1.0 Objectives

1.0 Establish the safety and efficacy of using stereotactic body radiotherapy (SBRT) to treat spine and para-spinal tumors in a single session.
1.1 Document frequency and severity of pain, symptoms and symptom interference, as well as quality of life before and after treatment.
1.2 Document changes in neurological function at defined intervals compared to pre-treatment neurological function

2.0 Background

Each year, approximately 200,000 cancer patients develop vertebral metastases [Schabert 1985]. Palliative treatment of bone metastases comprises a signficant portion of cancer care in that a large proportion of that expediture is spent on palliation of painful osseous metastases. Radiation therapy can be highly effective in relieving painful bone metastases given that almost 90% of patients will experience improvement in their pain, with complete pain relief in about half of treated patients (Janjan 1997). Unlike curative therapy which uses a high total dose of radiation to achieve tumor control, palliative therapy generally uses a lower total dose of radiation given over a shortened hypofractionated schedule.

A large collective experience has been described by the Radiation Therapy Oncology Group (RTOG) for bone metastases. The RTOG study concluded that low-dose, short-course treatment schedules were as effective as high-dose protracted treatment programs. For solitary bone metastases, there was no difference in relief of pain when 20Gy using 4 Gy fractions was compared to 40.5 Gy in 2.5Gy per fraction. In multiple bone metastases, 30Gy using 3Gy fractions was compared with 15 Gy using 3 Gy fractions, 20Gy using 4 Gy fractions and 25 Gy using 5 Gy fractions (Tong 1982). No differences were seen in the rate of pain relief between these treatment schedules. Partial relief of pain was achieved in 83% and complete relief occurred in 53% of patients . Multiple other studies have published benefits of hypofractionated radiation therapy for the treatment of bone metastases (Gaze 1997, Hoskin 1992, Jeremic 1998, Madsen 1983, Niewald 1996) and even in the face of spinal cord compression (Maranzano 1997). There are studies to support the effectiveness of single fractions of radiotherapy for bone metastases (Nielson 1999, 1998, Steenland 1999). The RTOG 97-14 study addressed the palliation of symptoms and quality of life for patients with osseous metastases by comparing 3 Gy x 10 fractions to 8 Gy x 1 fraction in a randomized trial involving 897 eligible patients with breast or prostate cancer and painful bone metastases. The complete response and partial response for pain for patients who received 8 Gy was 15% and 50%, compared to 18% and 48% for patients who received 30 Gy. In the preliminary report from this trial, it was concluded that palliative external beam radiation therapy is very effective in providing pain relief and that pain and narcotic relief is equivalent for both 30 Gy in 10 fractions and 8 Gy in a single fraction (Hartsell 2003).

While conventional radiation treatment is used to provide palliation for the vast majority of patients with spinal metastasis, there are at least 3 drawbacks. First, conventional irradiation is limited by the dose that can be tolerated by the spinal cord which may limit its ability to control disease. Second, excessive amounts of normal tissue are irradiated. Third, conventional irradiation is relatively inconvenient since most treatment courses last about 2 weeks.

In our experience from protocol ID02-446 which is evaluating SBRT given in 3 - 5 fractions for spinal metastases, patients find the option of non-invasive SBRT to the spine to be attractive when clinically indicated. However, the ability to give this treatment in a single fraction would be desirable if it could be done safely. This perception is confirmed by a study from Canada on 101 patients in which most participating patients indicated that an 8 Gy-in-one fraction regimen was favored, over a 2 week course of radiation treatment independent of the treated site. The convenience of the treatment plan and the likelihood of bone fracture were the most important facotrs influencing patients' choice (Szumacher 2005).

Stereotactic radiosurgery has been originally applied only to the brain. It is a routine procedure that delivers a single clinically significant focused dose of radiation into the tumor while delivering a clinically insignificant dose of radiation to the surrounding brain. The value of stereotactic radiosurgery in the brain has been established by numerous published reports (Auchter 1996). The linear accelerator (LINAC) based stereotactic radiosurgery program at U.T. M.D. Anderson Cancer Center was started in 1991 as a joint collaboration between the Departments of Neurosurgery, Radiation Oncology, and Radiation Physics. The program has been successful in treating patients afflicted with metastatic brain disease and has grown considerably since its inception. In the Fall of 1999, a dedicated stereotactic unit was installed that would be able to significantly improve the ability to handle the increasing number of referals for stereotactic radiosurgery. Over 200 patients are now treated routinely at MD Anderson Cancer Center on an annual basis with minimal degree of invasiveness and minimal complication rates of less than 1%.

Stereotactic body radiotherapy (SBRT) is based on radiosurgical principles applied to targets outside the head. In contrast to the brain which is an ideal model because it is rigidly contained within the bony confines of the skull, extracranial targets in the body do not afford the same luxury of immobilization. Stereotactic radiosurgery to extra-cranial sites has been hampered by difficulties with creating a robust system that produces highly reproducible body-immobilization. Preliminary experience with SBRT to the spine is summarized: Investigators at the University of Arizona reported on a prototype for stereotactic radiosurgery to the spine in 5 patients whose tumors that had failed to respond to spinal cord tolerance doses delivered by conventional radiation therapy to a median dose of 45Gy. Tumors were treated with single-fraction stereotactic radiosurgery with a median single fraction dose of 10Gy (range, 8-10 Gy). A short median follow-up of 6 months revealed no radiographic or clinical progression of the treated tumor in any patient. In 3 patients, there was CT or MRI documented regression of the treated tumor. A single complication of esophagitis occurred involving C6-T1 that resolved with medical therapy. Although the follow-up is short, all patients received significant palliation of pain (Hamilton 1996). An update to this series was reported on 9 patients presenting with recurrent disease to the spinal column. All patients had failed standard therapy consisting of surgery, external fractionated radiation therapy, and /or chemotherapy. Six of 9 patients had epidural compression, and 4 of the 9 had evidence of myelopathy. Two of 9 patients had radicular symptoms secondary to compression from the tumor. Patients were treated with

median radiosurgical dose of 8Gy (range 8-10 Gy), yet median dose delivered to the already prior irradiated spinal cord was 1.79 Gy. Three minor complications were reported including radiation-induced esophagitis, wound infection and one patient requiring an additional 24 hour hospitalization. No instances of radiation myelitis or neurological deterioration were observed. This phase I study demonstrated technical feasibility of spinal radiosurgery for the control of metastases to the vertebral column even in the face of epidural compression (Hamilton 1995).

Bilsky et al from Memorial-Sloan-Kettering Cancer Center, described preliminary experience in which intensity modulated radiation therapy (IMRT) was used to treat paraspinal lesions in patients who harbor locally recurrent tumors. The tumor received 20Gy in four fractions with 100% isodose to the tumor and 20% to the spinal cord. One year after IMRT, the tumor was well controlled with significant pain relief and there was no known evidence of radiation myelopathy (Bilsky 2001).

Murphy et al describe a new method for treating metastatic spinal tumors in which non-invasive image-guided frameless stereotactic radiosurgery is performed (Murphy 2001). The authors developed a system that coupled an orthogonal pair of x-ray cameras to a dynamically manipulated robot-mounted linear accelerator that guides the radiation beam to treatment sites associated with radiographic landmarks. Alignment of the treatment dose with the target volume was accurate to within 1.5mm. Four patients underwent spine radiosurgery with total prescription doses of 10 to 16 Gy in one or two fractions. The ability to deliver 16 Gy to the perimeter of an irregular target while limiting cord exposure to below 8 Gy was demonstrated (Murphy 2001).

At the University of Texas M.D. Anderson Cancer Center, a new stereotactic body radiation program to the spine was initiated in collaboration with the Department of Neurosurgery in November of 2002 to treat patients afflicated with spinal or paraspinal metastases. The program utlizes a system involving a Tyco/Radionics extracranial stereotactic body frame and a linear accelerator/“CT-on-Rails” system within in the Department of Radiation Oncology to deliver stereotactic body radiotherapy to the spine in the context of ongoing protocol ID02-446. Conformality to the tumor volume and protection of critical internal structures such as the spinal cord is theoretically assured by determination of treatment position and adjusting for any changes observed in treatment position using CT-on-rails imaging immediately prior to radiation treatment. The distinctiveness of this system is that it allows the patient to be scanned in the same treatment position on the same treatment couch within the same treatment room eliminating the need for transporting the patient to another room with a CT scanner.

The reproducibility of patient steup in our protocol ID02-446 has been published to be able to treat patients with an accuracy within 1mm [Shiu 2003]. The phase I results from our protocol ID02-446 was that the SBRT was safe and feasible to give in 5 fractions [Chang 2004]. Interim results from ID02-446 showing a crude tumor control rate of 87.3%, and no evidence of Grade 3-4 neurological toxicity will be presented at the American Society of Therapeutic Radiation Oncology meeting [Chang 2005]. In our interim analysis of data from ID02-446, we looked at the actuarial 1-year freedom from progression of spinal tumors, and found that the proportion of spinal tumors controlled in renal cell carcinoma patients compared to non-renal cell carcinoma patients was 95% compared to 56% (log-rank p = 0.02). Therefore, in this protocol that treatment plan will be stratified for renal cell carcinoma patients and non-renal cell carcinoma patients such that renal cell carcinoma patients will receive a higher dose, in the hopes of achieving a higher level of tumor control. The results from ID02-446 serve as a precursor and the basis for the proposed study of single session SBRT. This study is designed to establish the safety, and efficacy of single session SBRT for patients with metastatic spine disease.

3.0 Patient Eligibility

Inclusion Criteria:

1) Radiographically documented spine or paraspinal metastasis demonstrated on spine MRI within 4 weeks of registration
2) Maximum of 2 metastatic sites in the spine to be irradiated in single session
3) Informed consent for irradiation of spinal or para-spinal tumor (s)
4) Diagnosis of cancer including but not limited to lung (non-small cell and small cell), breast, prostate, renal cell, melanoma, gastrointestinal, and germ cell tumors, unknown primary tumors
5) Karnofsky performance status of at least 40 (ie not requiring active hospitalization)

Exclusion Criteria:

1) Worsening neurological status due to radiographic evidence of spinal cord compression requiring immediate surgical decompression or emergent conventional external radiation therapy.
2) Delay in initiation of radiation treatment would be potentially detrimental to neurological outcome
3) Prior irradiation to current site of interest in the spine
4) Spinal metastasis in the cervical spine are not eligible for treatment
5) Unstable spine requiring surgical stabilization.
6) Sites outside the spine (eg. lung, liver) are not eligible for treatment
7) Patients currently receiving, or who have received chemotherapy within 30 days are not eligible
8) Inability to tolerate lying flat on treatment couch for greater than 30 minutes.
9) Patient with multiple myeloma
10) Patients unable to undergo MRI of the spine
11) Patients with pacemakers

4.0 Treatment Plan

All patients will receive CT image-guided SBRT using intensity modulated radiation therapy to maximize conformality to the tumor while attempting to spare the spinal cord as much as possible. Patients will be stratified into two groups: 1) non-renal cell carcinoma patients 2) renal cell carcinoma patients.

Spinal Metastases

Non-renal cell metastases

For spinal metastases (spinal- thoracic, lumbar, sacral or paravertebral regions) other than renal cell carcinoma, the dose will be prescribed to the mean clinical target volume (CTV) or vertebral body such that 16 Gy will achieve 80-90% coverage of the CTV. The mean gross tumor volume (GTV) will be prescribed to receive 18 Gy with at least 90% coverage of the GTV if possible in a single fraction. Dose reduction may be necessary to respect spinal cord tolerance in the next section.

Renal-cell metastases
For renal cell carcinoma metastasis, the dose will be prescribed to the mean CTV or vertebral body such that 16 Gy will achieve 80-90% coverage of the CTV. The mean gross tumor volume (GTV) will be prescribed to receive 24 Gy with at least 90% coverage of the GTV if possible in a single fraction. Dose reduction may be necessary to respect spinal cord tolerance in the next section.

Paraspinal metastases
Non-renal cell metastases
For paraspinal metastases other than renal cell carcinoma, the dose will be prescribed to the mean GTV such that 18 Gy will achieve 80-90% coverage of GTV if possible in a single fraction. Dose reduction may be necessary to respect spinal cord tolerance in the next section.

Renal cell metastases
For paraspinal metastases arising from renal cell carcinoma, the dose will be prescribed to the mean GTV such that 24 Gy will achieve 80- 90% coverage of the GTV if possible in a single fraction. Dose reduction may be necessary to respect spinal cord tolerance in the next section.

Spinal cord dose constraint
Dose to the spinal cord will respect its tolerance such that the dose of the spinal cord will in general be limited to 8 Gy and the spinal cord + 2mm will be less than 12 Gy. No greater than 0.01 cc of spinal cord itself can exceed 10 Gy based on tabular dose volume histogram. Patients who have been previously irradiated to the spine in the same region of interest will not be eligible for this protocol.

5.0 Pretreatment evaluation

1) Patients will undergo a history and neurological exam. Neurologic function will be graded from 1 to 4 according to the McCormick classification scheme.
2) MRI of the spine must be performed within 1 month of registration.
3) A preatreatment CT scan will be obtained for treatment planning.
4) The SF-12v2 Health Survey, the M.D. Anderson Symptom Inventory (MDASI) and the Brief Pain Inventory (BPI Short Form), which includes assessment of pain medications will be administered for baseline assessment within 1 week of registration.
5) At the time of enrollment, patients will be noted to either have hepatic metastases present or absent.
6) Based on the radiation treatment plan, the gross tumor volume (GTV) representing the spinal or paraspinal metastasis, the clinical target volume (CTV) representing the GTV and the entire vertebral body for spinal metastases will be recorded.

6.0 Evaluation During Study

Patients will be evaluated at 1, 2, 3, and 4, and 8 weeks following completion of radiation therapy by telephone, fax, or mail. Patients will be seen for follow up visits at 3, 6, 9, 12, 18, and 24 months and then every six months thereafter; History, neurological exam, and neurologic function according to the McCormick scale will be assessed. MRI of the spine will be obtained at 3, 6, 9, 12, 18, and 24 months and then every six months thereafter. Included in the appendices, the Brief Pain Inventory (BPI) (Short Form), MD Anderson Symptom Inventory (MDASI) and SF-12v2 Health Survey will be administered at each clinic and telephone follow up. Pain medication requirements will be recorded on the BPI.

The BPI is a 17 item patient self rating scale assessing demogaphic data, use of medications, as well as sensory, and reactive components of pain (5). Reliablility has been demonstrated over short intervals using test retest item correlation; worst pain, r=0.93; usual pain, r=0.78; pain now, r=0.59. The BPI includes items that will adress components of sensory pain including severity, location, chronicity and degree of relief due to therapy. The BPI also has items that address reactive pain components including depression, suffering and perceived availablility of relief.

The MD Anderson Symptom Inventory (MDASI) is a flexible system for the assessment of symptoms experienced by patients with cancer (4). The MDASI consists of 13 core symptom items that are rated based on their presence and severity and 6 symptom interference items that are rated based on the level of symptom interference with function. With the MDASI, patients can rate their symptoms by completing a pencil-and-paper questionaire or by answering items presented in an interview. The study has been validated (4) and demonstrates that reasonably small numbers of symptom items can account for the majority of symptom distress in patients with different malignancies at various stages and that these items are sensitive to expected differences in symptoms and side effects. A major advantage of the MDASI is that it is easy for most to complete. It takes most patients less than 5 minutes to rate the core symptom severity and interference items. In an outpatient setting, less than 5% of patients refused or were unwilling to complete the questionnaire. Even patients with a high level of symptom burden were able to complete the MDASI. The use of simple designations for symptom and interference items makes the MDASI very easy to understand when presented in an interview format. Many patients find the 0-10 rating system of the MDASI easy and familiar, because this type of rating is ismilar to the 0-10 ratings of symptom severity often used in clinical practice. In addition translation of the MDASI into other languages should be simple and straightforward.

McCormick Neurologic Function Classification Scheme (17)

Neurologic Function	Clinical Definition
1	Normal to mild focal deficit
2	Moderate deficit; significant motor or sensory loss but able to function independently

3	Moderate to severe deficit; requires assistance to ambulate
4	Severe deficit; unable to function independently or to ambulate

7.0 Criteria for Response

Pain, Symptom and Quality of Life Instruments
Frequency and duration of complete pain relief will be the primary endpoint for efficacy of the study. The validated Brief Pain Inventory (BPI), MD Anderson Symptom Inventory (MDASI), and SF-12v2 Health Survey will be used to assess changes in these indicators compared to pre-treatment baseline. Response will be determined by follow-up questionaires. Time to maximal pain relief will be the time from the first day of irradiation until the lowest pain score for average pain after radiotherapy. The "worst pain score" from BPI will be used as the marker for treatment success or failure.

Treatment Failures
All the following are considered treatment failures:

1) A pain score greater than 0 that does not change within 8 weeks from start of radiation therapy.
2) A 2 point increase in "worst pain score" that is sustained at a higher level in the month following the first day of radiation therapy.
3) A pain score that drops by at least 2 points and subsequent sustained rise (*on 2 scucessive questionaires*) of pain score by at least 2 points.

Pain Relief

1) Patients experiencing a decrease of 2 points in the worst pain score for 2 consecutive analysis periods will be considered to have "partial pain relief."
2) Complete pain relief is defined as an average pain score of 0 for 2 consecutive analysis periods.

Radiographic Assessments.
MRI of the spine will be performed according to standard of care. These data will be collected on treated lesions and will be classifed as progressive defined as larger, stable defined as radiographically unchanged, or smaller.

The date of radiological progression will be recorded. Progression free survival based on time to event curves will be calculated.

8.0 Criteria for Removal from the Study

Toxicity monitoring will be focused on neurological, gastrointestinal, musculoskeletal, hematologic, and dermatologic systems. Toxicity will be graded according to NCI toxicity scale. Patients who have evidence of disease progression will be noted as tumor progression on the date progression is observed. Patients will be seen according to the follow up schedule for toxicity monitoring until death unless they withdraw consent for participation in the study in which case they will be removed from the study. For patients unable to return for follow-up clinic visits due to progressive disease or illness, these patients will be monitored via telephone follow-up until time of death.

9.0 Statistical Considerations

The advantage of stereotactic radiation given in a single session is one of convenience, both for the patient, and for the treatment team, since each treatment can last up to 2 hours. However, single fraction stereotactic body radiotherapy to the spine must be evaluated for safety in terms of avoiding spinal cord myelitis or myelopathy, since there is no opportunity to correct for positioning errors, and once radiation has been delivered, any spinal cord sequelae that occurs is likely to be irreversible. Data from our current protocol for 3 fraction stereotactic radiation to the spine has demonstrated that the 95% confidence interval of the probability of developing paralysis is between 0 and 10% based on the Clopper-Pearson analysis of approximately 70 patients treated so far, and no cases of paralysis have been observed to date. We wish to treat patients in a single fraction with stopping rules such that the trial will halt if the probability of paralysis exceeds 1%.

The statistical characteristics of this trial for single session stereotactic radiation to the spine are described below.
The primary issues in the trial are safety (proportion of paralysis) and effectiveness (tumor control, pain relief). The trial is intended to test the safety of giving stereotactic radiation in a single session and to determine tumor control based on spinal MRI. The prevalence and severity of spinal pain at pre-treatment baseline, and during longitudinal follow-up will be measured.
SAFETY
The trial will terminate (and a lower dose studied) if the investigator determines that there is evidence of paralysis (Grade 4 motor neuropathy) casued by radiation myelitis and not by tumor progression or spinal cord compression is at a rate of the treatment is greater than 0.01 (1%).
Sixty patients will be enrolled for the safety portion of the trial. The patients will be regularly monitored throguh follow-up visits for signs and symptoms of neurological toxicity. The probabilities of such termination as a function of the toxicity probability is shown below.

Design of the Trial

		High	
Num Subj	Cont	Pr Quit	Cum Probability Quit
15.	1.	0.00963	0.00963
30.	1.	0.02652	0.03615
45.	2.	0.00247	0.03861

60.	2.	0.00809	0.04670

Properties of the Design Assuming the Null Hypothesis
(p = 0.0100)

Quit If Evidence That Theta > H0

Prob Event	Prob Quit	Expected N	Expected N Given Quit
0.0100	0.0467	58.73	32.87

Properties of the Design Assuming Other Values of p

Quit If Evidence That Theta > H0

Prob Event	Prob Quit	Expected N	Expected N Given Quit
0.0500	0.6381	43.06	33.45
0.1000	0.9566	27.67	26.21
0.1500	0.9969	20.76	20.64
0.2000	0.9998	17.70	17.69

RESPONSE RATE
Assuming that safety concerns are met, the purpose of the trial is to estimate the response (pain relief) rate. All 60 patients entered will be used for this purpose.

Tumor control will be based on spinal MRI showing absence of progression. Actuarial and crude rates of tumor control will be calculated.

Pain relief will be assessed by items on the BPI that measure severity, location, chronicity, and degree of relief due to therapy by demographic data that will track use of narcotic and non-narcotic pain medications. For previously unirradiated patients as are in this trial, 46% of patients should demonstrate complete sensory pain relief and 90% should have some pain relief reported as a decrease in severity rating and use of pain medicatons and increase in the pain relief rating (Blitzer 1985).

The expected change in these indicators should occur within 1 month from the end of radiation therapy based on experience with 3 fraction SBRT on protocol ID02-446. Forty percent of patients should demonstrate complete sensory pain relief by 6 months from the end of radiation therapy as reported by the same indicators. Duration of sensory pain relief should approach a mean of 24 weeks for those patients reporting some relief and 13 weeks for those patients reporting complete relief. For patients surviving one year or more, 60% should report sustained relief based on results with standard radiation therapy.

Pain, Symptom and Quality of Life Instruments
The MD Anderson Symptom Inventory (MDASI) is a measure of symptom severity and symptom interference while the SF-12v2 Health Survey is a measure of health status. Because changes in symptom severity are usually associated with changes in health status, we are interested in assessing the relationship of symptom severity and symptom interference on health-related functional status of life using the SF12's physical and mental component scores. We will regress the MDASI with the component scores of the SF12 and examine the overlap in variability between the measures.

The "pain worst" item from the BPI will be used as the marker for treatment success or failure. Previous studies have shown that pain severity can be categorized into mild, moderate or severe based on how pain interferes with daily functions (Serlin et al, 1995, Mendoza, et al 2004). We will calculate the proportion of patients who responded to treatment. We expect 80% of patients to respond to declare success. A responder will be defined as a patient whose "pain worst" changed from moderate or severe (5 or greater on the) to none or mild (0–4) at 1 month after enrollment. This range was selected because previous studies have shown that patients who report pain of 5 or greater on this item experience significantly greater pain-related interference with function than those with mild or no pain [Cleeland et al, 1994, Serlin et al, 1995, Wang et al, 1999].

The following are secondary considerations in determining treatment failures and pain relief.

Treatment Failures
All the following are considered treatment failures:

1) A pain score greater than 0 that does not change within 8 weeks from start of radiation therapy.
2) A 2 point increase in "worst pain score" that is sustained at a higher level in the month following the first day of radiation therapy.
3) A pain score that drops by at least 2 points and subsequent sustained rise (*on 2 scucessive questionaires*) of pain score by at least 2 points.

Pain Relief

1) Patients experiencing a decrease of 2 points in the worst pain score for 2 consecutive analysis periods will be considered to have "partial pain relief."
2) Complete pain relief is defined as an average pain score of 0 for 2 consecutive analysis periods.

10.0 Reporting Requirements

Adverse events will be reported to the IRB according to the guidelines setup forth in the appendices including serious adverse events classified as NCI Grade 3 and 4 toxicity as well as hospital admissions related to treatment occurring within one month of treatment.

11.0 Standard Monitoring Plan

INSTITUTIONAL RESOURCES AVAILABLE FOR DATA AND SAFETY MONITORING

The Office of Protocol Research (OPR)
The Office of Protocol Research is the centralized office of institutional support for human subjects research. This Office provides support for all the processes related to the clinical trial submission, review and approval of NCI sponsored clinical trials. It is also the center for the education of all research personnel, monitoring and auditing of clinical trials.

OPR consists of three major sections:

The Protocol Approval and Regulatory Affairs Group provides support for the Scientific Review Committees (see below) and the Institutional Review Boards; inputs protocol set-up information, adverse events and protocol status/tracking information into the Protocol Data Management System (PDMS); and provides administrative support for the processing of protocol modifications and all other aspects of protocol management.

The Quality Assurance Office provides extensive training in Good Clinical Practice, federal regulations, research compliance and data management. This group includes highly trained, experienced individuals who constitute the monitoring and auditing teams. In addition to their monitoring role, they also conduct random audits and for-cause audits on clinical trials at the request of the IRB, the principal investigator or UTMDACC as IND sponsor.

The Research Administration Information Systems Group (RAIS) develops and implements the central information systems used for clinical trial development, submission, protocol data management and electronic transfer of clinical trial information to industry sponsors and the NCI. This group also maintains a website, www.clinicaltrials.org, on the UTMDACC homepage to enhance public access to clinical trials information.

The Protocol Data Management System (PDMS)
The Protocol Data Management System (PDMS) is the database used to track the review and approval process of each protocol; the patients registered to each protocol; the adverse events submitted to the IRB for each protocol; and other protocol-specific data and information that will be discussed throughout this document.

PDMS functions as the central repository for certain required patient data. Protocol information (e.g., eligibility criteria, randomization schemes, dose escalation, accrual rates) is extracted from each submitted protocol and is entered into the PDMS by the protocol coordinators in OPR. Information about the protocol status such as submission dates, committee review and approval dates, Informed Consent approval date, IRB continuing review dates, approved maximum accrual and expected accrual rates are kept current by the OPR protocol coordinators. In addition the system has interactive modules used by the research teams for patient registration, entering on-study dates, off-study dates, evaluability and adverse event information.

Protocol activation is a separate step in the protocol life cycle. Prior to activating the protocol in PDMS, the system will not allow participants to be registered in the PDMS database. Furthermore, a stamped and dated IRB-approved Informed Consent document is not prepared and released to the principal investigator (PI) until the study is activated. The protocol activation step ensures that no participant signs a consent form prior to the study being ready for accrual. (IRB approved, monitoring plan in place, drug in pharmacy, etc.)

All participants that sign consent forms for clinical studies at UTMDACC **must** be registered to the protocol in the PDMS or the pharmacy will not release drugs to treat the patient. As additional safety measures, PDMS has an interactive patient registration process that will only allow individuals 100% eligible for the study to be registered.

To ensure that the most recent IRB-approved informed consent document is used during the consent process, the PDMS displays the IRB approval date on the screen during the registration process. The registrant can compare the date on the screen to the date on the paper form a patient is being asked to sign to ensure the document is the correct one.

The Clinical Research Committee
The first step of the clinical trial review process occurs during the scientific review of the protocol by the Clinical Research Committee (CRC) The CRC reviews all therapeutic protocols. The CRC is faculty-run and faculty-led committees whose members are selected to provide equal representation of all academic departments while trying to maintain gender and racial balance.

Ensuring patient safety on clinical trials of any phase begins during the protocol review and approval process, long before any patients are accrued to the studies. The CRC begin the process with the initial protocol review. This includes:

- Ensuring the protocol is based on sound, high quality science
- Ensuring that the protocol contains a clear description of the DSM plan
- Ensuring that a protocol priority list is submitted with each protocol
- Ensuring that the statistical design is adequate
- Determine if a data monitoring committee is required; and if so, is there an adequate explanation of which DMC has oversight of the protocol.

All NCI sponsored trials must include a DSM plan in the body of the protocol or as an appendix to the protocol or they are not accepted into the review process. The PI should use the matrices beginning on page 11 to guide the design of the plan The CRC makes the initial determination of whether the plan is appropriate for that particular protocol to be forwarded to the IRB for complete review. Protocols without DSM plans, or with obviously inadequate plans, cannot be forwarded to the IRB for final review.

In addition, the CRC reviews the scientific merit of all protocols. Special attention is given to the statistical design of the study to ensure there is adequate statistical power to answer the specific aims of the study and if applicable, that the early stopping rules are clear and provide the maximum protection for the participants.

All Principal Investigators (PI) of UTMDACC investigator-initiated protocols are required to have a UTMDACC biostatistician as a collaborator on the protocol and to follow the guidance of this collaborator during the protocol development phase. The statistical sections of protocols developed outside of UTMDACC are pre-reviewed by the Department of Biostatistics prior to the CRC. Ensuring appropriate statistical power and stopping rules is the first step to insuring that trials with higher risk/benefit ratios are monitored closely and stopped at the appropriate time.

There are two CRCs and each committee meets once per month on either the second or fourth Wednesdays of the month.

THE INSTITUTIONAL REVIEW BOARDS

After being approved by the scientific review committee, all protocols are forwarded to the IRB. UTMDACC has two IRBs. Both committees meet two times per month on the first and third Wednesdays of the month.

The Institutional Review Boards provide the following services to meet the requirements of the DSM plans for all NCI funded trials:

- Determining the level of risk of each protocol
- Determining if the DSM plan is appropriate for each protocol
- Reviewing serious adverse events on a real time basis
- Reviewing audit reports from the OPRQA audit teams
- Making determinations of any required actions based on the audit reviews
- Reviewing monitoring reports from OPRQA and external monitoring teams
- Making determinations of any required actions based on the reviews of the monitoring reports
- Reviewing safety and efficacy reports submitted by principal investigators at pre-arranged intervals for high risk protocols

Criteria Used to Determine the Level of Risk of Each Protocol Therapeutic Trials:
The IRB uses the following criteria to determine the level of risk of each therapeutic trial they review. IRB #1 is responsible for new protocol review and approval. This committee is the final arbiter of the level of risk inherent in each protocol and the appropriateness of the DSM plan. The required components of a protocol's DS&M plan can be determined from the "Therapeutic Plan Matrix" based on the responses to the following questions.

- Has the agent been previously used in human subjects?
- If No, the pre-clinical pathology/toxicology data are reviewed. If Yes, the prior clinical data are reviewed
- Is the dose and route of administration of the agent the same as that previously used in humans?
- If not, how are the differences expected to impact the safety of the patient
- Has the agent been used in similar patient populations
- Is the agent developed or manufactured at UTMDACC?
- Is the agent being used in combination with one or more other agents
- If so, what is the combined toxicity expected to be based on past clinical used of all agents
- Does the trial involve recombinant DNA?
- Does the trial have early stopping rules?
- Is the study blinded?
- Is the study being conducted under an IND?
- If Yes, is UTMDACC the sponsor

Using these criteria, the highest risk protocols are Phase I and trials using rDNA therapies.

Once the IRB reviews each protocol and determines the risk, the DSM plan is reviewed to ensure that the appropriate plan has been submitted that meets the needs of the study.

Reviewing Adverse Events:
Patient safety is continually monitored during the course of each trial by a real time review of serious adverse events (SAE) submitted to the IRB. All protocols are required to have the NCI Common Toxicity Criteria (CTC) as an appendix as a guide in reporting SAEs. All SAEs must be reported to the IRB according to the UTMDACC policy for reporting adverse events (Appendix F). SAE review at UTMDACC is considered part of the IRB Continuing Review of protocols that is required by HHS under 45CFR§46.109(e) and the FDA under 45CFR§46.109(e).

When an SAE is submitted to the IRB, the IRB coordinator enters the SAE information into the PDMS and prints out a report of all prior SAEs reported for that particular protocol. If the SAE report is for an SAE that occurred outside UTMDACC and is being submitted by a sponsor as a Safety Report, the SAE is entered into the PDMS in a file created for that particular agent or therapy. The new SAE report along with the report of prior SAEs is reviewed by a Vice Chairperson of the IRB. There are multiple individuals in the position of Vice Chairperson whose job it is to review either internal or external SAEs. The SAE reviewer contacts the PI for additional information as needed. Protocol and/or informed consent document changes requested by the IRB in response to SAE reports are made in accordance with requests from the IRB.

This functionality of PDMS allows SAEs to be reviewed as part of the entire SAE history for the protocol, not in a void as a single event. The review process enables the SAE reviewer to determine trends or recurring SAEs as soon as they occur. All SAEs are listed as part of the IRB agenda for each meeting, and the Vice Chair who reviews them presents SAEs of note to the committee for discussion. Any modifications to the protocol or informed consent document resulting from SAE review that are requested by the IRB are conveyed in writing to the PI. Those issues of a serious nature are conveyed immediately by verbal communication and then in writing.

In addition to submitted all SAEs to the IRB as dictated by policy, investigators must also report AEs to their sponsors and to the NCI according to the NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents. The research team submits the expedited reports directly to NCI. For events reported via routine reporting, the information is entered into PDMS and is submitted electronically by the RAIS group.

The FDA co-ordinator in OPR is responsible for submitting AEs to the FDA for studies conducted under UTMDACC INDs and to the Institutional Biosafety Committee and the NIH Office of Biotechnology Activities (if MDACC sponsors the IND) if rDNA therapies are involved.

In addition to reviewing serious AEs, all other AEs documented in PDMS and reported via routine reporting are reviewed by the medical reviewer on the OPRQA monitoring team.

Reviewing monitoring reports from the OPRQA monitoring teams :
Any monitoring report prepared by an OPRQA or other monitoring team that indicates any safety issues or issues of non-compliance with GCP, federal regulations or IRB policies is provided to the IRB for review and determination of an action plan. The ORPQA monitoring teams and monitoring reports are discussed in full in the section entitled "OPRQA Monitoring Process." on page 8 and in Appendix H, entitled "The OPRQA Guidelines for Monitoring."

If the IRB, or the Chairperson or Vice Chairperson acting as its authorized representatives are presented with a monitoring report indicating the need to immediately suspend a study, either permanently or until further review, they will immediately contact the principal investigator of the study to inform her/him of the situation. The monitoring report will then be discussed at the next IRB meeting, an action plan will be proposed, voted on and then conveyed to the principal investigator.

Depending on the severity or type of demonstrated toxicity, the action plan dictated by the IRB may include any of the following:

- updating the informed consent document to include the new expected toxicity
- modifying the protocol to reflect an adjusted dosing schedule
- closing the protocol due to unacceptable toxicity

If the monitoring report indicates any issues of non-compliance, based on the severity of the results, the action plan dictated by the IRB can include, but is not limited to:

- additional education for the investigator or research team member
- temporary suspension of clinical research privileges
- assigning a mentor to provide oversight of the PIs clinical research activity
- permanent suspension of clinical research privileges

What ever action is taken by the IRB, the necessary and appropriate notifications of such actions to the institution's administration, funding agency, NCI or other sponsor will of course be carried out.

Also, as required by the Code of Federal Regulations at 21CFR § 56.113, 45CFR§46.113, the IRB has a written policy and procedure for suspension or termination of IRB approval of research that includes the requirement of notifying and federal funding agency involved with the protocol. If the protocol is NCI-sponsored, the Program Director will also be notified.

Reviewing audit reports from the OPRQA auditing teams:
Any audit report, resulting from a random or directed audit, prepared by an OPRQA or other audit team that indicates any safety issues or issues of non-compliance with GCP, federal regulations or IRB policies is provided to the IRB for review and determination of an action plan. The ORPQA audit teams, audit reports and audit processes are discussed in full in The OPRQA Audit Manual in Appendix D.

Depending on the severity or type of demonstrated toxicity, the action plan dictated by the IRB may include any of the following:
- updating the informed consent document to include the new expected toxicity
- modifying the protocol to reflect an adjusted dosing schedule
- closing the protocol due to unacceptable toxicity

If the audit report indicates any issues of non-compliance, based on the severity of the results, the action plan dictated by the IRB can include, but is not limited to:
- additional education for the investigator or research team member
- temporary suspension of clinical research privileges
- assigning a mentor to provide oversight of the PIs clinical research activity
- permanent suspension of clinical research privileges

What ever action is taken by the IRB, the necessary and appropriate notifications of such actions to the institution's administration, funding agency, NCI or other sponsor will be carried out. (See the IRB policy and procedure for suspension or termination of IRB approval of research in Appendix G)

Reviewing safety and efficacy reports
As required by the IRB for certain high risk protocols, the investigator will be required to submit to the IRB, a detailed report of any demonstrated toxicities and efficacy after treating a defined number of patients. The IRB will review the data supplied by the investigator, determine if the study is safe to continue as written, needs modification prior to continuing, or if the study should remain closed.

The Office of Protocol Research Quality Assurance
The Office of Protocol Research Quality Assurance (OPRQA) is part of the Office of Protocol Research and reports to the Vice President for Research Administration through the Chief Research and Regulatory Affairs Officer. The function of this office is further augmented by the OPRQA Oversight Committee, consisting of UTMDACC faculty members. This official body operates within a medical review-advisory capacity and reports to the president of UTMDACC.

OPRQA provides the following services to meet the requirements of the various DSM plans:
- to verify the accuracy and integrity of the research data collected
- to monitor protocol compliance using source documentation
- to verify adherence to federal and institutional requirements
- to enhance the delivery of accurate and reliable clinical trials data and results according to Good Clinical Practice
- to provide educational support to the clinical research staff regarding issues related to data management and quality assurance
- and to monitor quality indicators regarding protocol performance.

The OPRQA Audit Program
The OPRQA Audit Program assures that the data used to analyze study results (e.g., database spread sheets, Protocol Data Management System (PDMS), case report forms) is an accurate reflection of the primary data source. The audit program assesses protocol compliance

in the following categories: informed consent, eligibility, treatment, response, toxicity, general data quality, and compliance with the institutional guideline and federal regulations for the protection of human subjects. A focused audit may occur to address protocol compliance in any of the specified area(s) of clinical trial performance. Random audits are performed to spot check the quality of the clinical research conducted at UTMDACC and to assess the level of compliance attained by research teams.

The OPRQA Audit Manual which describes the auditing program, the audit process, how audits are conducted and reported is attached in Appendix D. Also in Appendix D is a list of the OPRQA staff members that make up the audit teams and their qualifications. Each audit team, as discussed in the Manual, also includes a faculty member that serves as the medical reviewer. The staff members of OPRQA that make up the audit teams report directly to the OPR which is an independent centralized resource within the institution that has no affiliation with any division or department. Therefore, these individuals have no conflicted research role with any clinical trial.

The OPRQA Monitoring Program

Monitoring the progress of clinical trials
For each protocol, the maximum accrual approved by the IRB and the current number of individuals accrued is available in PDMS. Since each patient is registered to the protocol in the database, monitoring the progress of the research by examining protocol accrual is a simple and routine process carried out by OPRQA. Reports have been programmed that search for and sort protocols based on the number of participants registered to the study during the previous six month period.

Every six months these reports are generated for categories of Low Accrual, No Accrual and for IRB approved but not yet activated studies. The PI of any protocol that falls into one of these categories is sent a memo requesting input on why the protocol is not accruing at the expected rate or why an IRB- approved protocol has not been activated. The outcome of these accrual audits and the PI responses are reviewed by the IRB. Depending on the response from the PI, the protocol is either closed, or the protocol may continue for six months and be re-reviewed at that time if accrual is still falling short of targets. The outcome of these accrual audits is available to the monitoring teams also, although the teams review the accrual rates at each monitoring visit which is generally far more frequent than every 6 months.

Monitoring the conduct of clinical trials and safety of participants
OPRQA provides on-site monitoring of NCI sponsored clinical trials that do not have an industry sponsor. The OPRQA monitoring teams discuss the frequency of monitoring with the PI and his/her research team during the pre-activation meeting. The frequency and % of patients monitored is described in the DSM plan approved by the IRB for that particular protocol.

The monitoring teams consist of one or more staff members from OPRQA depending on the rate of accrual and the complexity of the study design and documentation. Two to three faculty members with clinical research experience and expertise in the disease site of the protocol, serve as the medical reviewers on the monitoring team. The medical reviewers, like the other members of the monitoring team, are independent and objective. The medical reviewers cannot be collaborators on the protocol or members of the same academic department as the principal investigator nor can they have any other involvement with the protocol. The members of OPRQA also have no conflicts as they are also independent of all academic departments in the institution.

The monitoring teams review the following elements for each case they monitor: informed consent document, eligibility, pre-therapy requirements, treatment administrations, study evaluation and follow-up, all toxicities, response, general data quality. In addition to reviewing the elements described above for the selected patients, all AEs of each study participant, not just the participant/charts selected for in-depth review, is reviewed using the PDMS. All AEs, serious, non-serious, expected and unexpected, are reviewed in the report generated by PDMS by the monitoring team. The information that is entered in PDMS and reviewed in this report includes the date of onset of event, the grade, the suspected causality to treatment, the date the event resolved and if the event required treatment. A more detailed discussion of the monitoring process can be found in the OPRQA Guidelines for Monitoring (See Appendix H). The staff members in OPRQA that make up the monitoring team are also included in this appendix.

Pre-activation meetings are held for NCI sponsored trials with PIs, their research teams and representatives of OPRQA to discuss the data and safety monitoring plan for that protocol. At these meetings, the monitoring plan is discussed and templates for data collection are distributed. These templates are prepared by OPRQA on a case-by-case basis after reviewing the protocol. After being completed by the research team, the templates become a permanent part of the participants' medical records.

A monitoring report is prepared by the monitoring team after each monitoring visit. A copy of this monitoring report is included in Appendix H. The completed report is given to the research team and they have one week to review the report and provide data not found by the monitoring team. A final monitoring report is then prepared. If the report does not indicate the incidence of unexpected AEs or issues of non-compliance with GCP, federal regulations or institutional policies, the monitoring report is reviewed by the OPRQA oversight committee.

If a monitoring report does indicate the incidence of unexpected AEs or non compliance with GCP, federal regulations or institutional policies, it is forwarded to the IRB for review and action.

The OPRQA Oversight Committee
The OPRQA Oversight Committee is an officially constituted committee of the University of Texas M.D. Anderson Cancer Center. The OPRQA Oversight Committee reports to the President of The University of Texas M.D. Anderson Cancer Center, through the Vice President for Research Administration.

The purpose of the OPRQA Oversight Committee is to monitor and review clinical trials for adherence to patient quality measures established by the institution and the federal government; to advise the Vice President for Research Administration and the Chief Academic Officer on decisions regarding clinical research privileges; to ensure that high quality clinical research data is collected under Institutional Review Board approved protocols; and, to ensure that voluntary patient informed consent is obtained.

For NCI sponsored trials, the role of the Oversight Committee is to review monitoring reports prepared by the monitoring team only if no unexpected AEs or issues of non-compliance with GCP, federal regulations or institutional policies were found during the monitoring visit. If a monitoring report does indicate the incidence of unexpected AEs or non compliance with GCP, federal regulations or institutional policies, it is forwarded to the IRB for review and action.

The UTMDACC Data Monitoring Committee (DMC)

The Institution has a Data Monitoring Committee that oversees the data and patient safety issues for randomized Phase III clinical trials and blinded studies that have an MDACC principal investigator as the PI or data coordinator; and other MDACC sponsored studies identified by the principal investigator as requiring oversight by the DMC. The primary objectives of the DMC are to ensure that patients in a trial are protected and that patients' interests are not made secondary to the interests of the scientific investigation. A complete description of the organization, purpose, responsibilities and membership of the DMC can be found in the attached by-laws (Appendix E)

The intervals at which these studies should be reviewed by the DMC must be clearly delineated in the body of the protocol in the Data and Safety Monitoring Section. The timing of the DMC review as well as the design of any stopping rules are planned by the principal investigator and biostatistician collaborator and fully vetted prior to protocol approval. The timing of DMC review is protocol specific and therefore cannot be defined in this document. The outcome of the DMC review is communicated directly to the PI. If the committee decides the study should be closed, or requires any changes in the conduct of the study, that information is also communicated to OPR and the IRB and the status of the protocol will be changed to Closed to New Patient Entry until the required changes are submitted, reviewed and approved by the IRB. Each protocol should clearly indicate who prepares the information for the DMC review and who the DMC review results are communicated to.

Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant

The PDMS flags all NCI-sponsored trials and trials conducted under an MDACC IND. Any status change of a clinical trial becomes part of the permanent electronic protocol file in PDMS. Therefore, anytime a protocol is halted by IRB, DMC, the PI or other agent, OPR is made aware of any regulatory agency that needs to be notified. This notification process is also facilitated by the fact that the Office of Research Grants and Compliance also reports directly to the Vice President of Research Administration. Having both the grants office and protocol office report to the same person ensures the free flow of information related to protocols and their supporting grants.

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