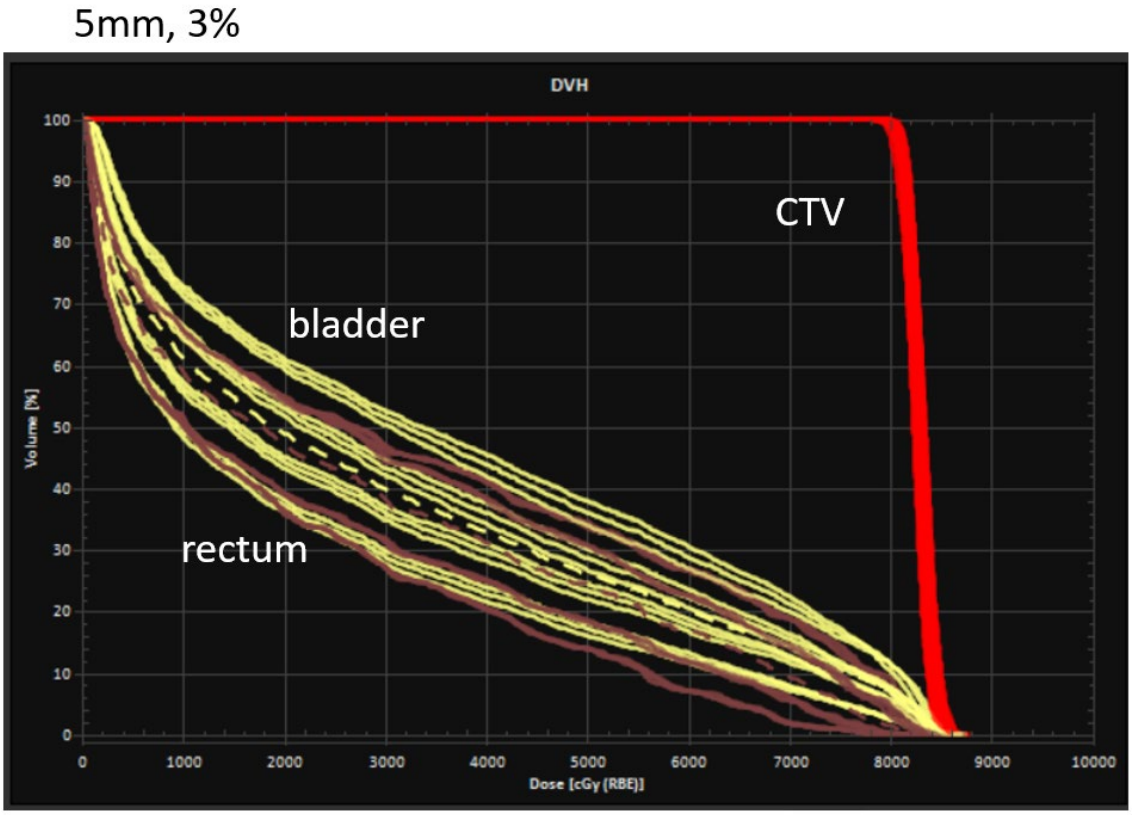
Fig. 1 Proposed online adaptive proton radiotherapy workflow

The process initiates with the daily acquisition of CT images using our in-room CT-on-rails system. These images are imported into RayStation, where adjustments to contours and volumes are made by our dosimetry team with an overseeing physician. A physician is present at the machine to review, approve these contours and adjust contours as needed. Subsequently, the plan undergoes reoptimization and passes through an in-house physics quality assurance (QA) algorithm. The physician then conducts a final review of the adapted plan and grants approval. A formal treatment plan is generated and loaded onto the

treatment machine. To ensure no significant setup changes have occurred during the adaptation process, an additional CT image is acquired.

Investigation into the technical and logistical feasibility of the proposed workflow has been performed through an in-silico analysis. This study utilized patients who underwent proton therapy for rectal cancer recurrence as part of the IMPARC clinical trial (NCT04827732). Specifically, eight patients with rectal or other pelvic malignancies, previously treated on a proton dose escalation trial over five fractions, routinely received daily CT-on-rails imaging prior to each fraction.

We determined that the average time required to complete the online adaptive process ranged from 33 to 45 minutes.[13] In typical proton planning, robust optimization and evaluation are employed, incorporating a 5mm setup uncertainty and a 3% proton range uncertainty for non-adaptive proton plans. However, for adaptive plans, we have the flexibility to eliminate setup uncertainty and optimize and evaluate with only a 3% proton range uncertainty, thereby reducing the dose to organs at risk (OAR) (figure 2).



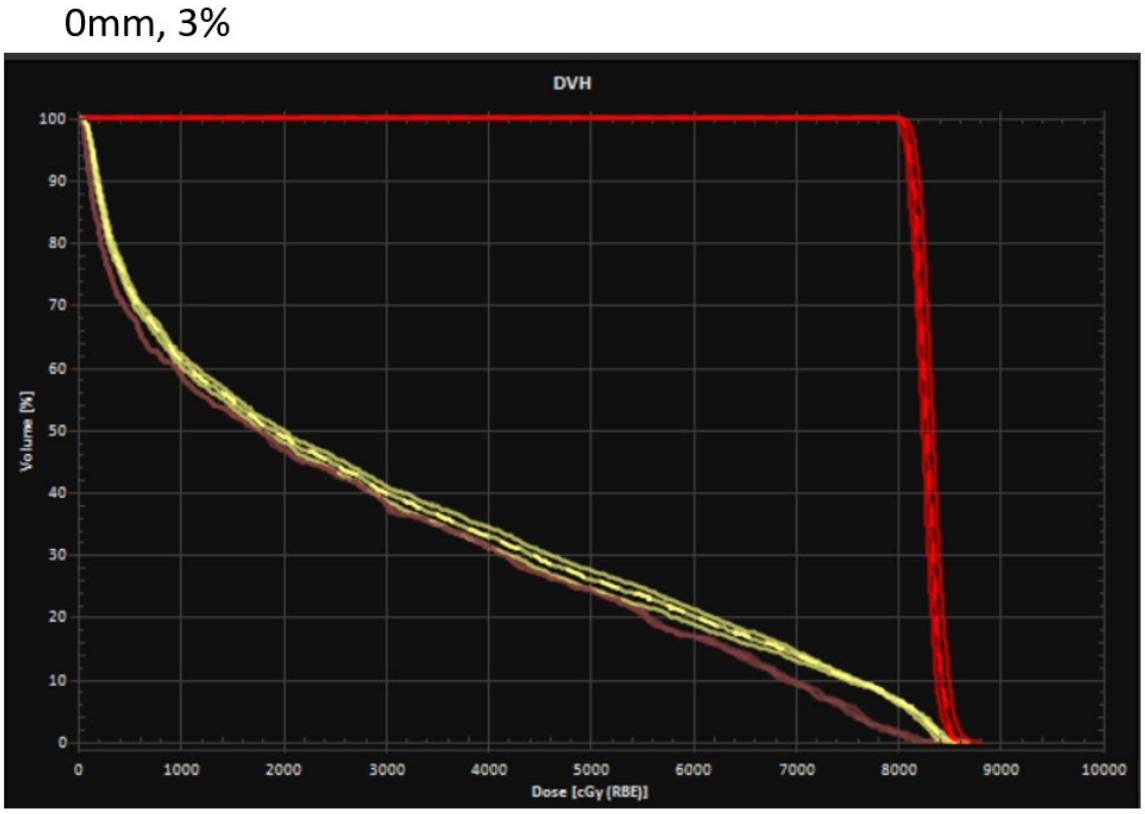


Fig 2. 5mm setup uncertainty and a 3% proton range uncertainty for non-adaptive plans vs 0mm setup uncertainty and 3% proton range uncertainty for adaptive plans

1.5 Study Rationale

Building upon our initial preliminary study and drawing from our institutional experience in online adaptation, as well as our capability to acquire high-quality CT scans while the patient is on the treatment table, the focus of this study is to demonstrate the feasibility of implementing this workflow for clinical use.

By using an online adaptation approach, we will combine the advantages of proton dosimetry while addressing the dosimetric challenges posed by proton therapy due to daily anatomical and tissue density variations. Establishing this workflow has the potential to enhance the effectiveness of proton therapy while simultaneously minimizing the adverse effects and radiation-related toxicity.

This study's objective is to demonstrate clinical feasibility and safety of the Proton Adaptive RadioTherapY (PARTy) workflow for patients who are suitable candidates for proton therapy and who could benefit from online adaptation based on anatomical considerations. We aim to demonstrate successful completion of the PARTy workflow in at least 70% of adaptive treatment fractions throughout the treatment delivery process.

1.6 Overall Design

This is a pilot study evaluating the feasibility of implementing an online adaptive workflow for patients undergoing treatment with proton radiotherapy.

1.6.1 Scientific Rationale for Study Design

The aim of this pilot study is to evaluate the feasibility of implementing an online adaptive workflow for patients receiving proton therapy in order to provide data for a larger evaluation of online adaptive proton therapy.

1.7 Risk/Benefit Assessment

1.7.1 Known Potential Risks

The medical risks from participating in this study revolve around exposure to proton radiation and increased time required per treatment to allow for day of plan adaptation. Treatment options for patients enrolled in this study include irradiating with online adaptive stereotactic body radiation treatments (SBRT) over 5 days every day or every other day to a dose of 25-50 Gy. All patients undergoing five fractions or fewer fractions with protons would be evaluated for eligibility for this study during a twice weekly proton triage meeting. Patients enrolled in this study would be deemed appropriate for non-adaptive proton SBRT by the treating radiation oncologist.

Adaptive radiation planning enables improved target coverage by accounting for daily changes in anatomy. This results in a higher integrated dose to the tumor, which has the potential of increased radiation toxicity. However, similar studies of photon based radiation adapted planning have shown this approach to be safe, with comparable levels of acute toxicity seen in both adapted and non-adapted conventional plans.

With online adaptation radiation treatment plans, the time a patient spends lying on treatment table may be extended (45-90 minutes) compared to non-adapted conventional plans (20-30 minutes).

1.7.2 Known Potential Benefits

Online adaptation has the potential to modify the treatment plan based on set up and anatomical changes that may occur between initial simulation and days of treatment. Online adaptation can enable improved target coverage and ability for better OAR sparing leading to more precise treatment delivery with reduced toxicity.

1.7.3 Assessment of Potential Risks and Benefits

Given the above potential risks and benefits, we believe that the benefits of performing online adaptation for patients receiving proton therapy outweigh the risks.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the feasibility of online proton adaptive radiotherapy based on successful delivery of more than 70% of attempted fractions where treatment adaptation is indicated.	Successful completion of online adaptive proton radiotherapy workflow through treatment delivery in at least 70% of planned adaptive fractions. Success will be defined as PARTy plan creation and delivery of the fraction using the study workflow in one on-table attempt. Unsuccessful planning and workflow delivery will be defined as multiple attempts of the PARTy workflow for one treatment fraction without treatment delivery such that the study workflow is abandoned.
Secondary	
1. To assess the safety of online proton adaptive radiotherapy.	1. Grade 2+ radiation-related toxicity at 3 months as measured by CTCAE v5.0.
Exploratory	
1. To assess patient tolerability and satisfaction with online proton adaptive radiotherapy process. 2. To assess dosimetric differences for target coverage and organ at risk (OAR) sparing between adaptive and non-adaptive proton therapy.	1. Patient reported experience measures (PREMs). 2. Dosimetry evaluation and comparison to non-adapted pre-plan.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

Patients must meet all of the below criteria in order to be enrolled to this study.

1. Oligometastatic or primary malignancy planned for proton SBRT. Disease site should be biopsy-proven primary disease of solid tumor histology with the exception of Hepatocellular carcinoma (HCC). HCC does not need to be biopsy proven if imaging and clinical findings are consistent with the diagnosis.

2. Must be deemed medically fit for proton SBRT by the treating physician.

3. Prior radiation therapy is allowed.

4. At least 18 years of age.

5. Karnofsky ≥ 70% (see Appendix A).

6. Because radiation therapy is known to be teratogenic, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, or a male suspect he has fathered a child, s/he must inform the treating physician immediately.

7. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

Patients must not meet any of the criteria below in order to enroll to the study.

1. Histology of small cell carcinoma. Mixed histologies with a predominantly small cell component are also exclusionary.

2. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3. Medical contraindication to proton therapy or any other condition that in the opinion of the treating radiation oncologist, renders the patient unfit for SBRT

4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

5. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days of study entry.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION AND ENROLLMENT PROCEDURES

The following steps must be taken before enrolling patients on this study:

1. Registration of patient in the Siteman Cancer Center database
2. Assignment of unique patient number (UPN)
3. Confirmation of patient eligibility

Patients must not start any protocol intervention or procedures prior to signing of informed consent.

4.1 Registration in OnCore Database

Patient registration to the Siteman Cancer Center OnCore database must occur within one business day of the patient signing consent.

4.2 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. The UPN must not include patient initials or other identifying information. All data will be recorded with this identification number on the appropriate CRFs.

4.3 Confirmation of Patient Eligibility and Enrollment

Patient eligibility will be confirmed using the information listed below

1. Completed eligibility checklist, signed and dated by a member of the study team
2. Copy of appropriate source documentation confirming patient eligibility

4.4 OnCore Subject Status Definitions

Note: subject status should not be updated in OnCore until the subject is actively in that status; future dates are not allowed.

Subject Status	Definition
Consented	Patient has signed an IRB approved consent for the trial.
Eligible	Patient eligibility has been confirmed by Washington University PI or delegate.
Not Eligible	Patient did not meet eligibility criteria for the trial. Note that if a patient is determined to be eligible but never initiates study participation, they are not considered a screen fail.
On Study	Patient is confirmed eligible for the study and enrolled.
On Treatment	Patient is receiving study therapy. On Treatment date should be the date of the first study treatment.

Off Treatment	Patient has discontinued study therapy. Off Treatment date should be the last day any study treatment was administered.
On Follow Up	On Follow Up date is the same as the Off Treatment date
Off Study	Patient has fully discontinued all study procedures (including any follow-up procedures and/or review of medical record for outcomes data).

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.6 Strategies for Recruitment and Retention

Patients will be accrued on basis of presentation to the radiation oncology clinic amenable to proton SBRT. Potential participants will be identified in the inpatient and outpatient radiation oncology clinic setting, as well as from the multidisciplinary spine tumor board. Patients will be approached regarding participation at or around the time of their radiation oncology consultation visit. Patients will be treated at a single facility, at the S. Lee Kling Proton Therapy Center, as the technology required for this study is confined to this center. We anticipate an accrual rate of approximately 10 patients per year, or an estimated study accrual period of 8-12 months. There will be no compensation or incentives offered for study participation.

5.0 TREATMENT PLAN

The treatment will consist of stereotactic body radiation therapy, administered as 5 fractions. All patients will undergo standard initial consultation, pre-treatment simulation, and planning in accordance with institutional standards. When patients present for each treatment, the initial pre-plan will be generated and assessed for safety and coverage of the treatment area. In addition to this, a new adapted plan will be generated. Both plans will then be compared, and the plan deemed to be most appropriate will be carried out. This process will occur for each treatment.

5.1 Radiation Therapy Guidelines

5.1.1 Dose and Fractionation

Radiotherapy will consist of stereotactic body therapy, to be given over five fraction course, delivered once daily or once every other day for a period of one to two weeks, for a total of five treatments. Patients will be planned for an initial

prescription dose at the discretion of the treating physician, delivered in five total fractions to the PTV, with dose adaptation based on safety constraints that are already approved of to prevent OAR injury.

5.1.2 Patient Positioning

All patients will undergo CT simulation in positioning appropriate for the specific treatment site for proton therapy. When medically feasible and applicable, patients may be simulated with IV and/or small bowel contrast (for non-thorax cases).

5.1.3 Treatment Volume Definition: Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Planning Target Volume (PTV)

Gross Tumor Volume (GTV) should include all gross recurrent disease including lymph node metastases as determined by CT, PET/CT, MRI, or biopsy.

The treatment target volumes and creation of the CTV and PTV are disease site specific and will be at the discretion of the treating radiation oncologist. Initial treatment pre-plan based on CT simulation will thus be generated with above target information. Additional treatment volumes including PTV_Opt and ring optimization structures may be generated for the purpose of adaptive treatment plan optimization. The decision to use PTV_Opt will be dependent on site of disease and anatomical location. This will be decided during initial treatment planning with treating radiation oncologist and physicist after simulation but prior to treatment start.

5.1.4 Organs at Risk Contours and Dose Constraints

OAR/normal structure contours and dose constraints will be disease site specific and to the discretion of the treating radiation oncologist. Generally, dose constraints will adhere to standard of care institutional dose constraints employed here at WashU/BJC Radiation Oncology Department.

5.1.5 Initial Treatment Planning

Coverage goal will be for 95% of the target volume or optimization volume to be covered by 95% of the dose. In situations where a critical structure is violated, reduction of dose or volume will be allowed in areas of overlap.

5.1.6 Adaptive Treatment Planning

When patients present for each proton treatment session, the initial treatment pre-plan will be generated based on the anatomy of the day. In addition to this, a new adapted treatment plan will be generated and re-optimization will be performed for dose adaptation to allow for acceptable sparing of normal structures (i.e., not violating the predetermined hard constraints based on safety constraints that are

already approved of for routine, clinical use). Dose adaptation can also be done in cases where on the volumetric imaging attained, there is noted to be violation of previously met hard constraints.

The supervising physician will review the adapted plan and prior non-adapted scheduled plan. Comparison will be made with initial pre-plan assessing for meeting OAR constraints and/or improvement of target coverage. The decision to proceed with the adaptive radiation is under the treating physician's clinical discretion where they feel tumor coverage may be impacted by interfraction motion of patient's anatomy and adaptive treatment may improve coverage based on pre-specified criteria (typically improvement in radiation dose coverage of the tumor or reduction of excess dose to a nearby organ which would increase toxicity) Subsequently, decision will be made if treatment will proceed with adapted plan or with initial pre-plan.

5.1.7 Quality Assurance of the Adaptive Plan

Patient specific QA will be performed at each fraction prior to delivery of the adaptive treatment plan. Given that dose measurements will not be possible with the patient on the table, this will be achieved by performing an independent Monte Carlo dose calculation on the image of the day, using the exported beam parameters, and mapped electron density. The independently calculated dose distribution will be compared to the dose distribution exported from Raystation, proton therapy planning system, looking at dose volume histograms and 3D gamma analysis of all voxels within the patient. An in-house plan integrity verification algorithm will be utilized to evaluate plan quality and integrity via plan parameters including contours, beam angles, segments, and monitor units. After completion of the automated checks, a final review by physics will be required prior to proceeding to treatment delivery. Following the completion of each treatment fraction, there will be an additional QA process conducted offline to verify the integrity of the delivered treatment and ensure that the dose administered aligns with the expected dose.

5.1.8 Dose Constraints

As this is a feasibility study, patients participating in the trial will have various types of malignancies in different anatomical locations, clinical circumstances, and different prescribed doses and treatment schedules. The dose constraints for each patient will be specific to their individual anatomy and will be determined during the initial treatment planning process by the treating radiation oncologist. Specific dose constraints will be established on a case-by-case basis. Generally, dose constraints will adhere to standard of care institutional dose constraints employed here at WashU/BJC Radiation Oncology Department. Below is suggested dose constraints for 5 fraction SBRT. The dose constraints listed below may be modified based on individual patient's clinical scenario and discretion.

Structure	Goal	Variation
Brachial Plexus	D0.1cc < 30.5Gy	D 0.1cc < 32Gy
Chest Wall	D0.1cc < 43Gy	
Spinal Cord	D0.5cc < 25Gy	
Lungs	V20Gy < 10%	V20Gy < 15%
Esophagus	D0.5cc < 33Gy	D0.5cc < 36Gy
Heart	D0.1cc < 29Gy	D0.1cc < 38Gy
Liver - GTV	Critical Volume >700cc < 15Gy V10Gy < 70%	
Kidney	Bilateral mean <15 Gy	
Stomach	D0.5cc < 33Gy	D0.5cc < 36Gy
Duodenum	D0.5cc < 33Gy	D0.5cc < 36Gy
Small Bowel	D0.5cc < 33Gy	D0.5cc < 36Gy
Large Bowel	D0.5cc < 33Gy	D0.5cc < 36Gy
Rectum	D0.1cc < 38Gy	
Bladder	D0.1cc < 38Gy	

5.2 Definitions of Evaluability

Endpoint	**In order to be evaluable for this endpoint, a patient must…**
Primary: feasibility of online proton adaptive radiotherapy	Have received at least one fraction of SBRT.
Secondary: G2+ toxicity at 3 months	
Exploratory: dosimetry evaluation and comparison to non-adaptive workflow	
Exploratory: PREMs	Have received at least one fraction of SBRT and completed PREMs.

5.3 Concomitant Therapy and Supportive Care Guidelines

It is **preferred** that patients do not receive systemic therapy within 2 weeks of starting and ending SBRT. However, given that select systemic agents are appropriate with concurrent radiation and that some patients may need treatment more urgently, the decision to treat will be at the discretion of the treating radiation and/or medical oncologist.

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum or urine pregnancy test within 14 days prior to the start of SBRT.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during SBRT.

If a patient is suspected to be pregnant, SBRT should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during SBRT, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for a total of 5 fractions of SBRT or until one of the following criteria applies:

- Documented and confirmed disease progression
- Intercurrent illness that prevents further administration of treatment
- Death
- Unacceptable adverse event(s)
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient decides to withdraw from the study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will have a single follow-up visit at 3 months post-end of SBRT.

5.7 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for the 3 month follow up visit and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 3 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 DOSE DELAYS

No dose delays are expected. If necessary, dose delays may occur on a case-by-case basis following discussion with the PI and will follow institutional standards.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines. All investigators treating patients on this study are responsible for ensuring that serious adverse events (as defined in Appendix B) are reported to the Sponsor-Investigator within an adequate timeframe for the event to be assessed by the Sponsor-Investigator for reporting to HRPO, QASMC, and/or FDA.

Adverse events will be tracked from start of treatment through 3 months post-end of SBRT. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Grade 1 AEs regardless of relatedness
- Grade 2-4 AEs that are unlikely related or definitely not related to treatment

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 WU PI Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment

PREM Form	Completion of treatment
Follow Up Form	At 3 mos follow-up
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

8.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

9.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually. The first report is required either 30 days after the enrollment of the 5th participant (if sooner than 6 months after study activation) or 6 months after study activation (provided at least one patient has been enrolled; if zero patients have been enrolled at the 6-month mark, the first report will be required one year after accrual opens provided at least one patient has been enrolled).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- Study demographic information (local protocol number, protocol title, list of primary study team members, study sites, primary and secondary sponsors, IND/IDE status, date of most recent QA audit, and study status and history (including activation and suspension dates)
- Accrual information, including study-wide target accrual and actual accrual, anticipated and/or actual accrual end date, and accrual by year by site (if applicable)
- Subject status information presented in both cumulative format (total number of subjects who consented, enrolled, screen failed, started intervention, discontinued intervention, went off study, expired) and current format (number of subjects in screening, on intervention, in follow-up, or off study at time of report)
- Protocol objectives and the number of participants who are evaluable for each objective
- History of study (including summaries of substantive amendments, accrual suspensions and reasons, protocol exceptions, errors, and breaches of confidentiality)
- Summary of exceptions, noncompliance reports, and unanticipated problems reported to the IRB
- Early stopping rules and data describing whether the stopping rules have been met (if applicable)

- Interim analysis plans and the results of the interim analysis (if applicable)
- Separate SAE and worst grade toxicity tables, each separated by site (if applicable) and arm/cohort/dose level (if applicable)
- Participant-level response and survival data by arm/cohort/dose level (if applicable)
- Summary of specimen collection (percentage of participants who have had specimens collected at each required time point)
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety of participants or the ethics of the study

Standardized DSM report tables are generated out of OnCore; study-specific DSM report tables are located in Appendix D.

10.0 Measurement of Effect

Because this study is a feasibility study and patients enrolled in this study will have distinct disease sits and heterogenous treatment plans, measurement of treatment response will be at the discretion of treating radiation oncologist.

11.0 STATISTICAL CONSIDERATIONS

11.1 Definition of Primary Endpoint

Feasibility: Feasibility will be defined as successful completion of online adaptive proton radiotherapy workflow through treatment delivery in at least 70% of planned adaptive fractions..

Success will be defined as PARTy plan creation and delivery of the fraction using the study workflow in one on-table attempt. Unsuccessful planning and workflow delivery will be defined as multiple attempts of the PARTy workflow for one treatment fraction without treatment delivery such that the study workflow is abandoned.

11.2 Definition of Secondary and Exploratory Endpoints

Secondary
Toxicity: This will be evaluated throughout treatment and at 3 months post-end of SBRT using CTCAE v5.0. Grade 2+ radiation-related toxicity will be collected.

Patient satisfaction: This will be evaluated using patient reported experience measures (PREMs, Appendix E) at the end of treatment.

Dosimetry evaluation: PARTy dosimetric evaluation will be completed with a goal of comparing the dose to OARs and target coverage in online adapted treatment plan with the non-adapted treatment plan.

11.3 Sample Size Calculation

As a pilot study, the sample size is determined based on clinical considerations rather than statistical power. For our primary objective, our goal will be to report the description of online adaptive proton therapy treatment workflows, adaptation, and the time to delivery of first treatment fraction. Goal accrual will be 10 evaluable patients. For the exploratory objectives, sample size is also based on clinical considerations rather than statistical power.

11.4 Statistical Analysis Plan

The primary objective is to demonstrate that online proton adaptive radiotherapy is feasible by confirming that adaptive treatment can be delivered in more than 70% of treatment fractions where treatment adaptation is indicated.

Our principal objectives in this trial will be to determine the feasibility for online proton adaptive radiotherapy. If we can successfully deliver treatments for more than 70% of treatment fractions where treatment adaptation is indicated while maintaining the safety, then we will consider this study as having provided sufficient pilot data to support more widespread study of online proton adaptive radiotherapy. Historical controls reference 70% as the definition of feasibility, so we have utilized that for our primary endpoint. Basic descriptive statistics will be used to evaluate feasibility. The long-term goals will be to improve patient outcomes and care by improving target coverage and decreasing radiation toxicity.

Regarding toxicity, we will report descriptive statistics for acute toxicity at a three-month time point. Toxicity rates are anticipated to be identical or improved to those of other linear accelerator based SBRT treatments. Other than the online adaptation component of the treatment plan, patients will receive disease site specific standard-of-care dose and fractionation treatment plan. Therefore, further prospective toxicity assessments are not indicated. Given that no prior data exists for online adaptive proton radiotherapy, we will report descriptive statistics. Descriptive statistics will be calculated on all variables. Frequencies will be computed for all binary/categorical variables, and continuous variables will be summarized using medians, quartiles, and ranges. Patient satisfaction measured with PREMS will be evaluated using descriptive statistics. As a pilot study we will establish these baseline parameters.

For the dosimetry exploratory endpoints, non-parametric equivalents (Wilcoxon test) will be conducted to compare plan quality between simulated pre-plans and online adaptive plans. Further analysis may be conducted with ANCOVA to estimate how the baseline covariates associated simulated pre-plans and online adaptive plans. The ANCOVA will be presented with least square (LS) mean estimate. Two-sided 95% confidence intervals for the mean changes and p-values will also be reported.

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APPENDIX A: Karnofsky Performance Status Scale

Able to carry on normal activity and to work; no special care needed	100	Normal, no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

APPENDIX D: Study-Specific DSM Tables

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
To assess the feasibility of online proton adaptive radiotherapy based on successful delivery of more than 70% of attempted fractions where treatment adaptation is indicated.	
Secondary	
To assess the safety of online proton adaptive radiotherapy.	
Exploratory	
To assess patient tolerability and satisfaction with online proton adaptive radiotherapy process.	
To assess dosimetric differences for target coverage and OAR sparing between adaptive and non-adaptive proton therapy.	

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? No
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? No

Patient Response			
UPN	**On Tx Date**	**# of fx completed**	**Patient feasible? (y/n)**

Patient Discontinuation and Survival			
Off Tx Date	**Reason for discontinuation**	**Vital status**	**If dead, cause**

APPENDIX E: Patient Reported Experience Measures (PREM) Form

Date of administration:_____ Patient ID:_____ HRPO:_____

Patient reports (1) not at all satisfied, (2) slightly satisfied, (3) moderately satisfied, or (4) very satisfied for the following procedures:				
Interval consult to treatment start	**1**	**2**	**3**	**4**
Treatment start to treatment completion	**1**	**2**	**3**	**4**
Treatment duration	**1**	**2**	**3**	**4**
Overall satisfaction with workflow	**1**	**2**	**3**	**4**