# PHASE II STUDY OF HIGH DOSE RADIOTHERAPY AND CONCURRENT TEMOZOLOMIDE USING BIOLOGICALLY-BASED TARGET VOLUME DEFINITION IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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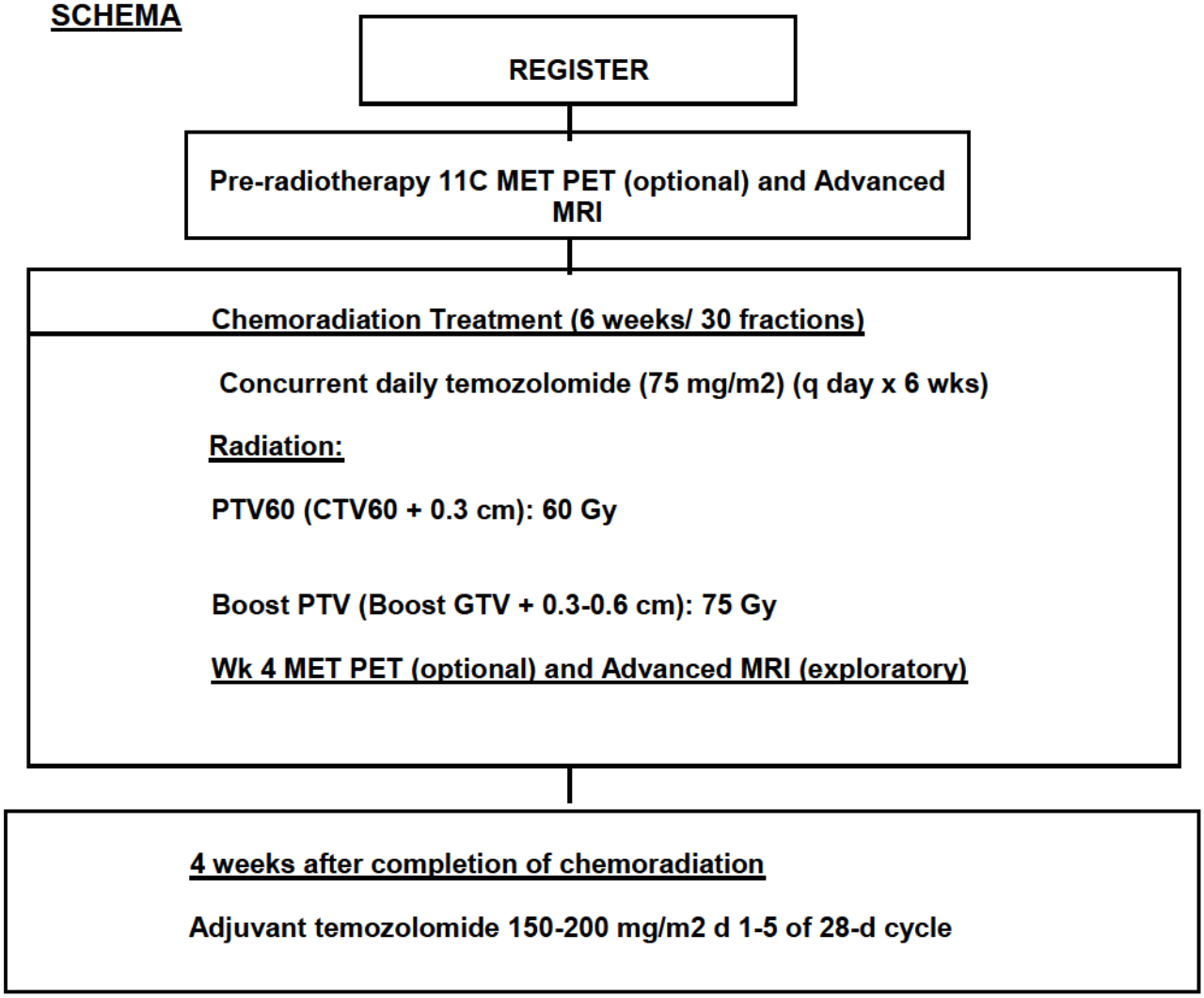
**SCHEMA**


REGISTER
Pre-radiotherapy 11C MET PET (optional) and Advanced MRI
Chemoradiation Treatment (6 weeks/ 30 fractions)
Concurrent daily temozolomide (75 mg/m2) (q day x 6 wks)
Radiation:
PTV60 (CTV60 + 0.3 cm): 60 Gy
Boost PTV (Boost GTV + 0.3-0.6 cm): 75 Gy
Wk 4 MET PET (optional) and Advanced MRI (exploratory)
4 weeks after completion of chemoradiation
Adjuvant temozolomide 150-200 mg/m2 d 1-5 of 28-d cycle

## 1.0 INTRODUCTION

Glioblastoma (GBM) is the most common primary brain tumor. Despite surgery, conventional radiotherapy and chemotherapy, the prognosis remains poor, with a median survival of 16 months. [1-2]

A phase III trial randomized 573 patients with newly diagnosed GBM to radiation therapy (RT) alone (60 Gy in 30 fractions) versus the same RT plus concurrent temozolomide followed by 6 months of adjuvant temozolomide. The combination arm demonstrated a statistically significant improvement in overall survival (14.6 vs 12.1 months) with a greater number of survivors at 2-5 years. Chemoradiation was well tolerated with an incidence of grade 3 or 4 hematologic toxicity of < 4%. This regimen is currently the standard of care for patients with newly diagnosed GBM.[3-4] However, the majority of patients continue to fail locally.[4-5] Thus, further intensification of local therapy is needed in conjunction with effective chemotherapeutic agents such as temozolomide.

Prior dose escalation studies with RT alone show that the pattern of failure can be altered with sufficiently high RT doses.[6-8]Several dose escalation studies have shown that high-dose conformal RT may improve local control; however, they were also associated with a higher rate of toxicity, predominantly symptomatic brain necrosis.[7-8] These studies used conventional contrast enhanced MRI for target volume definition, with large treatment margins, thereby leading to the delivery of high dose RT to large volumes of non-involved brain.

Important obstacles needed to be addressed in order to improve outcomes: 1) Better definition of tumor extent. 2) The ability to predict prior to radiation or during radiation which parts of a tumor are most likely to progress so that radiation may be intensified against these sub-regions. These two important issues will be addressed in this protocol.

### Metabolic PET Imaging

Recent advances in RT such as intensity-modulated radiation therapy (IMRT) offer the ability to deliver higher radiation doses to the most resistant regions of the tumor while reducing dose to the surrounding normal structures. However, advanced imaging is required to identify these resistant regions of the tumor.

Conventional contrast-enhanced T1-weighted and T2-weighted magnetic resonance imaging (MRI) used for radiation planning reflects only anatomic rather than molecular or biologic properties of the tumor. In contrast, advanced imaging with amino acid PET using carbon-11 ($^{11}$C) labeled methionine (MET PET) and advanced MR imaging may improve our ability to better define tumor extent and delineate the regions at highest risk for failure in high-grade gliomas.[9]

FDG-PET has demonstrated relatively less sensitivity in smaller tumors, intrinsic uptake within normal gray matter and reduced uptake in radiotherapy treated areas compared

to MRI.[10] In contrast, promising results have been obtained with L-methyl-$^{11}$C-methionine.$^{11}$C-methionine is an amino acid tracer with increased uptake in high grade gliomas related to increased activation of carrier-mediated transport at the blood-brain barrier and subsequent elevated protein synthesis.[11-12] Animal studies have shown that reduction in $^{11}$C methionine uptake after radiation precedes the development of tumor necrosis and tumor shrinkage, and the extent of the response seems to correlate with outcome.[13] Clinical evidence now suggests that MET PET identifies glioma beyond the region identified by conventional MRI.[14-15] A phase II trial in recurrent gliomas showed improved outcome when comparing conventional MRI to biologic target volume definition using MET PET.[16]

We have assessed the ability of MET PET to define tumor volume in a dose escalation study of GBM in which the targets were defined based on standard MRI. Pre-radiation MET PET was obtained in all patients. The majority of patients' MET PET showed uptake beyond the contrast-enhanced MRI.[17] We found that in addition to better demonstration of the extent of tumor compared to standard MRI, MET PET prior to treatment is a better modality to identify sites of future tumor recurrence. Twenty-six patients were evaluated and 19 had appreciable (>1cc) volumes of increased MET PET activity pre-therapy. In 5 patients the tumor target based on conventional MRI did not fully encompass the MET PET-defined tumor and all 5 patients had non-central failures contiguous with the MET PET defined tumor, compared with 2/14 patients whose MET PET-defined tumors were encompassed by the high-dose targets and had non-central failures. **Thus, inadequate MET PET coverage was associated with increased risk of non-central failures ($p<0.01$).**

**Functional MR Imaging**

Given the biologic heterogeneity of glioblastoma, non-central tumor recurrences are still seen even with adequate coverage of both contrast-enhancement on conventional MRI, as well as regions of MET PET uptake. To complement these modalities, functional MRI may be used to capture additional facets of tumor biology and growth that may not be completely visualized with a PET tracer.

**The use of advanced diffusion-weighted MRI to define tumor extent allows accurate spatial localization, is easy to implement in clinic, and may be complementary to the biologic information provided by amino acid PET.** Recently, we have reported on the value of a novel MRI technique that may identify dense regions of tumor that may be differentiated from edema or normal brain tissue, and potentially predict for tumor progression. Using diffusion-weighted (DW) MRI, a technique to measure the mobility of water within tissues that is sensitive to the tumor microenvironment and that could be easily implemented into widespread clinical practice, a b-value of 3000 s/mm$^2$ allowed the identification of solid tumor regions that was distinguishable from the signal from edema and normal grey and white matter, beyond standard T1-gadolinium enhanced or T2/FLAIR abnormality. Spatial analysis of patterns of failure in relation to radiation therapy dose volumes in 22 patients demonstrated that <90% coverage of the abnormal volume identified by high b-value

thresholding DW-MRI was associated with a non-central failure pattern. Moreover, patients with rapid tumor progression within a 6 month period had recurrent tumor involving at least 2/3 of abnormal volume on high b-value imaging, and inadequate coverage of the abnormal volume was associated with worse progression-free survival.[18]

More recently, we evaluated the relationship between high b-value diffusion MRI and perfusion MRI (Wahl DR, IJROBP 2016). Of 35 patients with newly diagnosed GBM, the abnormality identified by high b-value diffusion MRI ($TV_{HCV}$) and that identified by perfusion MRI ($TV_{CBV}$) defined spatially distinct regions of tumor with mean overlap of only 21%, with 40% of each of these volumes falling outside of the standard gadolinium-enhanced tumor region. On univariate analysis, increasing $TV_{HCV}$ and $TV_{CBV}$ were associated with inferior progression-free survival, while $TV_{HCV}$ was the most important imaging-defined variable associated with inferior progression-free survival on multivariate analysis. On evaluation of patterns of failure, areas of progressive GBM generally coincided with the HCV, CBV or volume of overlap between the two, with the highest positive predictive value (77%) for the percentage of a given volume of interest coinciding with the area of contrast-enhancing progression being the overlap between $TV_{HCV}$ and $TV_{CBV}$ (unpublished data, Figure). Thus, spatially distinct subvolumes of GBM were identified using a combination of advanced imaging technologies that each contained prognostic information, and potentially represent varying biologic phenotypes with distinct genetic alterations that could be use to guide therapy.

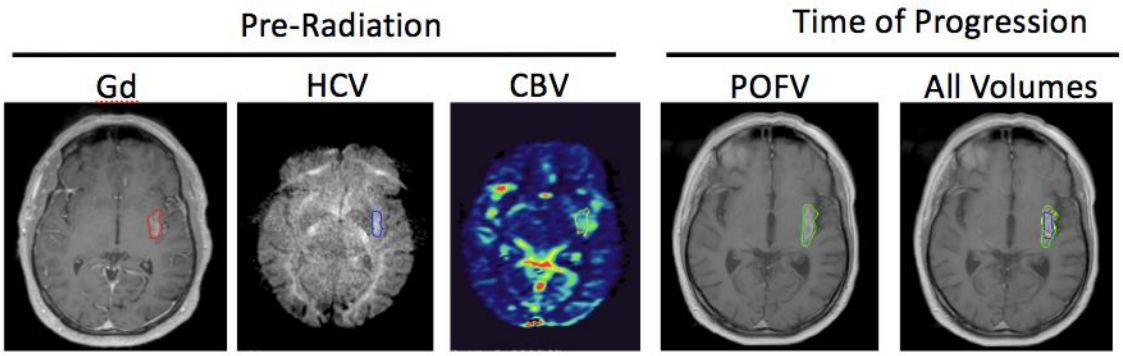



**Figure. MR imaging of pretreatment volumes of interest and correlation to patterns of failure.** Prior to radiation (left), underwent conventional T1-post gadolinium contrast imaging to define the volume of abnormal enhancement (Gd). They also underwent high b-value diffusion imaging to determine the hypercellular volume (HCV) and T1-weighted dynamic contrast enhanced perfusion images to define the cerebral blood volume (CBV). Following treatment (right), a multidisciplinary team defined the pattern of failure volume (POFV) where the GBM recurred. Images were co-registered and volumes overlaid to assess overlap.

Summary

Conventional MR imaging is inadequate in defining the extent of tumor growth and high-risk tumor regions that are likely to recur. **Advanced imaging techniques such as MET PET and high b-value DW-MRI and perfusion MRI capture tumor extent and identify regions at increased risk for recurrence, and may provide complementary information about the tumor that can be used to direct therapy.**

**Early imaging changes: Predicting response to therapy**

Recent evidence suggests that it may be possible to predict response in glioma early in treatment using either PET or MRI techniques such as diffusion-weighted MRI.[19] The hypothesis underlying this approach is that changes in tumor water diffusion that occur following successful treatment can be attributed to increases in the extracellular space, resulting from necrosis and/or apoptotic processes. The change in cellularity due to cell kill, along with tissue reorganization, leads to heterogeneous changes in the underlying tissue morphology (e.g. ratio of intra- to extra-cellular water) resulting in spatially varying changes in tumor apparent diffusion coefficient (ADC) values. Multiple papers by us and by others have described the utility of diffusion MRI to detect early response to therapy (radiation, chemotherapy, gene therapy) in experimental tumors of various histologies and sites. [20-22]

These initial results were validated in a prospective, single institutional study at the University of Michigan. Sixty patients with high grade gliomas undergoing RT were enrolled in a study of intra-treatment MRI at Week 1(Wk) and 3 (mid-course) of RT. Fractional tumor volume with increased diffusion on $PRM_{ADC}$ Wk 3 was the strongest predictor of patient survival at one-year, with larger volume predicting longer median survival (17.8 vs. 8.9 months, log-rank, $p<0.003$, HR 2.7(95% CI: 1.5-5.9). These results remained significant when limited to GBM patients.[23]

In addition, perfusion MRI allows an estimation of blood flow, blood volume, and vascular permeability, which can be a surrogate marker of the integrity of the blood-brain-barrier, and which may provide imaging evidence of tumor response to therapeutic interventions including anti-angiogenic therapy.[24-27] We have also reported on the use of perfusion imaging as a biomarker to distinguish true progression from pseudoprogression in high-grade glioma.[28]

Moreover, we evaluated the extent and severity of vascular leakage, as defined by gadolinium enhancement on MRI, as evidence of tumor aggressiveness in high grade glioma. We hypothesized that the vascular leakage volume pre-RT, reflecting disorganized angiogenesis typical of glioblastoma, would predict clinical outcome. We studied prospectively 20 patients with newly diagnosed high grade glioma. When time to progression was tested as a dependent variable, both the vascular leakage volume and vascular permeability were significant predictors.[29] In addition, early temporal changes during RT in heterogeneous regions of high and low perfusion in gliomas were found to predict response to RT.[29]

These extensive studies demonstrate the prognostic importance of various parameters tested by MET PET and functional MRI, open the opportunity to select or combine the

best available imaging modalities to identify treatment-resistant tumor subvolumes that may benefit from locally intensified RT. As of yet, there is no published data looking at the value of interim MET PET or high b-value diffusion weighted imaging to evaluate early changes in tumor during chemoradiation that may potentially predict for outcome. The study we propose herein will also evaluate potential early changes in treatment as seen on MET PET and functional MRI, and correlate these changes with outcome.

**Dose Escalation and Toxicity**

An important aspect of tumor dose re-distribution and intensification is the need to keep toxicity at a level that does not exceed the level observed following standard therapy.

We have recently summarized our phase I-II TITE-CRM radiation dose-escalation study concurrent with temozolomide for GBM. IMRT doses were escalated from 66 to 81 Gy over 6 weeks and targets consisted of the entire contrast-enhancing lesion on MRI. Thirty-eight patients were analyzed with median follow-up of 54 months for patients who are alive. **No radiation necrosis or late CNS toxicity was observed at or below 75 Gy.** Median OS was an encouraging 20.1 months (95% CI: 13.2, 34.3). The probability of central field recurrence decreased with increasing dose (logistic regression, $p<0.03$). These findings showed that GBM patients can safely receive dose-escalated RT delivered with IMRT with concurrent temolozomide.[30]

Functional imaging can aid in predicting sequelae of therapy. Diffusion tensor MRI (DT-MRI) has been shown to detect early structural white matter changes[31-32] that may correlate with late neurocognitive function after therapy in children[33-34] and in patients with low-grade gliomas.[35] We have examined whether early assessment of cerebral white matter degradation using diffusion-tensor MRI (DT-MRI) could predict late radiation toxicity. Twenty-five patients including 19 with GBM underwent DT-MRI prior, during, and following RT. DT indices including mean diffusivity of water, fractional anisotropy of diffusion, and diffusivity perpendicular and parallel to white matter fibers. In normal appearing large white matter fibers such as the genu and splenium of the corpus callosum, our study demonstrated that structural changes following RT were progressive, with early dose-dependent demyelination and axonal degradation. This study suggested DT-MRI as a potential biomarker for the assessment and/or prediction of radiation-induced white matter injury.[31] We have also analyzed an additional ten patients undergoing conformal fractionated brain RT who underwent DT-MRI and neurocognitive function testing before RT, at 3 & 6 weeks during RT, and 10, 30 and 78 weeks after RT. Parallel diffusivity decreased significantly and perpendicular diffusivity increased significantly following RT, implying axonal degradation and demyelination, respectively. The diffusivity changes were correlated with doses. Cingulum diffusivity changes at 3 and 6 weeks during RT predicted late changes in verbal recall scores by receiver operator characteristic analysis ($p<0.05$).[36]

**Summary**

**We are now aiming to build upon our prior results by improving the definition of the tumor target, as well as the tumor subvolumes at highest risk of local failure in each patient.**

Pre-radiotherapy high b-value DW-MRI and perfusion MRI will be used to determine the appropriate radiation target volume for RT boost intensification. All patients will receive a higher RT dose directed solely by biologic target volumes defined by these advanced imaging techniques. **We hypothesize that by distributing the high dose to the tumor subvolumes that are most likely to prove resistant, and reducing irradiated brain volumes, we will achieve higher rates of non-complicated local control.**

We will prospectively acquire baseline and interim MET PET and advanced MRI sequences during treatment and correlate imaging findings between modalities, and with subsequent patterns of failure, progression-free and overall survival. Outcomes among patients treated with individualized, biologic-based imaging will be compared to historical controls, and will be used for future randomized clinical trials in a multi-institutional setting.

## 2.0 OBJECTIVES

The overall goal of this study is to determine if the treatment regimen described in this protocol is sufficiently promising to advance to a definitive randomized trial.

### 2.1 Primary Objective

To estimate 12-month overall survival (OS) of GBM patients treated with high-dose RT based on high b-value DW-MRI and perfusion MRI planning, with concurrent temozolomide, in relation to historical controls

### 2.2 Secondary Objectives

2.2.1 To estimate progression-free survival (PFS), patterns of failure and response rates in relation to values from historical control patients

2.2.2 To assess the ability of pre-treatment and mid-treatment MET PET and advanced MRI to determine areas at high risk of recurrence

2.2.3 To prospectively compare tumor volumes defined by MET PET with high b-value DW-MRI and perfusion MRI.

2.2.4 To assess the ability of post-treatment advanced MRI to distinguish progression from pseudoprogression

2.2.5 To provide descriptive data regarding health-related quality of life (QOL), symptoms and neurocognitive function

## 3.0 PATIENT SELECTION

### 3.1 Eligibility Criteria

3.1.1 Newly diagnosed, histologically-confirmed supratentorial WHO grade IV gliomas including glioblastoma (all variants) and gliosarcoma.

3.1.2 Patients must be 18 years of age or older.

3.1.3 Karnofsky performance status ≥ 70

3.1.4 Minimal life expectancy of 12 weeks.

3.1.5 Adequate bone marrow reserve (Hemoglobin ≥ 10 g/dL, absolute neutrophils ≥ 1500/$mm^3$, platelet count ≥ 100,000/$mm^3$), acceptable liver function (total bilirubin ≤ 2 x upper limit of normal (ULN) (unless elevated bilirubin is related to Gilbert syndrome), and ALT/AST ≤ 5 x ULN) and renal function (serum creatinine ≤ 2.0 mg/dL) within 14 day prior to registration. Eligibility level for hemoglobin may be reached by transfusion.

3.1.6 Maximal contiguous volume of tumor based on high b-value diffusion MRI < 1/3 volume of brain

3.1.7 Patients must be registered within 6 weeks of most recent resection

3.1.8 Study-specific informed consent approved for this purpose by the IRB of the University of Michigan indicating that they are aware of the investigational nature of the treatment and the potential risks must be signed by the patient.

### 3.2 Ineligibility Criteria

3.2.1 Recurrent glioma, or tumor involving the brainstem or cerebellum. Prior low-grade glioma without prior RT, now with malignant progression are eligible.

3.2.2 Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment is not permitted. Prior chemotherapy for a different cancer is allowable if interval since last treatment cycle completion is >3 years.

3.2.3 Evidence of CSF dissemination (positive CSF cytology for malignancy or MRI findings consistent with CSF dissemination).

3.2.4 Evidence of severe concurrent disease requiring treatment

3.2.5 Prior invasive malignancy (except non-melanoma skin cancer or non-life limiting invasive malignancy that may not require treatment, such as low-risk prostate cancer) unless disease-free for a minimum of 3 years (for example, carcinoma in situ of breast, oral cavity or cervix are all permissible)

3.2.6 Patients unable to undergo MRI exams (i.e. patients with non-compatible devices such as cardiac pacemakers, other implanted electronic devices, metallic prostheses, or ferromagnetic prostheses [e.g. pins in artificial joints and surgical pins/clips], or unable to receive gadolinium for MRI, as per the standard UM Department of Radiology MRI screening criteria).

3.2.7 Patients treated with previous cranial or head/neck radiotherapy leading to significant radiation field overlap.

3.2.8 Females of child-bearing potential must have a negative pregnancy test within 14 days prior to registration. Patients with reproductive potential must agree to use an effective contraceptive method during treatment

3.2.9 Multifocal disease (>1 lobe of involvement) of discontiguous contrast enhancing disease as seen on conventional MRI

## 4.0 PRETREATMENT EVALUATIONS

4.1 Complete history and physical exam including assessment of Karnofsky performance status, and medication reconciliation to include steroid and anti-epileptic medication dose and schedule.

4.2 Complete neurologic exam and the Neurologic Assessment in Neuro-Oncology (NANO) Scale.[37]

4.3 Detailed neurological, QOL and symptom evaluation including Folstein mini-mental status examination (MMSE), quality of life questionnaire (EORTC QLQ-C30/BN-20) and MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT).

4.4 Laboratory evaluation within 14 days prior to registration, to include: CBC with differential, platelet count, comprehensive metabolic panel including BUN, serum creatinine, total bilirubin, SGOT or AST.

4.5 Preoperative CT or MR scan.

4.6 Contrast-enhanced post-operative MRI *(*preferably within 72 hours after the surgical procedure) must be obtained within the 5 weeks prior to initiating radiotherapy to determine tumor volume.

4.7 Neurocognitive testing including Controlled Oral Word Association (COWA), Trail Making A and B, and Hopkins Verbal Learning Test-Revised (HVLT-R). Testing will occur after adequate recovery from surgery, prior to initiation of RT.

## 5.0 REGISTRATION PROCEDURES

After informed consent is obtained and prior to the initiation of protocol therapy, all patients must be first registered with the UM-CCC Clinical Trials Office. Patients satisfying the inclusion/exclusion criteria will be eligible for registration into the study once an eligibility checklist is signed. A copy of the signed, institutionally approved informed consent together with copies of pertinent source documents and eligibility checklist will be needed to complete the registration process.

## 6.0 RADIATION THERAPY

### 6.1 Radiation Dose and Fractionation

Radiation therapy will be delivered once daily for a total of 30 fractions, five days per week. If treatment is interrupted due to a non dose-limiting adverse event or any reason other than toxicity, including holidays, weather, transportation, or treatment machine problems, the duration of treatment will be extended accordingly. An initial treatment plan will be designed to simultaneously deliver differing doses per fraction to 2 PTV volumes: 60 Gy to the conventional MRI volume (PTV_Low), which is the volume and dose used in standard practice. An additional simultaneous boost will be delivered to the combination of high b-value diffusion and perfusion abnormality alone (PTV_High, the area assumed to be at highest risk of tumor recurrence).

Patients with a negative postoperative high b-value DW-MRI and perfusion MRI following complete resection will be treated to the post-operative resection cavity and conventional T1 MRI contrast-enhancing region to a total dose of 60 Gy, as per standard of care, and will remain on study to be analyzed with the entire study cohort. A negative high b-value DW-MRI or perfusion MRI will be defined as a combined high b-value DW-MRI and perfusion target volume of 1 cc or less. Radiation dose will be prescribed to ensure that at least 95% of the PTV ($D_{95\%}$) should be covered by 100% of the prescription dose.

### 6.2 Target Volumes

Target volumes will be based on the postoperative conventional MRI, and high b-value diffusion as well as perfusion MRI. Pre-operative conventional MRI should be reviewed in correlation with the post-operative residual tumor bed as per standard of care. Target volumes for this treatment are as follows:

Gross tumor volume, conventional MRI (GTV_Low): shall be defined as the area of enhancement plus surgical cavity on pre-radiotherapy T1-gadolinium enhanced MRI, as per standard practice. If the conventional MRI does not show any abnormal enhancement, the GTV_Low will include the surgical cavity alone, as per standard practice.

Gross tumor volume, high b-value DW-MRI and perfusion MRI (GTV^HCV_perf): shall be defined as the area of abnormality on pre-radiotherapy high b-value diffusion MRI and perfusion MRI. The HCV target volume will be defined as previously published[18] on b=3000 s/mm$^2$ diffusion weighted imaging by a threshold technique (mean intensity plus 2 standard deviations) calculated from a volume of interest in the normal-appearing brain tissue in the contralateral brain from the tumor.

Clinical target volume, conventional MRI (CTV_Low): GTV_Low will be expanded by 1.7 cm to account for microscopic disease extension, and edited out of normal structures (e.g. calvarium, falx) as per standard of care.

Clinical target volume, high b-value DW-MRI and perfusion MRI (CTV^HCV_perf): CTV^HCV will be set equal to the GTV^HCV

Planning target volume, conventional MRI (PTV_Low): CTV_Low will be expanded by a margin of 0.3 cm, to account for daily patient set-up variability

Planning target volume, high b-value DW-MRI and perfusion MRI(PTV_High): CTV^HCV_perf will be expanded by a margin of 0.3-0.6 cm, or as appropriate to account for registration and daily patient set-up variability.

## 6.3 Treatment Planning and Localization Requirements

*Immobilization / Simulation:* A treatment planning CT and/or MRI will be obtained with the patient in the same position and immobilization device as for treatment. All patients will be positioned and immobilized with individualized thermoplastic masks to ensure precise localization methods.

*Treatment Planning:* All patients will undergo MR-guided treatment planning with a high b-value diffusion MRI-defined boost volume. GTV definition, CTV definition, and PTV margin are as described above. CTV and relevant normal tissues will be outlined on planning scan slices. The PTV margins will ensure adequate dose coverage by correcting for variability in treatment set-up and registration variability. Intensity modulated radiotherapy (IMRT) or rapid arc plans will be used to achieve the highest prescription dose to the target, while minimizing dose to the normal brain and other critical structures. The tumor and critical organ constraints are described in further detail below.

*Target Volume Coverage:* PTV_Low will be treated with a prescription dose of 60 Gy in 2 Gy fractions over 30 fractions, with a minimum dose of 95% of the prescription dose. Additionally, the volume of PTV_Low receiving a dose > 105% of the boost PTV prescription dose will be minimized based on achieving the PTV_Low dose prescription requirements.

PTV_High will be treated with a prescription dose of 75 Gy in 2.5 Gy fractions over 30 fractions. Minimum dose to PTV_High will be 95% of the prescription dose, and maximum dose should be no more than 105% of the prescribed dose (no plan that includes any dose greater than 110% will be accepted.)

*Organs at Risk:* The following critical normal tissues including the brain, brain stem, optic nerves, optic chiasm, and external surface will be outlined on the appropriate MRI/CT scans. Any compromises to the target because of physician decision to spare visual pathway or brainstem will be well-documented.

## 6.4 Radiation Toxicity

Toxicities will be assessed using diagnostic imaging and physical exam and neurologic testing including MMSE. Toxicities will be graded clinically according to Common Toxicity Criteria *(CTC)*.

### 6.4.1 Acute

Expected acute radiation-induced toxicities include hair loss; erythema or soreness of the scalp; nausea and vomiting; dry mouth; altered taste; fatigue; temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness; ear complications such as plugging of the ears, decreased hearing, or redness (erythema).

6.4.2 Early Delayed

Possible early delayed radiation effects include lethargy, transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

6.4.3 Late Delayed

Possible late delayed effects of radiotherapy include cataracts, and or eye damage leading to blindness, radiation necrosis, radiation leukoencephalopathy, radiation vasculopathy, pituitary dysfunction, radiation-induced neoplasms, and damage to the brainstem leading to significant motor or sensory deficits or even death.

## 7.0 DRUG THERAPY

### 7.1 Temozolomide

**7.1.1 Description:** Temozolomide is a methylating agent belonging to a group of compounds, imidazotetrazinones. Its chemical name is 8-carbamoyl-3-methylimidazo [5,1-d]1,2,3,5-tetrazin-4*(3H)*-one.

**7.1.2 Toxicology:**

Likely toxicities (occurring in >20% of patients) include: fatigue, nausea, vomiting, alopecia, headache, seizure, constipation, lymphopenia, anorexia.

Common toxicities (occurring in 3-20% of patients) include: confusion, memory impairment, blurred vision, allergic reaction, abdominal pain, diarrhea, stomatitis, arthralgia, thrombocytopenia, insomnia, coughing, dyspnea, dry skin, erythema, pruritis, rash, taste perversion, fever, back pain, peripheral edema, somnolence, myalgias, anxiety, depression, breast pain, upper respiratory infection, pharyngitis, sinusitis, urinary tract infection, increased urinary frequency, anemia, neutropenia, thrombocytopenia, decreased WBC.

Rare but serious toxicities (occurring in fewer than 3% of patients) include: anaphylaxis, erythema multiforme, toxic epidermal necrolysis/Stevens-Johnson syndrome, *Pneumocystis jiroveci* pneumonia, interstitial pneumonitis, alveolitis, pulmonary fibrosis, prolonged pancytopenia, aplastic anemia.

**Pharmacology**

**7.1.2.1 Mechanism of Action:** Temozolomide undergoes chemical degradation at physiologic pH to form MTIC *(3-methyl-[triazen-1-y1])* imidazole-4-carboxamide, the active metabolite of dacarbazine. The cytotoxicity of MTIC is thought to be primarily due to alkylation at the O6 position of guanine residues18 with additional alkylation occurring at the N7 position.

**7.1.2.2 Pharmaceutical Data:** Temozolomide is supplied in white opaque, preservative free, 2-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Capsules should not be opened or chewed. If capsules are accidentally opened or damaged, inhalation or contact with the skin and mucous membranes should be avoided.

**7.1.2.3 Storage and Stability :** The capsules are packaged in 30 cc 28 mm-48- Type I amber glass bottles *(30 capsules/bottle)* and should be stored between 2 and 30 degrees Centigrade. Capsules are stable for <u>at least</u> 30 months when stored in amber glass bottles at this temperature.

**7.1.2.4 Supplier:** Temozolomide is commercially available.

### 7.1.3 Recommended Concurrent Temozolomide Dose Modification:

Recommended dose modifications are as follows:

A weekly CBCPD will be drawn during concurrent temozolomide and radiotherapy treatment. Dose reductions may be made at the discretion of the treating physician, standardly not less than 67% of the starting dose (50 mg/m$^2$). Dose reduction, delay or discontinuation of temozolomide administration will be decided weekly according to hematologic and non-hematologic adverse events (AEs) as recommended below.* If the administration of temozolomide has to be interrupted, the radiotherapy will proceed normally. Missed doses of temozolomide will not be made up at the end of radiotherapy.

*If one of more of the following are observed

- ANC <1.5X10$^9$/L
- Platelet count <100 X10$^9$/L
- Grade 3 non-hematologic AE (except alopecia, nausea and vomiting while on maximum anti-emetic and fatigue)

Then treatment with concomitant temozolomide will be held until all of the following conditions are met:

- ANC ≥1.5X10$^9$/L
- Platelet count ≥100 X10$^9$/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting while on maximum anti-emetic and fatigue)

As soon as all of the above conditions are met, the administration of temozolomide will resume at the same dose as used initially.

If one of more of the following are observed:

- ANC <0.5X10$^9$/L
- Platelet count <75 X10$^9$/L
- Grade 4 non-hematologic AE (except alopecia, nausea and vomiting while on maximum anti-emetic, and fatigue)

Then temozolomide treatment concomitant with radiation will be permanently discontinued.

**7.1.4.2** A CBCPD will be obtained prior to each cycle of adjuvant temozolomide. A nadir CBCPD count will be drawn on day 22 (+/- 5 day window) of each cycle. These lab tests may be drawn at laboratories outside the University of Michigan provided the results sent to University of Michigan for toxicity assessment and dose modification.

Recommended dosing is based on adverse events during the prior treatment cycle. If multiple AE's are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

| Dose Level | Temozolomide Dose, mg/m2/day | Remarks |
|---|---|---|
| -2 | 100 | Reduction if prior AE |
| -1 | 125 | Reduction if prior AE |
| 0 | 150 | Starting dose cycle 1 (adjuvant) |
| +1 | 200 | Escalated dose at cycle 2, for cycles 2-12 in absence of AE |

**Delay**

On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x $10^9$/L, platelet count ≥ 100 x $10^9$/L and all treatment-related grade 3 or 4 non-hematologic AEs (except alopecia, nausea, and vomiting) must have resolved (to grade ≤ 1).
If AEs persists, treatment should be delayed by 2 weeks for up to 4 consecutive weeks. If, after 4 weeks of delay, all AEs have still not resolved: then any further adjuvant treatment with temozolomide should be stopped.

**Dose escalation**

If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100 x $10^9$/L and ANC ≥ 1.5 x$10^9$/L: then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (3-12).

**Dose reductions**
If any non-hematologic AE observed was grade > 2 (except alopecia, nausea and vomiting) and/or if platelets < 50 x $10^9$/L and/or ANC < 1 x $10^9$/L, then the dose should be reduced by one dose level. For patients who would require dose reductions to a dose level < 100 mg/m2/day, temozolomide will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then temozolomide will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea and vomiting) then adjuvant temozolomide treatment should be stopped.

*Subsequent cycles (3-12):* Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

*Important:* If the dose was reduced or delayed for adverse events, there will be no dose escalation.

The reason(s) for dose reduction and/or delay must be documented in the CRF.

Summary of Recommended Dose Modification or Discontinuation During Post-Radiation Temozolomide

| **Worst Non-Hematologic AE (except alopecia, nausea and vomiting) During the Previous Cycles** | |
|---|---|
| **Grade** | |

| | |
|---|---|
| **0-2** | No dose modifications for non-hematologic AEs. Dose escalations (only for cycle 2) or reductions based on ANC and platelet counts are applicable. |
| **3** | Reduce by one dose level (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. No further escalation is possible. If the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then stop. |
| **4** | Stop (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. |

| Nadir Values | | Platelets | | |
|---|---|---|---|---|
| | | **≥100 x $10^9$/L** | **50 – 99 x $10^9$/L** | **< 50 x $10^9$/L** |
| **ANC** | **≥ 1.5 x $10^9$/L** | Escalation to DL 1 (cycle 2 only) | Dose unchanged | Reduce by 1 dose level |
| | **≥1 & <1.5 x $10^9$/L** | Dose unchanged | Dose unchanged | Reduce by 1 dose level |
| | **< 1 x $10^9$/L** | Reduce by 1 dose level | Reduce by 1 dose level | Reduce by 1 dose level |

| **Hematologic AE on Day 1 of Each Cycle (within 72 hours before)** | |
|---|---|
| **AE** | **Delay** |
| ANC < 1.5 x $10^9$/L and/or Platelet count < 100 x $10^9$/L | Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible. |

| **Non-Hematological AE (except for alopecia, nausea and vomiting) on Day 1 of Each Cycle (within 72 hours before)** | |
|---|---|
| **Grade** | **Delay** |
| **2-3** | Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible. |

## 8.0 SURGERY

8.1 The extent of surgical resection shall be documented as a) biopsy, or b) subtotal resection or c) gross total tumor resection as described by the operative report and by postoperative imaging.

8.2 If post-radiation imaging demonstrates changes concerning for tumor progression versus treatment-related change and the clinical situation warrants, a biopsy or repeat resection for diagnostic and/or therapeutic purposes may be performed at physician discretion as per standard clinical practice. Surgery would be performed as part of standard care and is not part of this study. Hospitalization for this procedure (part of routine clinical practice) may not be considered an SAE.

8.3 $O^6$-methylguanine-DNA methyltransferase (MGMT) promoter methylation status and IDH-1 (assessed as part of standard practice) will be documented.

## 9.0 OTHER THERAPY (WHICH IS STANDARD FOR PATIENTS WITH GBM)

9.1 Steroids and anti-seizure medications may be given as clinically indicated. The total dose must be recorded pre-treatment, and at the time of each treatment evaluation. Steroids will be used in the smallest dose that will afford the patient satisfactory neurologic function and the best possible quality of life.

9.2 Prophylactic pneumocystis jirovecii pneumonia (PCJ) prophylaxis is a matter of physician judgment. If prophylaxis is offered during the concurrent phase, the use of monthly aerosolized pentamidine is recommended.

9.3 Analgesics and any other medications are to be specified and their dose recorded.

9.4 Data will be collected (for example, start date, total duration) on whether patients receive Novo-TTF (Optune) after radiation therapy, which is part of standard treatment for patients with GBM

## 10.0 PATIENT ASSESSMENTS

### 10.1 Study Plan

10.1.1 Patients will receive concomitant temozolomide (75 mg/$m^2$ daily for 6 weeks) with radiotherapy as per standard of care.

10.1.2 Temozolomide will be taken orally prior to RT. The physician will discuss with the patient any eating restrictions, when other medications should be taken, and when temozolomide should be taken on the days without RT as per standard of care.

10.1.3 Adjuvant temozolomide 150-200 mg/$m^2$ D1-5 q28 days (+/- 5 days) for six cycles will be started approximately 4 weeks following completion of radiotherapy. Additional cycles may be continued at investigator's

discretion. The first cycle will be prescribed at 150 mg/m$^{2,}$ then increase to 200 mg/m$^2$at cycle 2, toxicity permitting, as per standard of care.

10.1.4 Patients will receive RT at the University of Michigan or one of its affiliate centers. The patient will be considered eligible to receive concurrent and adjuvant chemotherapy through outside physicians closer to his/her home with continued follow-up at the University of Michigan per study guidelines

| **10.2 Study Specific Calendar** | Pre-Rx Evaluation | During XRT | Prior to Each Chemotherapy Cycle | Follow-up Evaluation[a,g] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Month | | | | | |
| | | | | 1 | 3 | 5 | 7 | 13 | 19 |
| History & Physical Exam | x | | | x | x | x | x | x | x |
| KPS & Neurological Exam | x | x[b] (wk 6 of RT | | x | x | x | x | x | x |
| QOL Evaluation/MDASI/MMSE[c] | x | x[c] (wk 6 of RT) | | x | x | x | x | x | x |
| CBC w/ Diff, Platelets | x | x[d] | x[d] | | | | | | |
| Comprehensive metabolic panel | x | | x[d] | | | | | | |
| Neurocognitive evaluation | x[b] | | | x | | | x | | x |
| Gadolinium enhanced Brain MR [e] | x | | | x | x | x | x | x | x |
| Advanced MRI | x | x[f] (wk 4 of RT) | | | x[f] | | | | |
| 11C MET PET | X[i] (optional) | x[f] (wk 4 of RT) | | | | | | | |
| Toxicity Notation | x | x | | x | x | x | x | x | x |

a) Timing of follow ups (1 month = 28 days): As per standard of care, patients will typically be seen in follow-up 1 month after completion of chemoradiation, then every 2 months +/- 2 week window. At the physician's discretion, after the first 6 months, follow-up visits may be approximately every 3 months. If a patient's temozolomide cycles are prolonged due to time for blood count recovery or other factors, assessments may be delayed in accord with the temozolomide cycles. At follow-up visits, history and physical exam, KPS and neurologic exam, and toxicity evaluations will be undertaken.

b) KPS and recording of steroid and anticonvulsant dose will be required during week 6 of radiotherapy. NANO evaluation will be required at baseline

and at the time of advanced imaging follow-up (3 months post-RT and/or at the time of suspected progression).

c) QOL/MDASI/MMSE evaluations will be undertaken at baseline, , 6 weeks (end RT), 1 month, 7 month, 13 month, 19 month (+/- 6 weeks) after the end of chemoradiation, typically at the time of standard clinical follow-up and preferably close to the date of imaging if imaging is obtained. Neurocognitive evaluation will be undertaken at baseline, 1 month, 7 months, and 19 months after chemoradiation (+/- 6 weeks).

d) CBCD to be drawn weekly during radiation, and prior to every cycle of adjuvant chemotherapy, beginning with first cycle as per standard of care. Comprehensive metabolic panel will be drawn at least every 8 weeks, or more frequently at primary oncologist's discretion, as per standard practice.

e) Clinical gadolinium enhanced MRI brain scans will be obtained as per standard clinical practice approximately every 8 weeks after chemoradiation, or per the treating physician's discretion as per standard practice.

f) Up to 10 patients will optionally receive MET PET during Wk 4. All patients will receive advanced MRI (see appendix for details) at Wk 4 (between fractions 17-20), and an additional advanced MRI scan will be obtained 3 months (+/- 1 week) after completion of chemoradiation and/or at the time of suspected tumor recurrence.

g) Patients will be followed for tumor progression and survival for up to 5 years from the end of radiotherapy. Tumor progression and date and cause of death will be documented, if known. Studies available in the clinical setting may also be used for study purpose as indicated under study aims.

i) Only the first 30 patients total will optionally receive pre-radiotherapy MET PET

## 10.3 Evaluation during Study

10.3.1 A neurologic examination including NANO evaluation, performance status, Folstein MMSE, QOL questionnaires and symptom survey shall be performed according to the Study Calendar schedule (10.2).

10.3.2 A contrast enhanced MRI of the brain shall be obtained prior to radiotherapy as part of standard care. Clinical brain MRI will be obtained as part of standard follow-up as stated in the study calendar above. Additional MRI and MR spectroscopy (if elected and clinically indicated) studies may be obtained at times of neurologic deterioration to document tumor progression versus radiation necrosis.

10.3.3 Standard clinical time points for laboratory evaluation will be employed. Standardly, weekly blood counts shall be obtained while radiation with concomitant chemotherapy is administered. During adjuvant chemotherapy, CBCPD will typically be obtained at day 22 of the cycle

(nadir) and the day of/prior to each chemotherapy cycle, and as required based on hematological toxicity in prior cycles.

### 10.4 Criteria for Removal from Study

10.4.1 All patients will be followed for survival, and for progression of neurological symptoms and for evidence of treatment failure by MRI. Patients who have tumor progression, as defined below, will not be removed from the protocol and will continue to be followed endpoints including survival, salvage therapies, etc. Date and cause of death will be documented, if known.

10.4.2 Therapy may be discontinued at any time by the request of the patient.

### 10.5 Evaluation Criteria and Endpoints

Standard RANO criteria will be used primarily to evaluate objective tumor response. Measurable disease is defined as bi-dimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI scan. Non-measurable disease is defined as either uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm. Formal RANO assessments for the following time points will be obtained after baseline assessment: approximately 1 month, 3 months, 7 months, and 13 months after chemoradiation.

10.5.1 Complete Response (CR): Complete response requires all of the following including complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; and patient must be off corticosteroids or on physiologic replacement doses only, and stable or improved clinically.

10.5.2 Partial Response (PR): Partial response requires all of the following: ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and patient must be on a corticosteroid dose not greater than the dose at time of baseline scan and is stable or improved clinically.

10.5.3 Stable Disease (SD): Stable disease occurs if the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status.

10.5.4 Progression (PD) is defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of non-measurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

## 11.0 STATISTICAL CONSIDERATIONS

This is a study of concurrent temozolomide and high dose radiation using biologic based target volume definition in patients with newly diagnosed glioblastoma (GBM).

The overall goal of this study is to determine if the treatment regimen described in this protocol is sufficiently promising to advance to a definitive randomized trial. Treatment for patients treated under this protocol will differ from standard care in the following ways:

1) High b-value diffusion-weighted and perfusion MRI will be used in target volume definition

2) The radiation dose to the boost volume will be 75 Gy based on earlier data demonstrating the safety and potential efficacy of this approach.

**11.1 Primary objective:** *To improve overall survival at 12 months compared with published historical controls.*

The final test addressing this aim will occur when the last enrolled patient completes 12 months of follow-up. If patients drop out or are lost to follow-up prior to 12 months, we will utilize the Kaplan-Meier approach to estimate OS at 12 months. Otherwise we will use the simple binomial proportion of patients who are alive within 12 months of treatment. We will test the null hypothesis that the true 12 months OS is equal to 0.65, based on recently reported survival rates from RTOG 0525 and RTOG 0825.[38-39] The alternative hypothesis will be that 12 months OS is greater than 0.65. The test will be one-sided at an alpha=0.10 level. We will additionally use the Kaplan-Meier approach to estimated OS over time for all patients and according to MGMT and IDH1 status.

For example, MGMT status is an established prognostic factor in this setting with hazard ratios of approximately 2 for an endpoint of overall survival. On average we would expect a similar proportion of methylated patients in this trial as was observed for RTOG 0525 and RTOG 0825 (30%). However, with a sample size of 40, it is possible that the proportion of methylated patients will differ from 30% by a non-negligible amount. To account for this in the statistical analysis, we will weight patients so that the

weighted proportion of methylated patients is equal to 30%. Specifically, if p* denotes the observed proportion of methylated patients in this trial, the new weights will be .3/p* for methylated patients and (1-.3)/(1-p*) for unmethylated patients.

**Sample size considerations:**

We anticipate enrolling 40 patients eligible to undergo a boost of radiation (>1 cc combined high b-value DW-MRI and perfusion MRI abnormality) at our institution. A similar protocol will be opened at a second center and treat an additional 40 patients in an identical fashion. This approach was chosen over a single multi-institutional trial protocol for logistical and financial reasons. Nevertheless, we expect to jointly analyze the data from all 80 patients following trial completion. Center will be included as a stratification variable in the analyses. Allowing for 10% of these patients to be non-evaluable for the primary endpoint, 40 (80) enrolled patients will provide greater than 80% power to detect an improvement in 12 month OS from 65% (based on historical controls) to 82% (40 patients) or 78% (80 patients). These results are based on an exact 1-sided test at alpha=0.10. Once completed, this trial will determine if the treatment is sufficiently promising to warrant further investigation in a multi-center, randomized trial.

**11.2 Secondary objective:** *To estimate progression-free survival, patterns of failure and response rates in relation to values from historical control patients.*

Progression Free Survival is defined as the time from study enrollment till the first of death from any cause or progression. Kaplan-Meier estimates of PFS will be generated for all patients on this trial and according to MGMT/IDH1 status. Additionally we will compare the observed PFS at 6 months and 1 year to published values from historical control patients.

**Patterns of failure and response rates** - Failures will be classified as central, in-field, marginal or distant, based on previously published criteria.[40] Our hypothesis is that including high b-value diffusion and perfusion MRI in treatment planning will reduce the proportion of central failures within the high-dose radiation region. We will explore whether this appears to be the case by comparing this proportion to prior dose escalation studies based on conventional MRI planning alone.

**Response rates** - The proportion of complete, partial and any responders will be calculated along with 95% likelihood ratio confidence intervals using RANO criteria.[41] The proportion of any responders will also be compared to published values from historical controls.

**11.3 Secondary objective:** *Assess the ability of pre-therapy and week 3 MET PET scans and advanced MRI to determine sub-volumes at high risk of recurrence.*

Several approaches are possible, ranging from very ad hoc qualitative analysis to complex voxel level image analysis. Here we describe an empiric approach to assessment of the ability of an image to predict volumes at highest risk of recurrence. The goal is to compare the probability of the imaging defined subvolume recurring with the probability of the rest of the tumor recurring. This comparison must take into account two potential confounding variables. First, these two (absolute) volumes will typically be different for a given patient and thus any analysis regarding location of recurrence must be weighted by volume. Second, the imaging defined volume may receive higher (or lower) dose than the rest of the tumor. One means to do this is to stratify the analysis on dose received. For example, assume we categorize the initial PTV in terms of high-dose and low-dose regions. Then for each region (strata) we could compute the following quantities

1) P1=Proportion of the imaging sub-volume overlapping with recurrence volume (rVOI )
2) P2=Proportion of the non-imaging sub-volume overlapping with rVOI

Evidence for success of the imaging at goal to '*determine tumor sub-volumes at high risk of recurrence*' would be given when P1>P2. Across the population of patients, we could perform a stratified test whether E[P1] > E[P2]. Metrics such as sensitivity and specificity will be used to quantify the spatial predictive ability and will be calculated as proportions of volumes. For example, for sensitivity we will calculate the proportion of the rVOI contained in the imaging subvolume. Predictive values (PPV and NPV) could be calculated in a similar manner.

Summary statistics will also be generated describing the volumes of each of these imaging defined sub-volumes and their overlap.

**11.4 <u>Secondary objective</u>**: To prospectively compare tumor volumes defined by baseline MET PET with baseline high b-value DW-MRI and perfusion MRI
A conformality index[42] will be calculated that compares the MET-PET defined tumor volume with high b-value DW-MRI and perfusion MRI defined tumor volume. Non-overlapping regions of MET-PET tumor volume and MRI tumor volume as well as the overlapping regions will be calculated for each patient and used to calculate conformality indices. Assuming the endpoint is normally distributed, the 95% confidence interval for the mean has half-width = 1.96*Standard error of the mean.

**11.5 <u>Secondary objective</u>:** *To assess the ability of post-treatment advanced MRI to distinguish true progression from pseudoprogression*

Patients will undergo follow-up advanced MRI (including high b-value MRI) within 1-4 months after completion of chemoradiation. Pseudoprogression is the appearance of progression later determined to be treatment effect, rather than actual progression, and typically occurs within the first 3 months after chemoradiation. True progression status at 12 months will be centrally reviewed by a team of neuro-oncologists, neurosurgeons, neuro-radiologists and radiation oncologists. This gold standard assessment at 12

months will identify patients as 'progressors' or 'non-progressors'. There are several ways to analyze this data. In the first, we will simply assess to what extent the advanced MRI imaging metrics obtained shortly after treatment (1-4 months) can predict the true progression status at 12 months. Because there is little uncertainty surrounding patients who have not progressed at 12 months, the second analysis will only involve apparent 'progressors' at 12 months. The outcome will still be the true (or at least gold standard) assessment of progression status at 12 months and the predictors will again be advanced MRI metrics obtained shortly after treatment. This analysis will directly assess the extent to which the advanced MRI imaging can distinguish 'true' from 'pseudo' progressors. Standard ROC type metrics will be reported, including AUC, sensitivity, specificity as well as negative and positive predictive value for defined thresholds. The key metric from the high b-value MRI and perfusion is the quantity of 'abnormal volume'. Although multiple thresholds will be studied we will consider less than 1 cc abnormal volume on 3 month follow-up high b-value MRI and perfusion to be indicative of pseudoprogression whereas >1 cc abnormal volume will be considered indicative of true progression. While of great clinical interest, the proposed study is not powered to provide definitive answers to these questions and these analyses will be hypothesis generating.

**11.6 Secondary objective:** *To provide descriptive data regarding neuro-cognitive function, health-related quality of life and symptoms related to radiation dose received.*

Patients will complete neurologic exam, mini mental status exam and EORTC global QOL questionnaire and specific brain module and MDASI-BT before, during and after treatment. The results will be summarized descriptively over time as well as by radiation dose. The relation between these outcomes and survival will be assessed by using QOL numbers as (possibly time dependent) predictors in a Cox regression model. Every effort will be made to avoid missing data. Missing data will be carefully considered as to whether it is missing at random or not. Mixed models with subject level random effects can provide valid estimation and inference under certain patterns of informative missingness and will be utilized where warranted. We will also perform simple checks whether for example subjects with decreased QOL are more likely to drop out. For example, we will compare observed QOL at time t amongst patients who did or did not drop out (i.e. decline to provide QOL data) by time t+1.

**11.7 Interim analysis:**

Due to a possible increased incidence of grade 3 or higher CNS toxicity (possibly, probably, or definitely related to treatment), we will analyze the data 6 months after the 20$^{th}$ patient completes radiation. At this point approximately 29 patients, out of the planned total of 40 patients eligible for radiation boost, will have been enrolled on the trial. It is possible that 6 patients will experience toxicity prior to this time point, in which case, the trial would be halted as soon as the 6$^{th}$ patient experiences toxicity. If the number of patients, out of the first 20, with toxicity (as defined above) is 6 or greater, the trial will be stopped due to possible safety concerns. The operating characteristics of this stopping rule are given in Table 1 below. When the true toxicity rate is 10%, just

1% of trials will stop early. On the other hand, if the probability of toxicity is 40%, 87% of trials will stop early. We note here that we do not expect to see excessive toxicity in this study because the volume of brain treated with the experimental (boost) dose of radiation will be limited to 1/3 the volume of brain, shown to be safe based on our prior dose-escalation study based on standard MRI alone.[30]

Table 1. The proportion of trials stopping

| True P(tox) | 10% | 20% | 30% | 40% |
|---|---|---|---|---|
| Proportion of Trials Stopping Early | 1% | 20% | 58% | 87% |

## 12.0 STUDY MONITORING

### 12.1 Adverse Event Reporting Guidelines

#### 12.1.1 Reporting Procedures

Serious adverse Events (SAE's) that are unexpected and/or definitely, probably or possibly related to protocol therapy should be reported to:

Principal Investigator: Michelle Kim, MD
[redacted]

The data manager will complete the CTO SAE Report form. The Clinical Trials Office (CTO) staff will coordinate the reporting process between the Investigator and the IRBMED as well as any other applicable reporting. Copies of all related correspondence and reporting documents will be maintained in the subject research chart and/or regulatory file as appropriate.
Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Data on adverse events will be collected from the time of the initial intervention through 30 days following the completion of radiation therapy. Serious Adverse Events (SAEs) will continue to be followed until resolution or clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal

investigator to ensure that all staff involved in the trial are familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial investigation agent/intervention administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history and recorded in the appropriate section of the case report form.

All adverse events occurring from the initial investigational agent/intervention administration through 30 days following the last dose of the investigational agent/intervention (end of RT) must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the investigational agent/intervention.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins taking the investigational agent/intervention is also considered an adverse event.

### 12.1.2 Definitions

Adverse event
Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse reaction
An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected
An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Serious
An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor (UNIVERSITY OF MICHIGAN), it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient’s medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Life-threatening
An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event

or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

12.1.3 The following adverse events are excluded from SAE reporting:

12.1.3.1 All moderate events (grade 2) or hematologic serious events (grade 3) due to the patient's cancer or the treatment which are common toxicities and expected, including but not limited to alopecia, fatigue, lymphopenia, headache, nausea, vomiting, and anorexia. These will be noted in the patient's medical records. Events which are unexpected and possibly, probably or definitely related will be reported in 15 days (grade 2) or 7 days (grade 3).)

12.1.3.2 Hospitalization secondary to expected cancer morbidity:

12.1.3.3 Admission for palliative care or pain management

12.1.3.4 Planned hospitalizations for surgical procedures either related or unrelated to the patient's cancer.

12.1.3.5 Emergency Department visits not related to study treatment including accidental injury.

12.1.4 Adverse Event Characteristics

CTCAE terminology

Adverse events (AE's) will use the descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 4.03.

Attribution of the AE:

The investigator is responsible for assignment of attribution.
Definite – The AE is clearly related to the investigational agent/intervention.
Probable – The AE is likely related to the investigational agent/intervention.
Possible – The AE may be related to the investigational agent/intervention.
Unlikely – The AE is doubtfully related to the investigational agent/intervention.
Unrelated – The AE is clearly NOT related to the investigational agent/intervention.

### 12.2 Data Safety and Monitoring

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan.

The study specific Data and Safety Monitoring Committee (DSMC), consisting of the protocol investigators, data manager or designee, and other members of the study team involved with the conduct of the trial, will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness.

At the regular DSMC meetings, the protocol specific Data and Safety Monitoring Report form will be completed. The report will be signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) on a quarterly basis for independent review.

**References:**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**Appendix 1:**

| | |
|---|---|
| 100 | Normal; no complaints; no evidence of disease |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 80 | Normal activity with effort; some sign or symptoms of disease |
| 70 | Cares for self; unable to carry on normal activity of do active work |
| 60 | Requires occasional assistance, but is able to care for most personal needs |
| 50 | Requires considerable assistance and frequent medical care |
| 40 | Disabled; requires special care and assistance |
| 30 | Severely disabled; hospitalization is indicated, although death not imminent |
| 20 | Very sick; hospitalization necessary; active support treatment is necessary |
| 10 | Moribund; fatal processes progressing rapidly |
| 0 | Dead |

**Appendix 2:**

Advanced and anatomic MRI (Final technique at the discretion of study neuroradiologist)

Advanced MRI will include the following series:

3D pre-Gd gradient-echo T1 weighted images, ~4 min
2D T2 FLAIR images, ~4 min
Triple gradient-echo images (min TE and min TR), ~3 min
Diffusion weighted images (3 directions, b=0,1000,3000), ~4:50 min
Diffusion tensor images ~5 min
Dynamic-susceptibility contrast images, ~3 min
3D post-Gd gradient echo T1 weighted images, ~4 min

Approximate scan time: 35 minutes

## Appendix 3: $^{11}$C-Methionine (MET) PET/CT imaging protocol (guidelines, subject to update with machine upgrade)

PET/CT imaging will be performed on a Siemens Biograph mCT TrueV PET/CT scanner with an extended field of view and with time-of-flight (TOF).[43] The reconstructed resolution of this state-of-the-art scanner was measured at 4.1 mm at full-width half-maximum (FWHM).

The $^{11}$C-radioactivity in the syringe prior to injection is measured. A radioactive dose of 16 mCi (592 MBq) of $^{11}$C-methionine will be administered as slow intravenous bolus injection over about 10 seconds. Deviations of up to ± 20% of the administered dose will not be considered protocol deviations. After injection of the study drug, the cannula and injection system must be flushed with 10 mL saline solution.

With the start of the tracer injection, a 30 min dynamic list mode study is acquired of the brain. Summed image data obtained between 10 and 30 minutes post-injection will be used for analysis. Abnormal MET uptake will be defined by automatic segmentation using a threshold as in published literature by normalizing the lesion activity by the mean activity of the normal cerebellum.[17]

While final acquisition parameters may vary, the proposed PET acquisition parameters are as follows:

Dynamic sequence (0 – 30 min.) 6 x 10 sec., 4 x 15 sec., 6 x 30 sec., 2 x 150 sec., 4 x 300 sec. (=22 time frames)
CT scan parameters: Eff. mass 40; keV 120; Slice thickness 3 mm; Pitch 1 (with Care dose and kV dose)
Image reconstruction: Ordered subset expectation maximization (OSEM) trueX and time-of-flight (TOF)

## Appendix 4. Neurologic Assessment in Neuro-Oncology (NANO) Scale

Neurologic Assessment in Neuro-Oncology (NANO) Scale

**Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.**

Date Assessment Performed (day/month/year): _____

Study time point (i.e. baseline, cycle 1, day 1, etc):_____

Assessment performed by (please print name): _____

| **Domains** | **Key Considerations** |
|---|---|
| Gait<br>0 ☐ Normal<br>1 ☐ Abnormal but walks without assistance<br>2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.)<br>3 ☐ Unable to walk<br>☐ Not assessed<br>☐ Not evaluable | • Walking is ideally assessed by at least 10 steps |
| Strength<br>0 ☐ Normal<br>1 ☐ Movement present but decreased against resistance<br>2 ☐ Movement present but none against resistance<br>3 ☐ No movement<br>☐ Not assessed<br>☐ Not evaluable | • Test each limb separately<br>• Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups<br>• Score should reflect worst performing area<br>• Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb |
| Ataxia (upper extremity)<br>0 ☐ Able to finger to nose touch without difficulty<br>1 ☐ Able to finger to nose touch but difficult<br>2 ☐ Unable to finger to nose touch<br>☐ Not assessed<br>☐ Not evaluable | • Non-evaluable if strength is compromised<br>• Trunk/lower extremities assessed by gait domain<br>• Particularly important for patients with brainstem and cerebellar tumors<br>• Score based on best response of at least 3 attempts |
| Sensation<br>0 ☐ Normal<br>1 ☐ Decreased but aware of sensory modality<br>2 ☐ Unaware of sensory modality<br>☐ Not assessed<br>☐ Not evaluable | • Recommend evaluating major body areas separately (face, limbs and trunk)<br>• Score should reflect worst performing area<br>• Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception<br>• Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas |

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration

Nayak L, DeAngelis L, Wen P et al. The neurologic assessment in neuro-oncology (NANO) scale: A tool to assess neurologic function for integration in the radiologic assessment in neuro-oncology (RANO) criteria. Neurology Apr 2014; 82(10) supplement S22.005.

## Appendix 5. Mini mental status examination (MMSE)

# Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions: Score one point for each correct response within each question or activity.***

| Maximum Score | Patient's Score | Questions |
|---|---|---|
| 5 | | "What is the year? Season? Date? Day? Month?" |
| 5 | | "Where are we now? State? County? Town/city? Hospital? Floor?" |
| 3 | | The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. |
| 5 | | "I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …)<br>Alternative: "Spell WORLD backwards." (D-L-R-O-W) |
| 3 | | "Earlier I told you the names of three things. Can you tell me what those were?" |
| 2 | | Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them. |
| 1 | | "Repeat the phrase: 'No ifs, ands, or buts.'" |
| 3 | | "Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.) |
| 1 | | "Please read this and do what it says." (Written instruction is "Close your eyes.") |
| 1 | | "Make up and write a sentence about anything." (This sentence must contain a noun and a verb.) |
| 1 | | "Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)<br>  |
| 30 | | TOTAL |

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**Appendix 6.** European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Quality of life questionnaire

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

---

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

### During the past week:

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |



Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993 Mar 3;85(5):365-76.

**Appendix 7.** European Organization for Research and Treatment of Cancer (EORTC) QLQ-BN20 Quality of life questionnaire Brain tumor module

ENGLISH

## EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

| During the past week: | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 31. | Did you feel uncertain about the future? | 1 | 2 | 3 | 4 |
| 32. | Did you feel you had setbacks in your condition? | 1 | 2 | 3 | 4 |
| 33. | Were you concerned about disruption of family life? | 1 | 2 | 3 | 4 |
| 34. | Did you have headaches? | 1 | 2 | 3 | 4 |
| 35. | Did your outlook on the future worsen? | 1 | 2 | 3 | 4 |
| 36. | Did you have double vision? | 1 | 2 | 3 | 4 |
| 37. | Was your vision blurred? | 1 | 2 | 3 | 4 |
| 38. | Did you have difficulty reading because of your vision? | 1 | 2 | 3 | 4 |
| 39. | Did you have seizures? | 1 | 2 | 3 | 4 |
| 40. | Did you have weakness on one side of your body? | 1 | 2 | 3 | 4 |
| 41. | Did you have trouble finding the right words to express yourself? | 1 | 2 | 3 | 4 |
| 42. | Did you have difficulty speaking? | 1 | 2 | 3 | 4 |
| 43. | Did you have trouble communicating your thoughts? | 1 | 2 | 3 | 4 |
| 44. | Did you feel drowsy during the daytime? | 1 | 2 | 3 | 4 |
| 45. | Did you have trouble with your coordination? | 1 | 2 | 3 | 4 |
| 46. | Did hair loss bother you? | 1 | 2 | 3 | 4 |
| 47. | Did itching of your skin bother you? | 1 | 2 | 3 | 4 |
| 48. | Did you have weakness of both legs? | 1 | 2 | 3 | 4 |
| 49. | Did you feel unsteady on your feet? | 1 | 2 | 3 | 4 |
| 50. | Did you have trouble controlling your bladder? | 1 | 2 | 3 | 4 |

**Appendix 8**. MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT)

**Date:** _____ **Institution:** _____

**Participant Initials:** _____ **Hospital Chart #:** _____

**Participant Number:** _____

## MD Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

**Part I.** How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

| | Not Present 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | As Bad As You Can Imagine 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Your **pain** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 2. Your **fatigue (tiredness)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 3. Your **nausea** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 4. Your **disturbed sleep** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 5. Your feelings of being **distressed (upset)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 6. Your **shortness of breath** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 7. Your problem with **remembering things** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 8. Your problem with **lack of appetite** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 9. Your feeling **drowsy (sleepy)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 10. Your having a **dry mouth** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 11. Your feeling **sad** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 12. Your **vomiting** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 13. Your **numbness or tingling** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 14. Your **weakness** on one side of the body at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 15. Your difficulty **understanding** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 16. Your difficulty **speaking (finding the words)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |





MDASI-BT - 2006

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

| | Not Present 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | As Bad As You Can Imagine 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 17. Your **seizures** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 18. Your difficulty **concentrating** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 19. Your **vision** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 20. Your change in **appearance** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 21. Your change in **bowel pattern (diarrhea or constipation)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 22. Your **irritability** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Part II.** How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

| | Did Not Interfere 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Interfered Completely 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 23. **General activity?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 24. **Mood?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 25. **Work (including work around the house)?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 26. **Relations with other people?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 27. **Walking?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 28. **Enjoyment of life?** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Appendix 9.** Hopkins Verbal Learning Test-Revised (HVLT-R)

## HOPKINS VERBAL LEARNING TEST - REVISED (Form 1)

**Instructions**

**Free Recall (Part A): Trial 1:** "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?" *[Read the list to the patient at the approximate rate of one word every two seconds]* "OK. Now tell me as many of those words as you can remember" **Trial 2:** "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time." **Trial 3:** "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."
*[20 minute delay]*

**Delayed Recall (Part B):** *[Do NOT read the list of words again]*. "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

**Delayed Recognition (Part C):** "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [ word ] on the list?" *[Read down the columns of words]*

**1. Free Recall**

| | Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|
| LION | ☐ | ☐ | ☐ |
| EMERALD | ☐ | ☐ | ☐ |
| HORSE | ☐ | ☐ | ☐ |
| TENT | ☐ | ☐ | ☐ |
| SAPPHIRE | ☐ | ☐ | ☐ |
| HOTEL | ☐ | ☐ | ☐ |
| CAVE | ☐ | ☐ | ☐ |
| OPAL | ☐ | ☐ | ☐ |
| TIGER | ☐ | ☐ | ☐ |
| PEARL | ☐ | ☐ | ☐ |
| COW | ☐ | ☐ | ☐ |
| HUT | ☐ | ☐ | ☐ |

Free Recall (Part A) Stop Time

_____:_____

Delayed Recall (Part B) Start Time

_____:_____

**2. Delayed Recall** ☐

**3. Delayed Recognition**

| Y | N | | Y | N | | Y | N | | Y | N | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | HORSE | ☐ | ☐ | house | ☐ | ☐ | HUT | ☐ | ☐ | TENT |
| ☐ | ☐ | ruby | ☐ | ☐ | OPAL | ☐ | ☐ | EMERALD | ☐ | ☐ | mountain |
| ☐ | ☐ | CAVE | ☐ | ☐ | TIGER | ☐ | ☐ | SAPPHIRE | ☐ | ☐ | cat |
| ☐ | ☐ | balloon | ☐ | ☐ | boat | ☐ | ☐ | dog | ☐ | ☐ | HOTEL |
| ☐ | ☐ | coffee | ☐ | ☐ | scarf | ☐ | ☐ | apartment | ☐ | ☐ | COW |
| ☐ | ☐ | LION | ☐ | ☐ | PEARL | ☐ | ☐ | penny | ☐ | ☐ | diamond |

**4. Discontinued:** Testing Discontinued? ☐ Yes ☐ NO

## HOPKINS VERBAL LEARNING TEST - REVISED (Form 2)

**Instructions**

**Free Recall (Part A): Trial 1:** "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?" *[Read the list to the patient at the approximate rate of one word every two seconds]* "OK. Now tell me as many of those words as you can remember" **Trial 2:** "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time." **Trial 3:** "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."
*[20 minute delay]*

**Delayed Recall (Part B):** *[Do NOT read the list of words again]*. "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

**Delayed Recognition (Part C):** "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [ word ] on the list?" *[Read down the columns of words]*

**1. Free Recall**

| | Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|
| FORK | ☐ | ☐ | ☐ |
| RUM | ☐ | ☐ | ☐ |
| PAN | ☐ | ☐ | ☐ |
| PISTOL | ☐ | ☐ | ☐ |
| SWORD | ☐ | ☐ | ☐ |
| SPATULA | ☐ | ☐ | ☐ |
| BOURBON | ☐ | ☐ | ☐ |
| VODKA | ☐ | ☐ | ☐ |
| POT | ☐ | ☐ | ☐ |
| BOMB | ☐ | ☐ | ☐ |
| RIFLE | ☐ | ☐ | ☐ |
| WINE | ☐ | ☐ | ☐ |

Free Recall (Part A) Stop Time

_____:_____

Delayed Recall (Part B) Start Time

_____:_____

**2. Delayed Recall**

| |
|---|
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |
| ☐ |

**3. Delayed Recognition**

| Y | N | | Y | N | | Y | N | | Y | N | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | spoon | ☐ | ☐ | harmonica | ☐ | ☐ | knife | ☐ | ☐ | WINE |
| ☐ | ☐ | PISTOL | ☐ | ☐ | can opener | ☐ | ☐ | RUM | ☐ | ☐ | lemon |
| ☐ | ☐ | doll | ☐ | ☐ | SWORD | ☐ | ☐ | trout | ☐ | ☐ | SPATULA |
| ☐ | ☐ | whiskey | ☐ | ☐ | pencil | ☐ | ☐ | BOMB | ☐ | ☐ | BOURBON |
| ☐ | ☐ | FORK | ☐ | ☐ | gun | ☐ | ☐ | PAN | ☐ | ☐ | beer |
| ☐ | ☐ | POT | ☐ | ☐ | VODKA | ☐ | ☐ | gold | ☐ | ☐ | RIFLE |

**4. Discontinued:** Testing Discontinued? ☐ Yes ☐ NO

## HOPKINS VERBAL LEARNING TEST - REVISED (Form 3)

**Instructions**

**Free Recall (Part A): Trial 1:** "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?" *[Read the list to the patient at the approximate rate of one word every two seconds]* "OK. Now tell me as many of those words as you can remember" **Trial 2:** "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time." **Trial 3:** "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."
*[20 minute delay]*

**Delayed Recall (Part B):** *[Do NOT read the list of words again]*. "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

**Delayed Recognition (Part C):** "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [ word ] on the list?" *[Read down the columns of words]*

**1. Free Recall**

| | Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|
| SUGAR | ☐ | ☐ | ☐ |
| TRUMPET | ☐ | ☐ | ☐ |
| VIOLIN | ☐ | ☐ | ☐ |
| COAL | ☐ | ☐ | ☐ |
| GARLIC | ☐ | ☐ | ☐ |
| KEROSINE | ☐ | ☐ | ☐ |
| VANILLA | ☐ | ☐ | ☐ |
| WOOD | ☐ | ☐ | ☐ |
| CLARINET | ☐ | ☐ | ☐ |
| FLUTE | ☐ | ☐ | ☐ |
| CINNAMON | ☐ | ☐ | ☐ |
| GASOLINE | ☐ | ☐ | ☐ |

Free Recall (Part A) Stop Time

_____:_____

Delayed Recall (Part B) Start Time

_____:_____

**2. Delayed Recall**

☐
☐
☐
☐
☐
☐
☐
☐
☐
☐
☐
☐

**3. Delayed Recognition**

| Y | N | | Y | N | | Y | N | | Y | N | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | pepper | ☐ | ☐ | ball | ☐ | ☐ | TRUMPET | ☐ | ☐ | KEROSINE |
| ☐ | ☐ | GARLIC | ☐ | ☐ | salt | ☐ | ☐ | basement | ☐ | ☐ | VANILLA |
| ☐ | ☐ | WOOD | ☐ | ☐ | priest | ☐ | ☐ | CINNAMON | ☐ | ☐ | GASOLINE |
| ☐ | ☐ | drum | ☐ | ☐ | chair | ☐ | ☐ | FLUTE | ☐ | ☐ | sand |
| ☐ | ☐ | oil | ☐ | ☐ | COAL | ☐ | ☐ | electricity | ☐ | ☐ | piano |
| ☐ | ☐ | SUGAR | ☐ | ☐ | CLARINET | ☐ | ☐ | moon | ☐ | ☐ | VIOLIN |

**4. Discontinued:** Testing Discontinued? ☐ Yes ☐ NO

## HOPKINS VERBAL LEARNING TEST - REVISED (Form 4)

**Instructions**

**Free Recall (Part A): Trial 1:** "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?" *[Read the list to the patient at the approximate rate of one word every two seconds]* "OK. Now tell me as many of those words as you can remember" **Trial 2:** "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time." **Trial 3:** "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."
*[20 minute delay]*

**Delayed Recall (Part B):** *[Do NOT read the list of words again]*. "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

**Delayed Recognition (Part C):** "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [ word ] on the list?" *[Read down the columns of words]*

**1. Free Recall**

| | Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|
| CANARY | ☐ | ☐ | ☐ |
| SHOES | ☐ | ☐ | ☐ |
| EAGLE | ☐ | ☐ | ☐ |
| BLOUSE | ☐ | ☐ | ☐ |
| NAILS | ☐ | ☐ | ☐ |
| CROW | ☐ | ☐ | ☐ |
| BLUEBIRD | ☐ | ☐ | ☐ |
| SCREWDRIVER | ☐ | ☐ | ☐ |
| PANTS | ☐ | ☐ | ☐ |
| CHISEL | ☐ | ☐ | ☐ |
| SKIRT | ☐ | ☐ | ☐ |
| WRENCH | ☐ | ☐ | ☐ |

Free Recall (Part A) Stop Time

_____:_____

Delayed Recall (Part B) Start Time

_____:_____

**2. Delayed Recall**

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**3. Delayed Recognition**

| Y | N | | Y | N | | Y | N | | Y | N | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | BLUEBIRD | ☐ | ☐ | chapel | ☐ | ☐ | NAILS | ☐ | ☐ | CANARY |
| ☐ | ☐ | shirt | ☐ | ☐ | SCREWDRIVER | ☐ | ☐ | socks | ☐ | ☐ | apple |
| ☐ | ☐ | CHISEL | ☐ | ☐ | CROW | ☐ | ☐ | child | ☐ | ☐ | SKIRT |
| ☐ | ☐ | EAGLE | ☐ | ☐ | sparrow | ☐ | ☐ | SHOES | ☐ | ☐ | saw |
| ☐ | ☐ | chocolate | ☐ | ☐ | WRENCH | ☐ | ☐ | hair | ☐ | ☐ | silver |
| ☐ | ☐ | robin | ☐ | ☐ | PANTS | ☐ | ☐ | hammer | ☐ | ☐ | BLOUSE |

**4. Discontinued:** Testing Discontinued? ☐ Yes ☐ NO

## HOPKINS VERBAL LEARNING TEST - REVISED (Form 5)

**Instructions**

**Free Recall (Part A): Trial 1:** "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?" *[Read the list to the patient at the approximate rate of one word every two seconds]* "OK. Now tell me as many of those words as you can remember" **Trial 2:** "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time." **Trial 3:** "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."
*[20 minute delay]*

**Delayed Recall (Part B):** *[Do NOT read the list of words again]*. "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

**Delayed Recognition (Part C):** "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [ word ] on the list?" *[Read down the columns of words]*

**1. Free Recall**

| | Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|
| TEACHER | ☐ | ☐ | ☐ |
| BASKETBALL | ☐ | ☐ | ☐ |
| LETTUCE | ☐ | ☐ | ☐ |
| DENTIST | ☐ | ☐ | ☐ |
| TENNIS | ☐ | ☐ | ☐ |
| BEAN | ☐ | ☐ | ☐ |
| ENGINEER | ☐ | ☐ | ☐ |
| POTATO | ☐ | ☐ | ☐ |
| PROFESSOR | ☐ | ☐ | ☐ |
| GOLF | ☐ | ☐ | ☐ |
| CORN | ☐ | ☐ | ☐ |
| SOCCER | ☐ | ☐ | ☐ |

Free Recall (Part A) Stop Time

_____:_____

Delayed Recall (Part B) Start Time

_____:_____

**2. Delayed Recall** ☐

**3. Delayed Recognition**

| Y | N | | Y | N | | Y | N | | Y | N | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | TENNIS | ☐ | ☐ | GOLF | ☐ | ☐ | BASKETBALL | ☐ | ☐ | carrot |
| ☐ | ☐ | football | ☐ | ☐ | DENTIST | ☐ | ☐ | doctor | ☐ | ☐ | ENGINEER |
| ☐ | ☐ | PROFESSOR | ☐ | ☐ | LETTUCE | ☐ | ☐ | CORN | ☐ | ☐ | glove |
| ☐ | ☐ | spinach | ☐ | ☐ | spider | ☐ | ☐ | baseball | ☐ | ☐ | SOCCER |
| ☐ | ☐ | lawyer | ☐ | ☐ | water | ☐ | ☐ | TEACHER | ☐ | ☐ | POTATO |
| ☐ | ☐ | submarine | ☐ | ☐ | BEAN | ☐ | ☐ | snake | ☐ | ☐ | tulip |

**4. Discontinued:** Testing Discontinued? ☐ Yes ☐ NO

## HOPKINS VERBAL LEARNING TEST - REVISED (Form 6)

**Instructions**

**Free Recall (Part A): Trial 1:** "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?" *[Read the list to the patient at the approximate rate of one word every two seconds]* "OK. Now tell me as many of those words as you can remember" **Trial 2:** "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time." **Trial 3:** "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."
*[20 minute delay]*

**Delayed Recall (Part B):** *[Do NOT read the list of words again]*. "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

**Delayed Recognition (Part C):** "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [ word ] on the list?" *[Read down the columns of words]*

| **1. Free Recall** | | | | | **2. Delayed Recall** |
|---|---|---|---|---|---|
| | Trial 1 | Trial 2 | Trial 3 | | |
| SHARK | ☐ | ☐ | ☐ | | ☐ |
| WALL | ☐ | ☐ | ☐ | | ☐ |
| HERRING | ☐ | ☐ | ☐ | Free Recall (Part A) Stop Time | ☐ |
| RAIN | ☐ | ☐ | ☐ | _____:_____ | ☐ |
| FLOOR | ☐ | ☐ | ☐ | | ☐ |
| HAIL | ☐ | ☐ | ☐ | | ☐ |
| CATFISH | ☐ | ☐ | ☐ | Delayed Recall (Part B) Start Time | ☐ |
| ROOF | ☐ | ☐ | ☐ | _____:_____ | ☐ |
| SALMON | ☐ | ☐ | ☐ | | ☐ |
| STORM | ☐ | ☐ | ☐ | | ☐ |
| CEILING | ☐ | ☐ | ☐ | | ☐ |
| SNOW | ☐ | ☐ | ☐ | | ☐ |

**3. Delayed Recognition**

| Y | N | | Y | N | | Y | N | | Y | N | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ☐ | ☐ | HAIL | ☐ | ☐ | window | ☐ | ☐ | HERRING | ☐ | ☐ | SHARK |
| ☐ | ☐ | bass | ☐ | ☐ | CEILING | ☐ | ☐ | SALMON | ☐ | ☐ | hurricane |
| ☐ | ☐ | SNOW | ☐ | ☐ | canyon | ☐ | ☐ | tornado | ☐ | ☐ | elbow |
| ☐ | ☐ | bank | ☐ | ☐ | RAIN | ☐ | ☐ | trout | ☐ | ☐ | CATFISH |
| ☐ | ☐ | FLOOR | ☐ | ☐ | ladder | ☐ | ☐ | melon | ☐ | ☐ | WALL |
| ☐ | ☐ | mustard | ☐ | ☐ | STORM | ☐ | ☐ | ROOF | ☐ | ☐ | door |

**4. Discontinued:** Testing Discontinued? ☐ Yes ☐ NO

**Appendix 10**. Controlled Oral Word Association (COWA)

## CONTROLLED ORAL WORD ASSOCIATION – Form 1

**Instructions:** "I am going to say a letter of the alphabet and I want you to say, as quickly as you can, all the words that you can think of which begin with that letter. You may say any words except proper names, such as the names of people or places (so, you would not say Rochester or Robert). Also, do not use the same word again with a different ending, such as eat and eating."

"For example, if I say S, you can say son, sit, shoe or slow. Can you think of other words beginning with the letter S?" *[If the patient succeeds in giving two appropriate words beginning with the demonstration letter, say: ]* "That is fine. Now I am going to give you another letter, you say all the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up. You will have one minute for each letter. The first letter is C." *[Start timing as soon as the letter cue is given - Allow exactly 1 minute for each letter]*

| | "C" | "F" | "L" |
|---|---|---|---|
| 01 | _____ | _____ | _____ |
| 02 | _____ | _____ | _____ |
| 03 | _____ | _____ | _____ |
| 04 | _____ | _____ | _____ |
| 05 | _____ | _____ | _____ |
| 06 | _____ | _____ | _____ |
| 07 | _____ | _____ | _____ |
| 08 | _____ | _____ | _____ |
| 09 | _____ | _____ | _____ |
| 10 | _____ | _____ | _____ |
| 11 | _____ | _____ | _____ |
| 12 | _____ | _____ | _____ |
| 13 | _____ | _____ | _____ |
| 14 | _____ | _____ | _____ |
| 15 | _____ | _____ | _____ |
| 16 | _____ | _____ | _____ |
| 17 | _____ | _____ | _____ |
| 18 | _____ | _____ | _____ |
| 19 | _____ | _____ | _____ |
| 20 | _____ | _____ | _____ |
| 21 | ☐ | ☐ | ☐ |
| 22 | ☐ | ☐ | ☐ |
| 23 | ☐ | ☐ | ☐ |
| 24 | ☐ | ☐ | ☐ |
| 25 | ☐ | ☐ | ☐ |
| 26 | ☐ | ☐ | ☐ |
| 27 | ☐ | ☐ | ☐ |
| 28 | ☐ | ☐ | ☐ |
| 29 | ☐ | ☐ | ☐ |
| Total: | _____ | _____ | _____ |

**Discontinued:** Testing Discontinued? ☐ Yes (Complete the Neurocognitive Tests Discontinued/Not Done CRF)
☐ NO

## CONTROLLED ORAL WORD ASSOCIATION – Form 2

**Instructions:** "I am going to say a letter of the alphabet and I want you to say, as quickly as you can, all the words that you can think of which begin with that letter. You may say any words except proper names, such as the names of people or places (so, you would not say Rochester or Robert). Also, do not use the same word again with a different ending, such as eat and eating."

"For example, if I say S, you can say son, sit, shoe or slow. Can you think of other words beginning with the letter S?" *[If the patient succeeds in giving two appropriate words beginning with the demonstration letter, say: ]* "That is fine. Now I am going to give you another letter, you say all the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up. You will have one minute for each letter. The first letter is C." *[Start timing as soon as the letter cue is given - Allow exactly 1 minute for each letter]*

| | "P" | "R" | "W" |
|---|---|---|---|
| 01 | _____ | _____ | _____ |
| 02 | _____ | _____ | _____ |
| 03 | _____ | _____ | _____ |
| 04 | _____ | _____ | _____ |
| 05 | _____ | _____ | _____ |
| 06 | _____ | _____ | _____ |
| 07 | _____ | _____ | _____ |
| 08 | _____ | _____ | _____ |
| 09 | _____ | _____ | _____ |
| 10 | _____ | _____ | _____ |
| 11 | _____ | _____ | _____ |
| 12 | _____ | _____ | _____ |
| 13 | _____ | _____ | _____ |
| 14 | _____ | _____ | _____ |
| 15 | _____ | _____ | _____ |
| 16 | _____ | _____ | _____ |
| 17 | _____ | _____ | _____ |
| 18 | _____ | _____ | _____ |
| 19 | _____ | _____ | _____ |
| 20 | _____ | _____ | _____ |
| 21 ☐ 24 ☐ 27 ☐ | | | |
| 22 ☐ 25 ☐ 28 ☐ | | | |
| 23 ☐ 26 ☐ 29 ☐ | | | |
| Total: | _____ | _____ | _____ |

**Discontinued:** Testing Discontinued? ☐ Yes (Complete the Neurocognitive Tests Discontinued/Not Done CRF)
☐ NO

## **Appendix 11**. Trail Making A and B

### TRAIL MAKING TEST DATA SHEET

**PART A**

**Sample Instructions:** "On this page (point) are some numbers. Begin at number 1 (point to '1') and draw a line from 1 to 2 (point to '2'), 2 to 3 (point to '3'), 3 to 4 (point to '4'), and so on, in order, until you reach the end (point to circle marked END). Draw the lines as fast as you can. Ready, begin. (If the patient makes a mistake, point out the error and explain it. If the patient completes Sample A correctly, say "Good! Let's try the next one." Proceed with the test and repeat instructions above. Start timing as soon as the instruction is given to "begin." Watch closely in order to catch any errors as soon as they are made. If the patient makes an error during the test, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred. DO NOT STOP TIMING. The patient must complete the test in 3 minutes or less.)"

**Test Instructions:** "On this page are numbers from 1 to 25. Do this the same way. Begin at number one (point to '1') and draw a line from one to two (point to '2'), two to three (point to '3'), three to four (point to '4'), and so on, in order until you reach the end (point to circle marked 'End'). Remember, work as fast as you can. Ready! Begin!"

I. Trail Making Test Part A:

1. Did the patient do Sample A before attempting Part A? ☐ Yes ☐ No
2. Total amount of time the patient was tested: _____ : _____ _____(min:sec)
3. Did the patient reach the "END" of the test?
   ☐ Yes
   ☐ No, tested for 3 minutes OR ☐ No, tested for <3 minutes
   If No, specify the last number reached on the test: _____

Comments: _____

**PART B**

**Sample Instructions:** "On this page (point) are some numbers and letters. Begin at number 1 (point to '1') and draw a line from 1 to A (point to 'A'), A to 2 (point to '2'), 2 to B (point to 'B'), B to 3 (point to '3'), 3 to C (point to 'C') and so on, in order, until you reach the end (point to circle marked 'End'). Remember, you first have a number (point to '1'), then a letter (point to 'A'), then a number (point to '2'), then a letter (point to 'B'), and so on. Draw the lines as fast as you can. Ready, begin. (If the patient makes a mistake, point out the error and explain it. If the patient completes Sample B correctly, say "Good! Let's try the next one." Proceed with the test and repeat instructions above. Start timing as soon as the instruction is given to "begin." Watch closely in order to catch any errors as soon as they are made. If the patient makes an error during the test, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred. DO NOT STOP TIMING. The patient must complete the test in 5 minutes or less.)"

**Test Instructions:** "On this page are both numbers and letters. Do this the same way. Begin at number one (point to '1') and draw a line from one to A (point to 'A'), A to two (point to '2'), two to B (point to 'B'), B to three (point to '3'), three to C (point to 'C'), and so on, in order, until the end (point to circle marked 'END'). Remember, first you have a number (point to '1'), then a letter (point to 'A'), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready! Begin!"

II. Trail Making Test Part B:

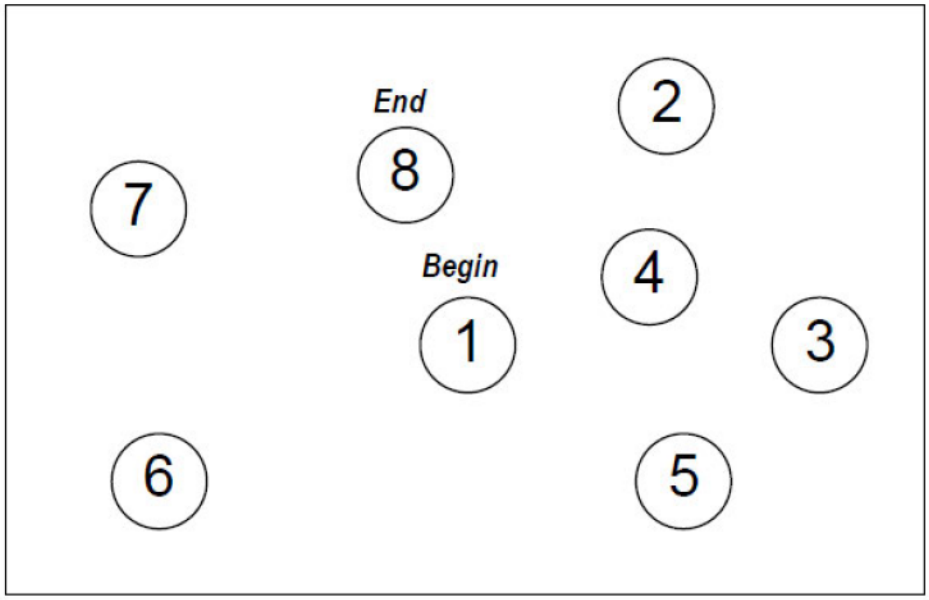
1. Did the patient do Sample B before attempting Part B? ☐ Yes ☐ No
2. Total amount of time the patient was tested: _____ : _____ _____(min:sec)
3. Did the patient reach the "END" of the test?
   ☐ Yes
   ☐ No, tested for 5 minutes OR ☐ No, tested for <5 minutes
   If No, specify the last number/letter reached on the test: _____

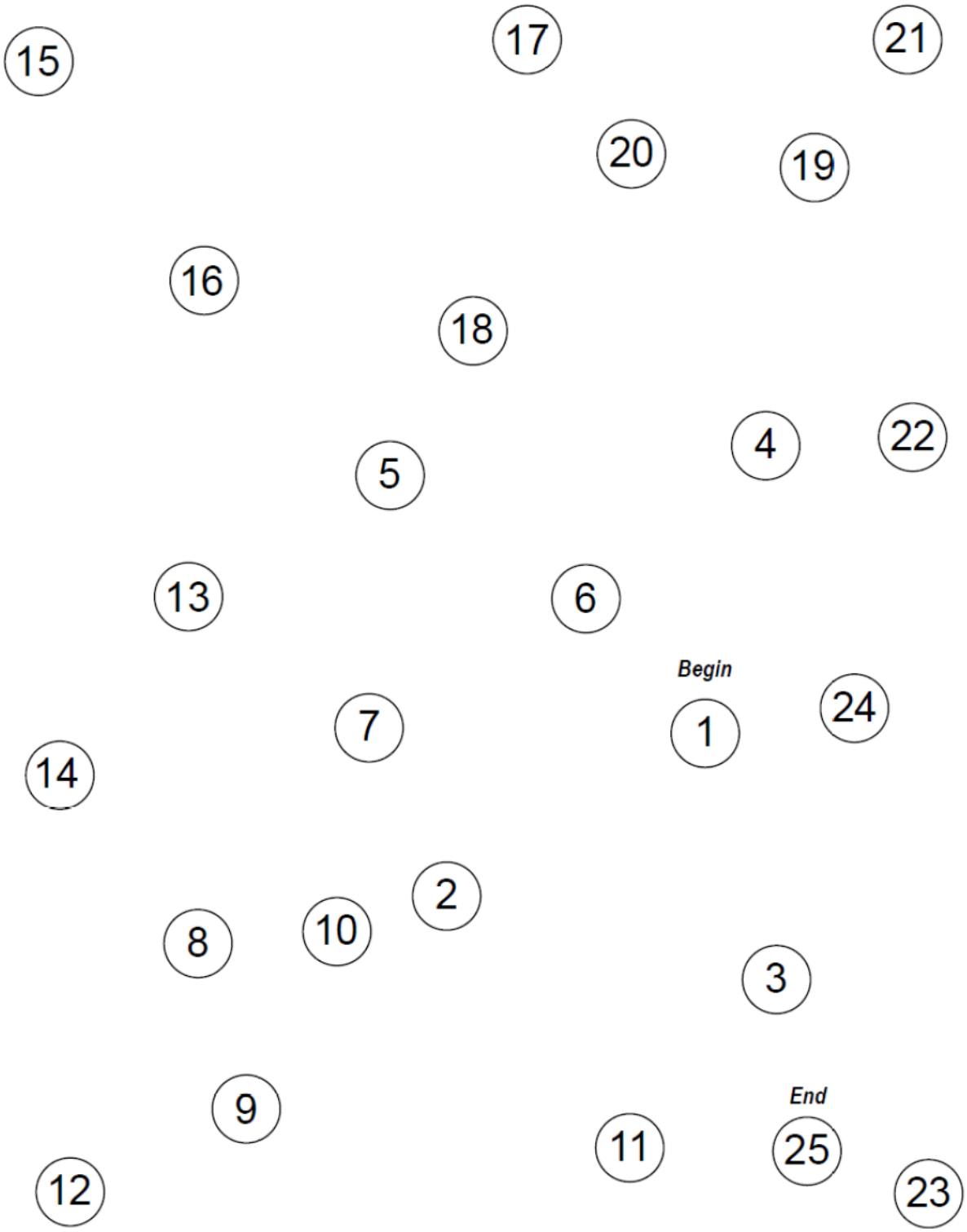
Comments: _____

# TRAIL MAKING

## Part A

### Sample

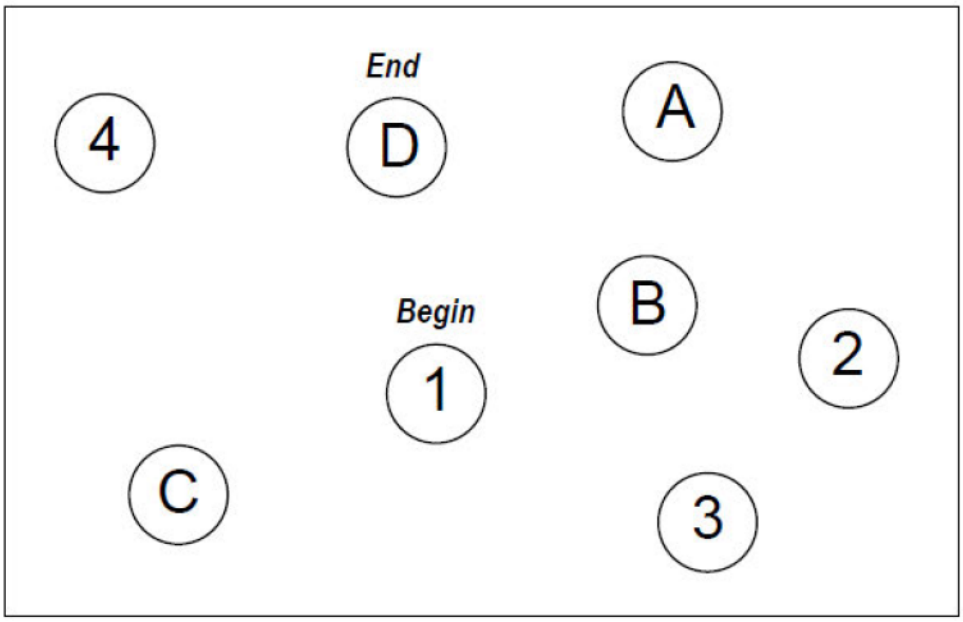


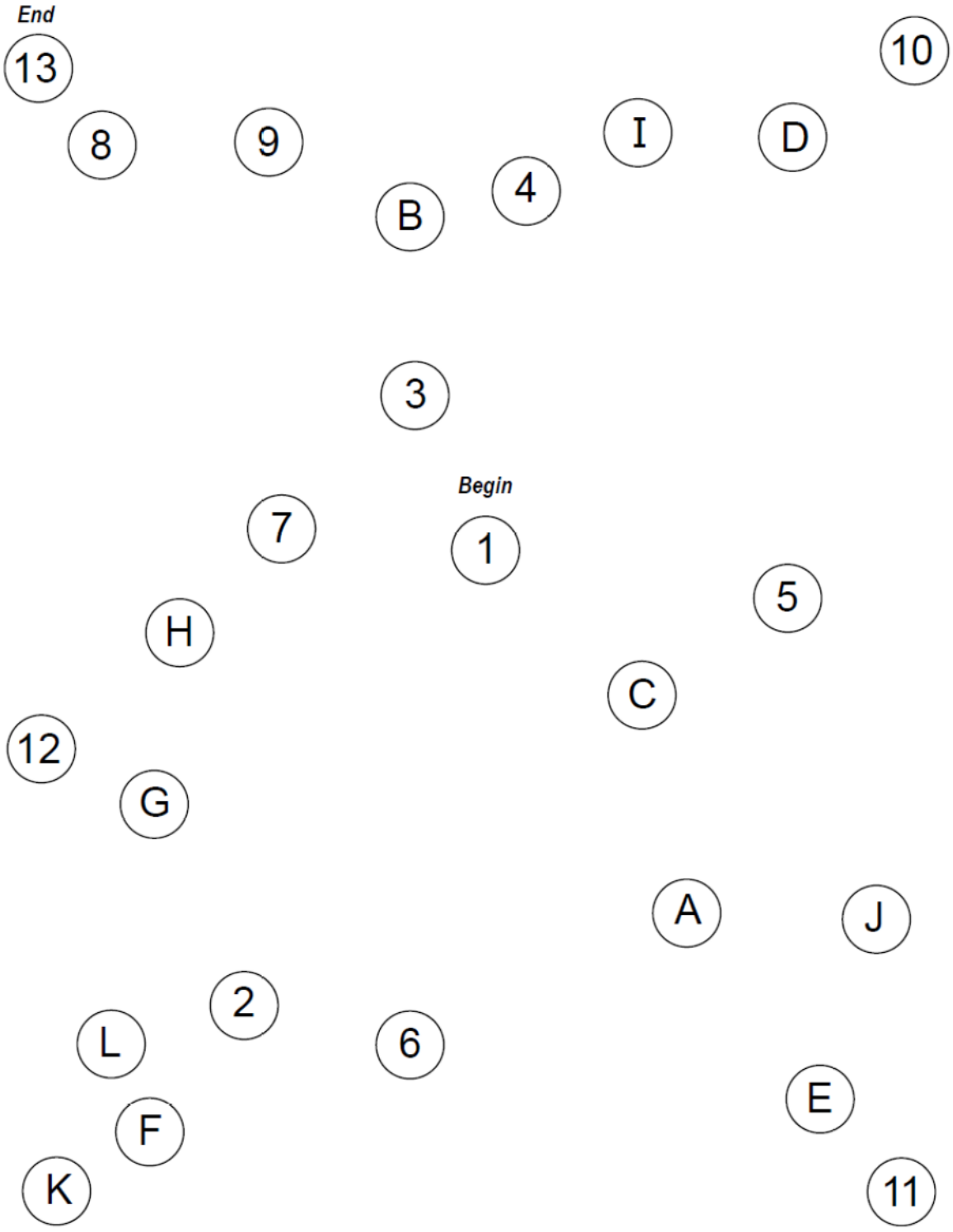

15
17
21
20
19
16
18
4
22
5
13
6
Begin
24
7
1
14
2
10
8
3
9
End
11
25
12
23

# TRAIL MAKING

## Part B

## Sample




End
13
10
8
9
I
D
4
B
3
Begin
7
1
5
H
C
12
G
A
J
2
L
6
E
F
K
11