\section{Study team}

\begin{multicols}{2}
\subsection{Principal Investigator (Neurosurgery)}
\lipsum[66]
\subsection{Co-Investigator (Neuro-Oncology)}
\lipsum[66]
\columnbreak
\subsection{Neurosurgery:}
\lipsum[75]
\subsection{Neuro-Oncology:}
\lipsum[75]
\subsection{Radiation Oncology:}
\lipsum[75]
\end{multicols}

\section{Schema}
\label{sec:sc}

\begin{tikzpicture}
\matrix [column sep=5mm, row sep=7mm]{
    \node [blockC] (c1) {\textbf{Enroll:}}; & \\
    First recurrence of GBM \& Age \geq 18 \& KPS \geq 70 \& Text greater 1 month since RT \& Prior conventional treatment \& Decompression not required \& Resection possible; & \\
    \node [blockC] (s1) {\textbf{Stratify: NRG scale}}; \& \\
    \quad \textbf{0 vs. 1 vs. 2 vs. 3}; \& \\
    \textbf{KPS \& $\leq 80$}; \& \\
    \textbf{tumor volume $\geq 50$ cm$^3$}; \& \\
    \textbf{2 cortical areas involved:\}; \& \\
    \textbf{Motor}; \& \\
    \textbf{Speech}; \& \\
    \textbf{MCA (affected areas adjacent to \& quad quad the M1/M2 areas of the Middle Cerebral Artery)}; & \\
    \node [blockC] (r1) {\textbf{Randomize}}; & \\
    \node [inner sep = 0pt] (dummy) {}; & \\
    \node [blockC] (b1) {Open biopsy \& Bevacizumab}; & \\
};
\end{tikzpicture}
\begin{itemize}
\item History of \texttt{gbm}\{glioblastoma multiforme\}
\item \texttt{mr}\{mri\}\{magnetic resonance imaging\}
\item \texttt{ct}\{ct\}\{computer automated tomography\}
\item \texttt{kps}\{kps\}\{karnofsky performance status\}
\item \texttt{wcc}\{wcc\}\{white cell count\}
\item \texttt{anc}\{anc\}\{absolute neutrophil count\}
\item \texttt{hb}\{hb\}\{hemoglobin\}
\item \texttt{ast}\{ast\}\{aspartate transaminase\}
\item \texttt{alt}\{alt\}\{alanine aminotransferase\}
\item \texttt{uln}\{uln\}\{upper limit of normal (defined for institution)\}
\item \texttt{inr}\{tnr\}\{international normalized ratio\}
\item \texttt{egfr}\{egfr\}\{estimated glomerular filtration rate (MDRD method)\}
\item \texttt{bhcg}\{bhcg\}\{beta human chorionic gonadotropin\}
\item \texttt{ivlg}\{ivlg\}\{intravenous immune globulin\}
\item \texttt{vegf}\{vegf\}\{vascular endothelial growth factor\}
\item \texttt{bsa}\{bsa\}\{body surface area\}
\item \texttt{rt}\{rt\}\{radiation therapy\}
\item \texttt{bp}\{bp\}\{blood pressure\}
\item \texttt{rplfs}\{rplfs\}\{reversible posterior leukoencephalopathy syndrome\}
\item \texttt{presp}\{presp\}\{posterior reversible leukoencephalopathy syndrome\}
\item \texttt{gls}\{gls\}\{gastrointestinal\}
\item \texttt{mos}\{mos\}\{not otherwise specified\}
\item \texttt{ncl}\{ncl\}\{national cancer institute\}
\item \texttt{tmz}\{tmz\}\{temozolomide\}
\item \texttt{mos}\{mos\}\{median overall survival\}
\item \texttt{pfs6}\{pfs-6\}\{progression free survival at 6 months\}
\item \texttt{ctepaers}\{ctep-aers\}\{cancer therapy evaluation program adverse event reporting system\}
\item \texttt{irb}\{irb\}\{institutional review board\}
\item \texttt{ae}\{ae\}\{adverse events\}
\item \texttt{mab}\{mab\}\{monoclonal antibody\}
\item \texttt{rtog}\{rtog\}\{radiation therapy oncology group\}
\item \texttt{speer}\{speer\}\{specific protocol exceptions to expedited reporting\}
\item \texttt{caerp}\{caerp\}\{comprehensive adverse event and potential risks list\}
\item \texttt{iv}\{iv\}\{intravenous\}
\item \texttt{dhs}\{dhs\}\{department of health and human services\}
\item \texttt{fda}\{fda\}\{food and drug administration\}
\item \texttt{fsh}\{fsh\}\{follicle-stimulating hormone\}
\item \texttt{cns}\{cns\}\{central nervous system\}
\item \texttt{crp}\{crp\}\{urine protein creatinine\}
\item \texttt{wnl}\{wnl\}\{within normal limits\}
\item \texttt{hr}\{hr\}\{hazard ratio\}
\item \texttt{rrg}\{rrg\}\{nih recurrent gbm scale\}
\end{itemize}

\printglossary[type=\acronymtype, title=Abbreviations, toctitle=Abbreviations]

\section{Eligibility}
\label{sec:eligibility}
\begin{center}
\textbf{Eligibility checklist}
\end{center}

\begin{enumerate}
\item History of \texttt{gbm}\{glioblastoma\}
\item \texttt{age}\{age\}\{first recurrence\}
\item \texttt{gls}\{gls\}\{kps \geq 70\}
\item \texttt{age}\{age\}\{1 month since \texttt{rt}\}\{radiation therapy\}
\item \texttt{prior}\{prior\}\{conventional treatment\}
\item \texttt{resection}\{resection\}\{possible\}
\item \texttt{sign}\{sign\}\{diffuse spread of disease or leptomeningeal disease\}

\item 14 days prior to enrollment:
\begin{enumerate}
\item \textbf{History} & physical exam
\item Brain imaging shows probable signs of progression of disease. \(\text{GLS}^{\text{MRI}}\) scans are preferred but \(\text{GLS}^{\text{CT}}\) is acceptable if there is a contraindication to the use of \(\text{GLS}^{\text{MRI}}\)
\item \textbf{Steroid dose stable or decreasing for at least 7 days}
\item \textbf{BP} - systolic \textless 160, diastolic \textless 90. Use of antihypertensives permitted
\item \textbf{WCC} \textgreater 3,000/mm^3
\item \textbf{ANC} \textgreater 1,500/mm^3
\item Platelets \textgreater 100,000/mm^3
\item \textbf{Hb} \textgreater 10 g/dL
\item \textbf{AST}, \textbf{ALT}, \textbf{Bilirubin} \textless 3 \textbf{ULN}
\item \textbf{INR} \textless 1.5 \textbf{ULN}
\item \textbf{eGFR} \textgreater 60mL/min/1.73m^2
\item If potentially pregnant - serum \(\text{hCG}\) negative
\end{enumerate}

\item \textbf{1 month} prior: \(\text{No}\) major surgery
\item \textbf{3 months} prior: \(\text{No}\) history of non-healing wounds, ulcers or bone fractures
\item \textbf{6 months} prior:
\begin{enumerate}
\item \(\text{No}\) unstable angina or myocardial infarct
\item \(\text{No}\) heart failure requiring hospitalization
\item \(\text{No}\) stroke or transient ischemic attack
\end{enumerate}

\item \textbf{3 years} prior: \(\text{No}\) other malignancy (not including completely excised basal or squamous cell skin cancer)
\item If sexually active, agrees to practice adequate contraception during study and for 6 months thereafter
\item \(\text{No}\) major autoimmune condition requiring immune suppression e.g. etanercept, infliximab, ivig
\item \(\text{No}\) prior treatment with anti-VEGF targeted treatments e.g. bevacizumab, cediranib, vandetanib, aflibercept, sunlinib, sorafenib
\end{enumerate}

The Eligibility Checklist must be completed in its entirety prior to registration. The completed, signed, and dated checklist used at study entry will be retained in the patients study file.

\newpage

\section{Registration}

\subsection{Procedure}

Patient registration will be conducted in accordance with routine hospital protocol. Enrolled patients will be further registered in a de-identified database maintained by the Research Nurse.

\subsection{Data collection at registration}

\begin{Form}
\begin{itemize}
\item \textbf{Checklist for study enrollment}
\end{itemize}
\end{Form}

\begin{enumerate}
\item Name of person randomizing case
\item Eligibility checklist completed
\item Investigator considers patient eligible
\item Informed consent:
\begin{enumerate}
\item For trial participation
\item For tissue and blood to be kept for use in research to learn about, prevent or treat cancer
\item To allow someone from this institution to contact him or her in the future to take part in more research
\end{enumerate}
\item Patient:
\begin{enumerate}
\item Initials
\item Identification number
\item Gender
\item Date of birth
\item \texttt{GLS(kps)}
\item \texttt{Weight}
\item \texttt{BSA}
\end{enumerate}

\textbf{Physicians:}
\begin{enumerate}
\item Neurosurgeon
\item Oncologist (Neuro-Oncology or Medical Oncology)
\item Radiation Oncologist
\end{enumerate}

\textbf{Dates:}
\begin{enumerate}
\item First resection
\item Started radiation
\item Completed radiation
\item Started temozolomide
\item Completed temozolomide
\item Registered for this trial
\item Randomized for this trial
\end{enumerate}

\newpage
\section{Rationale}
\subsection{Background}

\texttt{GLS(gbm)} (World Health Organization Grade IV astrocytoma), is the most common primary brain tumor in adults and portends a very poor prognosis. \cite{Louis2007} Its incidence is estimated to be 3.2/100,000 in the United States. \cite{RBTR2012}

Standard therapy for patients with newly diagnosed \texttt{GLS(gbm)} usually involves maximal surgical resection, followed by \texttt{GLS(rt)} (typically 60 Gray, given in 30 fractions) with concomitant and adjuvant \texttt{GLS(tmz)} for at least 6 months. The addition of \texttt{GLS(tmz)} to \texttt{GLS(rt)} has increased \texttt{GLS(mos)} from 12.1 months to 14.6 months, and 2-year survival from 10\% to 26\%. \cite{Stupp2005}

Recurrence of \texttt{GLS(gbm)} is almost inevitable. A meta-analysis of 8 Phase II studies involving 225 patients with recurrent \texttt{GLS(gbm)}, \texttt{GLS(mos)}, after disease recurrence was 25 weeks and the \texttt{GLS(pfs)} was 15\%. \cite{Wong1999}

Accurately diagnosing recurrence remains a challenge. Pseudo-progression occurs on follow-up imaging in 20-30\% of patients imaged at 2 months when treated with standard adjuvant \texttt{GLS(rt)} and \texttt{GLS(tmz)}. \cite{TAN2008}. In order to differentiate tumor recurrence from radiographic pseudo-progression, a surgical specimen remains the gold standard.

\subsection{Surgery}

In some cases surgery is essential in order to relieve mass effect caused by tumor growth. However in most cases, once recurrence of tumor has been confirmed (typically by frozen-section performed at the time of surgery), surgery proceeds with the goal of removal of as much of the remaining tumor as possible.

There has been considerable debate about the merits of such a
strategy. This is reflected, for example, in the Canadian recommendations for the treatment of recurrent or progressive GBM, which states

\begin{quote}
In the absence of level 1 evidence, the decision to re-operate should be made according to individual circumstances, in consultation with the multidisciplinary team and the patient.
\end{quote} \cite{basaw2011}

By contrast the National Comprehensive Cancer Network guideline for recurrent (local) GBM favors resection when possible. \cite{NCCN2013}

A recent review of literature on the subject, the most comprehensive to date (evaluating 11 studies), concluded that there is no established role for surgery in this setting. \cite{branden2013} Age and \texttt{KPS} were identified as generally important prognostic predictors and to a lesser extent, size of tumor.

\subsection*{Bevacizumab}

Regardless of the decision on whether to proceed with surgery (of whatever extent), some form of additional chemotherapy at recurrence is generally agreed to be worthwhile where possible. Although no one agent has yet been endorsed by existing guidelines, all of them give prime consideration to bevacizumab.

Although no phase III trial has been performed to validate this strategy, it has been approved by the \texttt{FDA} on the basis of two phase II studies, both published in 2009. In that by Friedman et al., those using bevacizumab alone had a \texttt{PFS} of 43\% and \texttt{OS} of 48 (95\% CI 35.6-64.5) weeks. \cite{friedman2009}

That by Kresyl et al. showed a \texttt{OS} of 31 (95\% CI 21-54) weeks. \texttt{PFS} was 57\% (95\% CI 44-75). \cite{kresyl2009} This was a favorable outcome with respect to historical controls, for example those treated with temozolomide alone.

\section*{Objectives}

\subsection*{Primary objectives}

\texttt{Evaluate the impact of biopsy versus extensive resection on time to progression after first recurrence of \texttt{GBM}}

\subsection*{Secondary objectives}

\texttt{Evaluate the impact of biopsy versus extensive resection on \texttt{PFS}}

\texttt{Assess the impact of biopsy versus extensive resection on quality of life, as measured by \texttt{KPS}}

\section*{Surgery}

\subsection*{Resection}

Patients randomized to microsurgical resection will undergo routine, image-guided cytoreduction targeting the contrast-enhancing portion of the lesion on T1-weighted contrast-enhanced \texttt{MRI}. Intraoperative adjuncts, including and not limited to, S-aminolevulinic acid, intraoperative \texttt{MRI}, and intraoperative mapping techniques, will be included as needed per the primary neurosurgeon.\texttt{Gliadel wafer} (carmustine) wafers will not be placed.

\subsection*{Biopsy}

Patients randomized to open biopsy will undergo routine, image-guided, open biopsies using a minimal craniotomy and open microsurgical techniques. (This does \texttt{not} include stereotactic needle biopsy).

\section*{Drug treatment: bevacizumab}

\subsection*{Overview}

In both treatment arms, patients will be treated post-operatively with bevacizumab. The first treatment will be administered on post-operative day 28.

\subsection*{Dose}

Bevacizumab will be administered at a dose of 10 mg/kg every 2 weeks. Doses will be adjusted if there is a \texttt{GREAT} than 10\% change in weight. While every effort will be made to keep bevacizumab infusions exactly 14 days apart, it is acknowledged that occasionally a dose must be given off schedule due to logistical reasons. A window of 4 days for bevacizumab dosing is acceptable.

\subsection*{Administration}

Bevacizumab will be administered intravenously as per current institutional guidelines, with associated pre-medications where required.
Treatment with bevacizumab will continue until progression of disease or significant toxicity occurs. Treatment may be held for grade 3 toxicities as defined in section:ref{subsec:ae}. If the patient does not meet criteria to resume treatment within 28 days of the date of the toxicity, they will be removed from the study treatment.

**Description and packaging**

Bevacizumab is a humanized IgG1 mab that binds all biologically active isoforms of human VEGF with high affinity. The mab consists of a human IgG1 framework and the antigen-binding, complementarity-determining regions from the murine anti-VEGF mab A.4.6.1.16-18. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection.

**Administration**

Bevacizumab should be administered as a continuous intravenous infusion using a rate regulating device per institutional guidelines. Pre-medications (e.g. ondansetron, diphenhydramine, dexamethasone) will be given as per local guidelines. It should not be administered as an IV push or bolus.

The first dose should be given over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be given over 60 minutes. If no adverse reactions occur, subsequent doses can be given over a minimum of 30 minutes.

Infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

**Storage**

Vials contain no preservative and are suitable for single use only.

**Supply**

Bevacizumab is available commercially.

**Glialae**

For studies with participating centers in the USA and registered with the gle(ncl), this is done through the gle(cetepaers). To facilitate reporting, a list of reported and/or potential gle(ae) associated with an agent is provided by gle(caepn). This uses a uniform presentation of events by body system.

In table :ref{tab:ae} below, these are shown for bevacizumab. In addition to the comprehensive list, a subset subset of gle(ae) is shown which are protocol specific exceptions to expedited reporting to the gle(ncl) via gle(cetepaers). These are the gle(speep). This list is based on a recent gle(rto) study involving bevacizumab. :cite{stog0823}

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>20%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Glialae** should be reported expeditiously by investigators to the gle(ncl) via gle(cetepaers) only if they exceed the grade of the event listed in parentheses after the event.
<table>
<thead>
<tr>
<th>Disorders</th>
<th>&amp; Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; &amp; Blood and lymphatic system disorders - Other (renal thrombotic</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>microangiopathy)</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; Febrile neutropenia &amp; &amp; 3</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>Supraventricular tachycardia &amp; &amp; 3</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; &amp; Acute coronary syndrome</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; &amp; Ventricular arrhythmia</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; &amp; Ventricular fibrillation</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>Abdominal pain &amp; &amp; 3</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; Colitis &amp; &amp; 3</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; Constipation &amp; &amp; 3</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; Colitis &amp; &amp; 3</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; Diarrhea &amp; &amp; 3</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; Dyspepsia &amp; &amp; 2</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td>&amp; Gastrointestinal fistula</td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Gastrointestinal hemorrhage</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Gastrointestinal perforation</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Gastrointestinal ulcer</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Infusion-related reaction</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Non-cardiac chest pain</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Allergic reaction</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Anaphylaxis</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Infections and infestations - Other (peri-rectal abscess)</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Gastrointestinal anastomotic leak</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Wound dehiscence</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>&amp; Blood and lymphatic system disorders</td>
</tr>
</tbody>
</table>
& \textcolor{gray}{alt} increased & & 3 & & \textcolor{gray}{ast} increased & & 3
& Blood bilirubin increased & & 2
& Alkaline phosphatase increased & & 3
& Cardiac troponin I increased & & \textcolor{gray}{tabularnewline}
& \textcolor{gray}{anc} decreased & & 3
& Weight loss & & 3
& \textcolor{gray}{wcc} decreased & & 3
\multicolumn{4}{l}{\textcolor{gray}{(c)}}{Metabolism and nutrition disorders}
& \textcolor{gray}{cellcolor[gray]{0.9}}{Metaphyseal and connective tissue disorders}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& Arthralgia & & 3 & & \textcolor{gray}{tabularnewline}
& Musculoskeletal and connective tissue disorder - Other (bone
& \footnote{Metaphyseal dysplasia was observed
& in young patients who still have active epiphyseal growth
& plates.)} & & \textcolor{gray}{tabularnewline}
& Myalgia & & 3 & & \textcolor{gray}{tabularnewline}
& Osteonecrosis of jaw \footnote{Cases of osteonecrosis of the jaw
& have been reported in cancer patients in association with
& bevacizumab treatment, the majority of whom had received prior
& or concomitant treatment with \textcolor{gray}{iv} bisphosphonates.}
\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(c)}{Nervous system disorders}
& \textcolor{gray}{cellcolor[gray]{0.9}}{Peripheral sensory neuropathy}
& \footnote{Increased rate of
& peripheral sensory neuropathy has been observed in trials
& combining bevacizumab and chemotherapy compared to chemotherapy
& alone.}
& \textcolor{gray}{tabularnewline}
& Dizziness & & 2 & & \textcolor{gray}{tabularnewline}
& Headache & & 3 & & \textcolor{gray}{tabularnewline}
& Intracranial hemorrhage & & \textcolor{gray}{tabularnewline}
& Ischemia cerebrovascular & & \textcolor{gray}{tabularnewline}
& Peripheral sensory neuropathy \footnote{Increased rate of
& peripheral sensory neuropathy has been observed in trials
& combining bevacizumab and chemotherapy compared to chemotherapy
& alone.}
& \textcolor{gray}{tabularnewline}
& Syncope & & \textcolor{gray}{tabularnewline}
& \textcolor{gray}{(c)}{Renal and urinary disorders}
& \textcolor{gray}{cellcolor[gray]{0.9}}{Acute kidney injury}
& \textcolor{gray}{tabularnewline}
& Hematuria & & 3 & & \textcolor{gray}{tabularnewline}
& Proteinuria & & 2 & & \textcolor{gray}{tabularnewline}
& Renal and urinary disorders - Other (Nephrotic Syndrome)
& \textcolor{gray}{tabularnewline}
& Urinary fistula & & \tabularnewline
& \textcolor{gray}{(c)}{Reproductive system and breast disorders}
& \textcolor{gray}{cellcolor[gray]{0.9}}{Reproductive system and breast disorders - Other (ovarian failure)}
& \footnote{Ovarian failure, defined as amenorrhea lasting 3 or more
& months with \textcolor{gray}{vgs} fsh elevation ($\geq 30 \text{ mIU/mL}$), was
& increased in patients receiving adjuvant bevacizumab plus
& mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After
& discontinuation of bevacizumab, resumption of menses and an
& \textcolor{gray}{vgs} fsh level $<27$ mIU/mL was demonstrated in 22%
& (7/32) of these women. Long term effects of bevacizumab exposure
& on fertility are unknown.}
& \textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& Respiratory, thoracic and mediastinal disorders
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& Respiratory, thoracic and mediastinal disorders - Other
& (nasal septal perforation)
& \textcolor{gray}{tabularnewline}
& Respiratory, thoracic and mediastinal disorders - Other
& (tracheo-esophageal fistula)
& \textcolor{gray}{tabularnewline}
& \textcolor{gray}{(c)}{Skin and subcutaneous tissue disorders}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& Vascular disorders
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& Hypertension & & 3 & & \textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& Thromboembolic event & & 3 & & \textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& \textcolor{gray}{(0.9)}\textcolor{gray}{tabularnewline}
& Vascular disorders - Other (arterial thromboembolic event)
& \footnote{Arterial thromboembolic event includes visceral arterial
ischemia, peripheral arterial ischemia, heart attack, and stroke.) \tabularnewline 
\end{longtable}
\end{center}
\columnbreak

The following have also been reported with bevacizumab but causality has not been established.
\begin{center}
\begin{longtable}{|c|c|}
\hline
\texttt{Body system} & \texttt{Adverse event} \\
\hline
\texttt{Body system} & \texttt{Adverse event} \\
\hline
\endfirsthead
\caption{Possible adverse events (continued)}\tabularnewline
\hline
\texttt{Body system} & \texttt{Adverse event} \\
\hline
\endhead
\endfoot
\endlastfoot

Blood and lymphatic system disorders & Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura) \\
& Disseminated intravascular coagulation \\
Cardiac disorders & Pericardial effusion \\
General disorders & Gait disturbance & Sudden death (not otherwise specified) \\
Hepatobiliary disorders & Hepatic failure \\
Infections and infestations & Infections and infestations - Other (aseptic meningitis) \\
Investigations & Platelet count decreased \\
Metabolism and nutrition disorders & Hyponatremia \\
Musculoskeletal and connective tissue disorders & Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone) \\
& Musculoskeletal and connective tissue disorder - Other (myasthenia gravis) \\
Nervous system disorders & Dysgeusia \\
& Peripheral motor neuropathy \\
& Seizure \\
Psychiatric disorders & Confusion \\
Respiratory, thoracic and mediastinal disorders & Adult respiratory distress syndrome \\
Pneumonitis & Pneumothorax \\
& Pulmonary hypertension \\
Skin and subcutaneous tissue disorders & Palmar-planter erythrodysesthesia syndrome \\
& Skin ulceration \\
\end{longtable}
\end{center}
\subsubsection{Bevacizumab Dose Modifications}

There will be no dose reduction for bevacizumab. Treatment should be interrupted or stopped for certain adverse events, as described in table \ref{tab:dm}. If bevacizumab is interrupted for \texttt{greater} 8 weeks, the patient should stop bevacizumab treatment on protocol.

\begin{center}
\begin{longtable}{|c|l|}
\hline
\texttt{Event} & \texttt{Grade} & \texttt{Action to be taken} \\
\hline
\end{longtable}
\end{center}
\textsc{Event} & \textsc{Grade} & \textsc{Action to be taken} \\
--- & --- & --- \\

Acute infusional reactions/ cytokine release syndrome} & Grade 1-3 & If infusion-related or allergic reactions occur, premedications should be given with the next dose and infusion time may not be reduced for the subsequent infusion. \\
& For patients with grade 3 reactions, bevacizumab infusion should be stopped and not restarted on the same day. At the physician's discretion, bevacizumab may be permanently stopped or re-instituted with premedications and administered patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions. \\
& Grade 4 & Stop bevacizumab \\

Venous Thrombosis & Grade 3 or asymptomatic grade 4 & Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is textless 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. \\
& If the planned duration of full-dose anticoagulation is textgreater 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if remp[all] of the criteria below are met: \\
& -- The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin or be on a stable dose of heparin prior to restarting bevacizumab \\
& -- The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions) \\
& -- The subject must not have had hemorrhagic events while on study \\
& If thromboemboli worsen/recur upon resumption of study therapy, stop bevacizumab \\
& Grade 4 (symptomatic) & Stop bevacizumab \\

Hypertension & Definitions \begin{description} \\
\item [grade 1] asymptomatic, transient (textless 24 hours) increase by \textgreater 20 mmHg (diastolic) or to \textgreater 150/100 if previously \glsaw{w}l; intervention not indicated \\
\item [grade 2] recurrent or persistent \textgreater 24 hours or asymptomatic increase by \textgreater 20 mmHg (diastolic) or to \textgreater 150/100 if previously \glsaw{w}l; monotherapy may be indicated \\
\item [grade 3] requiring more than one drug or more intensive therapy than previously \\
\item [grade 4] life threatening (eg, hypertensive crisis) \end{description} \\

& \multicol[2]{p[12cm]}{\textsc{Treat with antihypertensive medication as needed. The goal of BP control should be consistent with general medical practice.}} \\
& Grade 1 & Consider increased BP monitoring \\
& Grade 2 asymptomatic & If diastolic BP \textless 100 mmHg: begin anti-hypertensive therapy and continue bevacizumab \\
& Grade 2-3 & If symptomatic or diastolic BP \textgreater 100 mmHg: hold bevacizumab until symptoms resolve and BP \textless 160/90 mmHg \\
& Grade 4 & Stop bevacizumab \\

Congestive Heart Failure & Grade 3-4 & Stop bevacizumab \\

Proteinuria & \multicol[2]{p[12cm]}{Proteinuria should be monitored by urine analysis for \glsaw{up}c ratio prior to every other dose of bevacizumab} \\
& \glsaw{up}c ratio \textless 3.5 & Continue bevacizumab
& $\text{\texttt{\textbackslash gla\{upc\} ratio}} \geq 3.5$ & Hold bevacizumab until $\text{\texttt{\textbackslash gla\{upc\}}} \textless 3.5$
\tabularnewline
& Grade 4 or nephrotic syndrome & Stop bevacizumab
\tabularnewline
\hline
\text{Hemorrhage ($\text{\texttt{\textbackslash gla\{cns\}}} \text{ or pulmonary}$) & Grade 2-4 & Stop bevacizumab}
\tabularnewline
\hline
\text{Hemorrhage (non-$\text{\texttt{\textbackslash gla\{cns\}}} \text{; non-pulmonary}$) & Grade 3 & Patients receiving full-dose anticoagulation should stop bevacizumab}
\tabularnewline
& For patients not on full-dose anticoagulation, hold bevacizumab until all of the following criteria are met:
\tabularnewline
& & - the bleeding has resolved and Hb is stable
\tabularnewline
& & - there is no bleeding diathesis that would increase the risk of therapy
\tabularnewline
& & - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
\tabularnewline
& & Patients who experience recurrence of grade 3 hemorrhage should stop study therapy
\tabularnewline
& Grade 4 & Stop bevacizumab
\tabularnewline
\hline
\text{Glasunset(pres) & show PHES as abbrev first time}
\tabularnewline
\text{\texttt{\textbackslash gla\{rplis\}}} or \texttt{\textbackslash gla\{pres\}} & \texttt{\textbackslash multicolumn\{2\}{p\{12cm\}}\{myTwoCol\}Hold bevacizumab if symptoms/signs suggestive of \texttt{\textbackslash gla\{rplis\}}; subsequent management should include \texttt{\textbackslash gla\{mri\}} scans and control of hypertension. Stop bevacizumab upon diagnosis of \texttt{\textbackslash gla\{rplis\}}}
\tabularnewline
\hline
\text{\texttt{\textbackslash multicolumn\{2\}{p\{5cm\}}}Wound dehiscence requiring medical or surgical intervention} & Stop bevacizumab
\tabularnewline
\hline
\text{\texttt{\textbackslash multicolumn\{2\}{p\{5cm\}}}GI perforation, GI leak or fistula} & Stop bevacizumab
\tabularnewline
\hline
\text{Bowel obstruction & Grade 2 requiring medical intervention} & Hold bevacizumab until complete resolution, with a minimum of 4 weeks after surgery
\tabularnewline
& Grade 3-4 & Hold bevacizumab until complete resolution
\tabularnewline
& If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at Investigator’s discretion
\tabularnewline
\hline
\text{\texttt{\textbackslash multicolumn\{2\}{p\{4cm\}}}\{\raggedright Other unspecified bevacizumab-related AEs (except controlled nausea/vomiting)\}}
\tabularnewline
\hline
\text{\texttt{\textbackslash gla\{kps\}}} will be assessed at each visit.
\tabularnewline
\hline
\text{\texttt{\textbackslash gla\{cns\}}} will be repeated every 2 months, or more frequently if there are new symptoms or signs concerning for disease progression. \texttt{\textbackslash gla\{kps\}} will be assessed at each visit.
\tabularnewline
\hline
\text{Patients will follow up with their Oncologist at monthly intervals. }$\text{\texttt{\textbackslash gla\{mri\}}}s$ will be repeated every 2 months, or more frequently if there are new symptoms or signs concerning for disease progression. \texttt{\textbackslash gla\{kps\}} will be assessed at each visit.
\tabularnewline
\hline
\text{At time of subsequent progression, the patient will be re-evaluated at our multidisciplinary conference. Decisions will be individualized but will include the options of further surgery, further $\text{\texttt{\textbackslash gla\{rt\}}}$, a change in chemotherapy, treatment with electrical fields (NovoTTF \textregistered) and Palliative care.
\tabularnewline
\hline
\text{The primary objective of this study is to determine whether extensive resection plus bevacizumab (experimental arm) will improve the overall survival compared to open biopsy plus bevacizumab (control arm). The division into experimental and control arms is somewhat arbitrary as both are established treatments at the time of progression and neither has clearly been shown to be superior.
\tabularnewline
\text{Essentially, this is a Phase III design. The randomization of
\textbackslash end\{longtable\}\textbackslash end\{center\}\textsection{Monitoring}
\textsection{Treatment at time of progression}
\textsection{Statistical considerations}
\textsubsection{Sample size and power justification}
experimental and control arms is 81:19. The null hypothesis is that the median PFS for both arms will be 18 weeks, based on data from two Phase II trials of bevacizumab at time of recurrence. \cite{Friedman2002, Kresyva2009}. The alternative hypothesis is that patients treated with \text{an attempt at complete resection} plus bevacizumab will have an improvement in overall survival to 23 weeks ($\text{hgs(hr)}$ of 1.3). This is based on a review of existing literature (retrospective series) on this subject, which is detailed in the article describing this trial.

Following the methods of Therneau, we assume that the survival distributions will be exponential. \cite{Therneau2000} The $\text{hgs(hr)}$ is thus the reciprocal of the ratio of median survival times. We aim for a power of 80\% and a significance level of 0.05 (two-sided). This would result in a sample size of 456 (assuming all patients are treated as assigned and followed until to progression). A typical range of power and sample sizes is illustrated in table \ref{tab:pwr} for the above significance level, following the method of Schoenfeld. \cite{Schoenfeld1983}

\begin{table}[h]
\begin{tabular}{@{}llll@{}}
\toprule
Power & 1.2 & 1.4 & 2.0 \\
\midrule
70\% & 742 & 218 & 51 \\
80\% & 945 & 277 & 65 \\
90\% & 1264 & 376 & 87.5 \\
\bottomrule
\end{tabular}
\end{table}

Given the risks associated with overestimating the effect size in the study, which would lead to the study being underpowered, we prefer the more conservative margin of a $\text{hgs(hr)}$ of 1.2. Thus, we aim for for a sample size of 945.

Following a review of cases over the preceding 3 years (2009-2012), we estimate that our institution sees 50-70 cases/year of first recurrence of \text{gbm} who had previously received standard of care (the Stupp regimen, i.e. concurrent \text{rt} and \text{tmez} followed by adjuvant \text{tme}). \cite{Stupp2005} This numbers seem appear to be stable over this time period. We will include those who were receiving this regimen as part of another trial. We estimate that 60-70\% will be eligible for entry, and agreeable, to participation in the study, giving approximately 40 entrants/year.

Given the more optimistic threshold of a $\text{hgs(hr)}$ of 1.3, the trial would take 11 years to accrue. With the more conservative $\text{hgs(hr)}$ of 1.2, the trial would need to run for \text{c.8} 23 years.

\subsection{Patient accrual}
This study is projected to accrue 3-4 patients/month. If the average accrual is 2 patients/month (6 months after trial activation), the study will be re-evaluated with respect to feasibility.

\subsection{Patient selection and randomization}
All cases will be reviewed at our weekly weekly Multidisciplinary Central Nervous System Tumor Conference. Enrollment will be considered for all patients meeting the eligibility criteria. \ref{sec:sec}

Patients will be stratified at the time of enrollment; this will be followed by randomization, as shown in the study schema \ref{sec:sec}.

\subsection{Analysis plans}
In general, comparisons between groups will have a significance (type I error) of $p < 0.05$ (2-sided).

Progression-free and overall survival rates will be estimated using the Kaplan-Meier method. \cite{Kaplan1958} Differences between treatment arms will be tested with the log-rank test. \cite{Mantel1966} $\text{hgs(pfs6)}$ and $\text{hgs(mos)}$ will be measured from the date
of randomization to the date of death or, otherwise, to the last follow-up date on which the patient was known to be alive.

Proportions/rates will be modelled using an exact binomial distribution, with 95\% confidence intervals. These are: \text{\texttt{gls}(pfs6)}, objective response, grade 3+ toxicities and acute or delayed \text{\texttt{gls}(cns)} toxicities. For secondary endpoints, no adjustment is planned for multiple comparisons as these are exploratory tests.

\text{\texttt{gls}(mos)} and \text{\texttt{gls}(pfs6)} will also be modelled with multivariate analyses using the Cox proportional-hazards model. The planned covariates of interest are:

\begin{itemize}
  \item Protocol treatment (biopsy or extensive resection)
  \item Age
  \item Tumor volume at time of recurrence
  \item \text{\texttt{gls}(kps)}
  \item \text{\texttt{gls}(nrg)}. Number of critical areas of cortex involved (0-3)
  \end{itemize}
\footnote{These are}

\begin{itemize}
  \item Motor
  \item Speech
  \item MCA i.e. referring to affected areas adjacent to the M1/M2 areas of the Middle Cerebral Artery
  \end{itemize}

\item Time since original diagnosis
\end{itemize}

The assumption of proportional hazards will be checked using residuals and time-varying coefficients. If the data clearly do not follow proportional hazards, other statistical models will be used to fit the data instead. Possible alternatives are to use the stratified Cox proportional hazard model, accelerated failure model, or to partition the time axis into sections where proportional hazards assumption holds.

\subsection{Interim toxicity and futility analysis}
Interim analysis will be undertaken on an annual basis following the methods of O’Brien and Fleming. \cite{obrien1979} The study will be terminated of study should these initial results indicate a marked superiority of one treatment over the other.

\subsection{Significance Testing for Final Analysis}
The final analysis will be performed on an intention-to-treat basis, such that all eligible cases on the study will be included in the arm to which they were randomized, regardless of what treatment the patients actually received. The analysis to report the final results of treatment comparison between the experimental arm and the control arm will be undertaken once the required sample size has been accrued. If the \texttt{p} value is less than protocol-specified 0.05 (two-sided), the study Statistician will reject the null hypothesis and conclude that observing such a dataset would be highly unlikely if the outcome in both arms was really similar. Thus the data would support the hypothesis that the experimental arm improves progression-free survival. The final report will include all information reported in the interim analyses as well as treatment compliance and adverse events.

\section{Data collection}

\subsection{Data storage and analysis}
The Research Nurse assigned to this study will tabulate, store, and secure data in a single password-protected Excel database located on a password-protected computer in their locked office. Data analysis will be completed by the Principal Investigator and Statistician.

\subsection{Data safety monitoring plan}
The Data Safety Monitoring Plan is written to ensure the safety of the participants and verifying the validity and integrity of the data. All adverse events will be reported to the \texttt{irb} and \texttt{fda} in an expedited manner within 10 days of occurrence. The Investigator will continue to follow or obtain documentation of the resolution course of such an event.

\subsection{Ethical considerations and protection of human subjects}
For patients that meet the inclusion criteria, informed consent will be obtained at the time of consent for brain tumor surgery. The option to enter the trial will be presented to the patient, if he/she is able to consent, or to the legal guardian/durable power of attorney in all other circumstances.

For all patients, the risks, benefits
and alternatives of the trial will be discussed separately from those associated with the planned operation. Refusal to participate in the trial will not affect management strategies or therapeutic options.

\subsection{Potential risks}
The risks of study inclusion are similar to the risks of open neurosurgical tumor resection. This includes, but is not limited to, death, coma, infection, blood loss, and permanent neurological deficit.

\subsection{Potential benefits}
While the study provides no direct benefit to the patient, its findings may clarify the value of greater extent of resection for patients with recurrent glioblastoma.

\subsection{What other alternatives are there?}
If you decide not to participate in this research study, this will not affect the care to which you are entitled and will not influence your doctor in any way. If you decide not to participate, your doctor will discuss alternative treatment options with you. Some of these options may include open surgery, open biopsy, needle biopsy, and observation.

\subsection{Protecting confidentiality}
Each consented participant will be assigned a study identification number. All data will be collected and stored under this identification number, with no other identifying information such as name, date of birth, or social security number. All collected data will be stored on premises of the Hospital in a password-protected desktop computer located in a locked office accessible only to the Principal Investigator and Study Co-ordinator. A list of corresponding medical record numbers will be similarly tabulated and protected.

\subsection{Costs}
There will be no additional supply or equipment costs incurred to the patient or the hospital by this study. All proposed therapies are within the acceptable standards of current care options and will be billed to the patients insurance company, as would otherwise be the case.

\appendix
\setcounter{secnumdepth}{1}
\begin{center}
{\bf APPENDIX}
\end{center}

\section{Sample consent form}

\subsection{Why am I being asked to participate in this research study?}
You have been identified as a possible candidate for participation in a clinical research study called 'Biopsy vs Extensive Resection for first recurrence of Glioblastoma: The BERG trial'. A research study is performed when physicians try find new ways to diagnose and/or treat illness. Since this research study is experimental and the anticipated results have not been proven, you need to know enough about the risks and benefits to decide if you want to participate. This process is called informed consent.

The Research Nurse working with the Principal Investigator for this research study, will discuss this study with you in detail. The Informed Consent document explains what will be expected of you and what risks or benefits you may anticipate if you agree to participate. You should read this document very carefully and ask as many questions as you need to fully understand what your involvement in this study means. Please understand that by signing this document you agree to participate in this experimental study.

\subsection{How many people will take part in this study?}
This Hospital is sponsoring this research study. It is being conducted only at this Hospital. A target of a total of $945$ patients will participate.

\subsection{Why is this study being done?}
This research study is designed to better understand the value of greater extent of resection when your tumor shows signs of recurrence. By randomizing patients to extensive resection vs. open biopsy, we will determine whether one has more clinical value than the other. This remains an unresolved question. All proposed treatments are already \textit{fda}-approved and are not experimental.
What is involved in this study?

If you choose to participate in this study, you will be selected for either open biopsy (where a small hole is made in the skull to take a piece of the abnormal tissue and make a diagnosis) or microsurgical resection (where an opening in the skull is made to expose all the abnormal tissue and remove everything that is safe). These are both currently standard therapy options for patients with your diagnosis. The purpose of the study is to determine which provides more clinical benefit. Following surgery, you will recover as you would normally and then, if the tissue that is removed is diagnosed as recurrent tumor, receive bevacizumab, an anti-tumor agent that commonly given to patients at the time of recurrence. Your clinical follow-up after this will be no different than if it would be otherwise, with routine appointments to see your Neuro-Oncologist and Neurosurgeon at regular intervals.

How long will I be on the study?

If you agree to take part in this study, we will continue up with you for at least 3 years. As stated above, no additional appointments will be needed during this time.

What are the risks of this study?

The risks of this study are similar to those that you would be faced with during routine management of your tumor.

Risks associated with brain surgery, include death, neurological problems such as weakness, difficulty seeing or using language, blood loss, and infection.

Risks associated with bevacizumab include wound infection, hematological abnormalities (low blood counts), and gastrointestinal problems.

Are there benefits to taking part in this study?

This study involves treatments which would be available to you outside the context of the study. However there may be benefits either to having a surgical resection or to having a biopsy alone in terms of quality of life and survival. Also, the knowledge gained from this study may benefit others in the future.

What other options are there?

If you decide not to participate in this research study, this will not affect the care to which you are entitled and will not influence your doctor in any way. If you decide not to participate, your doctor will discuss alternative treatment options with you. Some of these options may include open surgery, open biopsy, needle biopsy, and observation.

How will I be informed of additional information or new findings?

If you decide to participate, your doctor will keep you informed of any new findings that are discovered during the course of this study which may affect your continued willingness to participate in this study.

What about confidentiality?

Every attempt will be made to keep your participation in this research study and your records confidential. However, representatives from the DHHS, from the FDA, and the Hospital may inspect your research records to evaluate the results of this study. The results of this research study may also be published in scientific journals and/or may be presented at scientific meetings, but your identity will not be revealed.

A description of this clinical trial will be made available on http://www.ClinicalTrials.gov, as is required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What are the costs?

There are no additional costs for you that are associated with this trial. As always, you understand that you will be responsible for payment of any bills that your insurance may refuse to pay due to your participation in this research study.

What happens if I am injured while participating in the study?

If you experience an injury or adverse event, please contact the Principal Investigator at 123 456 78910. If the investigator determines that the injury or adverse event is due to your participation in this research, this will be treated, although you are always responsible for the financial costs associated with your care. This does not waive your rights in the event of negligence.

What are my rights as a participant?
You understand that your participation in this research study is voluntary and that you are free to withdraw from this study at any time. If you decide not to participate, your doctor will not hold it against you in any way. If you decide to withdraw from this study at a later date, please notify the Principal Investigator of your decision and to discuss your alternative treatment options.

\medskip
You understand that your doctor may also stop your participation on this study if it is felt to be in the best interest of your health. This may be done without your consent, but alternative treatment options will be discussed with you.

\subsection{Whom do I call if I have questions?}
If you have any questions about this research study or your participation in it, please feel free to ask them now. If you think of questions later or have concerns about your participation, please call the Principal Investigator at 123 456 7890.

\medskip
If you have any questions about your rights as a research subject or about the Institutional Review Board for Human Research (IRB) at the Hospital, the board has reviewed this informed Consent document for compliance with federal guidelines. They may be contacted at:

\subsection{Patient/representative signature}

\medskip
You are voluntarily deciding whether or not to participate in the research study described in this consent form. Your signature below indicates that you have read and understand the information provided, and that you have decided to participate. You will receive a copy of the signed informed consent document.
\section{Rights of human subjects in medical experiments}

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

\begin{enumerate}
\item Be informed of the nature and purpose of the experiment.
\item Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized
\item Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment
\item Be given an explanation of any benefits to the subject reasonable to be expected from the experiment, if applicable
\item Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits
\item Be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise
\item Be given an opportunity to ask any questions concerning the experiment or the procedure involved
\item Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice
\item Be given a copy of any signed and dated written consent form used in relation to the experiment
\item Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision
\end{enumerate}

I attest that I, or my representative, discussed this study with the above named participant or legal representative. This person had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participate in this study.

\section{Karnofsky performance scale}

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

\begin{thebibliography}{99}


Gilbert M. Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma. \texttt{http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0825}\ (Available online)
