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A PHASE II SINGLE-ARM STUDY OF TOTAL BODY IRRADIATION WITH LINAC BASED VOLUMETRIC MODULATED ARC THERAPY (VMAT) AND IMAGE GUIDED RADIATION THERAPY (IGRT)

Principal Investigator:	Naamit Kurshan Gerber, MD Associate Professor Department of Radiation Oncology at NYU Grossman School of Medicine 160 E. 34th Street New York, NY 10016 Naamit.gerber@nyulangone.org 212 731 5304
Biostatistician/ Co-investigator	Judith D. Goldberg, ScD Professor at NYU Grossman School of Medicine Division of Biostatistics, Dept. of Population Health, Dept. of Environmental Medicine and Perlmutter Cancer Center NYU Langone Health 180 Madison Ave, 4th Floor, 451 New York, NY 10016 jd.goldberg@nyulangone.org 646-501-3643
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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

PROTOCOL APPROVAL SIGNATURES

Protocol Title: **A PHASE II SINGLE-ARM STUDY OF TOTAL BODY IRRADIATION WITH LINAC BASED VOLUMETRIC MODULATED ARC THERAPY (VMAT) AND IMAGE GUIDED RADIATION THERAPY (IGRT)**

Protocol Number: s19-00664

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

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Signature

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Date

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List of Abbreviations

AAPM	American Association of Physicist in Medicine
ACR	American College of Radiology
AE	Adverse Event/Adverse Experience
ALL	Acute Lymphoblastic Leukemia
AP	Anterior-Posterior
ASCT	Allogeneic Stem Cell Transplantation
ASTRO	American Society of Radiation Oncology
BED	Biologically Effective Dose
BMT	Bone Marrow Transplantation
BID	Twice a Day
CBCT	Cone Beam Computed Tomography
cGy/Gy	Centigray / Gray
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
CT	Computed Tomography
Cy	Cyclophosphamide
DHHS	Department of Health and Human Services
DSMC	Data and Safety Monitoring Committee
EFS	Event Free Survival
EPID	Electronic Portal Imager Device
FDA	Food and Drug Administration
FFR	Federal Financial Report
FFS	Feet First Supine
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GVHD	Graft Versus Host Disease
HDR	High Dose Rate
HFS	Head First Supine
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IGRT	Image Guided Radiation Therapy
ILROG	International Lymphoma Radiation Oncology Group
IPS	Idiopathic Pneumonia Syndrome
IRB	Institutional Review Board
ISM	Independent Safety Monitor
kV	Kilovoltage
LDR	Low Dose Rate
MLC	Multi-Leaf Collimator
MOP	Manual of Procedures
MV	Megavoltage
N	Number (typically refers to participants)
NCT	National Clinical Trials
NIH	National Institutes of Health
OAR(s)	Organ(s) At Risk
OBI	On-Board Imaging
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
OSLD	Optically Stimulated Luminescent Dosimeter
OTV	On Treatment Visit
PA	Posterior-Anterior
PI	Principal Investigator
PTV	Planning Target Volume
PSQA	Patient Specific Quality Assurance
P&P	Policies and Procedures
QA	Quality Assurance
QC	Quality Control
QMP	Qualified Medical Physicist
RNV	Record and Verify
RTT	Registered Radiation Therapist
SAE	Serious Adverse Event/Serious Adverse Experience
SSD	Source to skin/surface distance
SOP	Standard Operating Procedure
TBI	Total Body Irradiation
TMI	Total Marrow Irradiation
TP	Treating Physician
TPS	Treatment Planning System

US	United States
UP	Unanticipated Problems
VMAT	Volumetric Modulated Arc Therapy

Protocol Summary

Title	A PHASE II SINGLE-ARM STUDY OF TOTAL BODY IRRADIATION WITH LINAC BASED VOLUMETRIC MODULATED ARC THERAPY (VMAT) AND IMAGE GUIDED RADIATION THERAPY (IGRT)
Short Title	TBI with linac based VMAT
Brief Summary	Single institution study of safety of linac based VMAT TBI for myeloablative treatment in hematologic malignancies
Phase	Phase 2
Objectives	Primary objective: To estimate the proportion of subjects who achieve excellent target coverage while sparing the lungs. Excellent target coverage requires that following 3 dosimetric parameters levels have been achieved: 1. V100%= >90% (90% of PTV volume getting 100% of the dose). 2. D98>85% (98% of the volume getting at least 85% of the dose). 3. Mean Lung dose <900cGy. Secondary objectives: 1) To estimate the cumulative incidence rate of idiopathic pneumonia syndrome in the first 100 days after transplant. 2) To estimate the cumulative failure rate (including acute GVHD, transplant related mortality or death) during the first 100 days post transplant following full-dose TBI delivered with linac based VMAT 3) To estimate the event Free Survival (EFS) 4) To estimate the following: a) Proportion of subjects who have achieved a mean does to each kidney (Dmean) < 11 Gy b) Proportion of subjects who have achieved a maximum dose to 2cc of the entire body (D2cc) < 130% of Rx dose. c) Proportion of subjects who have achieved a maximum dose to 0.03cc of OARs < 120% of Rx dose. 5) To summarize the subject -specific quality assurance (PSQA) for each treatment plan.
Methodology	Non-randomized phase II trial in which patients who consent to the trial will be treated with linac based VMAT TBI as part of their conditioning regimen for transplantation
Endpoint	Primary endpoint: meeting the dosimetric endpoints specified above
Study Duration	One-year from last subject enrolled. Accrual estimated over 15 months.
Participant Duration	One year
Population	35 subjects ≥ 10 years old requiring full dose TBI (defined as **≥**12 Gy) as part of their conditioning regimen for Allogeneic Stem Cell Transplantation (ASCT). Up to 70 prospective subjects or patients may sign consent in order to achieve 35 accrued subjects; this is to account for screen failures.
Number of participants	35
Description of Study Agent/Procedure	Use of linac based Volumetric Arc Therapy (VMAT) to deliver Total Body Irradiation (TBI)
Key Procedures	CT simulation and twice daily radiation treatments

Statistical Analysis	The proportion of patients who receive TBI that achieves excellent target coverage will be estimated with exact 95% confidence intervals.

1 Key Roles

The Principal Investigator is Naamit Kurshan Gerber, MD who is an associate professor of Radiation Oncology who specializes in hematologic and breast malignancies. The sub-investigators include her colleagues from radiation oncology (Benjamin Cooper) medical physics (Barbee, Hitchen, Teruel, Malin, Galavis, Osterman) her colleagues in medical oncology who specialize in blood and marrow transplantation (Al-Homsi, Abdul Hay, and her colleagues in pediatric bone marrow transplantation (Sharon Gardner).

Naamit Kurshan Gerber, MD- PI
Associate Professor
Department of Radiation Oncology at NYU Grossman School of Medicine
160 East 34th Street
New York, NY 10016
Naamit.gerber@nyulangone.org
212-731-5304

Judith D. Goldberg, Biostatistician/Sub-Investigator
Professor, Division of Biostatistics
Dept. of Population Health
Dept. of Environmental Medicine
Perlmutter Cancer Center
NYU Langone Health
180 Madison Ave, 4th floor, 451
New York, NY 10016
JD.Goldberg@nyulangone.org
646-501-3643

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Total Body Irradiation (TBI) continues to play an important role in myeloablative and non-myeloablative conditioning regimens for Allogeneic Stem Cell Transplant (ASCT). When TBI is used as part of a myeloablative regimen, it is combined with chemotherapy to eradicate malignant cells, as well as to immunosuppress the host to prevent rejection of donor hematopoietic progenitor cells (HPC)[1,2].

Historically at many institutions, myeloablative TBI has been prescribed as an umbilicus midline point dose of 10-16 Gy in 6-12 fractions of 1.2-2.0 Gy per fraction, with 2-3 fractions per day, minimally 4-6 hours between fractions. CT simulation was not performed and therefore, dose calculations did not include heterogeneity corrections. Given the risk of radiation-induced lung complications, total lung dose was typically limited by either positioning the patient's arms to act as tissue compensators or by using blocks to shield the lungs. Most frequently, TBI has been delivered at extended source-to-skin distance (SSD) with the patient standing or lying, resulting in a reduced dose rate from that typically used in therapeutic radiation. In vivo dosimetry has been utilized to measure delivered dose[1]. In 2017, the American College of Radiology (ACR) and American Society of Radiation Oncology (ASTRO) published a Practice Parameter for the performance of TBI, which stated that total lung dose is often limited to about 8-10 Gy[1].

At this institution, myeloablative TBI dose fractionation has been 12 Gy in 6-8 fractions of 2 to 1.5 Gy, delivered twice daily with minimum 6 hours between fractions. Beginning in 2017, CT Simulation has been performed with patient supine with optimal positioning/immobilization of the arms to limit lung dose, and rice bag compensation to improve dose homogeneity. Dose calculations have evolved from two-dimensional hand calculated point doses to three-dimensional CT based heterogeneity corrected dose distributions performed to target the body via 15MV static-gantry opposed lateral fields at 415 cm SAD, with solid water compensation superior to shoulders. Treatment has been delivered in accordance with the treatment plan with the patient positioned on an ancillary couch at 415 cm extended distance, using a linear accelerator (Varian TrueBeam®, Palo Alto, CA)[3], with an acrylic beam spoiler to improve dose coverage of superficial tissue. Image-guidance has not been used. In vivo dosimetry using optically stimulated luminescent dosimeters (OSLDs) has been performed for all fractions.

With the myeloablative TBI technique at this institution, the total lung mean dose has been routinely limited to 10.5 Gy. For most cases, dose to 98% (D98%) of the target (defined as the entire body cropped three dimensionally 1 cm from the surface) has been ≥80% of the prescription dose. Dose to the 95% (D95%) of the target has been ≥82% of the prescription dose. Target volume that received 100% (V100%) of the dose ranged based on patient anatomy and limiting dose to the lungs, with values between 25% and 65%. Target mean dose ranged between 95% and 105%. Kidney mean dose aligned with target mean dose for all cases. Maximum dose (hotspot) to the body was below 135%. While the values outlined above were met for most cases, small deviations to the mentioned dosimetric parameters have occurred in some cases due to patient anatomy and the need of target coverage and lung sparing.

Myeloablative regimens are associated with treatment-related or non-relapse-related mortality rates of approximately 20-30%[2]. The most common toxicity of TBI based conditioning regimens is radiation-induced interstitial pneumonitis[2,4]. When delivered as a single high-dose (8-10 Gy) fraction, TBI is associated with a 50% risk of radiation-induced interstitial pneumonitis with a 50% fatality rate[5]. Even with fractionation, pneumonitis can occur in up to 25% of patients though the risk of fatal events is reduced[2]. The reported incidence of non-infectious pneumonitis or idiopathic pneumonia syndrome (IPS) after TBI-based myeloablative conditioning regimens range from 7% to 35%[6–13]. In a recently published single institution series with 202 patients in which 13.2 Gy TBI was delivered with opposed lateral beams, IPS occurred in 21% of patients at a median of 16 days with a mortality rate of 45%. Those undergoing TBI with a high-dose rate (HDR) had a nearly 3-fold increase in IPS (29%) compared with those receiving low-dose rate (LDR) TBI

(10%). Lung shielding was not used. Other factors, aside from dose rate, associated with IPS on multi-variate analysis were use of lower energy, a higher comorbidity index, and the specific conditioning regimen used[14]. Another single institution series reviewed 77 patients receiving once-daily TBI between years 2000 and 2016[15]. In this study, the cumulative rate of pulmonary toxicity was assessed. Dose rate, total dose and conditioning regimen were significant factors for the development of pulmonary toxicity. It is important to note that the definition of HDR versus LDR is not standardized for different studies and while Gao et al., defined the HDR vs. LDR dose rate cut-off at 15 cGy/min, Kim et al., defined the dose rate cut-off at 6 cGy/min.

Lawton CA et al.,[16] evaluated the effect of partial renal shielding used in conjunction with TBI on the incidence of bone marrow transplantation (BMT) nephropathy. In this series, 157 patients older than 18 years of age, received 14 Gy TBI and survived at least 100 days post-transplant. In the 72 patients who received 14 Gy with no renal shielding the actuarial risk of developing nephropathy 30 months post-BMT was 29±7 %. In the 68 patients that received 14 Gy with 15% renal shielding (renal dose = 11.9 Gy), the risk was reduced to 14±5 % at 30 months. For the 17 patients that received 14 Gy TBI with 30% renal shielding (renal dose = 9.8 Gy) there was no incidence of nephropathy at 30 months follow-up. A meta-analysis evaluating 11 single institution series concluded that the frequently applied TBI of six fractions of 2 Gy at distance (dose rate 5-15 cGy/min) without renal shielding lead to a biologically effective dose (BED) of about 21-22 Gy and that renal impairment can be expected in >10% of these cases[17]. It was also concluded that regimens with BED for kidney tissue of ≤ 16 Gy can be applied without renal shielding. Example of such regimens include six fractions delivering 1.7 Gy or nine fractions delivering 1.2 Gy.

While the low dose rate recommended for TBI is achievable for treatments at extended distance (400-500 cm), initial experiences using helical Tomotherapy and linac based VMAT TBI at 100 cm are reporting favorable outcomes in terms of pulmonary toxicities[18–20]. A detailed summary of such studies is provided in section 2.2.2 of this document.

2.2 Name and Description of the Investigational Agent

TBI will be delivered using a Varian TrueBeam linear accelerator with photon beam VMAT capability. VMAT is a radiation technique combining dynamic photon fluence modulation using multi-leaf collimation (MLC) with gantry rotation to deliver a highly conformal dose distribution with improved target coverage and sparing of organs at risk (OARs). VMAT treatment is delivered with the patient on the linac couch, which enables utilization of on-board imaging (OBI) including kV projection imaging and cone beam CT (CBCT), MV imaging using the electronic portal imaging device (EPID), as well as certain record and verify (RNV) safety features, which are not available for the extended distance TBI technique. VMAT, OBI, EPID and RNV are highly validated and used clinically worldwide to treat a wide variety of malignancies.

Our current treatment planning system (Varian Eclipse v15.6)[21] provides the capability to optimize and calculate plans that encompass multiple isocenters and up to 20 individual beams per plan. This device is 510k cleared (clearance number K200608). These capabilities allow us to create treatment plans that target the whole body by creating matching and overlapping beams along the craniocaudal direction in a sequential manner. Two treatment plans will be created, one with head first supine (HFS) orientation and one with feet first supine (FFS) orientation. In combination, these plans deliver the prescription dose to the entire target volume in accordance with our dosimetric objectives (see section 4.2.2).

The complete workflow includes simulation, treatment planning, treatment plan QA, treatment delivery, and analysis of acquired in vivo dosimetry.

- CT Simulation will be performed with the patient head first supine (HFS) in the treatment position with customized thermoplastic immobilization devices. CT images with slice thickness of 1.5 cm or lower will be acquired and transferred to Varian Eclipse TPS[21].
- A treatment plan will be created by combining a lower body feet-first plan and an upper-body head first plan.. Planning description and dose objectives are described in the corresponding section of this document and will be in accordance with physician's written directives.

- Patient-specific QA will be performed prior to first treatment.
- Prior to initiating treatment, images will be acquired with the on-board imaging system including kV, MV and CBCT. Images will be reviewed by an attending radiation oncologist before the first treatment is delivered.
- Positioning shifts will be applied as deemed necessary to achieve correct patient positioning.
- Treatment will be delivered. During treatment, transit dosimetry will be obtained using the EPID.

2.2.1 Dosimetric (preclinical) Data

To the best of our knowledge, there are no in-vitro or animal studies pertaining to the current proposed technique. However, there are some feasibility studies evaluating expected dosimetric distribution using retrospective patient CT datasets. These are summarized below.

Symons et al.,[22] performed a retrospective analysis of a linac based VMAT TBI technique on five patients using CT images from the top of the skull to the mid-thigh. The treatment plans aimed to deliver 12 Gy to at least 90% of the PTV (V100%≥90%) and 11.4 Gy to at least 95% of the PTV (V95%≥95%), while limiting the total lung mean dose to less than 8 Gy, and the liver and total kidney mean doses to below 9 Gy. All dosimetric constraints were met for the five cases evaluated.

At NYU[23], we performed a feasibility study (NYU IRB S18-00659) based on four retrospective full body CT datasets to develop and validate our intended treatment planning technique (unpublished data). All plans were prescribed to 13.2 Gy and the PTV was defined as the body contour cropped three dimensionally 5 mm from the body surface and extended 3 mm into the lungs and kidneys. Dose objectives were volume of PTV that receives 100% of prescription dose (V100%) ≥ 90%; dose to 98% of PTV (D98%) ≥ 85%; total lung mean dose < 9 Gy; total kidney mean dose < 11 Gy; maximum dose to lungs and kidneys (D0.03cc) < 120% of prescription dose; maximum dose to the body (D2cc) < 130% of prescription dose. Dose objectives were met for all cases. Average total lung mean dose 8.51 Gy, average total kidney mean dose 10.82 Gy and PTV mean coverage V100% = 94.3% were achieved.

2.2.2 Clinical Data to Date

Clinical results for volumetric modulated radiotherapy have been reported for two different radiation delivery systems: Helical Tomotherapy and linac based VMAT[18–20].

Gruen et al.,[18] reported a series of ten patients including both pediatric and adult patients (age range 4 to 22 years old) treated with helical tomotherapy. Dose prescription was 2 Gy fractions delivered twice a day (BID) with an interfraction interval of at least eight hours on three consecutive days to a total dose of 12 Gy. The average dose covering 95% of the target (D95%) in all ten patients was 97.5% of the prescription dose. Average mean dose was 9.27 Gy and 9.25 Gy for the left and right lung respectively. High dose regions of up to 130% of the prescription dose were seen in small volumes. All plans were checked for high dose regions exceeding prescription dose by more than 107%, and accepted if only small volumes in non-critical structures were affected. Overall acute morbidity of TBI was low corresponding to only mild Grade 1-2 side effects including mucositis, fatigue, loss of appetite, diarrhea, erythema, conjunctivitis, nausea, headache and neck pain. Grade 3-4 side effects directly related to TBI were not observed. After 1 to 15 months follow-up, eight patients were in stable remission without radiation-related morbidity. One patient died after transplantation due to bacterial sepsis and consecutive multi-organ failure. A second patient died three months after transplantation due to uncontrollable graft versus host disease (GVHD) grade 4. No incidence of radiation induced pneumonitis was reported in this study.

Springer et al.,[20] reported results for seven adult patients receiving linac based VMAT TBI at their institution over a 12 month period. The planned dose to the PTV was 13.2 Gy (8 fractions of 1.65 Gy administered twice a day in four consecutive days). Dose to 95% of the PTV was ≥97% for all cases. Dose objective to the lungs was set to mean dose ≤10 Gy. The mean dose to one lung never exceeded 10.7 Gy. Lungs were the only dose constrained OARs with the exception of one patient with a previous history of renal insufficiency (mean

kidney dose < 8 Gy), and another patient with previous whole brain irradiation (mean dose <11.7 Gy with central brain area reduced to 6 Gy). Five patients received full dose while two patients received only 8 Gy due to general condition and performance status. The mean follow-up after TBI of all patients was 8 months (2.3 to 15 months). During radiotherapy, all patients suffered from slight to moderate fatigue and pre-existing anemia. Immediately after TBI, all patients suffered from grade 3 mucositis and received analgesic therapy. No modest or severe lung reaction was observed during follow-up. One patient was treated during relapse without obtaining remission after chemotherapy, died of refractory disease 2.3 months after TBI. One additional patient relapsed 8.8 months after treatment (mediastinum and neck nodes) and died after 13.4 months. The other five patients were disease free and without severe toxicities.

Tas et al.,[19] treated thirty patients using linac based VMAT TBI. Age ranged from 6 to 63 years old (19 male, 11 female). Prescription was set in such a manner that 90% of the clinical target volume (the whole body) received 12 Gy in six fractions (two fractions of 2Gy per day). Mean doses to total lung and total kidney were restricted to less than 10 Gy and the maximum dose to the lens was restricted to less than 6 Gy. Average total lung mean dose was 9.7 Gy, total kidney mean dose was 9.6 Gy and maximum lens dose was 4.5 Gy. Mean dose was 12.7 Gy (106% of prescription dose). Mean and median follow-up times were 16 and 18 months. TBI induced acute toxicity was low with only grade 1 and 2 morbidity including patchy mucositis in 16, nausea in 12, headache in 11, fatigue in 9, neck pain in 8, xerostomia in 7, loss of appetite in 6 and faint or dull erythema in 4 patients. Grade 3 or more acute radiation toxicity was not observed. All patients were still alive at follow-up, and no leukemia relapse was observed (mean follow-up time of 16 months).

2.2.3 Dose Rationale

According to the International Lymphoma Radiation Oncology Group (ILROG), when TBI is combined with myeloablative conditioning regimens, fractionated TBI to total doses of 12-13.5 Gy are commonly employed[2]. Gassas et al.,[24] compared the outcome of hematopoietic stem cell transplantation (HSCT) in pediatric acute lymphoblastic leukemia (ALL) conditioned with two different regimens: (1) single dose of VP16 (60 mg/kg over 4 h) and TBI (1200 cGy, in six fractions) or (2) Cyclophosphamide (Cy) 50 mg/kg over 1 h daily for 4 days followed by the same TBI dose. They reported that there were no significant differences in the prevalence of acute or chronic graft-versus-host disease (GVHD) and transplant-related mortality between the two groups. Marks et al.,[25] compared the outcomes of 298 patients with acute lymphoblastic leukemia in first or second complete remission (CR1 or CR2) receiving HLA-matched sibling allografts after cyclophosphamide and total body irradiation (Cy-TBI) conditioning with 204 patients receiving etoposide and TBI. Four groups were compared: Cy-TBI <13 Gy (n=217), Cy-TBI >13 Gy (n=81), etoposide-TBI <13 Gy (n=53), and etoposide-TBI >13 Gy (n=151). Their analysis concluded that for HLA-identical sibling allografts for acute lymphoblastic leukemia in CR2, there is an advantage in substituting etoposide for Cy or, when Cy is used, in increasing the TBI dose to >13 Gy.

2.3 Rationale

To confirm the safety and efficacy of linac based VMAT for myeloablative TBI treatment delivery in patients with hematologic malignancies. VMAT-based TBI can reduce the lung dose, improve target coverage, and reduce dose heterogeneity with the goal of improving the therapeutic ratio of TBI. VMAT-based TBI can take advantage of image guidance using OBI and EPID, as well as in-vivo dosimetry using EPID. In addition, since the patient is treated on the linac couch, certain RNV safety features become available.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

There are known risks of any ASCT with myeloablative regimens including TBI including death. There are also many known late risks of TBI such as cataracts, cardiac toxicity, pulmonary toxicity, sterility, endocrine

abnormalities, and secondary malignancy. These risks, especially secondary malignancy, are potentially higher for adolescents and young adults. This study introduces the added element of linac based VMAT TBI.

One potential risk of linac based VMAT TBI is that a higher dose rate will be used for treatment delivery as compared with conventional methods of delivering TBI and this could potentially result in higher rates of idiopathic pneumonia syndrome[8,14,15].

Another potential risk of linac based VMAT TBI is that the lower dose to the lungs and kidneys could result in an increased risk of relapse. It should be noted, however, that most conventional methods for TBI block dose to the lung using lung blocks or other methods so in that sense, the use of VMAT to limit dose the lung is not unique. Furthermore, there is some preliminary data on total marrow irradiation (TMI) in which organs such as the lungs and kidneys are intentionally spared completely and the preliminary outcomes show the validity of this approach[26–28].

There could be other risks associated with a novel-treatment approach including the risks for possible errors in treatment delivery. As detailed below, many measures are taken to ensure accurate and precise dose delivery to minimize the risk of any errors.

There could be other unknown or unanticipated risks with regard to toxicity and efficacy of linac based VMAT TBI that are not present with conventional methods of TBI delivery.

2.4.2 Other Risks of Study Participation

Additional risks to study participation include breach of confidentiality. Privacy protection procedures are in place and good clinical practice guidelines will be followed throughout the study to minimize the risks associated with breach of confidentiality.

2.4.3 Known Potential Benefits

A potential benefit of linac based VMAT TBI, as opposed to our current approach of using opposed laterals to deliver TBI, is that we can minimize the dose to the lungs, without compromising coverage in the thoracic region outside of the lungs. This will have the potential of reducing the risk of idiopathic pneumonia syndrome while maximizing the effectiveness of TBI. We limit the mean dose to the kidneys, which has the potential to prevent renal dysfunction.

Since the initial writing of this protocol, Stanford has published their VMAT TBI experience which includes primarily pediatric patients (23/35 patients <18 years old).[30] Their series includes 35 patients treated with VMAT TBI, 13 with doses of 12Gy or higher as per this protocol. Their dose objectives are similar to ours with a D90%≥100% for the PTV body a Dmax≤120%, Dmean of lungs ≤660cGy. Of note, they also constrict their kidney dose and lens dose for myeloablative regimens. Their toxicity data (unpublished, data courtesy of Dr. Hui and Dr. Hiniker) is very favorable with a 4% rate of grade 2 pneumonitis (n=1, present before RT), 4% rate of grade 1 nephrotoxicity (n=1, present before RT), 40% diarrhea (4% grade 3), 56% rate of fatigue (all ≤ grade 2), 76% rate of nausea (4% grade 3), 84% rate of mucositis (36% grade 3), and 16% rate skin toxicity (all ≤grade 1).

Also since the initial writing of this protocol, a review of dose rate and pulmonary toxicity was published which bears mention given its relevance to this protocol. Vogel et al summarize the literature on the effect of dose rate and pulmonary toxicity after conventional TBI.[31] Of a total of 53 studies which report risk factors for pulmonary toxicity after TBI, 13% report dose rate as an added risk. In one of the studies included (Barrett et al., 1982), dose rate is associated with incidence of pulmonary toxicity only for lung dose ≥9Gy. This review concludes that for TBI delivered with traditional planning techniques, a dose rate ≤15cGy/minute is ideal and that total lung dose is another relevant parameter. The clinical data using IMRT or VMAT techniques, in which dose rates tend to be much higher is more limited. A report of radiation-related toxicities using organ sparing total marrow irradiation delivered intensity modulated radiation therapy with tomotherapy (n=142 patients), the dose rate was 200cGy/minute and the crude rate of radiation pneumonitis was 0.7% at a median follow up of

2 years.[32] The Stanford group changes the dose rate from the 600MU/minute default to 100-200 MU/minute for the beams treating the lungs to keep the average lung dose rate <20cGy/minute. Thus, the limited data there is on TBI delivered with IMRT technique does not show a link between increased dose rate and pneumonitis.

3 Objectives and Purpose

3.1 Primary Objective

To estimate the proportion of subjects who achieve excellent target coverage while sparing the lungs. Specifically, excellent target coverage requires that the following 3 dosimetric parameters levels have been achieved:

1) V100%≥90% (90% of PTV volume getting 100% of the dose).
2) D98>85% (98% of the volume getting at least 85% of the dose).
3) Mean Lung dose <900cGy.

3.2 Secondary Objectives

1) To estimate the cumulative incidence rate of idiopathic pneumonia syndrome in the first 100 days after transplant.
2) To estimate the cumulative failure rate (including acute GVHD, transplant related mortality or death) during the first 100 days post transplant following full-dose TBI delivered with linac based VMAT
3) To estimate the event Free Survival (EFS)
4) To estimate the following:
    a. Proportion of subjects who have achieved a mean dose to each kidney (Dmean) < 11Gy.
    b. Proportion of subjects who have achieved a maximum dose to 2cc of the entire body (D2cc) <130% of Rx dose.
    c. Proportion of subjects who have achieved a maximum dose to 0.03cc of OARs < 120% of Rx dose.
5) To summarize the subject-specific quality assurance (PSQA) for each treatment plan.

3.3 Exploratory objectives

- To explore the dosimetric consequences on the PTV, lungs and kidneys as a result of subject setup variations
- To analyze the in vivo transit dosimetry using SNC PerFraction (Fraction N) for dose tracking and correlation with subject setup
- To compare the linac based VMAT TBI vs. conventional TBI for treatment planning time
- To compare the linac based VMAT TBI vs. conventional TBI for treatment delivery time
- To conduct a cost analysis of linac based VMAT TBI vs. conventional TBI
- To explore the dosimetric consequences on the PTV, lungs, and kidneys as a result of subject setup variations.
- To analyze the in vivo transit dosimetry using SNC PerFraction (Fraction N) for dose tracking and correlation with subject setup
- To compare the linac based VMAT TBI vs. department's previous cases for treatment planning time
- To compare the linac based VMAT TBI vs. department's previous cases for treatment delivery time
- To conduct a cost analysis of linac based VMAT TBI vs department's previous cases

4 Study Design and Endpoints

4.1 Description of Study Design

Non-randomized phase II single-institution trial in which patients who consent to the trial will be treated with linac based VMAT TBI as part of their conditioning regimen for transplantation. The investigators include doctors with expertise in both adult and pediatric bone marrow transplant as well as both adult and pediatric radiation oncologists. NYU Langone Health has both an adult and a pediatric bone marrow transplant program.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

To achieve excellent coverage while sparing the lung as quantified by meeting the following dosimetric parameters: (all parameters must be met).

1. V100%≥90% (90% of PTV volume getting 100% of the dose).
2. D98>85% (98% of the volume getting at least 85% of the dose).
3. Mean Lung dose <900cGy.

4.2.2 Secondary Study Endpoints

1. The occurrence of non-infectious pneumonia syndrome in the first 100 days after transplant.
   Non-infectious pneumonia syndrome is defined by the American Thoracic Society as at least 1 of the following (i, ii, iii) without concurrent infection detected on blood culture, broncoalveolar lavage, lung biopsy or sputumi. Multilobar infiltrates on chest radiograph or computed tomography (CT)
   ii. Symptoms and signs of pneumonia including dyspnea, cough, cyanosis, hypoxia or pyrexia
   iii. New or increased restrictive patterns on pulmonary function testing or increased alveolar to arterial oxygen difference[6]..
   - There must be no concurrent cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction.
2. Occurrence of acute GVHD, transplant related mortality, or mortality in the first 100 days following transplant
3. Event Free Survival (EFS): interval from day 0 to date of first objective disease progression or relapse or death from any cause. Subjects without these failures will be censored at the last date that they were assessed and deemed failure free. The date of disease progression or relapse will be determined by the transplant team (medical oncology investigators) as per each disease-specific definition of progression or relapse. Day 0 is the day of the transplant.

4. Additional Dosimetric parameters of the linac based VMAT TBI plan not included in the primary endpoint:
   - Mean dose to each kidney (Dmean) < 11Gy.
   - Maximum dose to 2cc of the entire body (D2cc) <130% of Rx dose.
   - Maximum dose to 0.03cc of OARs < 120% of Rx dose.

5. Subject-specific quality assurance (PSQA) for each treatment plan:

- A pass rate of higher than 90% of points using a gamma criterion 5% at 3 mm and a dose threshold of 10% is required between the delivered dose to an array of detectors and the planned dose for each individual VMAT field.

4.2.3 Exploratory Endpoints

- Dosimetric consequences on the PTV, lungs and kidneys as a result of patient setup variations
- Analysis of in vivo transit dosimetry using SNC PerFraction (Fraction N) for dose tracking and correlation with patient setup
- Comparison of linac based VMAT TBI vs. conventional TBI for treatment planning time
- Comparison of linac based VMAT TBI vs. conventional TBI for treatment delivery time
- Cost analysis of linac based VMAT TBI vs. conventional TBI
- Dosimetric consequences on the PTV, lungs, and kidneys as a result of patient setup variations.
- In vivo transit dosimetry using SNC PerFraction (Fraction N) for dose tracking and correlation with patient setup
- Linac based VMAT TBI planning time vs. department's previous cases for treatment planning time
- Linac based VMAT TBI treatment delivery time vs. department's previous cases for treatment delivery time
- Linac based VMAT TBI costs vs department's previous cases

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age ≥ 10 years
2. Patients undergoing related, unrelated (including cord blood) hematopoietic progenitor cell (HPC) transplant, in which the protocol requires **≥**12 Gray of TBI, as part of the conditioning regimen.
    a. For individuals ≥18 years old, conditioning regimens outlined per BMT SOP: CLNTX007: Selection of Conditioning Regimens for Blood and Marrow Transplantation – ADULTS.
    b. For individuals <18 years old, conditioning regimens outlined per pediatric BMT SOP: CLNTX014: Selection of Conditioning Regimens for Blood and Marrow Transplantation – PEDIATRICS. Individuals < 18 years old will be included are from New York, New Jersey and Connecticut.
3. Referral from the blood and marrow transplant (BMT) program for full-dose TBI, who meet inclusion and exclusion criterial per BMT SOPs.
    a. BMT program will initiate referral, utilizing Form: 170102, Radiation Oncology Consultation.
    b. Patients undergo pre-transplant testing, as defined in BMT SOPs:CLNAL002: Related (MRD, Haplo) Allogeneic Recipient Evaluation and Management or CLNAL011: Unrelated (MUD, MMUD, CBU) Allogeneic Recipient Evaluation and Management, per below.
        i. BMT SOP's include baseline pulmonary function tests (PFTs). Patient with decreased FVC, FEV1 and or DLCO (adjusted for hemoglobin) or pulmonary history will have pulmonary consult, at the discretion of the BMT physician prior to undergoing myeloablative radiation.
        ii. Medical history and physical by BMT provider.
        iii. The following laboratory tests (additional testing may be required for positive results):
            1. ABO group and Rh type
            2. Red Blood Cell Antibody Screen.
            3. HLA typing and confirmatory typing
            4. HLA antibody screen, class I and II, performed within 30 days of transplant.
            5. Complete blood count (CBC) with differential.

6. Basic metabolic panel, including glucose and to include at a minimum electrolyte evaluation of potassium, calcium, magnesium, and phosphorus.
7. Blood urea nitrogen (BUN)
8. Creatinine
9. Liver Function Tests including:
10. Total bilirubin
11. Alkaline phosphatase
12. Aspartate aminotransferase (AST)
13. Alanine aminotransferase (ALT)
14. Lactate dehydrogenase (LDH)
15. Albumin
16. Total Protein
17. Urinalysis

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patient receiving less than 1200 cGy of TBI
2. Previous history of thoracic radiation therapy including previous TBI
3. All premenopausal women who have undergone menarche will require a urine qualitative pregnancy test to exclude pregnancy. Pregnant women will be excluded from the study.
4. Prisoners
5. Patient not meeting transplant criteria per BMT physician.

5.3 Vulnerable Subjects

Anyone eligible for full-dose TBI based conditioning regimens as preparation for ASCT will be included in the study population and not meeting the exclusion criteria. This may include vulnerable subjects including elderly patients as well as minors ages 10-17.

Beginning in October 2020, NYU Langone Health began performing ASCT in the pediatric population. Since October 2020, 8 allogeneic transplants have been performed in the pediatric unit. NYU does not have a pediatric TBI program and thus 2 patients (both 13 years of age) who needed TBI as part of their conditioning for ASCT were referred to other institutions for their transplant. NYU's program received FACT accreditation effective 1/19/22. With the increasing volume of ASCT in our pediatric population and the FACT accreditation, it is crucial that NYU develop its TBI program to accommodate these patients. As such, we are amending this protocol to include patients ages 10 and up.

5.4 Strategies for Recruitment and Retention

The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They will also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

The Principal Investigator or investigators will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.
2. Determine patient or prospective subject eligibility (inclusion and exclusion criteria).

3. Submit registration to NYU Langone Health Perlmutter Cancer Center CTO.

4. Receive registration confirmation from NYU Langone Health Perlmutter Cancer Center CTO, including a unique study identification number assigned to the subject that will be distributed to the study team upon registration of the subject. Confirmation of subject registration must be obtained before any treatment is administered or study procedures are performed.

Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy. The informed consent process and documentation follows that established procedures of NYULH Human Subject Research Standard Operating Procedures (HSR 301 Informed Consent Process and Documentation).

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will not utilize EPIC to identify subjects.

Any recruitment information sent by email will utilize Send Safe email.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyulangone.org or 1-855-777-7858.

5.5 Study Duration

The study will continue until 1 year after the day of transplant for last subject enrolled. The primary endpoint is up to 100 days post-transplant and the secondary endpoint is up to 1 year post-transplant. Accrual estimated over 15 months.

5.6 Total Number of Participants

35 participants will be accrued for this study. Consenting, screening, and treatment visits will take place at NYU Langone Health PCC.

Recruitment will end when 35 participants are accrued. It is expected that fewer than 10% of patients or prospective subjects will not be evaluable for dosimetric evaluation. Up to 70 participants may sign consent in order to achieve 35 accrued subjects; this is to account for screen failures.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

Withdrawal from the study can be made in writing to the Principal Investigator, Dr. Naamit Gerber.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. Naamit Gerber and any regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

The study intervention is a VMAT based delivery technique using a 6 MV photon beam from a Varian TrueBeam® (Palo Alto, CA) equipped with a Millennium multi-leaf collimation (MLC) system[3]. In a VMAT treatment, the linear accelerator gantry rotates continuously around the patient with the MLC leaves and dose rate varying throughout the arc delivery to modulate the dose to the target while selectively blocking the OARs.

The study will employ a feet first treatment plan for the lower body and a head first plan for the upper body.. Plans will be adequately overlapped and modulated to provide satisfactory coverage at the junction of the plans.

6.1.1 Dosing and Administration

Radiation dose will be administered according to the physician's written directive. Treatment will be administered twice a day over four consecutive days with an interfraction daily break of at least 6 hours between the end of the first fraction and the start of the next fraction.

Treatment will be administered by registered radiation therapists (RTTs). Prior to administration, the imaging system will be deployed to acquire kV, MV orthogonal projection radiography image(s) as well as CBCT image(s) to confirm accurate patient positioning. Optimal patient positioning shifts will be calculated and applied as deemed necessary based on acquired imaging. The imaging will be performed prior to the actual first day of treatment for the first patient (films only day). After that subject, we will re-evaluate the need for subsequent films only days. During delivery, the electronic portal imager device will be deployed to record the dose delivered to the participant. This technique, known as transit dosimetry, will be used to evaluate the accuracy of the treatment delivery as mentioned above.

6.1.2 Dose Adjustments/Modifications/Delays

Subjects will be treated to full dose (>12Gy) as outlined above. Adjustments to the prescription may occur at the discretion of the treating physician due to comorbidities or the participant's general condition. Dose objectives are described in section 4.2.2. Adjustments to these dose objectives may be in place at the discretion of the treating physician due to special circumstances, such as pre-irradiation and/or comorbidities outside of the thoracic region. Any modification to the outlined protocol will be noted, recorded, and taken into consideration for disease outcomes.

In the scenario that the linear accelerator used for the treatment (True Beam 1) goes down and cannot be used, and the subject needs TBI before the machine is fixed, the subject will be treated on a different machine, with whatever plan is able to be delivered (VMAT, VMAT with AP/PA, or laterals).This would likely entail adjustment of the dose objectives for the entire course. Any modification to the outlined protocol will be noted, recorded, and taken into consideration for disease outcomes.

6.1.3 Duration of Radiation Therapy

Radiation Treatment will be administered twice a day over four consecutive days with an interfraction daily break of at least 6 hours between the end of the first fraction and the start of the next fraction.

6.1.4 Tracking of Radiation Dose

Dose tracking will be performed using two different methods:

1. Reference points will be placed in the plan using Varian Eclipse treatment planning system (TPS)[21] that tracks the prescribed dose per fraction as well as the dose at individual locations.

2. In-vivo transit dosimetry during treatment will be recorded using the electronic portal imager device (EPID). This cumulative dose images will be analyzed for each fraction to track dose delivered.

6.1.5 Device Specific Considerations

This study will employ an external device to deliver the radiation therapy[3].

- Device brand: Varian
- Device model: TrueBeam® linear accelerator v2.7 or later
- Device accessories employed in this study: MLC, OBI, EPID

6.2 Study Agent Accountability Procedures

Quality assurance for the linear accelerator, OBI, EPID and MLC system will be routinely assessed as part of the current department policy and procedures (P&P) in accordance with the American Association of Physicist in Medicine (AAPM) task group 142[29].

All upper body plans will include volumetric modulated fields and will undergo patient specific QA (PSQA) prior to treatment using the electronic portal imaging device (EPID). The recorded data will be analyzed using two systems: SNC PerFraction (Fraction 0 module) and Varian Portal Dosimetry. Each field will be required to pass, with a passing rate of at least ≥ 90% using a gamma criterion of 5% at 3mm using both tools, with a preferred passing rate of ≥ 95% using a gamma criterion of 3% at 3mm.

During treatment, in vivo transit dosimetry for all VMAT fields will be acquired using Varian EPID and evaluated using SNC PerFraction (Fraction N) for dose tracking.

A backup plan using a conventional treatment at extended distance will be in place in case the linac scheduled to deliver the radiation as outlined in this document becomes unavailable for technical issues that require extended maintenance incompatible with the preset treatment schedule. Backup delivery will only be considered if the linac or imaging capabilities are down. Unavailability of transit dosimetry will not prevent treatment.

6.2.1 Administration of Procedural Intervention

Radiation therapy will be delivered by the RTTs at the department of Radiation Oncology with a qualified medical physicist (QMP) present. Participants will be positioned head first supine on the linac couch using the immobilization devices prepared at time of simulation. Participants will be triangulated using tattoos or radiopaque markers placed at simulation. Imaging will be acquired for patient positioning verification with a minimum of MV-kV orthogonal in the pelvic and head region and CBCT in the thoracic region. Optimal imaging shifts will be calculated based on all imaging and shifts will be applied when deemed necessary for accurate patient delivery and according with our tolerance tables. Imaging will be approved by physician to the first treatment and prior to subsequent fraction for all other fractions. Subjects will be treated sequentially for four regions: head, thorax, abdomen and pelvis. Subjects will then be repositioned feet first. Imaging will be acquired as per policy for positioning verification and shifts applied as needed. After positioning and imaging, treatment will be delivered to the lower body.

Subjects will be treated twice a day (BID) over four consecutive days with an interfraction break of at least 6 hours from the end of the previous treatment to the start of the following treatment. Approximate duration of the treatment is expected to range from 1 to 1.5 hours depending on participant setup, need for re-positioning, imaging, shifts, and treatment delivery time. However, it might extend past 1.5 hours for some cases.

6.2.2 Procedures for Training of Clinicians on Procedural Intervention

The physics section of the department provided training to therapists in all aspects of treatment simulation and treatment delivery in the form of dry runs and training sections. Treatment planning, treatment simulation and treatment delivery will be provided in accordance with written policies and procedures established in our department for this protocol.

6.2.3 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

Compliance with procedural intervention will be assessed according to internal policy and procedure. This will include complete delivery of dose in the number of fractions and intervals described in the study, presence of all required documentation uploaded to ARIA and required approval of imaging by physician.

7 Study Procedures and Schedule

Activity	**Consult visit[a]**	**Simulation Visit**	**On treatment visit while receiving radiation**	Follow up[b] >100 days after transplant	**1 year follow up[c]**

			(routine practice)		
Study team procedures					
Consent	X				
Medical History	X			X	X
Physical Exam	X		X	X	X
Height	X				
Weight	X				
Vitals signs	X		X	X	X
Laboratory Assessments					
Urine Pregnancy test for premenopausal participants	X	X (if not performed at consult)			
Pulmonary function tests	(pre-transplant)				X
Imaging Assessments					
CT simulation scan		X			
Adverse Events			X	X	X

[a] If not obtained at Consult visit, an additional visit will be added to obtain Consent/conduct screening
[b] @ >100 days and <150 days Follow up visit after transplant, (± 14 days)
[c] At one year follow-up following transplant, (± 30 days)

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

- Consult
- CT-simulation
- TBI treatments
- Follow up

7.1.2 Standard of Care Study Procedures

The delivery of TBI as conditioning regimen for ASCT is considered an acceptable standard of care. As such, the novel aspect of this study is the way the TBI will be planned, i.e. with VMAT-based approach.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

A urine pregnancy test will be performed in all women of child-bearing potential prior to CT simulation.

Subjects will have daily laboratory evaluations immediately following ASCT as standard of care.

Imaging will be performed as SOC following ASCT including chest x-rays or cross-sectional imaging as clinically indicated.

As the primary endpoint is a dosimetric endpoint, no specific laboratory or clinical imaging is required. All laboratory and clinical examinations ordered as SOC will be considered in determining the etiology of any pulmonary symptoms and whether it meets criteria for the secondary endpoint.

7.2.2 Other Assays or Procedures

Imaging will be performed as SOC following ASCT as clinically indicated. PFTs will be performed one year out.

7.3 Study Schedule

7.3.1 Enrollment/Baseline

The transplant team notifies radiation oncology of patients requiring TBI with a formal consultation request form, which lists the dose of TBI required and the specified dates for TBI and the transplant. Once a TBI consult request is placed, the patient is scheduled for consult and simulation. For any patient for whom the transplant team is requesting full dose (≥12 Gy) TBI, the radiation oncology team will broach the prospective subject regarding trial participation at the time of consult.

Enrollment/Baseline Visit (Visit 1, radiation oncology consultation)

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Obtain urine pregnancy test.
- Obtain demographic information, medical history, medication history, alcohol and tobacco use history.
- Record vital signs, results of examinations, other assessments.
- Baseline PFTs

7.3.2 Intermediate Visits

CT Simulation
The simulation may take place on the day of radiation oncology consultation or on a different day. If on a different day, a urine pregnancy test will be obtained within 7 days of simulation for all women of child-bearing potential.

7.3.2.1 Visit 2-5

TBI treatments will be delivered as per the transplant team, usually BID for 4 days. The most common regimens used will be will be 150cGy BID x 4 days and 165cGy BID x 4 days.
Need to record conditioning regimen data

Visit 2-5 (Days of TBI)

- During at least one of the radiation treatments, a radiation oncology attending will see the participant for an on treatment visit (OTV) and assess the participant for any acute side effects.

7.3.2.2 Visit 6

Visit 6 (>100 days and <150 days post-transplant):

- The subject will be seen in follow-up between 100-150 days post-transplant for assessment of adverse events, with specific attention to non-infectious pneumonia syndrome. All interval thoracic imaging performed will be reviewed along with the interval history.

7.3.3 Final Study Visit

- Subjects will be seen one year after transplant (± 4 weeks) for assessment of relapse free survival. Progression or relapse will be determined by reviewing the medical history and/or consulting with the transplant team if applicable. All interval thoracic imaging performed will be reviewed along with the interval history.
- Pulmonary function test assessments

7.3.4 Withdrawal/Early Termination Visit

If a subject withdraws after total body irradiation but before their final study visit, their withdrawal will be documented. Adverse event data will be recorded at this visit regardless of the interval from transplant. All interval thoracic imaging performed will be reviewed along with the interval history.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect

- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The principal investigator and/or Sub-investigator(s) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study regimen.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. Treatment-related AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent, require documentation of onset and duration of each episode.

Adverse Events (AE) and Serious Adverse Events (SAE) are unexpected toxicities that occur in the transplant setting (i.e. hematologic, gastrointestinal toxicities are expected). The Common Terminology Criteria for Adverse Events, Version 5.0, will be used for assessing the severity of adverse events. The following will be reported and monitored:

- Grade 3 or higher, non-hematologic toxicity directly related to study drugs (such as peripheral neuropathy).
- Grade 2 or higher hepatic bilirubin.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until at least 100 days (for non serious AEs) or up to one year post transplant (for SAEs) after the last day of study participation. . At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome.

Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

The Common Terminology Criteria for Adverse Events, Version 5.0, will be used for assessing the severity of adverse events.

The following will be reported and monitored for IPS:

- Grade 1-Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2- Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
- Grade 3- Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL
- Grade 4- Life-threatening consequences; urgent intervention indicated
- Grade 5- Death

8.4.2 Serious Adverse Events and Unanticipated Problems Reporting

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum, those events that must be reported are those that are:

- related to study participation,

- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

Events should be reported using the NYU CTO Medical Events Form.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.
Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the overall principal investigator. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 10 working days and to the DSMC/study sponsor/medical monitor within 24 hours of the site awareness for all deaths and immediately life-threatening events, whether related or unrelated of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DSMC/study sponsor within 10 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 days of the IRB's receipt of the report of the problem from the investigator.

Serious adverse event reporting will begin in conjunction with the date of treatment administration. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the principal investigator, assigned medical monitor, with a notification email sent to NYUPCCsafetyreports@nyulangone.org and recorded on the case report form.

All fatal or life-threatening adverse events must be immediately reported to the Principal Investigator, via appropriate reporting mechanism and the NYU Langone Health IRB by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be emailed to NYUPCCsafetyreports@nyulangone.org whether full information regarding the event is known or not.

Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. For laboratory results, include the laboratory normal ranges.

All other serious adverse events must be reported to the principal investigator and DSMC's appointed medical monitor within 24 hours by e-mail (NYUPCCsafetyreports@nyulangone.org). The Serious Adverse Event Form must also be emailed to the principal investigator, assigned medical monitor and emailed toNYUPCCsafetyreports@nyulangone.org, this documentation will be forwarded to the appropriate additional personnel within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

Current contact information shall be maintained at the site within the regulatory binder.

All serious adverse events (SAEs) will be evaluated by the DSMC if meeting the requirements for

expedited reporting, the investigator is responsible for reporting all SAEs to the appropriate IRB, DSMC, and FDA.

Follow-up report:
As a follow-up to the initial report, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event.

Other Reportable events

- **Deviations from the study protocol**

Any protocol deviations that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the NYU's IRB as soon as a possible, but ***no later than 10 working days*** of the protocol deviation.

8.4.3 Reporting of Pregnancy

Should a pregnancy occur, it must be reported immediately to the principal investigator and DSMC appointed medical monitor NYUPCCsafetyreports@nyulangone.org in accordance with the procedures described below. Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that the investigational regimen may have interfered with the effectiveness of a contraceptive medication. This will be reported to the IRB if necessary.

8.5 Reporting Procedures- Notifying the IRB

Federal regulations require timely reporting by investigators to the NYULH IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

This section also specifies the NYULH IRB requirements for investigator reporting of unanticipated problems posing risk to subjects or others, including adverse events. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – improving Human Subject Protection".
The NYU IRB address is:

NYU School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report Promptly, but no later than 10 working days:
Researchers are required to submit reports of the following problems promptly but no later than 10 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related and harmful**

– *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB- approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
– *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
– *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 10 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- **Breach of confidentiality**
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

8.6 Reporting Procedures – Notifying the Study Sponsor (NYU Langone Health)

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the principal investigator, appointed medical monitor, as well as email notification to NYUPCCsafetyreports@nyulangone.org within 24 hours of site awareness. See Section 1, Key Roles for contact information.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DSMC/principal investigator and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.7 Reporting Procedures

The reportable events noted above will be reported to the IRB using the form: “Reportable Event Form” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

The Principal Investigator is responsible for reporting all unexpected problems involving risk to participants or others to NYU Perlmutter Cancer Center CTO.

8.8 Safety Oversight

Safety oversight will be under the direction of a DSMC composed of individuals with the appropriate expertise. The DSMC will meet at least annually to assess safety and efficacy data of the study. The DSMC will operate under the rules of an approved charter.

All Internal SAEs reported, occurring to subjects on clinical trials that are not monitored by any other institution or agency, are reported to the principal investigator, DSMC appointed medical monitor, and to the DSMC via email: NYUPCCsafetyreports@nyulangone.org and reviewed within 48 hours by the medical monitor. Based on the review, one of three determinations will be made:

- SAE report is considered to be adequate
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The committee may request a cumulative review of all SAEs on the study to date.
- Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next protocol review.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety monitoring plan detailed below. Serious adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC is notified of serious adverse events via email initially, reviewed offline by the designated medical monitor, and presented at the next DSMC monthly meeting. The DSMC will review the study at least annually. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.1.1 Data Monitoring Committee

This investigator-initiated study will be monitored by the Data and Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the 2017 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for interventional clinical trials conducted in the NYULH Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULH PCC.

Per the NYU PCC Institutional Data and Safety Monitoring Plan, this pilot trial will be monitored by DSMC *annually* (from the date the first patient is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. The Principal Investigator is required to attend the review of their study. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data annually. DSMC summary reports are available to facilitate the review and monitoring of this study. These reports include the following: patient listings and summary reports that describe study enrollment and accrual, eligibility, demographic characteristics, dose modifications,

adverse experiences, subject's death and additional external published data if applicable to the study. Cumulative toxicities, SAEs, and AEs are reviewed, to identify possible adverse events with elevated frequency that is unexpected. Once a recommendation is made if further action is required, the Investigator must respond within the time period designated by the DSMC.

10 Statistical Considerations

The study is designed to estimate the proportion of patients who achieve excellent coverage while sparing the lung as quantified by meeting the following dosimetric parameters: (all parameters must be met).

1. V100%= >90% (90% of PTV volume getting 100% of the dose).
2. D98>85% (98% of the volume getting at least 85% of the dose).
3. Mean Lung dose <900cGy.

The key secondary objective is to estimate the cumulative incidence of non-infectious idiopathic pneumonia syndrome (IPS) within the first 100 days post transplant.

Non-infectious pneumonia syndrome is defined by the American Thoracic Society as at least 1 of the following (i, ii, iii) without concurrent infection detected on blood culture, broncoalveolar lavage, lung biopsy or sputum.

i. Multilobar infiltrates on chest radiograph or computed tomography (CT)
ii. Symptoms and signs of pneumonia including dyspnea, cough, cyanosis, hypoxia or pyrexia
iii. New or increased restrictive patters on pulmonary function testing or increased alveolar to arterial oxygen difference

- There must be no concurrent cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction.

Additional secondary objectives include:

Time to the first occurrence of acute GVHD, transplant related mortality or death in the first 100 days will be estimated.

Event Free Survival (EFS): interval from date of transplant to date of first objective disease progression or relapse or death from any cause. Patients without these failures will be censored at the last date that they were assessed and evaluated as failure free.

Additional Dosimetric parameters of the linac based VMAT TBI plan not included in the primary endpoint:

- Mean dose to each kidney (Dmean) < 11Gy.
- Maximum dose to 2cc of the entire body (D2cc) <130% of Rx dose.
- Maximum dose to 0.03cc of OARs < 120% of Rx dose.

Patient-specific quality assurance (PSQA) for each treatment plan:

- A pass rate of higher than 90% of points using a gamma criterion 5% at 3 mm and a dose threshold of 10% is required between the delivered dose to an array of detectors and the planned dose for each individual VMAT field.

Exploratory endpoints are:

- Dosimetric consequences on the PTV, lungs and kidneys as a result of patient setup variations
- in vivo transit dosimetry using SNC PerFraction (Fraction N) for dose tracking and correlation with patient setup
- Linac based VMAT TBI treatment planning time

- Linac based VMAT TBI treatment delivery time
- Costs of linac based VMAT TBI
- Dosimetric consequences on the PTV, lungs, and kidneys as a result of patient setup variations.
- In vivo transit dosimetry using SNC PerFraction (Fraction N) for dose tracking and correlation with patient setup.

These dosimentric outcomes will be compared with conventional TBI outcomes.

10.1 Statistical and Analytical Plans (SAP)

Characteristics of patients at start of TBI will be summarized using descriptive statistics. Radiation dosimetrty parameters will be summarized with descriptive statistics. The proportion of patients who meet the criteria for excellent coverage based on the definition above will be estimated along with exact 95% confidence intervals.

The cumulative incidence of non-infectious idiopathic pneumonia syndrome (IPS) within the first 100 days post transplant. Additionally, the time to the first occurrence of acute GVHD, transplant related mortality or death in the first 100 days will be estimated.

Event Free Survival (EFS): interval from date of transplant to date of first objective disease progression or relapse or death from any cause. Patients without these failures will be censored at the last date that they were assessed and evaluated as failure free.

95% confidence intervals and time to event curves will be provided.

Sample size considerations. We consider the proportion of patients who achieve the specified dosimetric criteria, If the true rate of success with respect to the defined dosimetric criteria is 85% or greater, with 35 patients, the lower edge of the exact Clopper Pearson one sided 95% confidence interval would be ≥68.9%.

All treated subjects who receive a bone marrow transplant will be included in all analyses.

Distributions of patient disease and treatment regimens as well as other characteristics of patients who complete TBI and receive BMT will be compared with those of patients who do not complete TBI. Analyses of secondary and exploratory endpoints will be primarily descriptive.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

TrialMaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance (QA) specialists will provide quarterly interim monitoring visits for data entry accuracy.

Source documentation should be consistent with data entered into any electronic medical record or Trial master.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

This study will be monitored according to the monitoring plan detailed below. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.) as necessary. A risk-based, data-driven monitoring approach will be used to verify data for this trial, which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will regularly review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO of any audit requests by health authorities, and will provide the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYULH Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, annually

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit will conduct quarterly interim monitoring visits to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, assent forms, informed consent form, recruitment materials, and all participant materials will be submitted to the 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol

- Key Information Sheet
- Informed Consent
- Assent for subjects ages 7-11
- Assent for subjects ages 12-14
- Assent for subjects ages 15-17

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent/assent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

The consenting process and documentation will follow the guidelines and policies of the NYULH.

13.3.3 Informed Consent

Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the research study and consent process. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies or the SOP of the local institution.

For patients who cannot read; a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

13.3.4 Assent Procedures and Documentation

In accordance with guidelines in the Federal Register 48(17): 8951-8952, 1982 (January 27th), all patients are required to sign a statement of informed consent. This study involves research, which presents greater than minimal risk but which holds the prospect of direct benefit to individual patients (46.405 - 45 Code of Federal Regulations, Part 46). Whenever children or minors (less than 18 years of age) are involved in research, federal regulations require the assent of the child or minor.

Written Assent will be obtained for subjects who are minors by the site PI or a delegated sub- investigator on the trial. Where deemed appropriate by the clinician and the minor's parents or guardian, the minor will also be included in all discussions about the trial. Requirement for documentation of assent will be determined by the IRB of record. Participation in the research protocol is the sole decision of the subject or their parent/legal guardian (if a minor). In addition to ample time to review the IRB-approved consent form, the patient/child or their parent/legal guardian (if a minor) will be allowed to ask questions and will be given the physician's office number to call if they have any additional questions. The minor who is participating in the study will know that the study doctor can talk about the study with the child's parent/guardian, but will not talk about it with anyone else who is not working on the study unless the child and the parent/guardian say it is OK. The child who is a subject on the study can call the study doctor any time if he or she has any questions. The child will be informed that he or she can stop being on the study any time.

Out of respect for children as developing persons, a detailed written assent document provides the child with information that they can take home. The signature allows the child to feel that their decision matters, and including him/ her in the process enhances the ethical principal of respect, which should be present in all human subjects research. Assent, when appropriate, will be obtained according to institutional guidelines.

In the State of New York, Child means a person who has not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

In State of New Jersey, the age of majority is 18 years but there are many situations where minors may consent to their own treatment prior to turning 18. Whenever a minor can consent to treatment, the minor is not considered a child under the regulations and may consent for themselves provided that they have the capacity to protect their own interests and the research is related to the care for which they have consented.

In the State of Connecticut, children cannot legally give consent; however, they can provide assent. Only individuals who are 18 years old (the age of majority, Conn. Gen. Stats. § 1-1d) or older, may legally consent to participate in research. Adequate provisions should be made for soliciting the independent, non-coerced assent from children. In cases where assent is obtained from a child, permission must also be obtained from parents or legally authorized representatives.

The definition of a guardian means an individual who is authorized under applicable State or local law to consent on behalf of a Child to general medical care. The definition of parent means a Child's biological or adoptive parent.

Each subject will be given a copy of the signed consent/written assent document. The physician will retain the original signed informed consent/written assent forms for subjects consenting to participate in the protocol in a locked and secure area with limited access.

13.3.5 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

If a child reaches the age of consent while still a participant in the research study, legally effective informed consent of this now-adult subject must be obtained according to SOP #HSR-301 prior to continuing his/her participation in the research.

13.4 Posting of Clinical Trial Consent Form

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject, as required by the protocol. Per Institutional guidelines, SOP#:HSR-601, instructs the principal investigator on registration and results reporting on clinicaltrials.gov.

13.5 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents.. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Health. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Health research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Health.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The biostatistician will have no interaction with potential participants and will have access only to non-identifiable subject information.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs and expected adverse reactions data) and clinical laboratory data will be entered into Trialmaster, a 21 CFR Part 11-compliant data capture system provided by DataCore. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food

and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

The study will be funded by the NYU Langone Health Hematological Disease Management Group.

15.2 Costs to the Participant

There will be no costs to subjects for participation.

15.3 Participant Reimbursements or Payments

There will be no subject payments or stipends for participation in this study.

16 Study Administration

16.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study Chairman, the PI of the Coordinating Center, and designated members of the study team. The Steering Committee will meet monthly to discuss the trial's progress, these meetings may be facilitated by CTO's quality assurance specialists.

17 Conflict of Interest Policy

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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