PURPOSE AND BACKGROUND:

The purpose of this trial is to address the “promise of protons” via a pragmatic scientific randomized prospective approach. For this discussion, the “promise of protons” will be defined as attempting to link the underlying principle that dosimetry improvement based on beam characteristics leads to improved outcomes.

There are a number of high-quality studies that are being undertaken currently in the US and in Europe. They clearly will help in defining which patients benefit but they are not structured to mirror the “promise of protons”. The “promise of protons” argues that across a wide variety of cancers protons offer significant advantages due to improvements in dosimetry. However, in 30 years of evolving clinical use of proton therapy, this simple wide application has never been studied in a prospective randomized scientific manner.

To date, the study that mirrors this approach the closest is the “Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer” (Baumann B et al) (***“Proton Concurrent Study”***). The study retrospectively reviewed over 1400 patients undergoing concurrent chemotherapy and radiation and showed a significant reduction in toxicity. This ***Proton Concurrent Study*** represents the “promise of protons” across a broad patient cohort but it is hampered by its retrospective nature and many possible confounding arguments inherent within these types of studies.

The recently published “Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer” (Lin S et al) (“***Proton Esophageal Trial***”) and the 2018 “Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer” (Liao Z et al) (***“Proton Lung Trial”)*** represent the two largest current prospective randomized published literature comparing proton therapy to photon therapy. Both represent single disease sites and therefore a much less broad scope than the “promise of protons”.

The ***Proton Lung Trial*** showed no clear benefit to proton therapy compared to photon therapy. It was structured very differently than attempting to limit benefit to those plans that were significantly improved with proton therapy. In fact, it required both arms to meet specific criteria and that approach clearly demonstrated that a different approach was required for future studies.

The ***Proton Esophageal Trial*** approached the problem differently; using a total toxicity burden approach to attempt to better define toxicity rates and potentially separate the two treatment arms. In this study, the total toxicity burden was significantly less in the proton therapy arm, but again this study is hampered by significant issues. The total toxicity burden, although based on procedures and significant medical events, is a non-validated endpoint. The other primary

endpoint of progression-free survival was not different between arms. Further a number of other metrics showed no clear benefit leaving the benefit in a rather complex non-validated toxicity measurement.

This trial seeks to evaluate the “promise of protons” by evaluating higher than average risk patients (due to concurrent chemotherapy risk, age, and site location details) purposefully mirroring the ***Proton Concurrent Study.*** These patients will be randomized to either be treated with proton therapy or photon therapy and followed for short and term toxicity rates and disease-free survival. As was done in the Proton Concurrent Study, we will focus on validated CTCAE 90-day grade 3 toxicity and then use validated long-term toxicity measurements of ECOG, Charlson-Deyo Co-Morbidity scores, and EQ-5D-3L Patient Reported Outcomes.

OBJECTIVE:
Primary study outcome will be acute CTCAE 90-day grade 3 or higher toxicity and 3 year CTCAE grade 3 or higher toxicity. Site specific requirements are an attempt to choose patients at relatively high risk for toxicity.

ELIGIBILITY:

- **Age: 65 or older (>50 for insurance plans allowing trial enrollment and support of either arm).**
- **Concurrent Chemotherapy during radiation**
- **Traditional fractionation to definitive dosing (≤2.2 Gy or RBE(Gy))**
- **Definitive goal. (Can be pre-operative. Can have oligometastatic disease so long as the intent is to treat all disease in a definitive fashion.)**
- **Anticipated Main Sites: CNS, Head and Neck, Esophagus, Lung, Pancreas, Hepatobilliary, Colo-Rectal, Bladder, Anal**

SITE DETAILS:

- **CNS (Supratentorial, Disease >3cm)**
- **HN (Nasopharynx, Oropharynx)**
- **Esophagus (Thoracic or Abdominal)**
- **Lung (Disease at T7 or lower or bilateral mediastinal disease)**
- **Pancreas (Head or body or lymph node positive disease)**
- **Hepatobiliary (>3cm ITV)**
- **Colo-Rectal (Clear T3 disease or LN+)**
- **Bladder (T3 disease, requiring >60 Gy)**
- **Anal (>T1 disease)**

Primary Outcome: Reduced Toxicity (Acute and 3 yr)

- **Acute CTCAE: 90 - Day Grade 3 or higher toxicity**
- **3 year - CTCAE Gr3 or higher toxicity**

Secondary Outcomes:

- **OS - 3 yr and 90 day mortality**
- **90-day Grade 4 Lymphopenia**
- **DFS Strictly defined (0 NED - minimum of 6 month with no immunotherapy, chemotherapy, radiation or surgery., 1 Ongoing tx for cancer with any level of possible residual or low volume metastatic disease, 2 Clear evidence for metastatic / recurrent / or progressive disease development.)**
- **Prospective Dosimetry Metric evaluation and evolution**
- **Long Term Toxicity 3yr**
    - **ECOG score**
    - **Charlson-Deyo Comorbidity score**
    - **Eq-5D-3L Patient Reported Outcomes**

Randomization:
Patients will be randomized to receive either photon based or proton based treatment via block randomization based on the disease site:

- **Disease site (Pelvis | CNS | Thorax | Abdomen | HN | Anal)**

If ongoing RCT trials show clear benefit to a subset of patients (for example the esophageal or HN cancer trials that have been completed at MDACC) show strong benefit, patients will be informed of the results and the protocol team has opportunity to close trial to any site based on the new publication of data.

Statistical Power:
The current trial will require randomization and treatment of a minimum of 168 patients in order to be sufficiently powered. This anticipates a grade 3 toxicity rate of 11% with a standard deviation of 3% based on the stronger proton therapy data in the ***Proton Concurrent Study***. With this number of patients, the study will be powered to detect a difference of 1.5% overall reduction (to 9.5% or less) 90% of the time. The maximum number enrolled will be 312 patients which would power the study to detect a 10% reduction in grade 3 toxicity.

There will be an interval analysis performed after 80 randomized patients within the two treatment arms reach the 90 day follow up mark at an Alpha of 0.005. The interim analysis is powered to detect a 25% reduction in toxicity at that sample size.

Required Encounters: Pre-treatment, End of Treatment, 3 months, 6 months, 1 yr, 18 months, 2 yrs, 30 months, 3 yrs. **(9 total visits)**

Site Requirement:
Site requirements are based on literature and clinical experience attempting to select higher potential benefit locations or tumors that are not currently considered for stereotactic ablative therapy.

Age Requirement:
The goal is to take a high risk subset of patients and randomize those at high risk for complications. Age is a contributing factor to complications following concurrent chemotherapy and radiation. This basic age requirement ensures a high risk population and ensure a greater ability to ensure randomization resulting in equivalent treatment arms.

We hope to work with insurers to allow privately insured patients older than 50 to enroll. We believe these patients would benefit. To date, there is a known history of insurance pre-authorizations complicating and disrupting proton trial enrollment. If we can obtain approval by insurance to support randomization via contract language, those patients over 50 who are covered will be eligible.

Blood work:
Grade 4 lymphopenia has been shown to relate to both progression free and overall survival. All patients in the current trial will be receiving concurrent chemotherapy and most will likely undergo regular blood work to monitor counts. The trial does recommend one baseline and then weekly blood work to monitor for Gr4 lymphopenia. We also recommend performing significant due diligence at the 3 month follow-up visit to include all interval blood work results. Beyond 90-days, there is no intent to monitor blood counts. This blood work requirement approaches what is typical for many patients, on and off trial, to monitor blood counts during concurrent chemotherapy. It is structured on a more defined basis in this trial and therefore is included as a recommended part of the trial enrollment.

Comparative Plan Generation:
All patients, regardless of treatment modality will have a comparative plan completed prior to the completion of treatment. The two plans will then be used to apply the proposed dosimetry metrics to define whether the proton therapy plan appears to provide benefit over the IMRT plan by achieving one or more metrics that were not obtainable with photon planning.

Dosimetry Metrics:
The following Dosimetry Metrics are designed to predict toxicity based on published literature and have the potential to parse proton therapy plans and photon therapy plans into groups that 1) "potentially benefit" to a larger degree from proton therapy and 2) plans that appear to show "no clear benefit" from proton therapy.

1. CNS brain constraint >100cc diff in 10Gy
2. Hippocampus Highest Mean <10 Gy
3. Posterior fossa <10Gy mean
4. Pituitary <30 Gy
5. Cochlea Highest Mean dose <35 Gy
6. Oral cavity Mean dose reduction 50%
7. Parotid Highest mean <20 Gy
8. Esophagus Mean dose 20% reduction
9. Lung v5<55% (requiring a v20<20%)
10. Mean Heart Dose<10Gy
11. LAD v15 <10%
12. Liver 30% reduction mean dose
13. Bowel(within 5 cm of GTV) 30% reduction mean dose
14. Bone Marrow v20 50% reduction
15. Immune System 1 nomogram risk group reduction

Planned Dosimetry Metric Review:
It is acknowledged that the chosen metrics are far from clearly defined within the literature and that there is a clear lack of consensus regarding sites, dose, and cut points that would be selected. The metrics chosen have been purposefully chosen to attempt to allow a significant number of concurrent chemoradiation cases to be eligible based on a thorough review of the current literature.

Planned evaluations of the metrics will be performed in accordance with the procedure formally described in the **Evolving Metrics Process Document** (separate document).

Data Storage and Confidentiality:
All data will be kept on site at the treating location. The Oklahoma Proton Center is a HIPPA compliant medical facility delivering medical care with an on site Quality Assurance and Compliance Officer.

Risk / Benefit Assessment:
Risk: Greater than minimal. The trial design is an attempt to define the optimal standard of care cancer treatment for patients. Potential risks lie from one treatment being superior to the other option. This clearly carries physical, psychological benefits to the one treatment arm group compared to the other arm especially once the trial has been published. We have implemented stopping rules to look for large significant differences early in the trial to attempt to limit this risk.

While there are risks inherent with almost any trial, trial enrollment is generally associated with improved outcomes for all patients enrolled. Clearly, in the current practice of radiation oncology, patients are treated with both proton and photon approaches and those options are always available in a non-randomized, non-study approach.

Subject Identification:
New patients who meet eligibility criteria will be offered the opportunity for enrollment during the process of consultation at the Oklahoma Proton Center for the management of their cancer. Consent will be obtained by our clinic staff (physicians and nursing staff) per standard facility guidelines for consent. We have actively participated in national trials and registries for over 1 decade and have numerous policies and procedures in place regarding our ongoing process of trial enrollment.