A RANDOMIZED CONTROLLED TRIAL OF INDIVIDUAL PSYCHOSOCIAL INTERVENTIONS FOR CANCER PATIENTS

MSKCC NON THERAPEUTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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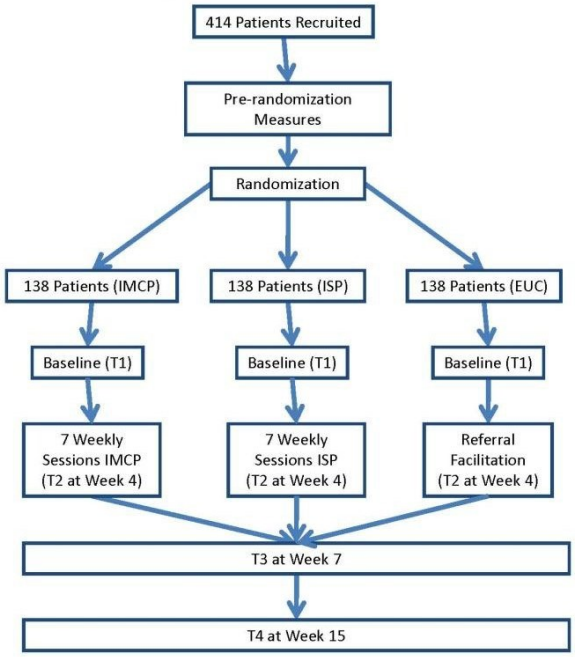
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Individual Meaning Centered Psychotherapy (IMCP), based on the principles of Viktor Frankl's Logotherapy, is designed to help patients with advanced cancer sustain or enhance a sense of meaning, peace and purpose as they approach the end-of-life. Preliminary findings from our pilot randomized control trial of IMCP suggest that IMCP significantly reduces psychological distress and desire for hastened death, and significantly increases spiritual well-being and a sense of meaning and purpose in life in a sample of patients with advanced cancer. This study is a larger randomized controlled trial which utilizes a repeated measures design to investigate the efficacy of Individual Meaning-Centered Psychotherapy (IMCP), compared to a standard Individual Supportive Psychotherapy (ISP) and an Enhanced Usual Care (EUC) arm on spiritual well-being, psychological distress, and quality of life in a sample of 414 ambulatory patients (138 per arm) with advanced cancer. (See Figure 1 below)

Figure 1 – Study Timeline



All patients with solid tumors with advanced disease receiving ambulatory care at MSKCC and its affiliates are eligible for participation. Recruitment of patients will take place at MSKCC, in ambulatory care areas treating solid tumors (i.e., prostate, breast, lung, colorectal, hepatobiliary, head and neck cancers, and palliative medicine) or through the mail using letter recruitment. Potential subjects for the study will be identified, by the research staff and participating oncology staff, by cancer diagnosis and stage. Potentially eligible patients will be administered the Distress Thermometer (DT), in order to determine whether the patient meets the requisite threshold for study participation in person or over the telephone. Patients who indicate a 4 or greater on the DT will be offered participation and randomized to one of the two 7-session interventions (IMCP or ISP) or to the EUC control condition. The Individual Meaning Centered Psychotherapy (IMCP) intervention will focus on enhancing meaning and purpose in patients' lives. The Individual Supportive Psychotherapy (ISP) intervention will focus on helping patients cope with cancer and express their feelings about it. In Enhanced Usual Care patients will be given targeted referrals based on screening and will receive psychoeducational materials. All participants will complete assessment batteries consisting of self-report questionnaires which will be administered at four time points: Baseline (T1, week 1), mid-way through the intervention (Midpoint (T2), week 4-7), immediately

following the last session of the intervention (Post-intervention (T3), week 7-14), and at post intervention (Follow-up (T4), 8-12 weeks post T3 assessment).

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Aim:

- To conduct a randomized controlled trial comparing the efficacy of Individual Meaning-Centered Psychotherapy (IMCP), a standardized Individual Supportive Psychotherapy (ISP) and Enhanced Usual Care (EUC) in improving meaning and spiritual well-being and overall quality of life and reducing psychological distress (depression and anxiety, hopelessness and desire for hastened death) in a sample of patients with advanced cancer.

Secondary Aims:

- To examine clinical and demographic variables that may correspond to differential responses to Individual Meaning-Centered Psychotherapy (e.g., potential moderating influences such as gender, race/ethnicity, religiosity, level of pre-intervention social support, optimism, physical symptom burden, prognostic awareness, and treatment dose).
- To assess the relative impact of Individual Meaning-Centered Psychotherapy on different aspects of meaning (e.g., purpose, coherence, existential vacuum), as well as on different aspects of spiritual well-being (meaning versus faith),
- To explore whether an enhanced sense of meaning ―explains‖ (mediates) improved psychological well-being (i.e., increased quality of life, decreased psychological distress).

3.0 BACKGROUND AND RATIONALE

Spiritual, Existential, Logotherapy, and Meaning-Based Psychotherapy in Cancer Populations:
A relatively small but growing literature is developing around psychotherapy interventions for cancer patients grounded in theoretical perspectives which address meaning and other existential concerns. These include interventions that incorporate the spiritual elements of yoga, meditation, Buddhist philosophy and religious belief (e.g., Cole, 2005; Lerner et al., 1987); those that use existential approaches based on the works of Yalom and others (De Vries, 1997); those based on concepts of self-transcendence (Coward, 1998; Chin-A-Loy & Fernsler, 1998; Hiatt, 1986); and meaning-based approaches based on Folkman‘s (1997) approach to ―meaning making‖ (Lee et al., 2006) and Frankl‘s Logotherapy (Lazer, 1984; Quirk, 1979; Zuehlke & Watkins, 1975). Self-transcendence has been shown, primarily in the nursing literature, to be associated with indicators of well-being and mental health in older adults, breast and prostate cancer patients, and AIDS patients (Coward, 1991, 1993, 1995, 1996, 1998; Chin-A-Loy & Fernsler, 1998; Reed, 1991a). However, all of these studies used group not individual intervention formats. The direct application of Frankl‘s original logotherapy to medically ill populations has been extremely limited (until our recent adaptation of Frankl‘s work in the form of Meaning-Centered Psychotherapy, described below). Lazer (1984) conducted logotherapeutic support groups for patients with cardiac disease, butno systematic assessment of the impact of these groups was conducted. Zuehlke and Watkins (1975) adapted individual logotherapy to patients with terminal cancer, meeting for 6 individual 45-minute sessions over two weeks. The logotherapy focused on: 1) enhancing rapport with therapist; 2) eliciting sources (e.g., activities, relationships) that provided meaning in the patient‘s life; 3) focusing on the impact of illness; 4) dealing with the fear of dying using the technique of ―dereflection‖; and finally 5) enhancing a sense of closure with

significant others in one's life as death approached. Patients who participated (N=6) experienced a stronger feeling of purposefulness and meaningfulness than controls (N=6),.

Interventions for Spiritual and Existential Suffering at the End of Life

Few empirically-supported psychotherapy interventions for spiritual suffering or distress at the end of life currently exist. Efforts to establish the efficacy of palliative care interventions are hindered by the many challenges researchers face in palliative care (Pessin et al., 2008). Palliative care practitioners have begun to deal with the issue of spirituality in the dying and interventions for spiritual suffering (Puchalski & Romer, 2000; Rousseau, 2000), but few have tested their efficacy experimentally. Psychotherapeutic techniques particularly adapted to the dying, such as life narrative and life review (Viederman, 1983), are found to be clinically beneficial. Recently, Chochinov et al. (2002, 2005) completed a multisite randomized controlled trial (RCT) to evaluate an individual psychotherapy for terminally ill patients called ―Dignity Conserving Psychotherapy,‖ whose central component is the creation of a ―generativity document.‖ What the work of Rousseau, Viederman, and Chochinov, as well as our work on Meaning-Centered Psychotherapy, suggest is the importance and potential utility of novel psychotherapeutic interventions aimed at improving spiritual well-being, sense of meaning and diminishing hopelessness, demoralization, and despair. Psychosocial interventions designed to relieve existential and spiritual suffering in advanced cancer patients are critically needed in order for clinicians to have the tools to effectively address these issues in their patients. It is essential that such interventions be tailored to the needs of patients with advanced illness, who may have difficulty participating in long-term or group psychotherapies. Individual Meaning Centered Psychotherapy (IMCP) has the potential to address the unmet need for one-on-one, flexible interventions critical to advanced cancer populations. It represents an important opportunity to provide an effective intervention for existential and spiritual suffering that can be practically delivered.

Meaning-Centered Psychotherapy for Advanced Cancer Patients

The importance of spiritual well-being and meaning in particular in moderating depression, hopelessness and desire for death in terminally ill cancer and AIDS patients demonstrated by our research group led us to look beyond the role of antidepressant treatment for depression in this population. We focused new efforts on developing non-pharmacologic (psychotherapy) interventions that could address such issues as loss of meaning, spiritual well-being and hopelessness in patients with advanced cancer. This effort led to an exploration and analysis of the work of Viktor Frankl and his concepts of logotherapy or meaning-based psychotherapy (Frankl, 1955, 1959, 1969, 1975). While Frankl's logotherapy was not specifically designed for the treatment of cancer patients or those with life threatening illness, his concepts of meaning and spirituality clearly apply in psychotherapeutic work with advanced cancer patients, who often seek help in dealing with existential issues (e.g. sustaining meaning and hope and understanding cancer and impending death in the context of their lives). Frankl's main contributions to human psychology have been to raise awareness of the spiritual component of human experience, and the central importance of meaning (or the will to meaning) as a motivating force in human psychology. His basic concepts include: 1) Meaning of life - life has meaning and never ceases to have meaning even up to the last moment of life, and while meaning may change in this context, it never ceases to exist; 2) Will to meaning - the desire to find meaning in human existence is a primary instinct and basic motivation for human behavior; 3) Freedom of will - we have the freedom to find meaning in existence and to choose our attitude towards suffering; 4) The three main sources of meaning in life are derived from creativity (work and deeds), experience (art, nature, humor, love, relationships, roles) and attitude (the attitude one takes towards suffering and

existential problems); 5) Meaning exists in a historical context, thus legacy (past, present and future) is a critical element in sustaining or enhancing meaning.

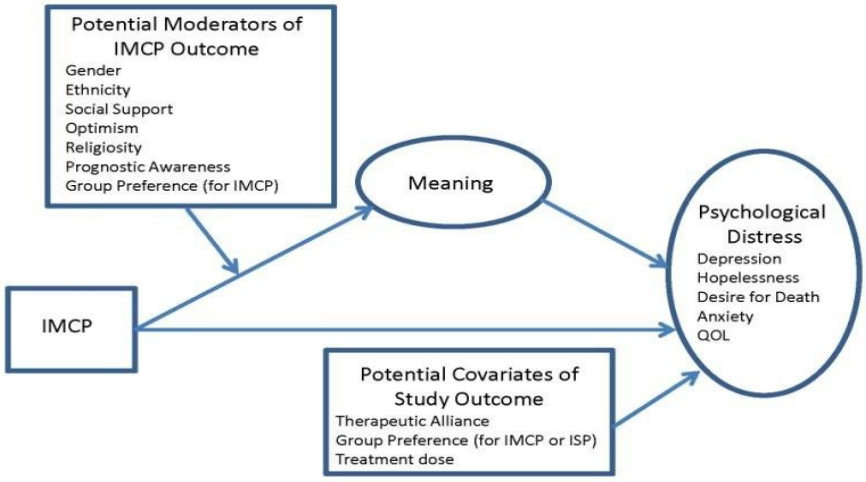
The innovative intervention we developed and call ―Meaning-Centered Psychotherapy‖ is based on the concepts described above and the principles of Frankl's logotherapy, and is designed to help patients with advanced cancer sustain or enhance a sense of meaning, peace and purpose in their lives even as they approach the end of life (Breitbart, 2002; Breitbart et al., 2004, 2009; Greenstein & Breitbart, 2000). We initially conducted an R21-funded pilot RCT of an eight-week (1.5-hour weekly sessions) Meaning-Centered Group Psychotherapy (MCGP) intervention, based on the concepts of meaning as elucidated by Viktor Frankl, which utilized a highly developed treatment manual incorporating a mixture of didactics, discussion and experiential exercises that focus on particular themes related to meaning and advanced cancer. MCGP proved to be a highly effective intervention, increasing a sense of meaning, spiritual well-being, and hope, while decreasing end of life despair. The positive results of this R21 (see Breitbart et al., 2009) resulted in the funding of an R01 study (1R01CA128287) conducting a larger randomized controlled efficacy trial of Meaning-Centered Group Psychotherapy (MCGP) currently beginning its fourth year of *funding*. It became quite clear to us during the course of the MCGP clinical trials that the group format for psychotherapy interventions in patients with advanced cancer posed many challenges and limitations. The rigid schedule necessary to conduct outpatient group sessions in this population resulted in high rates of missed sessions and high levels of attrition.

Theoretical Conceptual Model Underlying Meaning-Centered Psychotherapy

The central role played by meaning in diminishing psychosocial distress and end-of-life despair has led us to develop a meaning-centered intervention based on a theoretical model in which the enhancement of meaning results in improved quality of life and reduced psychological distress, despair and suffering at the end of life. Figure 2 depicts the model underlying our proposed IMCP intervention, in which enhanced meaning is conceptualized as the catalyst for improved psychosocial outcomes (improved quality of life, reduced psychological distress and despair).

Specifically, meaning is viewed as both an intermediary outcome, as well as a mediator of changes in these important psychosocial outcomes. Religious faith is not expected to directly impact psychosocial outcomes, but may moderate the intermediary outcome of meaning (see, for example, Nelson et al., 2002, indicating that religious faith does not provide a unique contribution to enhanced psychosocial outcomes after controlling for spirituality). This model also presumes that other factors will impact response to a meaning-based intervention, including prognostic awareness, psychosocial treatment preference, and therapeutic alliance. We recognize that the directionality of many of the variables included in this model could potentially be bi-directional; however, we are presenting the model we believe underlies the intervention.

Figure 2: Study Model – Mediators and Moderators of Treatment Outcome



Spiritual Well-Being/Meaning and Its Impact on Psychosocial Outcomes in Advanced Cancer

Brady et al. (1999) found that cancer patients who reported a high degree of meaning in their lives (as measured by the FACIT-Sp meaning/peace sub-scale) were able to tolerate severe physical symptoms better than patients who reported lower scores on meaning/peace. Patients with a high sense of meaning reported higher satisfaction with their quality of life than patients with a low sense of meaning, despite pain and fatigue. Our research group (Breitbart et al., 2000; Nelson et al., 2002) has demonstrated a central role for spiritual well-being (i.e., meaning) as a buffering agent, protecting against depression, hopelessness and desire for hastened death among terminally ill cancer patients. McClain, Rosenfeld, and Breitbart (2003) found that spiritual well-being, as measured by the FACIT-Sp, was significantly associated with end-of-life despair (as defined by hopelessness, desire for hastened death and suicidal ideation) even after controlling for the influence of depression. Moreover, when the FACIT-Sp was divided into two components, one measuring a sense of meaning and peace (the Meaning/Peace subscale) and another measuring spirituality linked to religious faith (the Faith subscale), the Meaning/Peace subscale was much more strongly associated with end-of-life despair than was the Faith subscale. We conducted two NIH-funded studies assessing the impact of pharmacologic treatment for depression in terminally ill AIDS and cancer patients on desire for hastened death. While the effective pharmacologic treatment of depression reduced desire for hastened death in depressed patients, our findings (Breitbart et al., 2000) also showed hopelessness and loss of meaning were often independent of depression as predictors of desire for death and are as influential on desire for death as depression. Such data suggest the critical need for development of psychosocial interventions for the terminally ill that address loss of meaning as a mechanism for improving psychosocial outcomes (e.g., quality of life, depression, anxiety, hopelessness, desire for death and end-of-life despair).

Individual Meaning-Centered Psychotherapy for Advanced Cancer Patients

We recognized that a brief and flexible individual format of Meaning-Centered Psychotherapy could have advantages over a group format in a population of patients with advanced cancer. We modified our original Meaning-Centered Group Psychotherapy intervention and developed an individual format intervention, (Appendices H & I). The overall goal of this proposed study is to examine the efficacy of IMCP.

Individual Meaning-Centered Psychotherapy is a flexible seven-session (1 hour weekly sessions) individual intervention that utilizes a mixture of didactics, discussion and experiential exercises that focus around particular themes related to meaning and advanced cancer. The session themes include: Session 1 – Concepts and Sources of Meaning; Session 2 – Cancer and Meaning; Session 3 – Historical Sources of Meaning: Legacy (past, present and future); Session 4 – Attitudinal Sources of Meaning: Encountering Life's Limitations; Session 5 – Creative Sources of Meaning: Creativity and Responsibility; Session 6 – Experiential Sources of Meaning: Connecting with Life via Beauty, Love, and Humor; and Session 7 – Transitions: Reflection, and Hopes for the Future. Patients are assigned readings and homework that are specific to each session's theme and which are utilized in each session. Of The IMCP format includes experiential exercises, didactics and discussions related to themes focusing on meaning; sources of meaning, and flexibility in moving from one source of meaning to another when cancer illness or treatment imposes obstacles and limitations. The IMCP Treatment Manual in Appendix I & J describes the intervention in detail.

Pilot Study of IMCP

We conducted a large pilot RCT of IMCP in a sample of 104 advanced cancer patients comparing Individual Meaning Centered Psychotherapy (IMCP) vs. Therapeutic Massage (T-M). This pilot study, funded by the Kohlberg and Fetzer foundations (MSKCC protocol # 04-089), established the feasibility, practicality, applicability, acceptance, and effectiveness of the IMCP intervention, and demonstrated powerful treatment effects for our individual format intervention that were even greater than those we were able to demonstrate in our group intervention study (Breitbart et al., under review) .

Methods: Patients with Stage III or IV solid tumor cancers (N=120) were randomly assigned to either a 7-session IMCP or 7 sessions of Therapeutic Massage (TM). Patients were assessed before and after completing the intervention, and again 2 months after completion. Outcome assessment included measures of spiritual well-being, meaning, hopelessness, anxiety, depression, overall quality of life, symptom burden and symptom-related distress.

Results: Study Completion: The flexibility of scheduling resulted in far less attrition and an ability to deliver the full dose of 7 treatment sessions to over 90% of the sample. Attrition was evaluated first as the proportion of patients who remained in the group throughout the 7-week intervention period (i.e., were available to provide post-intervention data), and second, by comparing the number of sessions attended across the two interventions. There was no difference in the number of sessions completed by participants in the two treatment arms, and the proportion of participants who completed all 7 weeks was comparable across both conditions. The IMCP participants attended an average of 5.28 sessions (s.d.= 2.6), whereas TM participants completed an average of 5.02 sessions (s.d.=2.9), t=0.53, p = .60. Of the 59 individuals who began IMCP, 39 (66.1%) attended all 7 scheduled sessions versus 33 (61.1%) of 54 individuals randomized to massage, chi-square = 9.41, d.f. = 7, p = .22. Attendance was not significantly correlated (using a Spearman correlation for ordinal data) with overall physical functioning, r_s = .17, p = .06.

Impact of Treatment on Spiritual Well-Being and Psychological Adjustment: Repeated measures ANOVA models were used to evaluate the differential impact of treatment on the measures of spiritual well-being and psychological functioning. In each of these models, treatment arm was entered as a categorical independent variable, along with baseline score on the outcome variable as a co-variate. These analyses revealed a significantly greater effect of treatment for IMCP compared to TM for overall spiritual well-being (FACIT-Sp Total score), b = 0.39 (95% CI: .18 - .59), t = 3.74, p = .0004, as well as for the Meaning/Peace and Faith subscales, b = 0.36 (95% CI:

.26 - .46), t = 3.48, p = .0008 and b = 0.39 (95% CI: 0.05 - 0.72), t = 2.27, p = .03, respectively. There were also significantly greater benefits for IMCP, compared to TM, in improving overall quality of life (MQOL), b = 0.70 (95% CI: 0.17 - 1.24), t = 2.58, p = .02, decreasing the number of physical symptoms endorsed (MSAS-Sx), b = 4.66 (95% CI: 1.53 - 7.79), t = 2.92, p = .005, and decreasing severity of physical symptom distress (MSAS-GDI), b = 0.42 (95% CI: 0.20 - 0.64), t = 3.77, p = .0003. There were no significant differences between these two interventions in terms of reducing anxiety (HADS-A), b = 0.04 (95% CI: -0.13 - 0.06), t = -0.72, p = .47, depression (HADS-D), b = 0.03 (95% CI: -0.09 - 0.14), t = 0.49, p = .63, or hopelessness (BHS), b = .13 (95% CI: -0.27 - 2.52), t = 1.59, p = .12.

In order to examine the basis for the group differences, simple change scores within each treatment arm were analyzed, along with paired t-tests to determine whether the change on each measure was significantly greater than zero. As evident in Table 1, participants in the IMCP arm demonstrated significant reductions in symptoms and improvement in quality of life/spiritual well-being across most of the study variables. Although many (but not all) of the effect sizes decreased somewhat during the follow-up period, most of these change scores remained significant. However, there was a markedly different pattern for participants receiving TM, with very few significant improvements (only hopelessness improved significantly following the TM intervention) at either the end of treatment at the 2-month follow-up.

We followed a similar approach for the analysis of the long-term benefits of treatment, using repeated measures ANOVA models to evaluate the differential impact of treatment on spiritual well-being and psychological functioning at the 2-month follow-up assessment. As with the post-treatment analyses, treatment arm was entered as a categorical independent variable and baseline score on the outcome variable was entered as a co-variate. These analyses revealed no significant differences in treatment efficacy for IMCP versus TM at the 2-month follow-up assessment, although a similar pattern of improvement was evident in the within-group analyses.

Table 1: Changes in Spiritual Well-being and Psychological Functioning Following IMCP

	M Pre	*M* Post	*d*	*p*	*M* F/U	*d*	*p*
Spiritual Well-being							
FACIT Total	2.24	2.72	1.21	.0001	2.60	0.69	.0005
Meaning/Peace	2.49	2.98	1.01	.0001	2.78	0.53	.006
Faith	1.69	2.15	0.66	.0002	2.25	0.63	.002
Psychological Functioning							
Anxiety	2.39	2.24	0.22	.17	2.16	0.48	.02
Depression	2.09	1.98	0.22	.18	1.89	0.51	.07
Hopelessness	7.57	4.70	0.80	.0001	4.84	0.63	.002
Physical Functioning/QOL							
Overall Quality of Life	5.89	7.18	0.94	.0001	6.88	0.71	.0003
Number of Symptoms	18.7	16.0	0.32	.06	17.5	0.14	.42
Symptom Distress	1.95	1.53	0.79	.0001	1.84	0.22	.22

Note: *M* pre: group mean at baseline; *M* post: group mean at end of treatment; *M* F/U: group mean at 2-month follow-up assessment; *d*, *p* correspond to effect size for comparison to baseline score (*M* pre)

Table 1 reveals that the therapeutic benefits of IMCP were somewhat more modest at the 2-month follow-up, but remained strong and statistically significant for most variables. In fact, some variables demonstrated more substantial improvements at the follow-up assessment (i.e., anxiety and depression). No such changes were evident in the TM treatment arm, with the ―null‖ findings continuing at the 2-month follow-up assessment.

Conclusions: IMCP appears to be a potentially beneficial intervention for patients' emotional and spiritual suffering at the end of life. Participants who received IMCP demonstrated substantial

and statistically significant improvements in spiritual well-being, a sense of meaning, hopelessness, overall quality of life, and symptom-related distress, and more modest effects for anxiety, depression and symptom burden. These treatment gains were sustained at the follow-up assessment, 2 months after completion of treatment. Patients who received TM, on the other hand, demonstrated little improvement in these outcome variables. When comparing the effects of these two treatments, IMCP resulted in significantly greater improvements in a number of variables studied. Further research that compares IMCP with other psychotherapeutic interventions, such as this current larger randomized control trial and includes a non-active control group, is needed to better understand the unique benefits of this treatment approach.

Potential Advantages of IMCP for Advanced Cancer Patients

Both Group and Individual formats of psychotherapy interventions have been studied and utilized in cancer populations as well as other populations with life-threatening medical illnesses (e.g., AIDS). The unique personal struggles that an individual patient faces when coping with cancer, especially as they near the end of life, suggest the importance of a one-on-one psychotherapeutic approach. Individual treatment allows the patient to engage in the therapeutic work on an intimate level and explore his/her distinct existential concerns. However, most clinical trials investigating psychosocial interventions for cancer patients have tested interventions that use a group format (e.g., Classen et al., 2001; Edmonds et al., 1999; Fawzy & Fawzy, 1998) and many have focused on or have included earlier-stage cancer patients and survivors (e.g., Dolbeault et al., 2009; Lee et al., 2006). While there may be clinical and financial utility in employing a group modality, the intensity and focus on each individual's experience may be diffused within this type of atmosphere. Multiple stories are often shared, and the individual and his/her personal meaning may become lost within the group dynamic. In contrast, a one-on-one psychotherapeutic approach permits at least two conditions that are of particular importance in working with vulnerable advanced cancer populations: flexibility and individualization. Being flexible in scheduling the location and time of the intervention is paramount when working with advanced cancer patients who may be in physical discomfort and limited in mobility in order to accommodate their needs. Group psychotherapy interventions can be effective for cancer patients, but have practical limitations in advanced cancer patients, imposed by requirements for an inflexible schedule where a critical mass of participants is required for ideal outcomes. This results in high rates of attrition and missed sessions (the full dose of the intervention is often not delivered). Individualization through tailoring treatments to address each patient's existential concerns and to identify personal sources of meaning is similarly crucial and may ultimately result in more potent and lasting positive effects than group interventions permit.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This study will utilize a randomized, controlled, repeated measures design to investigate the efficacy of Individual Meaning-Centered Psychotherapy (IMCP), compared to a standard Individual Supportive Psychotherapy (ISP) and an enhanced usual care (EUC) arm, on spiritual well-being, psychological distress, and quality of life in a sample of 414 ambulatory patients (138 per arm) with advanced cancer. All patients with solid tumors with advanced disease and significant distress who are receiving ambulatory care at MSKCC are eligible for participation. Recruitment of patients will take place at MSKCC, in all ambulatory care areas treating solid tumors (i.e., prostate, breast, lung, colorectal, hepatobiliary, head and neck cancers, and Palliative Medicine). In addition, patients may be recruited through letters.

Potential subjects for the study will be identified, by the research staff and participating oncology staff, by cancer diagnosis and prognostic indicators of advanced disease. Specific evidence of advanced disease to meet eligibility criteria includes documentation of one of the following: stage IV disease for breast, prostate, or colon cancers; solid tumor malignancies at other sites that are metastatic; locally advanced and unresectable cancer/tumors; locally recurrent ovarian cancer, or confirmation from the treating physician and documentation in the research medical record of advanced disease. The Screening Assessment (T0) will be conducted using the following: Patients will be assessed using the Karnofsky Performance Rating Scale (KPRS). Patients with a score below 60 or physical limitations sufficient to preclude participation will be excluded from the study. Potentially eligible patients will be administered the Distress Thermometer (DT), developed by the National Comprehensive Cancer Network (NCCN) Distress Management Clinical Practice Guidelines Panel (2009). This screening tool consists of a 0 to 10 visual analog scale in the form of a distress thermometer as well as a checklist of problem areas that may be contributing to distress (i.e., practical, family, emotional, spiritual/religious, and physical problems), in order to determine whether the patient meets the requisite threshold for study participation. Patients who indicate a four or greater on the DT will be informed of the nature of the study, the method, relevant risks and benefits, and offered participation. Demographic (age, race, education, SES, etc) and Health Status (cancer diagnosis, stage of disease), and pre-randomization preference (treatment preference) will also be collected (see Appendix A). Patients will then complete the informed consent.

Following informed consent, patients will be assigned a subject number and randomized to one of the two 7 session interventions (IMCP vs ISP) or to the EUC control condition. Randomization will be completed by MSKCC's Department of Biostatistics. After randomization, participants will be contacted and informed which randomization assignment they received and scheduled for the intervention. The intervention should begin within four weeks of randomization. Patients who cannot begin the intervention within 30 days of consent (because of conflict or illness), will be placed on a waitlist so they can be offered the intervention when they do not have any conflicts at which time patients will be re-consented.

After the patient has been randomized, they will complete a T1-Baseline Assessment (week 1) before the 1st session (see Appendix C). The assessment battery will be re-administered at 3 subsequent points: T2 (midpoint, at session 4, Appendix D); T3 (post-intervention, following the 7th session of the intervention or at the completion of 14 weeks, whichever occurs first, Appendix E) to assess changes over the course of treatment; and T4 (follow-up, 8-12 weeks post completion of T3, Appendix F) to assess maintenance of treatment gains. The EUC sample will also be administered the battery of questionnaires at approximately equivalent intervals. Please see Appendices A, C, D, E, & F and if it is overly burdensome to come to the counseling center for assessments patients will be given the option to complete them by mail, email the blank questionnaires to participants for them to print and complete at home (forms will be returned by mail), or administer the questionnaires over the phone. Figure 3, section 9.0 for specific measures)

All intervention sessions will be conducted at Ambulatory Counseling Center facilities of the MSKCC Department of Psychiatry and Behavioral Sciences or another Memorial Sloan-Kettering Cancer Center treatment facility. However, in rare circumstances if deemed appropriate by the interventionist (e.g., illness, emergency, transportation difficulties) telephone sessions will be permitted. All psychotherapy sessions will be audio recorded to be used for treatment integrity purposes. Portions of these audio recordings may be transcribed for academic, educational, or

training purposes with the participants consent. This will happen when a portion of a session is particularly compelling or represents a noteworthy example of Meaning-Centered Psychotherapy in practice. Transcription will be completed by research staff or Ubiqus, a transcription service company. Sessions may be observed with the participants' knowledge by trainees and/or study personnel through the two way mirror in the MSK Counseling Center for training, educational, supervision purposes or for treatment integrity. Finally, sessions may be video recorded with the participants consent and may be used for academic, educational, or training purposes.

We will be assisted on this project by Dr. Barry Rosenfeld from the Fordham University Department of Psychology. Dr. Rosenfeld is a Professor and Director of Clinical Training at Fordham with a faculty appointment at MSKCC. As Co-PI on the R01 grant that was awarded to support operations of this study, his primary role is to provide consultation for research design, research supervision, data analyses, and manuscript preparation. There is an established subcontract between MSKCC and Fordham University. All data that Dr. Rosenfeld receives will be de-identified.

4.3 Intervention

All eligible patients, meeting inclusion and exclusion criteria, who provide informed consent and voluntarily agree to participation in this psychotherapy intervention study will be randomly assigned to one of three study arms: the two psychotherapy interventions described below or the enhanced usual care condition. Individual sessions of either IMCP or ISP will be held in the MSKCC Department of Psychiatry and Behavioral Sciences ambulatory care facility: The MSK Counseling Center, MSKCC 54th Street. In rare cases therapist may see patients in other treatment facilities at MSKCC such as the Breast Center, Outpatient Treatment Center, or Inpatient Hospital if circumstanses such as severe illness preclude the patient from traveling to the MSKCC couseling center. On rare occassions at the discression of the P.I. and individual therapist, participants who become severely ill or hospitalixed may be pemitted to participate in individuals through teleconference in order to maximize therapeutic benefits to participants and minimize attrition. Participants will attend individual sessions weekly for 60 minutes. There will be seven individual sessions with an outside window of 14 weeks. Ideally, the psychotherapy will be completed in 7 weekly sessions. However, we have allotted a window of approximately 14 weeks to complete the 7 sessions, allowing for occasional meetings every 2 weeks in the event of medical illness in this advanced cancer population. The follow-up assessments will be 8 weeks after the last session.

Individual Meaning-Centered Psychotherapy (IMCP): IMCP is based on the principles of Viktor Frankl's Logotherapy, and is designed to help patients with advanced cancer sustain or enhance a sense of meaning, peace and purpose in their lives even as they approach the end of life. IMCP is structured as a 7-session (1-hour weekly sessions) individual intervention that utilizes a mixture of didactics, discussion and experiential exercises that focus around particular themes related to meaning and advanced cancer (See Appendices I & J for IMCP Treatment Manual and IMCP Participant Manual). The session themes include:

- Session 1 – Concepts and Sources of Meaning
- Session 2 – Cancer and Meaning: Identity Before & After Cancer Diagnosis
- Session 3 – Historical Sources of Meaning: Legacy (past, present and future)
- Session 4 – Attitudinal Sources of Meaning: Encountering Life's Limitations
- Session 5 – Creative Sources of Meaning: Creativity & Responsibility
- Session 6 – Experiential Sources of Meaning: Connecting with Life via Beauty, Love & Humor

- Session 7 – Transitions: Reflection, and Hopes for the Future

Patients are assigned readings (i.e. Man's Search for Meaning by Victor Frankl) and homework that are specific to each session's theme and which are utilized in each session. Participants may also complete an optional Legacy Project outside of the group based on these themes and discussion (ie. autobiography, artwork, photo album, family history, etc). While this intervention is primarily psychoeducational with the focus of each session on issues of meaning and purpose in life in the face of advanced cancer/limited prognosis, elements of support and expression of emotion are inevitable, but limited by the focus on experiential exercises, didactics and discussions related to themes focusing on meaning).

Individual Supportive Psychotherapy (ISP): The ISP intervention (see Appendix K for ISP Treatment Manual), utilized as the comparison treatment condition in this study, is adapted from the Supportive Group Psychotherapy manualized intervention developed by David Payne (1997) and adapted by Drs. Kissane, Breitbart and colleagues into the ISP manualized intervention. This intervention is a 7-session individual supportive psychotherapy utilizing an approach to supportive psychotherapy based on models described by Rogers (1951, 1980) and Bloch (1996). The essential components of supportive psychotherapy are integrated into this manualized intervention, including: reassurance, explanation, guidance, suggestion, encouragement, affecting changes in patient's environment, and permission for catharsis (Bloch, 1996). The ISP therapeutic process emphasizes Rogerian person-centered concepts: genuineness, unconditional positive regard, and empathic understanding. The ISP therapeutic content emphasizes maintaining focus on cancer, supporting patients in the here and now, fostering expression of emotion and discussion of difficult topics, and creating a sense of being understood (Payne, et al., 1997). The manual also contains specific instructions on how to avoid therapeutic techniques that are not exclusively supportive (e.g., interpersonal therapy, cognitive-behavioral therapy, meaning-centered therapy).

Enhanced Usual Care (EUC): The use of a usual care condition to increase the methodological rigor of this randomized controlled trial must be balanced with the need for beneficence and preventing harm in the care of patient participants. We are therefore including what we refer to as an ―enhanced‖ usual care arm to this randomized controlled trial to address the ethical issues raised by utilizing a usual care condition in a vulnerable advanced cancer population. The ―enhancement‖ to usual care in this study involves the inclusion of screening and targeted referral components as suggested by Reynolds et al. (2001). Participants will receive feedback about their level of distress (based on the DT administered at screening) and given appropriate targeted referrals based on levels of distress and problem areas endorsed. Participants will be given a letter with a list of appropriate referrals. Several referrals may be made based on identified problem areas, using the following guidelines:

- ―Practical Problems‖ - Social Work on their disease management team
- ―Family Problems‖- Family Clinic at MSKCC Counseling Center
- ―Emotional Problems‖ - MSKCC Counseling Center
- ―Spiritual/Religious Concern‖- Pastoral Care Counseling Services
- ―Physical Problems‖- MSKCC physician or MSKCC Palliative Care Service

In addition, patients may be offered community resources as well. Research assistants conducting the screening and providing feedback and referrals will be trained in the NCCN guidelines for distress management (NCCN, 2009; see Appendix G). Regardless of whether they indicate significant distress or any problem areas patients in the EUC will all be provided with informational brochures on psychosocial services available at MSKCC (i.e., the MSKCC Counseling Center Services Guide for Patients [MSKCC, 2007], psychoeducational materials (see

Appendix H) and a book entitled ―The Human Side of Cancer‖ by Jimmie Holland, M.D. EUC patients will be closely monitored at each assessment point for significant distress and highly distressed patients (i.e. 8 or above on DT or endorsement of suicidal ideation on BDI) will be referred to the counseling center or contacted by the PI for further assessment as needed.

Selection, Training and Supervision of Leaders: We have carefully considered the selection of therapists and intensive training and supervision of our treatment providers. The manualized research interventions for this protocol, IMCP and ISP, are highly structured, as therapists are provided with an outline of content for all study sessions. Therefore, we determined that therapists must have, at minimum, a Masters degree in Mental Health Counseling, social work, or psychology to qualify for consideration as an interventionist on this study. Clinicians with greater experience and more advanced skills will also be considered for the therapist role on this study. Therapists will be assigned to either the IMCP or ISP arms to maximize the differentiation between the formats. Supervision and training for IMCP and ISP will be conducted by the P.I. or Co-Investigator in charge of each treatment arm.

All research study counselors are either MSKCC-employed mental health clinicians or non-MSKCC employed mental health clinicians contracted to work on specific research studies. We use the services of non-MSKCC mental health clinicians as study counselors so that we can best accommodate participant schedules and availability to attend the study sessions.

All study interventionists will undergo extensive training in either IMCP or ISP, by the P.I. or Co-Investigator. Although some MSKCC clinicians are already experienced in providing IMCP or ISP from our pilot study period, the P.I. and Co-Investigator will lead periodic intensive training workshops in the delivery of these interventions for each distinct intervention therapists. All therapists will be provided with a copy of the treatment manual for the intervention they will be providing, describing in detail the philosophy, format, and techniques involved in the intervention. These training workshops will focus on the acquisition of skills in the conduct of each intervention. We will also provide ―booster‖ training to maintain standardized delivery of both treatment conditions to prevent ―provider drift.‖ To reinforce standardized treatment delivery, the P.I. or Co-Investigator in charge of the treatment arm will lead supervision sessions for the different treatment providers.

Therapists will be trained on an as needed basis for the duration of the study. If needed some therapists in training may conduct 1-2 training cases with patients who are not eligible to participate in the study due to stage of cancer, low distress or past participation. Therapists will receive intensive supervision and the therapist‘s competency in the intervention will be assessed to determine if they are ready to be study therapists. Participants who are consented as training cases will not be randomized and will not complete any assessments. Data collected on training cases will be used for training and supervision purposes on this study only. These records will not be shown outside of the study supervisors, therapist in training, and staff. Training will be approximately 7-14 weeks to allow for trainees to complete the 7 sessions of the intervention. The audio-recordings from the training cases will be kept for the duration of the study to train future therapists and will be destroyed after the study is completed. Training participants will be offered reimbursement for travel expenses.

Adherence to Intervention Format: We will institute several ―best practices‖ to enhance and monitor treatment fidelity, which include: careful attention to the study design, selection, intensive training and supervision of treatment providers, delivery of treatment, receipt of treatment, and ―real-life‖ enactment of treatment skills. With regard to study design, we will compare two

intervention conditions (IMCP and ISP) that are equivalent with regard to the number, frequency and duration of sessions. We will monitor session attendance using a diary log with names and session dates to track percentage of attendance and to account for absenteeism and reasons for missed sessions. We will make every effort to deliver the full treatment, but we expect some variation in treatment delivery dose as well as treatment drop-out. Reasons for attrition will be assessed with an open-ended question for enrolled participants who withdraw. Drop-out reasons will be categorized and then judged by independent raters. To reduce likelihood of treatment contamination, each of the treatment conditions (IMCP and ISP) will be delivered by distinct treatment providers. We have developed comprehensive treatment manuals for IMCP and ISP (see Appendices I, J & K) to facilitate standardized delivery of the treatment sessions. Therapists will monitor attendance and homework completion as part of their process notes. We will also collect information about EUC utilization of resource referrals. Deviations from protocol will be recorded, and discussed regularly during supervision. We will also externally monitor treatment sessions, feedback sessions for the EUC arm, and provide feedback to interventionists.

Treatment Integrity/Adherence to Intervention Format: We will establish several procedures to monitor treatment protocol adherence and improve standardized delivery of the treatment. First, we have developed standardized treatment manuals for each of the treatment conditions (IMCGP and ISP). To ensure that providers are adhering to the treatment protocol, we have developed a provider outline of intervention components for each treatment session, for both of the interventions that are included in each treatment manual. These checklists/outlines can be used to facilitate supervision. We have also developed ―Treatment Integrity Coding Manuals‖ (see Appendix L), adapted from Dr. Kissane's experience in developing treatment integrity assessment methodology in his work on Family Focused Grief Therapy (Chan et al. 2004), for each of the two interventions (IMCP, ISP). These ―Treatment Integrity Manuals‖ allow for independent raters to evaluate each session of both interventions for treatment adherence in terms of process and content. The MSKCC Department of Psychiatry and Behavioral Sciences will have available two psychotherapy conference and consult rooms with 2-way mirrors, audiotape recording capabilities which will enhance our ability to provide supervision, training and treatment integrity. All sessions will be audio-taped, with prior consent of the participants. A random sample of about 15% of all recorded sessions (approximately 1 session per IMCP/ISP case) will be evaluated and rated for treatment integrity (utilizing the Treatment Integrity Coding Manual). To prevent against therapist drift, treatment integrity ratings will be conducted regularly throughout the period of therapy within the study. All raters will be given the opportunity to offer written comments/feedback to individual facilitators regarding the specific individual session to enhance continued training and supervision in these individual interventions. Raters will be blinded to the therapist but not to the intervention arm or the specific session within that treatment arm, and required to achieve >80% inter-rater reliability. We will also use a patient-generated measure of treatment adherence, the ―Post-intervention Questionnaire‖, described in the Study Measures section.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

5.1 Subject Inclusion Criteria

- 21 years of age and older
- Able to communicate and understand English well enough to complete assessments and intervention**
- Patients with solid tumors with advanced disease (see section 4.1 for more specific description of evidence of advanced disease) receiving ambulatory care at MSKCC*
- Distress Thermometer rating of 4 or greater*

*Patients who do not meet these eligibility criteria may be offered participation as a training case (See inclusion criteria for Training Cases below).

Subject Inclusion Criteria - Training Cases

- 21 years of age and older
- Able to communicate and understand English well enough to complete the intervention**
- Patients with solid tumors with advanced disease (see section 4.1) receiving ambulatory care at MSKCC with a Distress Thermometer rating of 3 or less

  or

  Patients with solid tumors who do not meet eligibility criteria for advanced disease receiving ambulatory care at MSKCC

  or

  Patients with solid tumors with advanced disease (see section 4.1) receiving ambulatory care at MSKCC who have participated in a prior meaning focused intervention study

  or

  Patients with solid tumors with advanced disease (see section 4.1) receiving ambulatory care at MSKCC who have enrolled in this study, been assigned to the EUC arm, and completed all study requirements including follow-up assessments.

**The study treatment manual materials and assessments were designed and validated in English and are not currently available in other languages. Translation of the intervention and questionnaires into other languages would require reestablishing the reliability and validity of them. Therefore, participants must be able to communicate in English.

5.2 Subject Exclusion Criteria

- In the judgment of the treating physician and/or the consenting professional, presence of significant cognitive impairment (i.e., delirium or dementia) sufficient to preclude meaningful informed consent and/or data collection
- Baseline Karnofsky Performance Rating Scale (KPRS) score below 60 or physical limitations sufficient to preclude participation in a 7 session outpatient psychotherapy intervention
- In the judgment of the consenting professional, severe psychiatric disturbance sufficient that would preclude participation in the intervention (patients whose psychiatric disorder is well controlled on medication will be eligible)

6.0 RECRUITMENT PLAN

Screening for Recruitment: Potential candidates for the study who meet the eligibility criteria of cancer diagnosis and stage will be identified by the research staff and/or participating oncology staff or co-investigators. Study investigators in the Pain & Palliative Care Service the Breast Cancer Medicine Service, the Head & Neck Oncology Service, the Thoracic Medicine Service, the Gastrointestinal Oncology Service, and the Genito-Urinary Oncology Service will serve as liaisons to the Research Staff and help screen and identify potential subjects for the study. In addition for these services the study research staff may screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information to approach these patients. They may also make inquiries using database programs (i.e. Dataline) to identify appropriate patients for review of study eligibility criteria.

Recruitment Strategies: In order to maximize study enrollment several recruitment strategies will be utilized in this study. We will defer to our co-investigator' preferences as to which method(s) they would like us to use in their respective clinic. These include:

1) Potentially eligible patient who have an upcoming appointment at an MSKCC outpatient clinic may be contacted in person by the research staff in clinic. The research staff will discuss the study in detail, administer the screening instruments and seek informed consent for participation. The screening process for this protocol requires administration of screening questionnaires (Distress Thermometer, Mini Mental, Karnofsky). The Code of Federal Regulations Title 45, Part 46, Subpart A states that an IRB may waive the requirement for an investigator to obtain a signed consent form for some or all subjects if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In following the code, we request to waive consent, in accordance with these regulations, for the pre-screening measures, as they are conducted for screening in purposes only.

2) Patients may also be contacted by mail with their treating physician's assent. Patients who have been sent a recruitment letter (see Appendix O) and study brochure (see appendix P) will be contacted by phone one week post mailing the letter. Three attempts will be made to contact the patient one month after the mailing of the letter. Patients who do not respond to the letter will be considered _not interested‖ in the study and will not be contacted in the future. If the patient is interested the research staff will discuss the study in detail, administer the screening instruments, and seek informed consent for participation on the phone.

3) Flyers or study brochures (see Appendices M, P, & Q) with study contact information will also be distributed in ambulatory care areas treating solid tumors (i.e. prostate, breast, lung, colorectal, hepatobiliary, head and neck cancers, Palliative Medicine, and the Counseling Center) . Patients can call in to receive information or be screened for study eligibility over the phone. If patients request additional information about the study (i.e. study brochures or informed consents) these materials will be sent to them by mail or email.

If a patient is medically eligible, they will be contacted by the research staff to introduce the study, assess patient interest. If patients are interested, the study will be explained to them in detail and they will be asked to complete the Screening Assessment including the Distress Thermometer. If eligible, the patient will then complete the consent. Once an informed consent (either verbal consent over the phone or written consent in-person) is obtained patients will be assigned a subject number and informed that they will be contacted in the near future about which arm they have

been randomized to. If they have been randomized to IMCP or ISP, the start date for the intervention will also be discussed. Every effort will be made to schedule intervention sessions so that they will not interfere with participants' cancer treatment plans. For patients who express interest in participating in the study but require financial assistance for transportation to/from individual sessions, a $20.00 travel reimbursement per session (or assessment for EUC arm) will be offered (see Appendix N).

Patients who do not meet all of the study eligibility criteria and are thus ineligible may be offered a chance to take part in the study as a training case. Additionally, patients enrolled in the main study and assigned to the EUC arm may be offered the opportunity to participate as a training case for one of the other arms (i.e., meaning or support) once they have completed all study requirements and follow-up assessments. These individuals, if they are interested, will be consented as training cases and will receive 7 sessions of Meaning Centered or Supportive Counseling by one of the study therapists being trained to deliver the therapy (section 4.2).

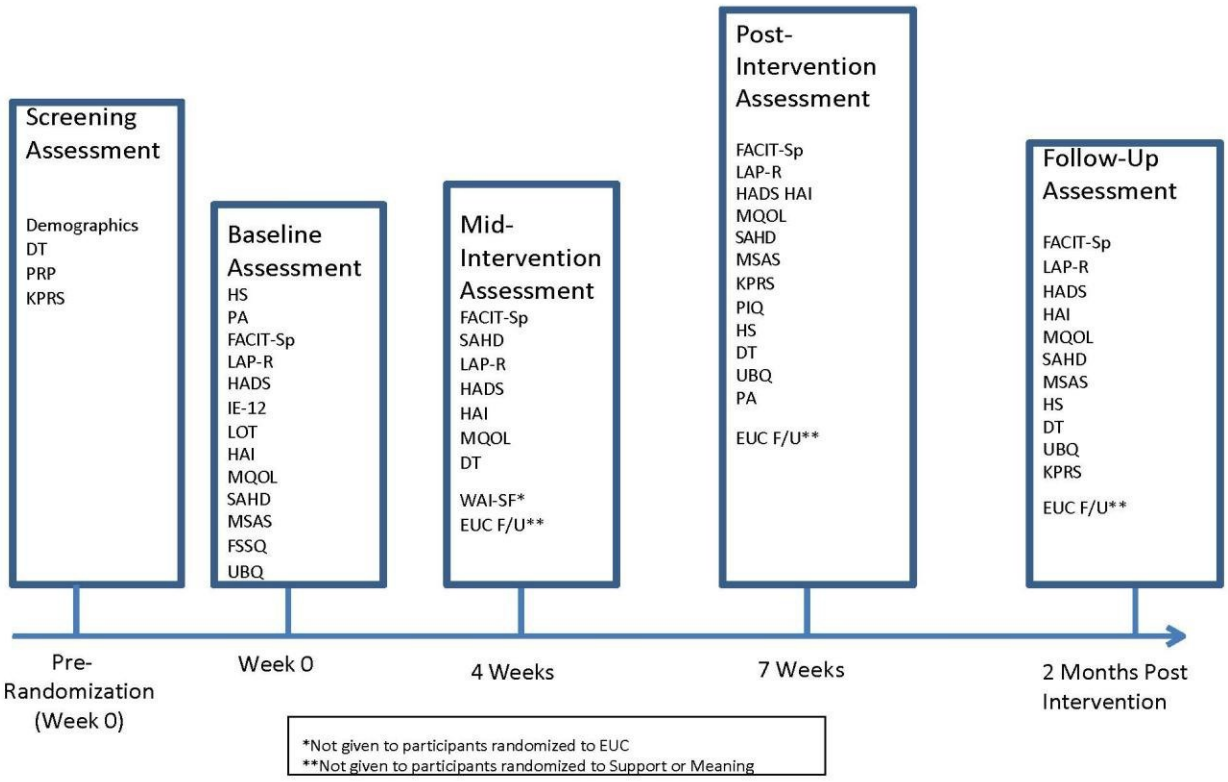
Maintaining of Recruitment Records: Research staff will use the information provided by the patient, medical provider and/or medical record to confirm that the patient is eligible. If the patient is ineligible for the research study, the research staff will destroy all information collected during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes for the duration of recruitment to make sure patients are no re-approached. At the completion of the study, all screening information will be de-identified.

Limited Waiver: The screening and recruitment process outlined above presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we have a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

7.1 ASSESSMENT/EVALUATION PLAN

Following completion of the screening assessment (T0), participants will be randomized to one of the 3 study arms (IMCP, ISP, or EUC) and informed of the intervention they have been assigned to receive. The assessment battery described above will be re-administered at four subsequent points (See Figure 3): T1 (baseline, before the intervention, week 1, Appendix C), T2 (midpoint, at session 4, Appendix D); T3 (post-intervention, following the 7th session of the intervention or at the completion of 14 weeks, whichever occurs first, Appendix E) to assess changes over the course of treatment; and T4 (follow-up, 8-12 weeks post completion of T3, Appendix F) to assess maintenance of treatment gains. Patients in the EUC arm will be re-administered the assessment battery at comparable time points. In addition to the T0, T1, T3, and T4 questionnaires, we will be asking patients in the IMCP arm to complete an optional weekly session rating survey (Appendix R). Patients who complete all 5 assessments will be eligible to receive a $20 Barnes and Noble gift card as a thank you for study completion. This will be delivered to the patient in person, by mail or email, depending on participant preference.

Figure 3: Study Assessment Timeline



When feasible and when the participant has given permission for us to contact his or her doctor during consent, the MSKCC oncologists for a subset of participants will be contacted by email to complete a prognostic awareness questionnaire. This e-mail, sent by the principal investigator no more than two weeks after patients complete their baseline assessment (T1), will contain a link to a survey introductory page that provides informed consent information. Potential participants will review study information and the risks and benefits associated with participation. Physicians who select the "next page" button will be informed that they are providing consent and will be taken to a webpage to fill out an 8-item questionnaire (see Appendix S for email, consent text, and questionnaire items). Contacted oncologists will be provided with a study ID number to connect the data they provide with the participant, and their responses will be otherwise de-identified. If the questionnaire is not completed after two weeks, a reminder email will be sent to the physician. If they do not complete the survey at that point, physicians will not be contacted again. The online questionnaire should only take about 5 minutes to complete, involves minimal burden, and is completely voluntary. Physicians are informed that the data they provide will not identify them and neither their patient nor his or her study therapist will have access to their responses.

The data collected from this Physician Prognostic Awareness Questionnaire will be managed through REDCap (Research Electronic Data Capture), a data management software system supported by the Core Informatics Group of the Clinical and Translational Science Center (CTSC) at Weill Cornell Medical College. The CTSC is funded by a CTSA NIH grant, which is led by Vanderbilt University and includes MSKCC. As a result of the Hospital‘s inclusion on this grant, we are able to use the CTSC‘s resources, including REDCap, even for projects on which they have no role. For this project, we are only using REDCap; we are not collaborating with anyone at the CTSC. Members of the Core Informatics Group supporting the REDCap software will only have

access to the de-identified data hosted by their servers for the purpose of ensuring the proper functioning of the database and the overall software system. REDCap is a tool for the creation of customized, secure data management systems including web-based data entry forms, reporting tools, and a full array of security features including user and group based privileges with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are kept in a locked server room with appropriate environmental modifications (e.g., special air conditioning), supported by an uninterrupted power supply, and backed up nightly with some backup tapes stored off-site. All connections to REDCap utilize encrypted (SSL-based) connections. Nationally, the REDCap software is developed, enhanced, and supported through a multi-institutional consortium led by the Vanderbilt University CTSA. Use of REDCap has been approved by the Department of Psychiatry & Behavioral Sciences' manager of IT Systems.

Subject Burden

In an effort to minimize patient burden, the assessment protocol has been designed to be as brief as possible in order to gather the required information. The assessment battery takes approximately one hour to complete, depending on the individual patient. Research staff will interrupt an assessment if a patient is fatigued or in significant pain. In an effort to ease patient burden, all self-report measures will be read to the patient if necessary.

Tests and Measures

Study participants will be assessed at baseline, midpoint, and follow-up assessments, using the following study measures (see Appendices A, C, D, E, & F for assessment questionnaires). The measures chosen have all been widely used with medically ill patients and have been used to study patients with cancer. In selecting these measures, an effort was made to limit subject burden. Assessments will be completed in person or if the patient is not able to complete the follow-up questionnaires in person, the research study team reserves the right to be able to mail or complete the questioners over the phone with the participant.

Screening for Eligibility Criteria:

1. Sociodemographic Questionnaire: Sociodemographic information will be obtained at the pre-randomization time point consisting of questions concerning age, gender, ethnicity, education, employment history, marital status and household composition, and religious affiliation and practices. Significant medical and other life events which occur during the course of treatment and follow-up will be recorded for each patient. (5 minutes; T0)
2. Distress Thermometer (DT): The Distress Thermometer (Roth et al., 1998) is a single-item visual analog scale used to screen cancer patients for the presence of psychological distress with a 0-10 range. The National Cancer Center Network (NCCN) Clinical Practice Guidelines for Distress Management recommend use of the DT, along with a 34-item problem checklist (NCCN, 2003, 2009). An extensive research literature has documented the utility of the DT as a screening tool for oncology settings, and has identified a cut-off of 4 or greater for identifying clinically significant psychological distress (e.g., Grassi et al., 2009; Jacobsen et al., 2005). (2 minutes; T0, T2, T3)
3. Karnofsky Performance Rating Scale (KPRS): Observer-rated scale used by physicians to report patient's level of physical performance with a range of 0-100. (Karnofsky & Buchenal, 1949; Coscarelli-Schag, 1984). KPRS is rated upon admission screening and at each assessment. (1 minute; T0, T3, T4)

Health Status Measures:

1. Health Status Interview (HS): Extent of disease, degree of medical co-morbidity, concomitant therapies, and significant medical events occurring during the study will be recorded for each patient. (5 minutes; T1)
2. Memorial Symptom Assessment Scale - Short Form (MSAS): The MSAS is a symptom checklist that elicits information about the intensity, frequency, and distress associated with 32 physical and psychological symptoms (Portenoy et al., 1994). Patients rate their symptoms during the previous week. The MSAS, which has been validated for use in cancer and AIDS patients (Breitbart et al., 1996), generates a global symptom distress index and two sub-scales that characterize physical symptom distress and psychological symptom distress respectively. We utilize an abbreviated version of the MSAS which assesses a single domain (usually distress) for each symptom, and provides calculations for sub-scales that are identical to those obtained for the original measure (range 0-4). This abbreviated version of the MSAS has also been demonstrated to have adequate levels of internal consistency (coefficient alpha =.83 for the Physical Symptom Distress subscale). (5 minutes; T1, T3, T4)
3. Prognostic Awareness (PA): PA will be assessed by using three approaches published in the literature on advanced cancer patients (Chochinov et al., 2000; Lichtenthal et al., 2009; Prigerson, 1992; Ray et al., 2006). Prigerson (1992) created a single-item assessment of prognostic awareness which we have adapted by our team for our population:― How would you describe your current disease status?‖ with response options: ―curable‖, ―likely curable‖, ―unlikely curable‖, or ―incurable‖. Chochinov et al. (2000) used semistructured interviews to assess patients‘ understanding of their illness, with interviewers ranking responses among three categories: 1 = No Awareness, 2 = Partial Awareness, and 3 = Complete Awareness (range 0-3). Finally, Temel et al. (in progress) are currently developing the Prognosis and Treatment Perceptions Questionnaire, a 13-item measure that assesses the following: perceptions of likelihood of cure, importance and helpfulness of knowing about prognosis, primary goal of cancer care, preferences for information about treatment, and satisfaction with quality of information provided regarding prognosis and treatment. We have adapted these measure and are utilizing a combined assessment of these three approaches which will be completed in two parts (Part 1- as self report questions during the assessment and a clinician rated assessment by the therapist. (5 minutes; T1, T3)
4. Physician Prognostic Awareness Questionnaire (8 items; See Appx S): When feasible, a subset of participants‘ oncologists (approximately 50) will be asked to complete a brief, face valid questionnaire, developed in collaboration with Fordham University. The questionnaire consists of 8 items assessing physicians‘ perceptions of the discussion about prognosis with their patients, including the patient‘s understanding of their prognosis and any potential barriers to their understanding. (5 minutes; T1)
5. Health Status and Outcome (Appendix T): HIS charts will be reviewed at the end of study or after death notification for the following information: DNR, hospitalization within one month of death, hospital death. (Chart Review; T4 and post-death)

Measures of Meaning:

1. Life Attitude Profile-Revised (LAP-R): The LAP-R is a 48-item self-report multidimensional measure of discovered meaning and purpose in life and the motivation to find meaning and purpose in life based on Frankl‘s work (Reker, 1992). Items are rated on a 7-point Likert-type scale of agreement. The LAP-R evaluates 6 dimensions: purpose, coherence, life control, death acceptance, existential vacuum, and

goal seeking, which are used to calculate two composite subscales: the Personal Meaning Index (having life goals and a sense of direction) and Existential Transcendence (degree to which meaning and purpose has been discovered) (range 8-56). The LAP-R has high internal consistency (Cronbach's alpha coefficients ranging from 0.77 to 0.91; Reker, 1992). (5 minutes; T1, T2, T3, T4)

2. Unfinished Business Questionnaire (UBQ): This 3-item measure asks participants to identify any matters in their lives (e.g., relationships, work) perceived as unfinished or unresolved (range 0-10). Participants who endorse ―unfinished business‖ are asked to provide a troubling example and to rate their distress related to this example. (under 5 minutes; T1, T3, T4)

Measures of Spiritual Well-Being:

1. FACIT Spiritual Well-Being Scale (FACIT-Sp): The FACIT Spiritual Well-Being Scale is a brief self-report measure designed to assess the nature and extent of individual's spiritual well-being (Brady et al., 1999, Peterman, Fitchett & Cella, 1996). This measure, which generates two sub-scales: Faith (the importance of faith/spirituality) and Meaning /Peace (sense of meaning and purpose in life) (range 0-4), has been demonstrated to have strong internal reliability for both the total score and each subscale (coefficient alpha = .87 for the total scale, .88 for the faith factor and .81 for the meaning factor). In addition, strong support for the external validity of this measure has been demonstrated in a several large samples of cancer and AIDS patients including patients with advanced and terminal illness (Brady et al., 1999, Breitbart et al., 2001; Nelson et al., 2002). (5 minutes; T1, T2, T3, T4)

Measures of Religiosity:

1. Intrinsic/Extrinsic Religiosity Scale (IE-12): The Age Universal I-E Scale is a 12 item self-report measure that assesses intrinsic and extrinsic religiosity (Maltby, 1999). Each item is anchored on a three point scale (range 0-2). Items on the intrinsic scale include ―My whole approach to life is based on my religion,‖ and ―It is important to me to spend time in private thought and prayer‖. Extrinsic religiosity items include ―I go to church because it helps me to make friends,‖ and ―Prayer is for peace and happiness,‖ (Allport & Ross, 1967). The measure has adequate internal consistency reliability (alpha range = .66 to .75) and has been increasingly used with elderly and medically ill populations (e.g., Nelson, 2002). (under 5 minutes; T1)

Measures of Psychological Distress and Quality of Life:

1. Hospital Anxiety and Depression Scale (HADS): Tis is a 14 item self-rated questionnaire, which has been well tested as a measure of overall psychological distress in cancer populations (range 0-42)., with Depression and Anxiety Subscales of seven items each (range 0-21).. It is considered particularly useful because of the absence of somatic items that often confound the determination of psychiatric problems among the medically ill. Strong test-retest reliability has been found in samples of elderly patients (Spinhoven et al., 1997) and HIV positive patients (Savard et al., 1998).(under 5 minutes; T1, T2, T3, T4)
2. Schedule of Attitudes towards Hastened Death (SAHD): This 20-item questionnaire (range 0-20) was developed by the responsible investigators as a self-report measure of interest in hastened death (Rosenfeld, Breitbart, et al., 1999; 2000). This measure has been administered to more than 300 patients with terminal cancer and HIV/AIDS, and has demonstrated high levels of reliability (alpha coefficient=.88 and median item-total

correlation=.43). In addition, the SAHD has demonstrated concurrent validity, correlating 0.88 with the clinician-rated Desire for Death Rating Scale (Chochinov et al., 1995), and somewhat more modestly (*r*=.47 to 0.65) with measures of depression and overall psychological distress. This range of scores and pattern of correlations with measure of depression is consistent with previous research (e.g., Chochinov et al., 1995; Breitbart et al., 2001). (under 5 minutes; T1, T2, T3, T4)

3. Hopelessness Assessment in Illness (HAI): The Hopelessness Assessment in Illness scale (HAI) is a brief, 8-item questionnaire specifically developed through a R01-funded research study (B. Rosenfeld, P.I.; W. Breitbart, Co-P.I.) to assess hopelessness in cancer patients with advanced disease and terminal illness (range 0-16). (Rosenfeld et al., in press). The HAI has demonstrated a high degree of internal consistency (coefficient alpha above .80) and construct validity (e.g., a correlation of.74 with clinical ratings of hopelessness). The HAI demonstrated incremental validity over and above existing measures of hopelessness, such as the Beck Hopelessness Scale, which our group has used in previous research studies. (under 5 minutes; T1, T2, T3, T4)
4. McGill Quality of Life Questionnaire (MQOL): A brief, self-report instrument designed to assess various domains of psychological, spiritual, and physical functioning among terminally ill patients (Cohen et al., 1995). Patients rate their current functioning on a scale of 0 to 10. The physical and psychological domains of the MQOL are highly correlated with other measures of quality of life, although the existential/spiritual domain assessed by this measure has not typically been included in other quality of life measures. This measure has demonstrated reliability (internal consistency > .70 for the subscales), and adequate levels of concurrent validity (e.g., correlation of .34 with the Spitzer Quality of Life Index) (under 5 minutes; T1, T2, T3, T4)
5. Duke-UNC Functional Social Support Questionnaire (FSSQ): As a measure of perceived social support we are utilizing an 11-item multidimensional, functional social support questionnaire (range 0-4). (Broadhead et al., 1988). The Duke-UNC is a reliable and valid self-report instrument that generates a total score representing overall social support, and two subscale scores corresponding to confidant support and affective support. This measure has adequate demonstrated levels of internal consistency and test-test reliability (> .60), as well as significant correlations with other measures of social functioning. (5 minutes; T1)
6. Life Orientation Test Revised (LOT-R): This 8-item measure of optimism has been widely used in studies of adjustment to stress and illness and depression (range 8-56). Studies have demonstrated high levels of reliability (e.g., alpha coefficients ranging from =.76-.80 and test-retest reliability of .79) as well as concurrent and discriminant validity (Scheier & Carver, 1985). While most studies have treated the LOT-R as a trait-like measure (dispositional optimism), Carver et al. (1993) found that LOT-R scores were influenced by situational stress in a sample of women with breast cancer. (2 minutes; T1)

Measures of Psychotherapy Preference, Process and Adherence:

1. Pre-Randomization Preference Questionnaire (PRP): A face valid questionnaire developed by the investigators to assess patients' preference for interest in participating in a psychotherapy intervention, and preferences regarding content and group assignment. Patients are asked to rate (on a 0-4 Likert-type scale) their preferences for 3 aspects of psychotherapy content: a) social support, b) expression of feelings, c) finding a sense of meaning and purpose in life. Patients are also being asked to indicate their preference for the meaning-centered vs. supportive psychotherapy vs. enhanced

usual care study arms (they are told that this information is solely for analytic purposes and will not influence group assignment). (1 minute; PR)

2. The Working Alliance Inventory-Short Form (WAI-SF): The original WAI is a 36 item instrument designed to measure variables affecting the degree of counseling success based on Bordin's (1979) conceptualization of the therapeutic alliance, independent of the counselor's theoretical orientation (Horvath et al, 1989). There are three sub-scales of the WAI (tasks, goals, and bonds) as well as a composite score (range 12-94). All items are rated on a seven point Likert Scale acceptable validity was demonstrated with the Counselor Rating Form (CRF) and the Empathy scale of the Relationship Index (Horvath et al, 1989). Cronbach's Alpha of the WAI composite score is 0.93 (Horvath et al, 1986). We will be utilizing a shortened version of the WAI (WAI-SF), which consists of 12 items total with four items in each of the three sub-scales (tasks, goals and bonds). Validity has been demonstrated for the WAI-SF based on a similar factor structure with the original 36 item WAI. Cronbach's alphas for the WAI-SF range from 0.83 to 0.98 (Busseri et al 2003). The WAI-SF self-report rating form will be administered to participants in the IMCP and ISP treatment arms at the post-intervention assessment. (under 5 minutes; T1, T2, T3: Not in EUC)
3. Treatment Integrity/Adherence to Intervention Format: We have developed a Treatment Integrity Rating Form based on the standardized treatment manuals for each of the treatment conditions (IMCP and ISP) which will allow for independent raters to evaluate each session of both interventions for treatment adherence in terms of process and content. There is one for form for all sessions. Content items will be rated on a Yes/No scale, and process items will be rated on a 0-2 scale. All sessions will be audio-taped, with prior consent of the participants. A random sample of 30% of these audio-tapes will be evaluated and rated for treatment integrity by two independent raters.
4. Post-Intervention Questionnaire (PIQ): A face valid questionnaire developed by the investigators to assess adherence to prescribed format and whether any concurrent psychiatric/psychological treatments have occurred during the intervening period (administered at the completion of the final individual psychotherapy intervention session). Treatment adherence is assessed by asking patients their opinion of the focus of content in the intervention they participated in. Patients are asked to rate (on a 0-4 Likert-type scale) the degree to which the psychotherapy they participated in focused on: a) social support, b) expression of feelings, c) finding a sense of meaning and purpose in life. They will be asked to answer an open-ended question: 1) ―What other forms of psychiatric/psychological treatment have you received during this study‖? (1 minute; T3; Not administered to EUC).
5. Optional Weekly Session Rating (Appendix R): A subset of the patients in the IMCP arm will be asked to complete an optional brief weekly session assessment. This will ask participants the extent to and ways in which the meaning-related topics covered in their sessions are helpful and/or applicable. Feedback from these questions will help us determine which meaning-related topics are most salient and helpful for patients to potential adapt the intervention. This survey will be handed out by the therapist immediately after each session, and the participant will be given the option to decline filling it out. (Optional: weeks 1-7, IMCP only)

8.0 TOXICITIES/SIDE EFFECTS

Minimal risk of psychological distress is posed by study questions that ask participants to identify their current problems. However, since study items were chosen to reflect what are likely to be

existing concerns, the present study is not expected to markedly increase participants' psychological distress above their routine concerns. Experienced personnel, trained in interviewing medically ill individuals, will administer all instruments, and will be supervised by the Principal Investigator or Project Coordinator. Participants' reactions will be observed and signs of significant distress will be followed up by the PI or study therapist with attention to presence of any serious psychological concerns. In the unlikely event of significant acute distress, participants will be referred to a staff member from the Department of Psychiatry and Behavioral Sciences. If a research participant indicates that s/he is acutely suicidal and poses a significant and acute risk of self-harm, this information will be shared with their attending physician so that timely and appropriate psychiatric assessment and care can be provided by the MSKCC Social Work or Psychiatry Service staff.

However, some subjects may become distressed or experience anxiety when discussing end-of-life care issues in the individual psychotherapy sessions or in response to filling out the self-report questionnaires that inquire about their illness, degree of depression, thoughts on end of life care, feelings of hopelessness, pain and physical symptoms, quality of life and social support. All patients will be monitored for severe distress and explicit suicidal ideation with plan or intent at each assessment point (including EUC). We will continue to utilize interviewers who have been trained to be sensitive to the nature of end-of-life care issues. When necessary, subjects who experience psychological distress related to filling out self-report questionnaires will be referred to appropriate care by the MSKCC Psychiatry Service.

There will be only one exception to the strict patient confidentiality policy, described above, which pertains to information obtained during the research assessment, which would indicate that the patient is seriously suicidal and may pose a significant and acute risk of self-harm. Subjects will be informed of this exception, and will also be informed that such information will be shared with the P.I. of the study and their attending physician so that timely and appropriate psychiatric assessment and care can be provided by the MSKCC Psychiatry Service.

There is a slight risk that participants may become fatigued or uncomfortable during the course of the self-report assessment. The assessment protocol has been designed to be as brief as possible in order to gather the required information. If necessary, the questionnaires will be read to the participant. The questionnaires should take approximately one hour to complete.

Expected Frequency of Side Effects/ Toxicity

In our previous studies involving over 500 cancer patients, using a very similar battery of questionnaires and assessment tools examining such issues as depression, hopelessness, suicidal ideation, pain, quality of life, etc., we have encountered little resultant emotional distress. Subjects in fact reported that they were relieved to be discussing such issues. We will, however, continue to utilize research personnel who have been clinically trained to be sensitive to issues of emotional distress, fatigue and subject burden.

9.1 PRIMARY OUTCOMES

The primary outcomes to be measured include measures of meaning (LAP-R), spiritual well-being (FACIT-Sp) and psychological distress (HADS, SAHD, HAI, MQOL). Specific measures are described above in section 7.0 and assessment timeline described below.

Figure 4. Schedule of Interventions & Assessments

Week	0	1	2	3	4	5	6	7	15
Screening and Randomization to Intervention	x								
Assessments	T_0	T_1			T_2			T_3	T_4
Interventions:									
Meaning Centered Psychotherapy (1 hour sessions)		x	x	x	x	x	x	x	
Supportive Psychotherapy (1 hour sessions)		x	x	x	x	x	x	x	
Enhanced Usual Care (Referral Facilitation)		x			x			x	

10.0 CRITERIA FOR REMOVAL FROM STUDY

Given the clinical course of patients with advanced cancer, not all patients entered into the study are expected to complete the entire trial. Subjects will be taken off study protocol under the following circumstances:

- Patient voluntarily withdraws from study
- Onset of severe cognitive difficulties that preclude participation in the intervention or accurate assessment in the judgment of the therapist and the P.I.
- Patient is unable to tolerate the intervention in the judgment of the therapist and the P.I.
- Infectious episode that is of sufficient severity to preclude further participation in the study.
- Non-compliance with the intervention without medical cause or reasonable explanation in the judgment of the therapist and the P.I.

11.0 BIOSTATISTICS

This project involves a parallel-arm randomized controlled clinical trial to compare the efficacy of three psychotherapy interventions: 1) Individual Meaning-Centered Psychotherapy (IMCP); 2) Supportive Individual Psychotherapy (ISP); and 3) Enhanced Usual Care arm (EUC). We plan to recruit altogether 414 patients (138 in each arm) with solid tumors with advanced disease. The primary outcomes include assessments of meaning (LAP-R), spiritual well-being (FACIT-Sp) and psychological distress (HADS, SAHD, HAI, MQOL).

Omnibus MANOVA for the primary aim**:**
The general paradigm for assessing the outcomes will be multivariate analysis of variance (MANOVA). MANOVA is appropriate because the primary psychosocial outcomes are highly correlated. The MANOVA method essentially combines the multiple dependent variables together into a weighted linear combination of canonical variates. The canonical coefficients provide the weights in this linear combination. The canonical weights have several advantages. The main advantage is that they inform the relative contribution of each outcome to the overall canonical function (i.e., whether or not meaning contributes more than spiritual well-being to the overall canonical function). MANOVA was chosen, rather than, for example, a mixed-effects modeling approach, primarily because of these considerations. In MANOVA, the combined canonical variate is analyzed in a manner similar to a univariate ANOVA.

The primary aim of this study will be evaluated in one omnibus, one-way MANOVA model against the null hypothesis that all three randomized arms entail comparable post-intervention outcomes in meaning, spiritual well-being, and psychological distress. Thus, the dependent variables will be the six primary outcome assessments (LAP-R, FACIT-Sp, HADS, SAHD, HAI, and MQOL) measured at the post-intervention time point (week 7). The sole independent variable is the randomized intervention assignment. Dunlop, Cortina, Vaslow & Burke (1996) showed that this method provides the most generalizable findings, findings that do not depend on the patients' baseline scores or other baseline characteristics. Thus, the omnibus MANOVA will test whether or not the psychotherapy groups differ in all six correlated outcomes of interest.

The T2 (mid-intervention) assessments are made because some patients may be too sick to complete the 7-session intervention. For these patients, we will use the T2 assessment to represent the most available data on intervention effect.

Sample size and statistical power considerations:

Two important hypotheses need to be established in this trial: 1) IMCP is superior to EUC; and more importantly, 2) IMCP is superior to ISP for improving psychosocial outcomes in patients with advanced cancer. Therefore, we have based sample size considerations on sufficient statistical power to detect these two differences. We have conservatively based our sample size calculations on a 0.20 standardized mean difference in the MANOVA canonical variates between the IMCP and ISP interventions. This 0.20 difference is what Cohen would consider a ―small‖ effect size in psychosocial research (Cohen, 1992), representing subtle group differences typically observed in psychotherapy clinical trials. Cohen (1992) distilled the findings of decades of psychosocial research and arrived at a classification of a ―small‖ effect (0.20 standardized mean difference), a ―medium‖ effect (0.50 difference), and a ―large‖ effect (0.80+ difference). This ―small‖ difference is also a sensible assumption, due in part to the small group differences in some of the psychosocial outcomes in our pilot IMCP trial (Table 1, e.g., psychological distress). Thus, we planned to have a sufficiently large sample size to detect subtle differences. Overall, this conservative estimate would accommodate outcomes in psychological distress which out pilot data showed a small difference. Based on these assumptions, we would need 104 participants in each arm at post-intervention (week 7) in order to obtain a power of 0.80. Other assumptions that go into this estimation included two *a priori* contrasts (IMCP vs. EUC and IMCP vs. ISP), and a two-sided, type-I error rate of 0.01 in the MANOVA test. The statistical power calculations were obtained from the computer program G*Power version 3.1 (Faul, Erdfelder, Lang & Buchner, 2007), for a MANOVA model with six correlated outcome variables. The output of the G*Power estimate is included below.

F tests - MANOVA: Global effects

Options:	Pillai V, O'Brien-Shieh Algorithm	
Analysis:	A priori: Compute required sample size	
Input:	Effect size $f^2(V)$	= 0.20
	α err prob	= 0.01
	Power (1-β err prob)	= 0.80
	Number of groups	= 2
	Response variables	= 6
Output:	Noncentrality parameter λ	= 20.8000000
	Critical F	= 2.9936309
	Sample size	= 104
	Actual power	= 0.8062691
	Pillai V	= 0.1666667

A sample size of 104 per randomization arm (138 at baseline) at post-intervention would accommodate a post-intervention attrition rate of up to 25%, which is within the attrition rate in our pilot IMCP trial. The estimated sample size at the follow-up time point (week 15) is 90 participants per intervention condition.

Based on our current IMCP Group psychotherapy intervention, we are currently recruiting at a rate of 5 – 6 individuals to participate. This study involves the IMCP individual therapy, which is more flexible in terms of enrolling patients quickly and scheduling for starting of the therapy sessions. Thus we are confident that we will be able to recruit at a rate of 8 – 9 individuals per month and complete the total enrollment of 414 within the 4-year recruitment period.

Data analytic plans for the secondary aims

To examine clinical and demographic variables that may correspond to differential responses to Individual Meaning-Centered Psychotherapy (e.g., potential moderating influences such as gender, race/ethnicity, religiosity, level of pre-intervention social support, optimism, physical symptom burden, prognostic awareness, and treatment dose).

We anticipate that several socio-demographic and clinical variables will moderate the impact of IMCP. For example, we expect that level of religiosity (based on the IE-12) at the baseline/pre-intervention assessment will be inversely related to treatment response (i.e., less religious individuals will be more likely to experience benefits from this intervention than more religious individuals). We also predict that level of social support will moderate improvement, with those patients reporting higher levels of social support receiving the greatest benefits (because of the emphasis on connectedness to others as a source of meaning in the IMCP intervention). On the other hand, we expect that patients with poorer physical functioning (e.g., lower Karnofsky score), greater pain severity and overall symptom burden (MSAS Global Distress Index scores) will be less likely to benefit from the interventions, in part because unmanaged physical symptoms may impede participation.

Analyses: Putative explanatory covariables will be identified and tested statistically using the method originally described by Baron and Kenny (1986), and more recently by MacKinnon (2008). Specifically, these will involve Multi-Variate Analysis of Covariance (MANCOVA) using the changes in the six primary outcomes (post intervention minus baseline) as a function of intervention condition, controlling as covariates the effects of gender, race/ethnicity, and baseline covariates in religiosity, social support, optimism, physical symptom burden, pain severity, and overall symptom burden. This analytic approach entails the following advantages: 1) change scores have the advantage of clearly identifiable direction of change, 2) psychosocial outcomes are measured on an interval scale (such as measures of temperature in the Fahrenheit or Celsius scales), so that change scores are less prone to problems associated with respondents using different internal psychological scales; and 3) precedence exists (Flay et al. 1995) in interventions designed for behavioral change. This method offers several advantages, both in terms of power as well as interpretation, to a traditional repeated measures design for analyzing data when both independent and dependent variables are assessed at two or more time points (Huck & McLean, 1975; Willet, 1988-9). Change score analyses will include the baseline score as a covariate if change is significantly correlated with baseline score (as is often the case).

To assess the relative impact of Individual Meaning-Centered Psychotherapy on different aspects of meaning (e.g., purpose, coherence, existential vacuum), as well as on different aspects of spiritual well-being (meaning versus faith):

Two additional MANOVA models will be carried out. In the first model, pre-post change scores of different aspects of meaning (e.g., purpose, coherence, existential vacuum) will be modeled by intervention conditions to examine to relative impact of IMCP on these outcomes. The canonical weights will be used to estimate the relative contribution of each mean components on the overall canonical function. Components of spiritual well-being will also be analyzed similarly, in a separate MANOVA model. Univariate ANOVA contrasts will be used to compare IMCP against ISP and IMCP against EUC.

To explore whether an enhanced sense of meaning ―explains‖ (mediates) improved psychological well-being (i.e., increased quality of life, decreased psychological distress:

This mediation analysis will be carried out using a MANCOVA model. The dependent variables will be the changes in psychosocial outcomes at the follow-up assessment time point (week 15 minus baseline) in quality of life and psychological distress as a function of intervention condition, adjusting for the post-intervention change in meaning (post-intervention LAP-R minus baseline LAP-R). Thus, the follow-up outcomes will be predicted by enhanced sense of post-intervention meaning. This lagged analysis is necessary because there is a potential confounding effect, for example, in using the post-intervention changes in meaning in predicting post-intervention quality of life. The lagged analysis between follow-up outcomes in quality of life and psychological distress and post-intervention changes in meaning preserves a plausible temporal ordering of causes and effects.

Intent-to-treat analyses and handling of missing data:
Intent-to-treat (ITT) analysis is the gold standard in evaluating the relative efficacy of therapeutic regimes for patients assigned to different treatment arms whether or not they comply with the full treatment plan as defined in the protocol. In contrast to studies that assess clinical outcomes that are observable whether or not patients comply with therapy, it is likely in this study that patients who fail to participate in particular counseling sessions will also be missing the corresponding outcome data. Thus, examination and imputation of incomplete data will be an integral part of our ITT analysis. Data for intermediate time points might be imputable by one of several available statistical techniques. However, it is more problematic to assess outcomes for patients who essentially drop out of the study, namely, who are missing the final (and possibly preceding) evaluations. Although we shall endeavor to obtain final evaluation-time data even for patients who discontinue the counseling, but because of the likelihood that premature withdrawal is related to deteriorating physical health, we cannot rely on this and will therefore use appropriate statistical methods. One preferred approach is the Pattern-Mixture Model (Hedeker & Gibbons, 1997), which assumes that patients can be grouped into a small number of implicit cohorts with different patterns of missing data. This method models the trajectories of responses within each cohort and combines results across cohorts to make overall comparisons between treatment arms. The Pattern-Mixture Model can be relatively easily applied in practice using a publicly accessible SAS macro. This approach will handle two potential, inter-related issues, namely, intent-to-treat analysis and missing data while making a global assessment of the overall efficacy of the two types of counseling. We anticipate that the majority of patients will complete most or all of the planned sessions and the corresponding assessments. However, our pilot data suggest that there may be sufficient attrition to warrant use of the above-described approach even if drop-out rates do not differ significantly between the two treatment arms.

Missing data:
Because attrition may significantly impact the MANOVA, we will utilize several techniques for dealing with missing data (Nich & Carrol, 1997; Singer & Willett, 1991). These techniques may

include estimating missing data, complete data analysis, and intention to treat analysis. Although missing data can be estimated using a number of powerful techniques (Graham, Hofer, Donaldson, MacKinnon & Schafer, 1997), we intend to use a multiple imputation procedure described by Schafer and Olsen (1997), which is capable of handling categorical data, continuous data, and any combination of the two. Graham et al. (1997) have argued that parameter estimates using this method are unbiased and have standard errors that are typically only slightly larger than those generated by other methods. In order to assess the effect of this imputation method, we will compare results based on imputed data to those based only on subjects who completed the study (this comparison allows for an assessment of the extent to which biases may have influenced study results). Finally, we can analyze data assuming that those subjects who dropped out of treatment had no change in either meaning or psychological distress.

Procedures to control False Discovery Rate (FDR):
One final issue is that of multiple statistical analyses. While the use of MANOVA models decreases the possibility of inflated type I error normally observed when several outcome measures are being evaluated, analysis of the individual dependent variables can also incorporate a multiple comparisons method, such as a the False Discovery Rate-controlling procedure (Benjamini & Hochberg, 1995).

12.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

12.3 Randomization

Participants will be randomized to one of the two 7-week interventions (Individual Meaning Centered Psychotherapy or Supportive Individual Psychotherapy) or the Enhanced Usual Care. After eligibility is confirmed and immediately after consent is obtained, patients will be registered in the MSKCC Protocol Participant Registration (PPR) system and randomized using the MSKCC Clinical Research Database (CRDB), by calling the MSKCC PPR Office at 646-735-8000 between the hours of 8:30 am and 5:30 pm, Monday - Friday.

Randomization is overseen by the MSKCC Biostatistics Service. Randomization will be accomplished by the method of random permuted block, and stratified by two dichotomized variables: 1) baseline Distress Thermometer (4 through 6 vs. 7 through 10); and 2) baseline Karnofsky score (60 through 79 vs. 80 or greater).

Patients who are registered and randomized, but cannot make their scheduled session time (because of conflict or illness) will be placed on a waitlist so they can be offered a spot when they are available in the future, in the same treatment assignment as randomized.

13.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team. The data collected for this study will entered into a secure database, the hard copies of the questionnaires will be kept in a locked, secured location and will only be accessible to study staff. Data will be stripped of any identifying information. A list, matching participants' names and case numbers will also be kept in a secure area at MSKCC. All questionnaire data completed by participants will be identified only with a study code number.

Study findings will be presented in aggregate form only, with no reference made to individual participant's data. The Principal Investigator and his research team will be responsible for identifying, reviewing and reporting all necessary adverse events to the institutional IRB as appropriate. Adverse events are identified through standard, routine protocol review and clinical assessment of each participant in the study. Minimal data set will be maintained in CRDB.

13.2 Quality Assurance

Reports will be generated to monitor patient accruals and completeness of registration data. Data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team.

13.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled ―Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional

committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

This trial is funded by the NCI/NCH and will comply with all of its requirements for Data and Safety Monitoring. This trial sponsor does not have an independent Data Safety Monitoring Process.

13.4 Regulatory Documentation

Participating sites/investigators who are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSKCC.

14.1 PROTECTION OF HUMAN SUBJECTS

Overall, the benefits of this study outweigh the risks. Patients participating in the study will all have the benefit of receiving seven individual psychotherapy sessions provided by trained staff of the MSKCC Psychiatry Service, free of charge, or a targeted patient referral sheet. The risks are primarily related to the potentially upsetting nature of some of the themes that will be raised in the individual psychotherapy sessions or in the self-report questionnaires which ask about mood, depression, hopelessness and end-of-life care issues

Potential Risks/ Risk Management
Some subjects may become distressed or experience anxiety when discussing end-of-life care issues in the individual psychotherapy sessions. In addition, some patients may become distressed or experience anxiety when filling out the self-report questionnaires which inquire about their illness, degree of depression thoughts on end of life care, feelings of hopelessness, pain and physical symptoms, quality of life and social support. All the psychotherapy individual interventions will be facilitated by highly trained, and qualified mental health professionals who have extensive experience with cancer patients and are sensitive to these issues arising during individual psychotherapy. Therapists will be supervised closely by the P.I., a senior clinician with close to 20 years of experience in the psychiatric care of advanced cancer patients. We will also utilize research staff that is experienced in obtaining research information on issues related to cancer illness and its impact, emotional distress, quality of life, and other issues of a sensitive nature. When necessary, subjects who experience psychological distress related to filling out self-report questionnaires will have appropriate care provided by The MSKCC Psychiatry Service.

There will be only one exception to the strict patient confidentiality policy, described above, which pertains to information obtained during the research assessment, which would indicate that the patient is seriously suicidal and may pose a significant and acute risk of self-harm. Subjects will be informed of this exception, and will also be informed such information will be shared with the P.I.

of the study and their attending physician so that timely and appropriate psychiatric assessment and care can be provided by the MSKCC Psychiatry Service.

Benefits
Patients participating in the study will all have the benefit of receiving a 7-week individual psychotherapy intervention provided by trained staff of the MSKCC Psychiatry Service, free of charge or a targeted referral sheet. Moreover, patients who are identified as having a major psychiatric disorder which would preclude them from participating in the psychotherapy study (e.g., untreated severe major depression requiring treatment) will be referred to the MSKCC Psychiatric Service for timely treatment.

Subject Burden
In an effort to minimize patient burden, the assessment protocol has been designed to be as brief as possible in order to gather the required information. The questionnaires take approximately one hour to complete, depending on the individual patient. Research staff will interrupt an assessment if a patient is fatigued or in significant pain. In an effort to ease patient burden, questionnaires can be mailed to patients, read to patients over the phone, or read to patients in person to help with completion if necessary.

Additionally, for patients who express interest in participating in the study but require financial assistance for transportation to/from individual sessions or to complete assessments, a $20.00 travel reimbursement per session will be offered.

14.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

14.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)

- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject‘s condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI‘s signature and the date it was signed are required on the completed report.

Severe distress as a direct result of the intervention, suicide attempt, or expressed suicidal ideation with plan or intent will be considered a serious adverse event and will be reported.

Hospitalizations and death are expected events for all patients involved in this clinical trial; We will not report events that are unrelated to participation in this study.

14.2.1

N/A

15.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign or verbally agree to an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing or verbally agreeing to the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form if the consent takes place in-person. If the verbal consent is used, the consenting professional will sign the attestation page documenting that the proper consent process took place and that the participants agreed to participate in the research project. The participant must receive a copy of the informed consent form.

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17.0 APPENDICES

Appendix A – Pre-Randomization Measures
Appendix C – T1 Questionnaire
Appendix D – T2 Questionnaire
Appendic E – T3 Questionnaire
Appendix F – T4 Questionnaire
Appendix G – EUC Materials-NCCN Guidelines
Appendix H – EUC Materials-Counseling Services
Appendix I – IMCP Therapist Manual
Appendix J – IMCP Patient Manual
Appendix K – ISP Therapist Manual
Appendix L – Treatment Integrity
Appendix M – Study Flyer
Appendix N – Payment Receipt
Appendix O – Study Letters
Appendix P – Study Brochure
Appendix Q – Study Flyer (with tabs)

Appendix R – Optional Weekly Session Rating
Appendix S – Prognostic Awareness Physician Questionnaire
Appendix T - Advanced Care Planning (Chart Review)