Dose-effectiveness RCT of preventive family therapy in advanced cancer: benefits for the bereaved

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DOI: 10.1200/JCO.2015.63.0582

IRB#: 05-120 A(19)

Randomized Controlled Trial of Family Focused Grief Therapy in Palliative Care and Bereavement

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TABLE OF CONTENTS

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This Randomized Controlled Trial (RCT) seeks to test the efficacy and dose responsiveness of a manualized family therapy intervention called Family Focused Grief Therapy (FFGT), which is delivered to families of patients with advanced disease and continued into bereavement. Randomization is to three arms: 6 sessions of FFGT, 10 sessions of FFGT or standard care. The study also explores the potential mediators of effective outcome, empowering further refinement of the intervention, and undertakes an analysis of health-related costs of bereavement care. It is a multi-site study involving Memorial Hospital for Cancer and Allied Diseases (a Comprehensive Cancer Center), Calvary Hospital (a dedicated palliative care hospital with home hospice care program), and Beth Israel (a medical center with a dedicated pain and palliative care department). Consenting families will be assessed at baseline through completion of questionnaires that appraise each individual's psychosocial well-being and perception of their family's functioning. Therapy will be delivered by family therapists (social workers, psychologists and psychiatrists), who will attend regular supervision sessions to sustain fidelity of the model of intervention. Follow-up of family members for psychosocial well-being, perceptions of family functioning and costs of heath-related care will occur at 3, 6, 9 & 13 months after the patient's death or completion of therapy sessions.

Schematic outline of main events and assessment points:

Informed consent of eligible patients & family members; baseline questionnaires & then randomization	<u>Three arms of RCT</u>: 1. 6 sessions of FFGT 2. 10 sessions of FFGT 3. Standard care	Follow-up of family members with outcome measures at 6 & 13 months after the patient's death or completion of therapy sessions; economic questionnaire at 3, 6, 9 & 13 months post death or completion of therapy sessions.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The overall objective of this randomized clinical trial is to test dose responsiveness of FFGT proportional to the level of family dysfunction and baseline level of distress, while also exploring potential mediators and mechanisms of change that contribute to effective outcome, empowering further refinement of the model.

The primary objectives are:

- To evaluate the efficacy and dose responsiveness of FFGT (family intervention) across all subjects and within family types in preventing complicated bereavement and depression compared with standard palliative care among high risk family members of patients dying from terminal cancer.

- To examine whether family type and pre-intervention distress moderate the impact of FFGT.

The secondary study objectives are:

- To evaluate whether family coping and communication mediate the impact of FFGT.

To examine the costs of FFGT and standard palliative care, and to assess whether the additional costs associated with FFGT delivery are offset by reductions in community health utilization and lost work days among family members
The following additional objectives focus on identifying therapeutic processes that occur during intervention sessions that contribute to improved quality of life at the end-of-life (EOL) (e.g., preparedness, closure, support) for participants receiving FFGT:

- **To examine whether changes in family members' cancer-related disclosure during sessions of FFGT are associated with corresponding changes in family members' quality of life at the EOL (i.e., preparedness, sense of life closure, support) .**

- **To investigate putative mediators of the association between in-session disclosure and family members' quality of life at the EOL ..** Specifically, we aim to determine whether in-session disclosure improves EOL outcomes through its impact on two dimensions of family sessions, as evidenced by observational coding of family behaviors during sessions: (1) Safety in the therapeutic system and (2) within-family Collaboration.

- **To examine the moderating effect of therapist characteristics on the association between in-session disclosure and quality of life at the EOL ..** We hypothesize that family member disclosure will be more strongly related to EOL outcomes when therapists evidence the following three skills: (a) engaging the family in the therapy process, (b) facilitating emotional connection and (3) establishing safety.

3.0 BACKGROUND AND RATIONALE

Cancer inevitably affects the entire family. The experience of a life-threatening illness causes considerable stress not only to the patient but also to the caregivers, who share in the grief and associated psychological distress. The family most commonly fills the role of primary caregivers for the patient with advanced cancer or other progressive illness, especially during palliative care. In recent years, there has been growing recognition that the care of a patient with cancer should encompass treatment of his or her whole family. Indeed, Lederberg has gone so far as to depict

family members as 'second order patients' (Rait & Lederberg, 1989), while the World Health Organization's definition of palliative care identifies the patient and family as the unit of care (WHO, 2002). The palliative care movement has embraced the desirability of family-centered care, but has struggled to devise models to do this effectively.

Review of the literature

Distress reverberates throughout the palliative care family, with moderate levels of psychosocial morbidity affecting up to half the patients, one third of their partners and, importantly, one quarter of their adult offspring. While patients' distress was found to be maximal at the time of first recurrence (Silberfarb et al, 1980), the phases of palliative and terminal care appear most demanding for the family (Cassileth et al, 1985). We identified eight studies of distress in the next of kin, with rates between 18 and 34 percent (Buckley, 1977; Plumb & Holland, 1977; Maguire, 1981; Gotay, 1984; Ell et al, 1988; Northouse, 1989; Kissane et al, 1994; Minagawa et al 1996). In six of these, rates approximated one third; moreover, in longitudinal studies, this distress endures for up to 18 months (Ell et al, 1988; Northouse, 1989).

Few studies have evaluated other family members, including children (Cassileth et al, 1985; Ell et al, 1988; Kissane et al, 1994) and parents (Plumb & Holland, 1977). We found a strikingly high level of distress in adult offspring (average age 28; 60 percent female), one quarter of who exhibited "caseness", a standardized marker of clinical concern, on measures such as the Brief Symptom Inventory (BSI) and Beck Depression Inventory (BDI) (Kissane et al, 1994).

Palliative care and the family: Palliative care as a discipline understands the need for family-centered care, but has struggled to find an effective model to accomplish this comprehensively. Higginson and colleagues (2003) recently conducted a meta-analysis of 26 studies of palliative and hospice care teams and contrasted a slightly positive effect size on index patient outcomes [26 studies, weighted mean 0.33, SE 0.12 (95%CI 0.10, 0.56)] with no proven benefit on caregiver and family outcomes [13 studies, weighted mean 0.17, SE 0.16 (95% CI -0.14, 0.48)]. Funnel plots (whose precision increases with sample size) suggested significant publication bias and statistical heterogeneity in studies reporting caregiver outcomes. One large US National Hospice study, for instance, failed to demonstrate an effect on caregivers (Greer & Mor, 1986). A major Norwegian study randomized patients to receive a comprehensive program of palliative care or conventional oncological care and did not find any difference in bereavement outcome despite efforts from the palliative care program to achieve this (Ringal et al., 2001).

A further systematic review on interventions to help caregivers identified 22 interventions, of which 9 focused on single index caregivers (Harding & Higginson, 2003). Provision of information and psychological support were considered priority needs. In the US National Hospice study, complicated bereavement was associated with increased physician utilization (Mor et al., 1985; McHorney & Mor, 1988). Intervention to promote problem solving skills in caregivers was only found to be effective for the distressed sub sample (Toseland et al., 1995). A series of pilot studies of caregivers groups have shown little promise of significant outcome in psychosocial well-being for caregivers (Heinrich & Coscarelli Scrag, 1985; Grahn & Danielson,

1996; Plant et al, 1987; Reele, 1994; Cawley et al, 1988; Robinson et al, 1998; Barg et al, 1998; Horowitz et al, 1996; Carlsson & Strang, 1996). Harding & Higginson concluded that broadly offered individual and group therapeutic interventions for caregivers lacks evidence to support benefit They note that caregivers value self-reliance and independence as important values and therefore, argue that greater promise lies with targeted interventions that identify a significantly distressed or depressed sub sample of caregivers and explore the benefits of intervention on outcome for these high risk individuals.

Family functioning & psychological adaptation: Communication between family members is the presumed method for disseminating information about an ill relative. Medical staff often assumes that such communication is adequate. Yet offspring differed significantly from their parents in their perception of the family's communication ($p < 0.001$) (Kissane et al, 1994) on the Family Environment Scale (Moos & Moos, 1981), tending to view such communication as inadequate. Family communication in the cancer setting was directly examined by Vess and colleagues (1985, 1988) and by Davies and colleagues (1986). Both studies showed the importance of family communication. Vess's study indicated that patterns of communication strongly influenced levels of cohesion and conflict in the family, as did how effectively roles were filled. Davies and colleagues (1986) found that functional coping was characterized by open discussion, mutual empathy, respect between family members, flexible adoption of roles and utilization of community resources.

Development of a family-centered model:
As caregiving has been progressively transferred back into the community, the roles of family caregivers have become more pronounced. The principal caregiver is the spouse in 70 percent of cases, children (daughters and daughters-in-law predominate) in 20 percent, and approximately 10 percent comprise friends or more distant relatives (Given & Given, 1989; Ferrell et al, 1991). The family comprises a fictive kin – namely, whoever the patients say their family is. A family-centered model of care is an essential requisite of responsible services to meet the needs of all the "patients" within the unit of care – the cancer sufferer and their key relatives - and thus to maintain effective support across the palliative care continuum into bereavement.

We believed that a system of classifying families was needed and have now consistently found this typology in 3 cohorts of families. In our previous work (Kissane et al, 1994; 1996a; 2003), we applied well-validated measures of family functioning to a cross-sectional sample of 102 families (342 subjects) and a second, longitudinal cohort of 115 families (269 subjects) and third cohort of 81 families (363 subjects). Each person completed the questionnaires independently, so that they presented their personal view, unbiased by the input of others. Based on three key dimensions of the Family Environment Scale (FES), cohesiveness, conflict, and expressiveness, five types of families were discerned. This classification was both consistent over time (found during palliative care, and at six weeks, six months and thirteen months of bereavement) and predictive of psychosocial morbidity. Particularly, we established that there was a strong relationship between the type of family functioning and the psychosocial status of individual members within the family. When the FES scores for cohesiveness, expressiveness and conflict

are summed (using a reversed conflict score), the total forms the Family Relationships Index (FRI). The short form of the FRI contains four items for each subscale, generating a possible maximum score for the FRI of twelve, which indicates an optimally functioning family in the eyes of the respondent. It is a suitable brief, 12-item, screening tool.

The ability of the FRI to discriminate healthy from unhealthy families has been well established in many studies, and confirmed in our earlier Melbourne studies with high concurrent validity with the family assessment device (Epstein et al, 1983). As a screening tool to detect 'at risk' families with an FRI threshold score of ≤ 9 or a cohesion subscale score of < 4, the FRI had a sensitivity of 0.86 and specificity of 0.45 (Kissane et al., 2003). In using screening tools, it is customary to privilege sensitivity over specificity so that true cases are not missed. Edwards and Clarke (2004) in following 48 patients and 99 relatives across 6 months of cancer care confirmed independently a sensitivity of 1.0 for the FRI to identify dysfunctional families using the FAD as gold standard, and a sensitivity for the FRI between 0.88 and 1.00 to detect beck depression inventory-fast screen "caseness" and between 0.77 and 1.00 for Spielberger State anxiety "caseness" in individual family members across three time points.

Classification of family types: We have applied descriptive names to the five types that form our typology of family functioning. Two clusters are well functioning in their characteristics, *Supportive* and *Conflict Resolving*; two are clearly dysfunctional, *Hostile* and *Sullen*; the final type, which has features intermediate between its well functioning and dysfunctional counterparts, we have termed *Intermediate*.

Supportive families have the characteristics of high cohesiveness, good expressiveness and absent conflict. Typical FRI scores generated by members of this family type are eleven or twelve: four for cohesiveness, four for reversed conflict and three or four for expressiveness. Members are intimate with each other, share their distress and provide mutual comfort. Unbridled conflict is absent from these families as they tolerate negative emotions, honestly disclose feelings and draw confidence from their knowledge of the family's closeness. Approximately one third of families in the palliative care system seem to function in this manner – they exhibit low levels of individual psychological morbidity and function competently in their social world.

Impressively, supportive families express grief openly but without adverse consequences, ostensibly because their cohesiveness facilitates sharing of distress, while at the same time fostering mutual consolation and caring. This pattern is consistent with the clinical observation that adaptive families grieve effectively together (Kissane, 1994). Further observation of family coping style via F-COPES (McCubbin et al, 1985) revealed that supportive families made regular use of mature coping strategies such as the use of community resources, social support and optimistic reframing of their predicament.

Conflict Resolving, the second type of well functioning family, exhibits moderate conflict, but high cohesiveness and above average expressiveness. Members carry low rates of psychosocial morbidity and the lowest levels of grief intensity. Approximately one fifth of families seem to have this pattern during palliative care. We surmise that their closeness and open communication are protective, providing the means to resolve differences. A degree of conflict is permissible for families to remain well functioning, but the key is surely the family's ability to tolerate this difference of opinion with respect, not unbridled conflict.

By contrast, the *Hostile* family is the most dysfunctional, characterized by high conflict, low cohesiveness and low expressiveness. Typical FRI scores lie in the range zero to four, with cohesiveness zero to one, expressiveness zero to one and reversed conflict score zero to two. Hostile families are fractured and chaotic, with members sometimes refusing to speak to each other for several years. They have the highest rates of psychosocial morbidity. Hostile families' scores on F-COPES are poorest, with members least able to make use of community resources, social support, cognitive reframing strategies or use of religion. Approximately six percent of families fall into this category during palliative care, but this rate doubles during the early months of bereavement. They need a defined treatment plan, strong working alliance with clinicians and increased support to contain their conflict and help them to focus on the tasks at hand.

We have termed the second type of dysfunctional family *Sullen* because of the muted anger and high rates of clinical depression found amid their members. These families are characterized by reduced cohesiveness, mild to moderate conflict and poor expressiveness, an across-the-field reduction in each dimension of family functioning. They display intense levels of grief during bereavement. Typical FRI scores for this type of family range from four to seven, with cohesiveness one to three, expressiveness one to two and reversed conflict one to three. Members show substantial psychosocial morbidity, just less than hostile families, but have the highest rates of depression (sometimes thought of psychodynamically as 'anger turned in'). Interestingly, sullen families exercise the highest level of control over family life, with greater rigidity and conformity to family expectations. In this compliant way, they are less dislocated than their hostile counterpart, but expression of genuine feelings may be blocked. They distinctly differ from hostile families on F-COPES, in seeking assistance, appearing needy and making the greatest use of community resources, social support, cognitive reframing and religion of all the family types. Roughly nine percent of palliative care families have sullen functioning, but this rate also doubles to 18 percent over the early months of bereavement.

The final class of family, *Intermediate*, is characterized by moderate cohesiveness, but they also carry high rates of psychosocial morbidity. Typical FRI scores range from seven to nine, with cohesiveness in the range three to four, expressiveness one to three, and reversed conflict three to four. Members within this cluster have the lowest levels of achievement orientation (an FES subscale reflecting personal ambition) and control over family life (the extent to which rules are used inflexibly). These characteristics bolster the validity of this cluster as a discrete group. Individuals in these families carry more symptoms of depression and anxiety and function less well socially than do well functioning families. Although they do not demand attention, they have

middling characteristics as "battlers", and could be regarded as families with potential and easily helped. Approximately one third of families display this type of functioning during palliative care.

Clinical utility of this classification: We hasten to add that we have never intended these names to be shared with the family. We do not label families clinically, which would not only be pejorative, but potentially harmful. They are predictive but not diagnostic categories. Nonetheless, the categories have utility in testing clinical theory. Health professionals can talk with a family about concerns over their functioning but would use the family's language to do so.

The classification was remarkably consistent across the four time points through to 13 months post death in repeated measures multivariate analyses. Its strong association with the individual psychosocial morbidity carried by family members pointed to its utility as a means to better recognize those at risk. It gave us a means to screen families and preventively intervene with those at risk using an empirically developed model, FFGT.

Economic analysis of psychotherapy and family therapy interventions: An important concern in the development of new medical and behavioral interventions is the economic cost of such programs. Methods of cost-identification, cost-effectiveness, and cost-benefit analysis, commonly used to evaluate the costs and outcomes of new medical technologies and health care programs, have also been applied to mental health interventions. Economic evaluations of psychotherapy interventions have focused predominantly on the treatment of affective disorders and schizophrenia (Gabbard et al., 1997). Economic assessments of family interventions have been limited to analyses of family therapy for schizophrenia (Langsley et al., 1968; Cardin et al, 1985; Tarrier et al., 1991) and family counseling for juvenile delinquency prevention (Lipsey, 1984).

Economic assessment of a family-centered intervention typically involves the estimation of intervention costs as well as potential cost offsets, such as reductions in both health care utilization and in lost productivity (Pike-Urlacher et al., 1996). Methods of estimating these economic inputs and outcomes have been well-described in the health economics literature (Drummond et al., 1997; Berger et al., 2001) and will be applicable to our evaluation of FFGT.

Identifying mechanisms of change:
Although the general objective of this study is to determine the efficacy of FFGT in preventing distress, we are also interested in learning about *how* families benefit from this kind of intervention – that is, what are the 'active ingredients' of the intervention itself. We therefore examine putative mechanisms by which conjoint family sessions help family members and patients achieve desired EOL outcomes.

Previous studies on end-of-life care have elicited patient and family perspectives on what constitutes a "good death" (Steinhauser, Clipp, et al. 2000). In addition to pain and symptom management, patients and caregivers described relational experiences that were valued at the end

of life, such as spending time with family, confiding in loved ones, saying goodbye, and ensuring that the family is prepared for the future (Steinhauser, Christakis et al. 2000 & Steinhauser, Bosworth et al. 2002).. A measure derived from these patient and caregiver accounts was validated by Steinhauser and colleagues (2002). This measure, the Quality of Life at the End of Life scale, is used in the present study to assess the range of concerns and experiences specific to the end of life phase, prior to the patient's death. An objective of the current study is to examine what therapeutic processes help families achieve these end-of-life outcomes.

Communication is recognized to play a vital role in the quality of end of life experiences among patients and their family (King, et al.2006). FFGT is designed to foster better communication (i.e., disclosure) among family members about cancer-related concerns and anticipated loss. However, the hypothesis that increased communication *among family members* will yield improved EOL outcomes remains largely untested. We therefore test this assumption by examining whether in-session disclosure about cancer-related concerns is associated with improved quality of life at the end of life. Family members are asked to report on how much they feel was disclosed at the end of each session. We further examine mediators and moderators of this association. Prior research on change mechanisms in family therapy has identified two dimensions of family therapy shown to be predictive of outcomes: (1) Therapeutic safety (i.e.,comfort with open communication within family sessions) and (2) Within-family collaboration (i.e., shared sense of purpose and cohesion within family sessions) (Friedlander, et al. 2008).. We hypothesize that in FFGT, cancer-related disclosure will bear its impact on EOL outcomes through systemic changes in family collaboration and feelings of safety. **We will measure these features of the intervention by using an existing, validated observational coding instrument to rate family behaviors in recorded sessions.** To further explore the conditions under which family members are most likely to benefit from cancer-related disclosure, we will examine whether specific therapist skills (engagement, emotional connection and safety with family) moderate the effect of in-session disclosure on EOL outcomes. **These therapist skills will also be measured using an existing observational coding instrument.**

Preliminary Studies:
In our phase 1 study of FFGT in Melbourne, Australia, 81 families gave informed consent, generating a cohort with 41 (176 individuals) intermediate families, 21 (96 individuals) sullen families, and 19 (81 individuals) hostile families. The socio-demographic characteristics of patients (and illness details) and relatives have been published (Kissane et al, 2003). Randomization in a 2:1 ratio assigned 53 families to intervention and 28 to control. Within the intervention arm, 45 (85%) families commenced FFGT, 2 withdrew after 1 session and 3 withdrew prior to termination, 40 (75.5%) families completing therapy fully. With the length of therapy titrated to apparent family need, the mean number of sessions was 7.

The global impact of FFGT analyzed on an intention-to-treat basis was a significant reduction in distress (BSI) at 13 months post bereavement [difference in change 0.11 (95%CI -0.01, 0.22), p = 0.02], with a small effect size of 0.26. However, effect sizes were greater for sullen families (d = 0.32) and smaller for hostile families (d = 0.18). Significant improvement in distress and

depression were also demonstrated for individuals with the top 10% of BSI and BDI scores at baseline. The effect size for the global reduction in BDI at 6 months post-death was a respectable 0.44 for sullen families and 0.30 for intermediate families. (Kissane et al, in press)

Sullen families appear to be the class most readily helped by FFGT. Our earlier work highlighted their interest in seeking help on F-COPES (Kissane et al, 1996) and their high rates of psychosocial morbidity. We omitted use of F-COPES in our recent RCT, but reintroduce it here to better explore its mediator effect on family outcome. Although the small numbers of sullen families with members carrying high distress at baseline limit definitive conclusions, our results offer preliminary evidence that this is the subgroup most suitable for a preventive family intervention.

For intermediate families, FFGT offers a modest but worthwhile prospect of benefit. Conflict tends to worsen in control families in this class, while those receiving FFGT improve, particularly across the first 6 months of bereavement. Distress is correspondingly reduced.

Our containment of hostile families may have been limited by an insufficient length of therapy for some. We will therefore examine this directly in this study through formal variation in the treatment dose between 6 and 10 sessions of intervention length. Moreover, hostile families tend to be help-rejecting (Kissane, et al. 1996). We have therefore extended our manualized therapy to explicitly explore any help-rejecting dynamic through examination of the advantages and disadvantages that such behaviors confer on the family. At the same time, we have increased emphasis in the manual and our training program about therapists being respectful of the need for distance between members of hostile families, their separation being a potentially homeostatic solution to conflict. This is a necessary caveat to avoid causing harm.

Importantly, no significant association was evident between the therapist who delivered FFGT and the outcome achieved, providing evidence that the model of therapy was, indeed, is generalized in being able to be taught to and delivered by a variety of family therapists.

Theoretical model underpinning FFGT: Our research has been guided by two theories relevant to bereavement: attachment theory (Bowlby, 1979) and cognitive processing theory in adaptation to trauma (Creamer et al, 1992). Attachment theory informs the relational nature of loss, ‘continuing bonds’ and adaptation in bereavement (Shaver & Tancredy, 2001), such relationships being concentrated socially in the family’s circle. Stroebe and Schut (2001) have emphasized the dual process model of such adaptation with loss-oriented and restoration-oriented components evolving in parallel. Thus, while emotional expression about the impact of the many losses associated with the illness and death is shared, coping responses are activated as members strive to re-establish some order and continuity in their ongoing lives. Our FFGT model facilitates both elements of the dual-process model through inviting sharing of grief alongside improved family functioning, in which communication, co-operation and mutual support are enhanced.

Successful cognitive processing involves achieving an understanding of the events, with modification of the person's assumptive world (Parkes, 1972 & 1998), a schema of ideas, values, attitudes and beliefs that each person organizes about their life in the world. Illness and death, like other trauma, disrupt this schema. At the family level, emotional disclosure and social sharing impacts on members' assumptive world views (Janoff-Bulman, 1992; Janoff-Bulman & Berg, 1998), leading to cognitive processing as positive and negative appraisal processes and confrontation/avoidance strategies unfold within the family. Family functioning through the family's basic communication processes and negotiation of differences impacts dynamically on members' cognitions. Families challenge negative rumination and model a pathway to finding positive meaning (Folkman & Moskowitz, 2000).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Study Design

A randomized controlled trial will compare intervention with FFGT and standard palliative care delivered to a cohort of 'at risk' families who have a relative receiving treatment for advanced or terminal cancer. Identification of eligible families will be based on routine screening for family functioning that has been introduced on admission to the collaborating services and extended into a routine family meeting that occurs shortly after this admission so that families are informed and educated about approaches to care provision. This psycho-educationally directed family meeting has been manualized and includes an information booklet about palliative care in an effort to standardize the baseline at study entry through optimizing the uniformity of this approach at each service. This phase of the study works to actively break down barriers to family assessment and care provision through this routine screening and educational approach that is normalized as our standard of practice.

A key feature of this design is its focus on 'at risk' families and, through this, an ability to reach 'at risk' individuals. This follows the principle of respecting well functioning families who have the internal resilience and wherewithal to cope independently with the challenges of illness and care provision for a dying family member. It also avoids a prominent methodological difficulty with many palliative care studies whereby an intervention is offered to all, and resultant effect sizes are small and fail to demonstrate benefit from the global approach. Targeted model is consistent with the philosophy, for instance, of prescribing analgesic medications only to those in pain, rather than to all patients. Screening the whole family during attendance at an educational meeting provides the means to both recognize and invite those in special need to join a study that seeks to explore the most responsive way of offering help. A stratified randomization process will assign families to 0, 6 or 10 sessions of FFGT and the usual palliative care delivered to each arm will be carefully monitored by an independent research study assistant blinded to the randomization status.

We define an i*ntermediate* family as a family where at least one member has a score on the FRI of 8 or 9. A s*ullen* family is defined as a family with at least one member having an FRI score of minimum score of 5 and not above 7; and finally, a *hostile* family is a family where at least one member scores a minimum of 0 and a maximum of 4 on the FRI scale.

Responding to the unique needs of palliative care populations, our therapy model was first developed with a degree of flexibility in terms of length of therapy or number of sessions, although the principle of assessment, active treatment, and consolidation and termination sessions was consistent. However, by now randomizing each family type to receive therapy of either of two prescribed lengths [either 6 sessions as the minimal dose or 10 sessions as a maximal dose]; we can explore the effect size achievable through differing treatment doses. In the process, we can examine the relationship between the dose of treatment and complexity of family issues to determine the optimal length of therapy needed to generate a satisfactory outcome for the family members involved.

The timing of death of the index family member is ultimately unpredictable. Defining a uniform post-treatment assessment point is thus impossible; this methodological challenge is overcome by standardizing outcome measurement related to the point of death, selecting 6 and 13 months post death as longitudinal follow-up points, the former being past the peak phase of bereavement distress across the first 2-4 months and latter being deliberately selected to avoid the anniversary phenomena of bereavement. In circumstances where patients live well beyond their predicted prognosis [5/81 (6.2%) patients remained alive in our preliminary study], longitudinal follow-up will correspond to 6 and 13 months beyond termination of their FFGT therapy. Where the estimation of prognosis has proven inaccurate, the trigger for the fallback position of follow-up occurring 6 months post-intervention would be that the patient is still alive at six months post-intervention.

The primary outcome analysis will involve a comparison of distress (BSI) and depression (BDI) scores for individual family members. In this sense, a family model is being applied to benefit vulnerable individuals, and those individuals with high baseline distress will be a component of secondary analyses. Other analyses will examine whether type of family functioning and family coping style mediates the primary outcome findings, while cost analyses will provide further insight into the relative utility of each model of care.

4.2 Intervention

Interventions: The FFGT intervention will have assessment, focused therapy, consolidation and termination phases. The first two sessions are assessment sessions and occur one week apart. There will be two or six focused intervention sessions depending on the predetermined length of therapy. The first focused intervention session is approximately two weeks after the last assessment session. Subsequent focused intervention sessions are expected to follow once every month. Finally, there will be two consolidation/termination sessions, which will occur one time each, approximately two months apart. The six session program is expected to extend over a

period of 6 months and the 10 session program over 10 months. The three phases of therapy are planned according to the following summarized schedules. The FFGT manual is attached as Appendix D. Considering that the families are in a period of stress and change, therapy sessions may not always occurred as planned, however all reasonable efforts will be made to adhere to the session schedule.

6 Session Schedule

	Assessment Phase of Therapy		**Focused Therapy**		**Consolidation and Termination Phases of Therapy**	
Session #	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24**
1	X					
2		X				
3			X			
4				X		
5					X	
6						X

10 Session Schedule

	Assessment Phase of Therapy			**Focused Therapy**					**Consolidation and Termination**	
Session #	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**
1	X									
2		X								
3			X							
4				X						
5					X					
6						X				
7							X			
8								X		
9									X	
10										X

FFGT goals

FFGT is a manualized, time-limited, focused intervention in which the family is the recipient of care and grief and family functioning are its predominant themes. Its focus is on two major goals: to improve family functioning and promote adaptive grieving. The first objective is relational and is explored through attention to cohesion, communication and conflict resolution. The second is intricately interwoven since sharing of grief is dependent upon effective communication. Family solidarity helps to counter aloneness, one of the most painful aspects of mourning. Strengths of the family are particularly affirmed as a pathway to harness relevant change in family functioning. A 'coping with cancer' and later 'coping with bereavement' focus is sustained to avoid being drawn into long standing problems that lie beyond the scope of this brief intervention.

Application of the model is dependent on the therapist achieving engagement through identification of relational issues or concerns, which the family then owns and agrees to target as the focus of their work together. Active problem solving, conflict resolution and acknowledgment and sharing of grief are the mainstay of the focused treatment. Change is affirmed in the consolidation phase, with response prevention strategies considered during termination.

The manual lays down conditions for the safe conduct of therapy in the home, the therapist selecting a neutral clinical office at the study site when these conditions are not met. Contraindications to therapy in the home include high family conflict (initial assessments of hostile class families), marked geographic disadvantage to the therapist and unsuitable environment. Liaison with the home care nurse provides ready information. We anticipate over two-thirds of the therapy occurring in the family home. When family members wish to be involved in therapy but are unable to present due to geographical inaccessibility, family members may participate in therapy via speaker phone. In the event of a patient's death during the intervention, the patient's family is expected to continue with the family focused therapy sessions as planned.

Session outline

Session 1. After identifying the hopes and expectations of family members for FFGT, the story of illness with cancer becomes the opening theme, including the emotional journey of each family member, understanding of the cancer treatment goals and prognosis. As data is collected, the therapist assesses family communication, cohesion and conflict. Roles, rules, values and beliefs are explored. The therapist makes use of open-ended or strategic, linear or circular questioning to glean information – 'questioning' is the primary mode of therapist intervention - and of offering summaries back to the family of what the therapist has understood so that consensus is reached with the family about their style of relationship. The manual provides lists of potential questions to explore all of the above.

Session 2. If a trans-generational picture of the family with attention to patterns of relationship and of coping with loss was not completed in session 1, this continues the assessment in the early part of session 2. Family strengths will receive special focus. Again, a summary of all that has been learned about the family is used to highlight strengths and to gain agreement about identified concerns, so that options for treatment can be considered and family consensus negotiated. A plan and timetable of focused treatment is then agreed upon.

Sessions 3-8. The agreed foci of family relationship issues are targeted with promotion of open communication, teamwork and conflict resolution. The family's ability to accept difference of opinion and reach a negotiated compromise to issues that cause conflict is promoted with formal problem solving strategies being taught. Themes of care provision, intimacy, the emotional challenge of suffering, discussion of death and dying, saying goodbye, the role of culture, religion or ritual, historical or trans-generational influences, and how the family shares grief are woven into these relational reviews and are all discussed as described in the attached manual. Summary and affirmation of progress, with balanced attention to family strengths are strategies common to every session. Progress with the agreed concerns is assessed and affirmed at each session.

Where a 6 session model is being applied, only 2 sessions focus on these agreed concerns, before time between sessions is extended to 8 week intervals as consolidation and then termination are moved towards. In contrast, with 10 sessions of therapy, an additional 4 sessions of focused work are incorporated, so that a sustained focus of endeavor is directed to the targeted concerns, before the consolidation & termination.

Last 2 Sessions. Progress is again reviewed, success affirmed and the re-emergence of old patterns acknowledged. Response prevention strategies are discussed. Hopes and expectations for the future are considered as the family is prepared to terminate therapy. Loss of therapy is grieved similarly to loss of the deceased family member; the family is left with reminders of its strengths, achievements and future hopes.

Usual care

Families assigned to the Usual Care Condition will receive standard psychosocial care which is based on the following patterns: Social work consultations are routinely provided to the cancer patients, but relatives are only seen during admissions or upon request. Referral to a psychologist or psychiatrist is provided if requested or thought clinically appropriate by treating clinicians. The study involves several research study assistants. Our follow-up procedure will assign a research assistant blinded to randomization to monitor through a standardized review process all such care received, including local community family doctor and specialist care and medications prescribed across both randomization conditions so that the impact of such potential confounders can be controlled for in outcome analyses.

We anticipate that 30% of patients will die at home and 70% will die in hospital. Place of death and time of death after randomization will therefore be ascertained so that these can be controlled for in data analyses.

Training procedures: Therapists will be drawn from the disciplines of psychiatry, psychology and social work and have achieved appropriate training within their discipline as a family therapist. Each therapist being engaged in this study will go through the following further training to ensure uniform understanding and application of the model of therapy as standardized and manualized for this trial.

Firstly, a therapist's workshop on FFGT will be delivered by Drs. Kissane, Zaider and Lederberg, who in turn will sustain supervision of this therapy throughout the study. Use is made of experiential role play in these workshops. Therapists will read and fully familiarize themselves with the appropriate manual. Each therapist will treat a family off study with the model of therapy, presenting process notes made from each session's audio-recording to the supervisors in a peer review group format. A fidelity assessment as described later will be made by staff of the MSKCC Psychotherapy Laboratory of this pilot work to establish competence with and adherence to the prescribed model. Training will be repeated until competence is established. Therapists will then be randomly assigned families in the RCT.

Five family therapists are trained in FFGT at MSKCC during January to July 2005 period and a further five will be trained from September 2005 to March 2006, drawing on staff and trainees of the Ackerman Institute through collaboration with its director, Dr. Ivan-Imber Black. Both Calvary Hospital and Beth Israel have social worker / family therapists, resulting in a team who will be with us during RCT. Additionally, we trained another 8 therapists in August 2008.

Supervision procedures: Continuing supervision will occur through weekly peer group supervision sessions for the therapists throughout the life of the study to ensure their continued conformity to the model. Each therapist will be invited to firstly listen to their previous session's audio tape, and to prepare a summary of process notes on the session (typically 3 pages long), including their formulation of issues, key interventions and perceived outcome. These process notes form the basis of material presented at twice- weekly peer group supervision sessions and form a complementary record of the therapy alongside audio tapes of sessions.

Treatment fidelity: Tapes of thirty percent of sessions will be randomly selected (but balanced between assessment, intervention and termination phases of intervention) to be rated for treatment integrity by two independent raters. Raters will be trained in assessment and use of the coding manual using tapes from pilot sessions and original Australian study. Weighted means of the percentage agreement for items within domains of integrity measure will be used to assess interrater reliability. To protect against therapist drift, treatment integrity ratings will be made six-monthly throughout the period of therapy within the study, feedback being provided to therapists and supervisors. Raters will be blinded to the therapist, required to achieve >80% inter-rater reliability, and will employ the following treatment integrity scales:

The *FFGT Treatment Integrity Measure* codes for content and process of therapy across the assessment, focused intervention and termination phases of family treatment (Chan et al, 2004). Its content items cover planning goals of therapy; understanding the family's style, history, ideology and strengths; and addressing key themes. Process-based domains include providing reassurance; problem solving and assisting the family; providing direction to sessions; maintaining the agreed focus; building rapport; and terminating therapy. Eleven items code the number of questions asked on specific themes. As not all themes are relevant to specific families, where not identified as a 'key concern' and thus not discussed, the item is coded as *not applicable* (N/A). The total item numbers for the assessment, intervention and termination subscales of the FFGT integrity measure are 35, 23 and 28 respectively (see Appendix D). Although items are generally therapist-oriented, because FFGT is a dynamic group process, some reflect family-as-a-whole behaviors. A coding manual (see Appendix E) defines each item of the integrity measure, including explicit guidelines for rating that item, exemplars of behaviors that should or should not be considered, and important distinctions between items.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

The proposed research is a collaborative, multidisciplinary effort between investigators at Memorial Sloan-Kettering Cancer Center (MSKCC), Calvary Hospital (Calvary), and Beth Israel Hospice Program (Beth Israel). Expertise includes Family Therapy, Nursing Social Work, Palliative Medicine, Health Economics, Psychiatry and Behavioral Sciences and Statistics. A minimum of 165 families from three participating sites will be included in this study. All patients with advanced cancer entering palliative care are eligible to participate. Patients will be recruited from Calvary Hospital's inpatient, home care and hospice programs, MSKCC inpatients & outpatients, and Beth Israel's hospice program and Pain and Palliative Care Department. Highly trained research study assistants will be recruiting participants, mostly from referrals and some from our study brochure/poster (see Appendix O).

5.1 Subject/Patient Inclusion Criteria

- Individuals with advanced disease/ Stage IV cancer who may be involved in palliative care treatment program
- Individuals with a poor prognosis

5.11 Patient and Family Member Inclusion Criteria

- Per investigator's judgment participants must have satisfactory cognitive functioning to provide valid informed consent and participate in family therapy.
- In the event that the index patient is declining or too frail to take part in family meetings, the family is able to participate without the index patient being involved in the study.

- For every enrolled family there must be at least 2 family members willing/ able to take part at the time of recruitment.
- The presence of FRI screening scores of ≤ 9 or cohesiveness subscale score < 4 based on the perception of any single family member, including the patient.

5.2 Patient and Family Member Exclusion Criteria

- Inability through language to complete the study questionnaires – inability to speak English with an English-speaking therapist.
- Age less than 12 years for a child.
- Patient and family member determined geographical inaccessibility to attend family sessions.
- Significant psychiatric disturbance sufficient, in the investigator's judgment, to preclude participation in a psychotherapeutic intervention.

6.0 RECRUITMENT PLAN

For Calvary Hospital, from 2,719 inpatient admissions in 2003, 714 survived greater than one month; for their home care program, from 513 admissions, 243 lived greater than 1 month; for their hospice program (average LOS 47 days), from 673 admissions, 285 patients remained on the program > 1 month and 52% died at home. Geographic county distribution for all Calvary patients was Bronx 37%, Queens 22%, Manhattan 14%, Brooklyn 14% and Westchester 12%. Better cognitive functioning is associated with longer stay. Thus combining hospice and home care programs at Calvary provides approximately 528 available community patients annually. Recruitment from both the inpatient and hospice/home care programs at Calvary hospital would offer 1242 patients annually with a length of survival of > 1 month.

For Memorial Hospital, its Palliative Care outpatient clinic had 1272 patients in 2003, of whom 342 unduplicated patients survived > 1 month; its inpatient Palliative Care Service had 78 admissions, with 60 patients surviving greater than 1 month. Therefore, 402 patients per annum would be available for recruitment with an estimated prognosis of > 1 month. From these, geographically accessible catchments include Manhattan 21%, Brooklyn 24%, New Jersey 12%, and Bronx 5%.

For Beth Israel Medical Center, its inpatient Palliative Care Service is comparable to MSKCC and Calvary Hospital.

Thus combining these 3 sites, more than 1644 patients would be screened annually for study eligibility, with more than 1329 residing in geographically accessible areas, an amply large pool of patients for study recruitment.

Routine screening with the Family Relationships Index (FRI) will occur at each collaborating study site and be administered by the nurse, social worker or admitting clinician as part of the routine initial assessment. This 12-item, true-false response format screening scale is derived from the short form of the Family Environment Scale (Moos & Moos, 1981) and has 3 subscales informing family function: cohesiveness (4 items), a measure of family connectedness and teamwork; expressiveness (4 items), a measure of communication of both thoughts and feelings; and conflict (4 items), a measure of expression of anger and hostility. The FRI score is derived from the sum of cohesiveness, expressiveness and the reversed conflict score. The short form has high correlation with its longer version and the FES has been used in over a thousand studies across more than 20 years.

The FRI scale will given to the patient and all available family members on a handheld tablet along with other Pain and Palliative Care Service assessments during the initial outpatient visit. The nurses will administer this questionnaire on the inpatient floor as well. The routine use of FRI screening and a routine introductory family educational meeting at each service breaks down the barrier of accessing families and recognizing those 'at risk' of a morbid outcome. With each collaborating site conducting a routine family informational and educational meeting for all available family members during the early phase of admission to the service, we have standardized the content of these sessions based on Hudson's work (Hudson et al, 2002) (see Appendix C). Nursing in-service training will be conducted at each site by Dr. Nessa Coyle to achieve uniformity and this in-service will be repeated every six months across this study. Our goal here is not to study the educational benefits of this family meeting, but to standardize baseline care as much as possible across sites and use the routine family meeting to overcome the barrier to screening reaching all family members. The FRI is administered in this session to any family member that has not previously been reached through the admission process.

Once the patient and family members complete the scales, the computer will generate the score. The FRI scores of less then or equal to 9, or a total score of above 9, but with a score less then 4 on the cohesiveness scale indicates potential eligibility for enrollment in the trial. The facilitator of the family meeting will provide information about the study and gain permission for the site research study assistant to make contact. Thus, the facilitator will be trained to comment about the FRI: "As a group you indicate good levels of communication, co-operation and teamwork. We're impressed by how well you work together as a family, and believe that this will prove to be a great source of support to [name of patient]." Or "We notice that some of you feel in your questionnaire responses that family communication [or family conflict] [or family teamwork] can be a challenge at times, and therefore we'd like to take this opportunity to tell you about a study we are conducting to explore better ways of assisting families as they strive to support their ill family member."

Eligible families will be given information about the clinical trial for each individual member, and will be contacted by the research study assistant to ascertain their interest in joining the study. Each individual family member will complete the informed consent and research authorization. As long two or more family members are consenting, the family is accepted into the study. Some

families will have some non-consenting individual members, their reasons for refusal being noted. This does not prohibit a family approach as systemic theory has long recognized the benefits of family intervention reaching indirectly to members choosing to not attend family sessions. Family members absent from the first meeting will be contacted by mail or phone regarding the study. Individuals interested in participating will either be consented face-to-face or by over the telephone. A copy of the informed consent and research authorization will be provided to all participants regardless of consent method. We have used these procedures successfully in prior studies, and learned that outreach by the telephone to adult offspring (with permission from their parent, the patient) is important to achieve their recruitment.

Once the informed consent is obtained, families will be randomized into one of three groups and family therapists will be assigned to conduct therapy sessions.

Family members will be reimbursed a total of $30 for any traveling or parking expenses related to attending therapy sessions.

In addition, individual participants will receive reimbursement in the sum of $25 after completing a 6 month follow up assessment and an additional $25 upon completion of the final 13 month assessment battery. This reimbursement will be given to all participants regardless the randomization (therapy arm vs standard care).

For clinical purposes, a family member is any and every person identified by the patient as belonging to the family. The construct of their 'fictive kin' allows for household residents of any gender, and includes married partners, de facto spouses and members of an extended family or friends who are designated to be close and relevant to care provision for the index patient. Partners, co-residents of a house or apartment, children and their partners, siblings, living parents, ex-spouses, relatives visiting from overseas and close friends would be eligible. The theoretical model presented by attachment theory suggests that the closer the relationship in life, the greater the propensity for grief in bereavement. Accordingly, our goal is to recruit the direct membership of the nuclear family of the patient with cancer firstly, and relevant members of their family-of-origin secondly. Representation of typically two generations and often three is achieved routinely. However, the principle of inclusivity prevails whenever the patient identifies an individual as close and hence worthy of incorporation as 'fictive kin'.

In most cases, the initial contact with prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined 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 seek 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) reviewing results of screening of patients and family members with the FRI, whether this is drawn from outpatient screening, screening at the time of inpatient admission or screening during a routine family informational and educational meeting; (3) conversing with

patients regarding possible enrollment; (4) handling of PHI contained within those records and provided by the potential subjects; (5) maintaining information in a screening log of patients approached.

In summary, routine screening with the FRI will be administered on a handheld tablet or using the paper version during the initial outpatient visit, inpatient admission process or routine family education session. All family members present on such occasions will be invited to complete the survey. If the scores indicate potential eligibility, the study will be introduced to eligible patient and family members, and an informed consent will be obtained from each person. In the event that not all family members are present at this time, patients will be asked to identify other family members, who will be contacted with regard to the study and informed consent will be sought for participation. Once consented, the families will be randomized into one of the three therapy arms and a therapist will be assigned.

7.0 ASSESSMENT/EVALUATION PLAN

Feasibility and Study Time Line: During 2005, each site will be receiving training in screening with the FRI, initially as pencil and paper tests, and hand held tablet screening with the FRI is planned for introduction and training in Oct.-Dec. 2005, drawing upon the experience of Dr. Ostroff. Nursing standardization of a routine family education session will be coordinated from September to December, 2005 with particular training assistance from Dr. Nessa Coyle. Finally, training of FFGT therapists has been proceeding with pilot family cases since early 2005.

Study accrual will proceed across the first 5.75 years of the study, so that therapy can be concluded during the first half of year 5 and follow up of participants concluded in the second half of year 5. Initial training of study research assistants will occur over the first two months of the study, while independent and masked assessors of FFGT fidelity will be trained and undertake rating appraisals every six months during years 1-4.5, thus providing regular feedback about uniform application of the model to avoid drift. Supervision of the therapy will take place weekly throughout the intervention phase of the study.

Pre-study year (2005): FFGT interventionists' and nurse educators' training.
IRB approvals at sites.

Years 1-2	Months 1-3: training of RSAs and initiation of recruitment. Completion of supervision of pilot family therapy. Months 4-24: active recruitment of subjects.
Years 2-3	Recruitment until year 5.75, active therapy continuing thereafter
Year 4-5	Completion of FFGT intervention and follow-up
Year 6	Completion of follow-up, data analyses and write-up.

Baseline assessment. Each consenting family member (including the patient) will complete measures of demographics, preference for treatment, distress (BSI), depression (BDI), social adjustment (SAS), family functioning (FES, FAD), family coping (F-COPES), and quality of life at the end of life (QUALE-M).

Support of therapists. Research study assistants will facilitate the set-up of family sessions and provide support to therapists through phone calls to family members the day before a session to confirm attendance.

Recording of interventions. All sessions of FFGT will be audio or video recorded; training, supervision and fidelity studies will be described below.

Follow-up assessments. This is standardized to occur for all relatives of the ill patient at 6 months and 13 months after the patient's death, the latter time period being deliberately after the anniversary of death. They will complete BSI, BDI, SAS, FES, FAD, F-COPES, the bereavement phenomenology questionnaire (BPQ), QUALE-M, and a measure of attendance at clinicians (family doctors, internists, specialists, psychologists/psychiatrists/social workers), bereavement groups, comparative alcohol usage and use of medications (psychotropics in categories of anti-depressants, tranquilizers or hypnotics). Where the estimation of prognosis has proven inaccurate, the trigger for the fallback position of follow-up occurring 6 months post-intervention would be that the patient is still alive at six months post-intervention. In the event that the patient survives longer than anticipated, the follow up assessments will be done at 6 and 13 months post completion of therapy sessions. For standard care families where the patient survives 8 months post baseline (the average therapy length) we will administer follow up questionnaires to the family 3, 6, 9 and 13 months post this 8 month survival date. Patients and family members who are randomized to receive therapy (6 or 10 sessions) will also be asked to complete brief questionnaires immediately following each meeting in order to elicit feedback on their satisfaction and experiences with the intervention session. These so-called 'intervention process' measures are described below and include the FTAS, FSDM, PANAS and QUALE-M.

Cost data collection and service utilization. Economic assessments will be completed in person or by mail at the planned evaluation times (baseline, 6 months, and 13 months post death or completion of therapy sessions). In order to minimize problems with recall, we will also administer the economic assessment by telephone on 2 intervening occasions (3 months and 9 months post death or completion of therapy)

8.0 TOXICITIES/SIDE EFFECTS

Psychological Risks. Some subjects may become distressed or experience anxiety when discussing cancer related emotional issues in the psychotherapy sessions. In addition, some patients may become distressed or experience anxiety when filling out the self-report questionnaires that inquire about their illness or their family member's illness. All the psychotherapy sessions will be conducted by highly trained, and qualified mental health professionals who have extensive psychotherapy experience with cancer patients and are sensitive to these issues arising during psychotherapy.

In the event that a participant experiences distress to either the interventions or filling out self-report questionnaires, they will be referred for to the MSKCC Psychiatry Service for care. There will be only one exception to the strict patient confidentiality policy, described below, 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 so that timely and appropriate psychiatric assessment and care can be provided by the MSKCC Psychiatry Service.

9.0 PRIMARY OUTCOMES

Measures	T1 Baseline	3-month	T2 6-month post death	9-month	T3 13 months post death
FRI (screening only)					
FES	√		√		√
FAD	√		√		√
F-COPES	√		√		√
BDI	√		√		√
BSI	√		√		√
SAS	√		√		√
BPQ			√		√
Economic and Medical Information	√	√	√	√	√
The Complicated Grief Assessment-Self Report (CGA-SR)			√		√
Medical Assessment Form	√				
Process Measures (therapy only)	After each therapy session				

Measures:

The questionnaires take approximately 40 minutes to complete. The length of the questionnaire depends on the time point of follow up. The following are measures that will be used for assessment during this study.

1. The Family Relationships Index (FRI) is a 12-item; true-false response scale derived from the short form of the Family Environment Scale (FES), a well-validated measure of an individual's perception of their family's functioning, including such constructs as interpersonal relationships and organizational structure (Moos & Moos, 1981). The FRI will be used for screening, while the FES is administered to family members enrolling in the trial. The cohesiveness, conflict and expressiveness (of both thoughts and feelings) subscales generate the FRI, a global measure of

family interaction. The Personal Growth dimension involves assessments of Independence, Achievement Orientation, Intellectual-Cultural Orientation, Active-Recreational Orientation, and Moral-Religious Emphasis. The System Maintenance dimension includes Organization and Control measures. The 40-item short form of the FES, for which population norms have been determined, has satisfactory consistency (alphas between 0.61 & 0.78), stability (2-month, 3-month and 12-month test-retest reliabilities from 0.52 to 0.91), and predictive and discriminant validity as evidenced in more than 150 research studies, many with adolescent family members

2. The Family Environment Scale (FES) is a well validated 40 item, true or false response scale described above will be administered only to families enrolled in this trial.

3. The Family Assessment Device (FAD) is a 60-item, well validated measure, which assesses family functioning on seven dimensions and distinguishes between healthy and unhealthy families (Epstein et al, 1985). It is employed to provide concurrent validity to the FES/FRI and as an independent outcome measure, since the FRI was used to determine study entry. As well as a general functioning dimension, the FAD has the following subscales: problem solving, communication, roles, affective involvement, affective responsiveness and behavior control. It is based on the McMaster Model of Family Functioning that emphasizes the accomplishment of essential functions and tasks to promote the development of family members. The FAD has been found to have good internal consistency (Cronbach's 0.72 – 0.92) and discriminant validity (Miller et al, 1985), including extensive use with adolescent populations.

4. The Family Crisis Oriented Personal Evaluation Scales (F-COPES) is a 30-item self-report designed to measure coping response patterns adopted by families in response to problematic or difficult situations. It has five subscales: use of social support, mobilizing the family to acquire help, seeking spiritual support, reframing, and passive appraisal (McCubbin et al., 1996). Test-retest at four weeks for the global measure was r = 0.81, Coefficient alpha 0.87, subscale reliabilities between 0.62 & 0.87.

5. The cognitive items of the Beck Depression Inventory-II (BDI) comprise its short 13-item form, which correlates satisfactorily with the full 21-item version and eliminates somatic items that are confounding in the medically ill (Beck et al, 1996). Psychometric evaluation confirms the reliability (internal consistency 0.92 and stability 0.93 across one week) and validity (content, concurrent, discriminant and construct) of the BDI.

6. The Brief Symptom Inventory (BSI) is a reduced 53-item version of the Hopkins Symptom Checklist-90, yields global ratings of psychological morbidity and scores on nine subscales: somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism (Derogatis, 1993). The BSI has established reliability (alphas between 0.71 & 0.85) and has shown convergent and predictive validity in many studies. Its General Severity Index is our primary outcome variable, for which community norms have been established, and whose test-retest reliability is 0.90.

7. The Social Adjustment Scale (SAS) was modified for use as a measure of change in social adjustment in the domains of housework, work, social and leisure activities, relationships with children and extended family, and overall social functioning, either with or without a partner

(Cooper et al, 1982). A 45-item self report measure, it correlated well (0.63 – 0.80) with the interview SAS and the spousal assessment (0.70).

8. The Bereavement Phenomenology Questionnaire (BPQ) is a 22-item self-report that rates the frequency of bereavement phenomena in the prior two weeks. Its Cronbach's alpha was 0.93 and for concurrent validity with a clinical interview, a Spearman's RHO of 0.45.

9. Medical information assessment form: The socio-demographic characteristics of each patient and their family members will be documented, including age, gender, occupational and current work status, marital status, religion and its use, country of birth, tumour types and major categories of anti-cancer treatment. Length of illness from diagnosis to death and survival from study entry to death will be calculated by reference to each patient's medical record.

10. Economic Assessment: In order to evaluate the economic impact of FFGT on families, we will administer an economic assessment questionnaire to all participating family members – those randomized to FFGT and those randomized to usual care. The assessment battery will include questionnaire regarding work status as well as attendance at primary care and specialist physicians, bereavement counselors, community bereavement groups, social workers, psychologists or psychiatrists, together with use of antidepressants, hypnotics and tranquilizers or other psychotropic medication will be recorded, alongside frequency and quantity of alcohol use. Economic assessments will be completed in person at the planned evaluation times (baseline, 6 months, and 13 months post death or completion of therapy). In order to minimize problems with recall, we will also administer the economic assessment by telephone on 2 intervening occasions (3 months and 9 months post death or completion of therapy). The Baseline and Follow-Up Economic Assessment Questionnaires will ascertain information regarding health care utilization and days of work lost. These endpoints have been used frequently in economic studies of psychotherapy interventions (Gabbard et al., 1997).

11. The Complicated Grief Assessment-Self Report (CGA-SR) is an 11-item patient-administered questionnaire designed to assess specific symptoms of complicated grief. Items correspond to the proposed DSM-V consensus criteria for complicated grief and were derived from the Inventory of Complicated Grief, a well validated measure with excellent internal consistency (Cronbach's α = .94) and test-retest reliability (r=.80) (Prigerson, et al., 1995). In a community-based sample of recently bereaved adults, the criteria assessed by the CGA-SR demonstrated both convergent validity and discriminant validity with respect to other mood and anxiety disorders (Prigerson, Vanderwerker, & Maciejewski, in press). In addition, at 6-12 months post-loss, "caseness" as determined by the criteria assessed by the CGA-SR predicted elevated risk for a host of adverse mental and social outcomes (Prigerson et al., in press). Patients completing this measure are asked to report on the presence and frequency of grief symptoms over the previous month, including yearning for the deceased, emotional numbness and feelings of emptiness and meaninglessness.

12. Intervention Process Measures

The following brief questionnaires are included in order to monitor change processes among family members undergoing family focused grief therapy (FFGT). They are designed to assess the following three components of therapy, all of which are hypothesized to contribute to the outcome of FFGT: (1) therapy alliance (the degree to which family members feel positively about the therapy and therapist); (2) disclosure during session (the degree to which family members shared information, feelings, thoughts) and (3) the patient's emotional experience during session. The set of questionnaires is expected to take 5-7 minutes to complete. The set of questionnaires listed below will be administered to each participating family member immediately following the family therapy session. Each participating family member will be given a stamped envelope in which to seal the questionnaires and return them by mail to the investigator.

In addition to these questionnaires, we will use an observational coding system (see SOFTA below) to rate family and therapist behaviors that are hypothesized to predict improved session outcomes. These ratings will be made by trained research assistants by observing recorded FFGT sessions.

The **Family Therapy Alliance Scale (FTAS)** is a 13-item sub-scale of the Systemic Therapy Inventory of Change (STIC), a self-report questionnaire designed to track patient change during couples and family therapy. The FTAS scale specifically inquires about the strength of alliance in family therapy. A confirmatory factor analysis conducted with this instrument (N=67) yielded three factors with good fit, represented by sub-scale items: (1) alliance between self and therapist (6 items, e.g., "the therapist understands my goals in this therapy"); (2) alliance between family and therapist (3 items, e.g., "the therapist has the skills and ability to help all the other members of my family") and (3) alliance within family (3 items, e.g., "some of the other members of my family and I do not feel safe with each other in this therapy"). One additional item inquires about the participant's satisfaction with the therapy. The STIC has shown moderate to strong correlations with measures of distress (e.g., Beck Depression Inventory, Beck Anxiety Inventory) and measures of family functioning (e.g., Family Assessment Device).

The **Family Session Disclosure Measure (FSDM)** was adapted from Laurenceau and colleagues (1998, 2005) and has been used in prior studies with breast cancer patients (e.g., Manne et al., 2004a). This measure is comprised of a total of 10 items classified into the following sub-scales: (1) perceived self disclosure of thoughts, information and feelings (3 items); (2) perceived disclosure of family members with regard to thoughts, information and feelings (3 items); (3) perceived family responsiveness (3 items). One additional item inquires about level of experienced closeness or intimacy. This measure has been used to assess disclosure as an empirically established component of felt intimacy in interactions with significant others (see Laurenceau, 1998) and has been sensitive to intimacy-enhancing interventions with breast cancer patients (Manne, unpublished data). This measure will be administered prior to the first session to obtain a baseline score, then immediately after each subsequent family session.

The **Positive and Negative Affect Schedule (PANAS)** is comprised of two 10- item mood scales. Positive Affect (PA) reflects the extent to which a person feels enthusiastic, active, and alert, whereas Negative Affect (NA) is a general dimension of subjective distress and unpleasurable engagement that subsumes a variety of aversive mood states, including anger, contempt, disgust, guilt, fear, and nervousness. The two factors roughly correspond with the dominant personality factors of extraversion and anxiety/neuroticism, respectively. Positive and Negative affect can be assessed for different time periods, such as the moment, today, past few days, past few weeks, past year, and in general. Cronbach alpha scores for the PANAS PA and the PANAS NA were significantly reliable ($p < .05$). For PA, $\alpha = .85$, for NA, $\alpha = .91$. Test-retest reliability scores ranged from .47-.68, $p < .05$ (depending on time instructions) for the PA scales and from .39-.71, $p < .05$ (depending on time instructions) for the NA scales. The PANAS demonstrates good external validity with the Hopkins Symptom Checklist (HSCL) and with the Beck Depression Inventory (BDI), both thought to pertain more to negative affect than to positive affect. The HSCL significantly correlates with the PANAS NA at $r = .74$ (Correlation with the PANAS PA was $r = -.19$). The BDI significantly correlates with the PANAS NA at $r = .56$ (Correlation with the PANAS PA was $r = -.35$). The significant negative correlations with the PANAS PA demonstrate convergent validity.

A modified version of the **Quality of Life at the End of Life measure (QUALE-M)** will assess the quality of patient and family members' EOL experiences during the course of therapy. Items for this measure were generated from focus groups of terminally ill patients, bereaved family, and health care practitioners. A survey was subsequently administrated to a large national sample to corroborate the themes identified in the focus groups. A further item reduction and factor analysis resulted in a final measure with five domains, three of which will be assessed in this study: Life Completion ($\alpha = 0.84$); Preparedness ($\alpha = 0.77$), and Affective Social Support ($\alpha = 0.60$). This measure demonstrated convergent and discriminant validity, and acceptability to seriously ill patients. Given the use of this measure also with family members in our study, symptom impact and heath care subscales were excluded. The QUALE-M will be administered to every participant in each of the three arms once prior to the start of the study as a baseline measurement. For those who are on a therapy arm, the QUALE-M will be administered once prior to the start of therapy and after each of the first 4 sessions. Although originally designed for administration to patients, we believe that the QUALE-M is a suitable choice for family members because it addresses general EOL concerns. Measures designed for family caregivers at the EOL (e.g., The Caregiving at Life's End Questionnaire) are composed of similar items but focus predominantly on caregiving burden and care tasks. The QUAL-E is relevant for family members regardless of their role in active caregiving.

The System for Observing Family Therapy Alliances (SOFTA-o) (Friedlander et al. 2004). will be used to code family and therapist behaviors as presented in recorded intervention sessions. Ratings will be made to derive scores on two dimensions of family alliance: (1) *Safety within the Therapeutic System*; and (2) *Withinfamily Collaboration*. Patients and family members' experiences of alliance are coded from verbal and nonverbal behaviors, as observed on recordings of family sessions. *Safety within the Therapeutic System* is operationalized as an individual's

level of comfort and openness in the presence of other family. *Within-family Collaboration* is defined by the family's tendency to share a common goal, offer to compromise and demonstrate mutual respect. A complementary therapist version of the SOFTA will be used to rate alliance-related behavior of the therapist, specifically: *(1) Engagement of the family (*e.g., "therapist pulls in quiet client"; *(2) Emotional connection* (e.g., "Therapist expresses empathy for client's struggle"); *(3) Facilitating safety* (e.g., "Therapist controls or manages overt hostility between clients"). Within each category, ratings are combined into a summation score reflecting each dimension. Scores will be entered into the statistical analysis as specified below. All dimensions of the SOFTA have demonstrated predictive and concurrent validity with outpatient couples and families (Friedlander, Escudero et al. 2006; Friedlander, Lambert et al. 2008; & Friedlander, Escudero et al. 2006a). A training manual developed by the authors is available (http://www.softa-soatif.com/), with an on-line tutorial and standardized videos with which to establish inter-rater reliability. As recommended, two raters (Dr. Zaider and a hired Research Assistant (RA)) will undergo 20 hours of training to achieve 90% reliability by one point or less (Friedlander et al. 2004). Only sessions 1 to 4 will be coded.

10.0 CRITERIA FOR REMOVAL FROM STUDY

Subjects will be taken off study protocol under the following circumstances: 1) patient voluntarily withdraws from study, 2) report of intolerable psychological difficulties resulting from the evaluation and treatment techniques (patients who experience an increase in psychological distress due to participation in the interventions will be offered referral to and treatment by the P.I. through the Psychiatry Service, at their own expense), 3) or if at anytime the patient is found to be ineligible for the protocol as designated by the section on Criteria for Patient/Subject eligibility.

If a patient develops delirium or is too ill to continue in family sessions, they may withdraw, but the family work continues and the therapist uses her discretion in gathering the family around the patient's bed at the beginning or conclusion of a family session where appropriate and accessible to the family meeting. If a family elects to withraw from therapy we will continue to follow up the participants who agree to complete questionnaires.

11.0 BIOSTATISTICS

Sample size calculations:
The primary endpoints of this study are the change from baseline to 13 months post-death (or termination) in the BSI-General Severity Index and the BDI-Total, providing evidence for prevention of complicated bereavement and depression compared with standard palliative care among high risk family members of patients dying from terminal cancer.

We plan to enroll a minimum of 55 families into each of the three study arms for a total of 165 families (predicting an average of four members per family for 660 individual participants). From our previous experience we expect that approximately 10% of these families will not return to fill out the follow-up questionnaires at 13 months post-death resulting in 150 families available for analysis.

Based on data from the previous FFGT study in Australia, for these sample size calculations, we assumed that the average family size will be three members in addition to the index patient and that the intra-cluster correlation between members of the same family will be 0.1. In order to adjust for the fact that there are two primary outcome measures, the BSI and the BDI, and to allow for pair-wise comparisons between the three arms for both of these measures, we conservatively fix the significance level of each test at 0.01 to provide some control on the overall Type I error rate of this study at 0.05. In the FFGT study in Australia, the control arm had a mean absolute difference between baseline and 13 months post death of 0.01 (SD=0.39) on the BSI-GSI and 0.10 (SD=4.5) on the BDI-Total.

Taking into account that this study involves cluster sampling and intra-class correlation between members of a cluster, with 150 families we will have 82% power for two-sided tests to detect an absolute difference of 0.19 (an effect size of approximately 0.45) on the BSI-GSI. We used Horton's simulation method to estimate the statistical power with a two-sided test at a 0.01 Type-I error rate (Horton, 2004). In the previous FFGT study with 6 therapy sessions, we observed a standardized difference of approximately 0.33 between the FFGT condition and the Control condition. A subset of families received 10 sessions of FFGT and showed an approximately 0.60 standardized difference in the BSI-General scores. Taken together, it is not unreasonable to estimate that FFGT therapy (6 and 10 sessions combined) will be superior to the Control condition by approximately a 0.45 standardized difference in the BSI-General.

Based on the FFGT study in Australia, we predict that of the 165 families enrolled in this study, 50% (83) will be intermediate families, 28% (47) will be sullen families, and 22% (36) will be hostile families. Allowing for 10% dropout, we should have approximately 75 intermediate families, 42 sullen families, and 32 hostile families available for analysis of the primary endpoints. Exploratory analyses will be carried out to estimate the extent to which FFGT entails differential effects by family type. These exploratory analyses will generally be carried out separately by three family types (intermediate, sullen, and hostile).

We estimate approximately 2034 families screened per annum across our sites. Of these, approximately 915 will be eligible, and with a recruitment rate of 44% based on our prior experience with FFGT, 402 families would be available per annum who might agree to participate in this study. Thus there is a sufficiently large pool of families from which we can recruit for study participation. Based on the rate of recruitment observed in the Department of Psychiatry and Behavioral Sciences, our ultimate recruitment may be between 150 and 200 families. Even though we have powered the study for 165 families, we will consider including additional families if they wish to participate and if there are enough funding and time resources. A larger

cluster size allows for more precise estimates on subtle differences (e.g., differential FFGT effects by family type). Another rationale for recruiting additional families is to have control over variabilities in family compositions. For example, in our statistical power estimation we assumed that each family cluster consists of four family members. However, in reality the families may be larger or smaller, and the within-cluster variability is typically greater in small families than in large families. Additional sample size reduces the potential impact of this variability.

Preliminary analyses and missing data - Before conducting statistical analyses, we will examine the distribution of variables included in each analysis and use appropriate transformations with procedures outlined for distribution analyses. Where questionnaires are returned with missing data, we will contact subjects to obtain missing data. As attrition introduces a bias, imputation of data will be achieved by employing (full information) maximum likelihood estimation on the available data, under the assumptions of missingness at random and normality (which are not testable with the collected data; eg. Shafer, 1997), for purposes of overall model testing and evaluation using the popular latent variable modeling program MPLUS (Muthen & Muthen, 2004). Furthermore, as an alternative approach, we will consider utilizing multiple imputation, under the same assumptions (eg. Little & Rubin, 2002). For the latter purposes, with the lack of a readily available software for conducting multiple imputation for hierarchical data of the kind this study would yield, we plan to carry out multiple imputation at each of the two levels involved, merge back by family identification code, carry out model evaluation for each of the so-generated sets, and aggregate parameter estimates and standard errors as described in the literature (eg, Little & Rubin, 2002). To clarify the degree of increase in Type 1 error introduced by such imputations (Gibbons & Hedeker, 1993), in our intention-to-treat analyses, we will compare the analysis using imputed data with the traditional analysis omitting incomplete datasets, which assumes such missing data is randomly distributed. Finally, patients and relatives who decline to participate or withdraw will be compared statistically on available socio-demographic and medical variable, with a planned post hoc analysis of predictors of intervention drop-out, to better understand the barriers to data interpretation and application of this model in care provision. Thus, if a higher attrition rate occurs for the more dose intense intervention, exploration of this will be undertaken.

Graphical methods and descriptive statistics such as the mean, median, range, and variance of the data will be used preliminarily to explore trends in the scales (BSI, BDI, SAS, BPQ) across time in the three study arms. For the primary aim of this study, the change in the BSI and BDI from baseline to 13 months post bereavement (or termination when the patient has not died) will be compared between the three arms. For each scale, generalized estimating equations (GEE) (Liang and Zeger, 1986) will be used to compare the mean change while adjusting for the correlation between responses of members of a family. Co-varieties to be included in the equation include participant characteristics (age, gender, ethnicity, relation to patient, income, prior psychiatric history), number of sessions attended, study site, family size, therapist conducting intervention, and patient characteristics (primary cancer, time since diagnosis). Preliminary descriptive analyses will explore the distribution of the mean changes and the correlation in the data in order help determine the proper choice of a link function and working correlation matrix.

To account for the fact that there are two primary outcomes and to allow for pair-wise comparisons between the three study arms, the significance level for each test will be set at 0.01 yielding an overall Type I error rate of 0.05 for this study. Secondary analyses will include (1) subgroup analyses looking at changes in the BSI and BDI separately for the three family types: intermediate, sullen, and hostile (2) studying the change in the BSI and BDI from baseline to 6 months post bereavement; (3) studying change in BSI & BDI for the 10% and 20% of individuals with high baseline scores; and (4) exploring changes between baseline and 6 months post bereavement and 13 months post bereavement for additional scales (including SAS and BPQ). These analyses will be carried out using GEE as described above.

Depending upon the distribution of the data, we may also use mixed effects models (Pinheiro and Bates, 2000) to further explore the longitudinal trends in the data. This approach would allow us to model the scores from baseline, 6 months and 13 months post bereavement

Analytic plans for additional research questions are described below:
Question 1a: Is FFGT efficacious in preventing complicated bereavement and depression compared with standard palliative care?

This is our primary research question, which will be addressed by comparing the change between baseline and 13 months post-bereavement BSI-General outcome between the FFGT condition (6-session and 10-session combined) and the Control condition in a GEE model controlling for family clusters and other covariates outlined above. From our preliminary data, FFGT could be predicted to help intermediate, sullen and hostile families, but what is the minimal effective length of therapy able to achieve this and how does length of therapy impact on effect size?

Statistical power and sample size considerations for our primary Aim. Our original criteria for power calculation were highly conservative, based on a small 0.33 effect size, rather than the potentially doubling of effect size when 10 sessions of therapy were delivered (Kissane et al., 2007). The 0.33 effect size weighted heavily the lowest effect size with only 6 sessions of therapy. In addition, we raised the difficulty in reaching statistical significance to 0.01, rather than the conventional 0.05. These conservative criteria were designed to detect subtle effects involving multiple comparisons. Based on progress to date, our ultimate recruitment may be between 150 and 200 families. If we recruit 165 families, and 10% do not complete the study, then we will have 150 family clusters per study arm for analysis. The table below shows an 82% and a 90% power if the final effect size is at 0.45 and 0.50, respectively.

	Original Effect Size Estimate = 0.33	Scenario 1: ES = 0.45	ES = 0.50	Nearly Double ES = 0.60
n = 150	52%	82%	90%	> 95%

Statistical power estimates were carried out using the simulation methods in Horton et al. (2004). We ran a simulated GEE model 400 times based on a 0.10 intra-class correlation between members of the same family cluster. This intra-class correlation is derived from our prior data (Kissane et al, in press). We also conservatively assumed that there will be a minimum of 4 members per family cluster.

Question 1b: Is 10-session FFGT more effective than 6-session FFGT and standard care for participants in dysfunctional families of differing types? Is 10-session FFGT more effective than 6-session FFGT and standard care for participants with higher pre-intervention levels of distress?

We hypothesize that the longer dose of FFGT is more effective for participants from dysfunctional families and participants with higher levels of pre-intervention distress. To assess the dose responsiveness of FFGT we will use the Jonckheere-Terpstra test, a nonparametric test for ordered differences among classes. The Jonckheere-Terpstra test is available in the SAS FREQUENCY procedure. Data will be permuted to account for the clustering when calculating the variance of the statistic.

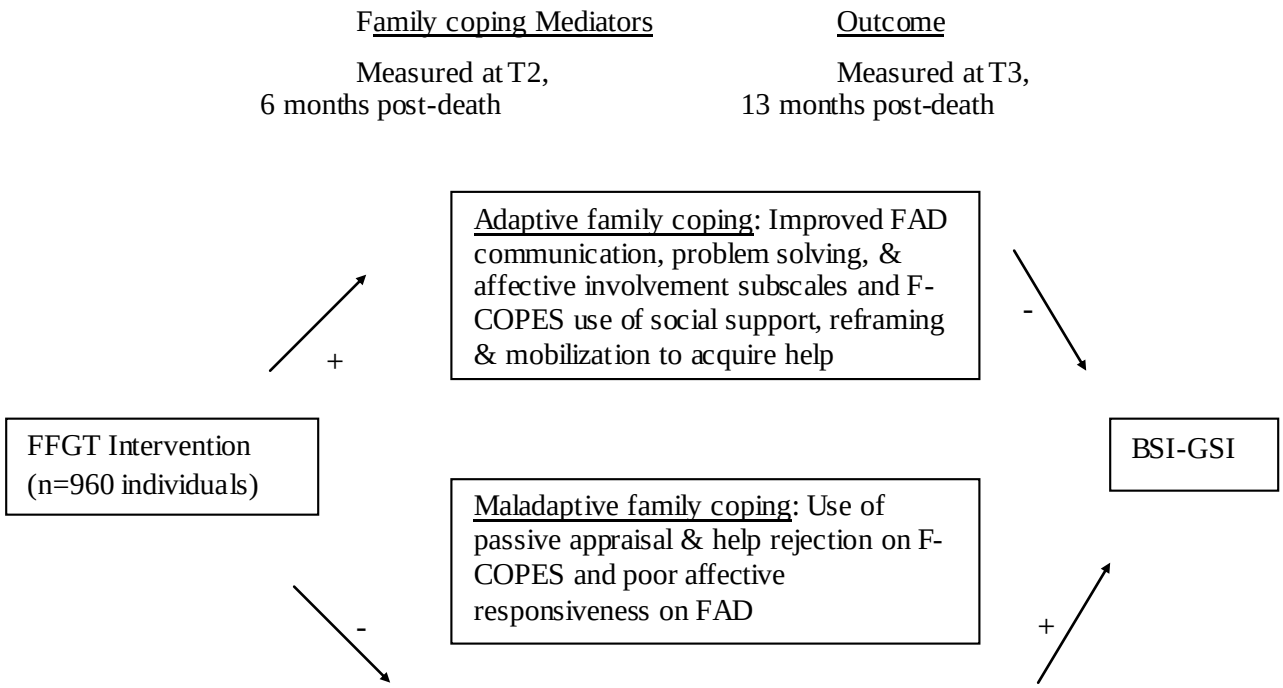
Question 1c: Does FFGT impact social functioning and bereavement reactions?

This research question will be addressed through the use of mean differences between the pooled FFGT arms (6- and 10-session conditions) and the control condition in a GEE model. The mean differences and confidence intervals will be obtained from the GEE coefficient coding whether or not the participant was assigned to FFGT or control. The outcome of social functioning will be based on the summary scores of the Social Adjustment Scale (SAS). Bereavement reactions will be based on the summary scores of the 22-item Bereavement Phenomenology Questionnaire (BPQ).

Question 2: Do family communication and adaptive family coping mediate the impact of FFGT?

Background: Exploring the mechanisms through which a psychological intervention works guides further refinement of the model and its application in clinical practice. Therefore, in this research question, we examine potential mechanisms for change within the two groups receiving FFGT, focusing on participants who received either 6 or 10 sessions of FFGT. In our original observational work evaluating the role of family functioning and bereavement (Kissane et al, 1996a & b), we found that hostile families tended to be help-rejecting on F-COPES in sharp contradistinction to sullen families, who were open to a range of adaptive family coping mechanisms, while intermediate families again tended to adopt better family coping approaches. Our intervention has been styled to promote problem solving, open up communication channels and optimize mutual support.

The model below illustrates the proposed coping mechanisms.



Analyses: We will evaluate the measures of change in adaptive family coping at T2 (FAD subscales –communication, problem solving, affective involvement – and F-COPES subscales – use of social support, mobilizing family to acquire help, reframing) as mediators of the bereavement distress (BSI-GSI) at 13 months post-death, as illustrated in the diagram above, and contrast these with change in maladaptive family coping. This analytic equation will be repeated for depression (BDI-total). To determine relevant control variables, correlations and one-way ANOVAs (for categorical variables) will be calculated between possible control variables (eg family member status as partner, offspring; gender) and distress or depression outcome. Intervention effects will then be evaluated using a hierarchical regression model predicting 13-month bereavement distress, and secondly depression. In these models, relevant control variables will be included on Steps 1 and 2, Baseline (T1) distress or depression will be included on Step 3, and study condition (FFGT intervention) on Step 4. The general approach to the analytic treatment of moderator and mediator models has been described by Baron and Kenny (1986) in the context of multiple regression models. We will also follow procedures outlined by Aiken and colleagues (1994) in their approach to testing mediation models for intervention design. To show mediation, it is first necessary to demonstrate that the variables to be mediated affect the various mediators and outcomes of interest. Thus, it must first be shown that the intervention has an effect on outcome distress or depression. If the mediation hypothesis is correct, the parameter estimate for the intervention will no longer predict distress. In addition, the parameter estimates for adaptive family coping as they affect distress will be significant. When possible, constructs used in the model having multiple indicators will be combined into single indicators using factor analysis. The analyses will be repeated for the outcome depression (BDI) at 13-months post-death.

As a complement to these analyses, we will address pertinent aspects of the research question also within the framework of latent variable modeling (e.g., Muthen, 2002). In this regard, it is first noted that we anticipate the interrelationships among the variables in the middle part of the above scheme to likely be explainable well by two underlying latent dimensions (factors; for the FAD- and F-COPES observed variables, respectively). This hypothesis can be explored if need be using exploratory factor analysis and is in particular testable by fitting a confirmatory two-related-factor analysis model to their variances and covariances (correlations). Assuming plausibility of the hypothesis is indicated with this analysis, a latent variable model will then be fitted to the data stemming from all variables appearing in that scheme. When specific questions are of concern with regard to bereavement distress and to depression separately, this model will be fitted considering in turn each one of them as a single outcome variable. An overall model will then be fitted using both these outcome variables, thus simultaneously evaluating their relationships with the variables displayed in the left and middle part of the scheme, as well as accounting for the interrelationship between these two outcome variables. Whether using a single or both outcome variables, the generic latent variable model will postulate the two latent factors mentioned above (representing the 6 adaptive family coping measures in the middle of the scheme) as mediators, thus allowing evaluation and testing of the direct as well as the indirect (mediated) effects of type of family upon the outcome variable(s). Thus, a main positive feature of this approach is the possibility to account for error of measurement in the mediating variables (formally, predictors of the outcome variables unless included in a latent variable model in the role of indicators of underlying latent dimensions as here); furthermore, with the pair of outcome criteria this model permits more precise evaluation of the relationships among all involved variables as it includes these interrelated criteria. In addition, within this latent variable modeling approach, using recent modeling advances interactions between variables other than the outcomes can be included and also estimated and tested, allowing in this way to address the question of possible moderator effects in relation to the constructs evaluated by the adaptive family coping indicators (measures).

All data analyses described here will be performed using the increasingly popular latent variable modeling program Mplus (Muthen & Muthen, 2004). Power analyses: Since this question is concerned with mediation, considerations of power are not required with regard to the regression-based analyses outlined in the first paragraph of the preceding analysis section, as power is met for the primary effect of intervention on outcome tested in Question1 above. With respect to the latent variable models outlined in the second paragraph of that section, using the method in MacCallum, Browne, & Sugawara (1996) it is directly found that at the proposed above sample size the power for testing the described confirmatory two-related-factor analysis model (for the 6 indicators of adaptive family coping in the middle part of the scheme in that section) will be in excess of .80. (This model will be fitted to 21 variances and covariances, has 13 parameters, and thus 8 degrees of freedom; at that sample size, the power evaluation approach in MacCallum et al., 1996, yields power higher than .80; e.g., Table 2, p. 141.) Similarly is found that the mediator as well as moderator effect models described in the preceding section will be associated with even higher power, as the latter is proportional to degrees of freedom yet the ones of these models are

higher than the degrees of freedom of that confirmatory factor analysis model (the latter is entirely embedded in the former, latent variable models, and has less further parameters than added data points).

Question 3: What are the costs of delivering FFGT, and is FFGT associated with reductions in health care utilization and lost productivity among family members over 13 months of bereavement following the death of a loved one from cancer? Background: In exploring any new model of intervention and especially one that seeks to prevent morbidity that is likely to otherwise lead to increased cost utilization over time, a prospective, comparative cost analysis is worthwhile for the subjects in each arm of the study. Analyses: The economic evaluation of FFGT will consist of two components: 1) estimation of intervention costs, and 2) assessment of economic impact on participating family members. Program costs will be estimated by recording the total time spent in FFGT sessions, multiplied by the average hourly wage of the provider delivering the intervention. We will also estimate the travel costs required for family members to attend the FFGT sessions. The cost of training providers to deliver FFGT will not be included.

We will estimate the costs of delivering the intervention, at both dose levels. Using data from the Economic Assessment Questionnaires, we will estimate health care utilization and lost productivity (i.e., lost work days) among participants in all arms of the study. Since cost data tend to be non-normally distributed and subject to substantial variability, and the economic outcomes are secondary to the psychosocial outcomes of the trial, we may not have adequate statistical power to detect significant difference between groups. However, we will compare health resource utilization and lost productivity across groups, and describe trends in these outcomes.

Question 4. The following additional research questions focus on identifying features of the intervention sessions that contribute to improved quality of life at the end-of-life (EOL) (e.g., preparedness, closure, support) for participants receiving FFGT. These questions about mechanisms of change will be analyzed using Linear Mixed-Effects Modeling (LME)(Murray et al. 1998; Laird & Ware 1982; Raudenbush & Bryk 2002; Murray et al. 2004), also known as multi-level modeling. Atkins (Atkins, 2005), specifically recommended this method for analyzing family therapy process data.

4a. Are changes in family members' cancer-related disclosure during sessions of FFGT associated with corresponding changes in family members' quality of life at the EOL (i.e., preparedness, sense of life closure, support)?

We hypothesize that overall increases in family members' cancer-related disclosure across sessions of FFGT will be associated with improvements in quality of life at the end of life. Using Raudenbush and Bryk's notation (Raudenbush & Bryk 2002), we describe mathematically the modeling of two levels of data (see below): At the so-called Level 1, the outcome for individual i of family j at session t is described as a function of an intercept and slope for that individual ($\beta 0i$ and $\beta 1i$), and an error term (eitj) that captures the degree to which the outcome at a given session deviates from that individual's mean EOL score. At Level 2, the trajectories of change in EOL over time, represented in the random, family intercepts ($\beta 0i$) and rates of change (slopes $\beta 1i$), are further explained by changes in session disclosure (FSDM). The Level 2 error term (r00i) allows for the effect of disclosure to vary among patients and family members within the same family.

(1) A. Level 1 (Repeated Measures) QUALE-Mijt = β0i + β1i(Time) + eitj
B. Level 2 (Individual) β0i = γ00 + γ01 (FSDM) + r00i
β1i = γ10 + γ11 (FSDM) + r10i

The parameter γ11 indicates the change in slope of time given one unit increase in FSDM scores. The hypothesis in Aim 1 will therefore be supported if this parameter is statistically significant.

Power Analysis: The primary outcome in these analyses is scores on the QUALE-M. We conducted a power analysis to determine the sample size needed to test the hypothesis stated in study Aim 1. In a validation study of the QUAL-E with a large sample of terminally ill patients, the ICCs between QUAL-E responses at baseline and those collected 1 week later ranged from 0.61 to 0.74 for subscales used in our study. We estimated an ICC of 0.66 within the participating family clusters. Using the formula specified in Donner and Klar (Donner & Klar, 1996), 40 clusters of families comprised of 3.5 members per family (based on composition of families accrued in RCT to date), will yield a 77% statistical power to detect a moderate (0.50) Cohen's effect size at a two-sided alpha error of 0.05. Estimation of a moderate effect size was based on effect sizes obtained for reduction of distress scores among family members receiving FFGT in a prior RCT(Kissane et al. 2006).

4b. Do family alliance processes mediate the association between in-session disclosure and family members' quality of life at the EOL .We hypothesize that family alliance processes, represented by summary scores on two subscales of the SOFTA, will mediate the association between disclosure (FSDM), and EOL outcomes (QUALE-M).
As is described above, a two-level model will be specified for this analysis, with Therapeutic Safety and Within family Collaboration scores tested separately:

(2) A. Level 1 (Repeated Measures) QUALE-M*ijt* = *β*0*i* + *β1i*(Time) + *eitj*
B. Level 2 (Individual) *β*0*i* = *γ00* + *γ01* (FSDM) + *γ02*(Within-Family Collab) + *r00i*
β1i = *γ10* + *γ11* (FSDM) + *γ12*(Within-Family Collab) + *r10i*

In the equation above, the *γ11* parameter is an estimate of the effect of disclosure on the change in EOL outcomes adjusted for the effects of Therapeutic Safety or Within-family Collaboration. We will estimate the mediation effect by comparing the change in the *γ11* parameter between two equations, one with the mediator (*β1i*= *γ10* + *γ11* (FSDM) + *γ12* (Collab) + *γ10i*) and the other without the mediator (*β1i*= *γ10* + *γ11* (FSDM) + *γ10i*). This "difference in coefficients" method (Mackinnon, Fairchild & Fritz, 2007) will be used to show that the influence of disclosure on QUALE is reduced if the mediator is present. The 95% confidence interval of the change in coefficient will be sought to gauge the extent of the mediation effect.

4c. Do therapist characteristics moderate the association between in-session disclosure and quality of life at the EOL . Referred to as a slopes-as-outcomes model (Raudenbush & Bryk 2002), the *slope* of disclosure (FSDM) on EOL outcome (QUALE-M) at Level 1 will itself be modeled as a function of one of the characteristics listed above (e.g., distress):

(1) A. Level 1 (Repeated Measures) QUALE-M$ijt = \beta 0i + \beta 1i$(Time) + $\beta 2i$(FSDM) + $eitj$
B. Level 2 (Individual) $\beta 2i = \gamma 00 + \gamma 01$ (BSI) + $r00i$
$B2i = \gamma 10 + \gamma 11$ (BSI) + $r10i$

Where the regression of the level 1 slope ($\beta 1i$) on the level 2 covariate (BSI) results in a cross-level interaction between Disclosure (FSDM) and Distress (BSI). Significance of the fixed regression coefficient $\gamma 11$ will indicate a moderation effect.

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.1 Research Participant Registration

Consenting and registration will always be conducted by an MSKCC consenting professional. Following the informed consent, the patient will be assigned a sequential subject number to ensure confidentiality and facilitate data collection and analysis. The project coordinators or research assistants will assign the subject number as appropriate. The list will be kept in a locked file cabinet in the designated research area.

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, including those who were recruited through Calvary Hospital or Beth Israel Medical Center, 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. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

12.2 Randomization

Patients at MSKCC and at participating sites will be randomized to one of three arms: (1) Usual care (0 sessions FFGT), (2) 6 sessions of FFGT, or (3) 10 sessions of FFGT. After eligibility is established using the baseline questionnaire packets and immediately after consent is obtained, patients will be registered in the MSKCC computerized Protocol Patient Accrual (PPA) system and randomized using the MSKCC Clinical Research Database (CRDB). Randomization is overseen by the MSKCC Biostatistics Service. Randomization will be accomplished by the method of random permuted block, and

patients will be stratified by recruitment site and family type (intermediate, sullen, or hostile). Stratification by site is necessary because family member characteristics may differ between sites on ethnicity and socio-demographics. Stratification by family types is necessary to ensure these families are balanced across the three arms.

13.0 DATA AND REGULATORY MANAGEMENT AND ISSUES

All data will be gathered by MSKCC staff and kept in a secured location and available only to members of the research study team, stored in a protected file and be secure from the rest of the network. Data will be kept stripped of any identifying information. The research team will create a key that assigns each participant to a generated code number. This list, matching participants' names and code numbers, will be maintained on a separate sheet of paper kept in locked storage. Confidentiality of each participant's data will be protected with utmost care with all questionnaire data identified solely by a code number. Study findings will be presented in aggregate form only, with no reference made to the individual participant's data. Aggregate data will never be sent to anyone unless in an encrypted file. The Principal Investigator and the research team will be responsible to identify, review, and report all necessary adverse events to the institutional IRB and NCI, as appropriate. Adverse events are identified through standard, routine protocol review and clinical assessment of each participant in the study.

13.1 Quality Assurance

Registration 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. All questionnaires will be audited for completeness. Accrual rates and extext 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, at a minimum of two times per year, more frequently if indicated.

13.2 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://cancertrials.nci.nih.gov/researchers/dms/index.html. 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://mskweb2.mskcc.org/irb/index.htm.

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.

13.3 Regulatory Procedures

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB of Record.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae/biosketch and medical license (if applicable) for each investigator and consenting professional
- Documentation of Human Subject Research Certification for investigators and key staff members
- Laboratory certifications and normals (if applicable)

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

13.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval from their IRB of record within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue, sites will not be permitted to continue enrolling new participants until IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

13.3.2 Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB must be submitted to MSKCC at the time re-approval is granted. The most current approved version of the consent form should also be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the research staff in charge of that participating site should report to MSKCC IRB as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Research Study Staff should report deviations and violations to the participating site's IRB as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.
Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

13.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

MSKCC research staff will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder at MSKCC.

A regulatory binder for each site will be maintained at MSKCC by MSKCC research study staff; this binder may be paper or electronic.

After study closure, the investigator will maintain all source documents, study related documents and CRFs for 3 years.

13.4 Noncompliance

If a participating site is found to be noncompliant with the regulatory requirements set forth in section 13.3, accrual privileges may be suspended and/or contract payments may be withheld (if applicable), until the outstanding issues have been resolved.

14.0 PROTECTION OF HUMAN SUBJECTS

The potential risks involve emotional distress which might accompany a patient being asked about the experience of illness or their family members being asked about their experience of this serious illness and eventually the patient's death. For subjects receiving FFGT, their reactions will be monitored during treatment, and the therapist will seek to address psychological distress in the sessions. There is a reasonable prospect of benefit from the FFGT intervention. The research assistants will examine questionnaires at baseline and the two follow-ups using the BSI and BDI. Participants rating suicidal ideation will be referred to the PI, an experienced psychiatrist, who will contact the participant and make a clinical referral if necessary.

In this study, both patients suffering serious illness and their family members and nominated friends will be consented and registered. Confidentiality of each subject's self-report information and each patient's medical information will be protected with the utmost care. Each study subject will be given a unique numeric identifier upon study entry. Data sheets collected from each subject will be identified solely by a code number. A list matching subject names and code numbers will be maintained on separate sheets of paper which will be kept in locked storage. Each sites IRB and HIPAA regulations concerning confidentiality will be strictly enforced. Hardcopies of the original questionnaires will be stored in locked file cabinets.

Through the use of password security measures, restrictions will be applied to each user commensurate with their needs to access the data. Confidential information will not be routinely available to all members of the research team but rather on a 'need to know' basis. As required at MSKCC, computer passwords will be regularly changed, and the institution's firewall will block inappropriate access. All Internet based data communications will be encrypted with 128 bit SSL (Secure Socket Layer) and use X.509 security certificates to provide additional protection. All current and new personnel will be instructed in the ethics of electronic data access, as well as receive training in both HIPAA issues and human subjects training.

14.1 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.

14.2 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 containing the following information:

Fields populated from the 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 information:
  - 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.

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.

Responsibility of MSKCC and Participating Sites

- The MSKCC Research Staff is responsible for submitting all SAEs which occur at participating sites to the MSKCC IRB
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs as they occur.

15.0 INFORMED CONSENT PROCEDURES

Families are identified by screening of the patient and any available family members with the FRI as they attend outpatients or during admission procedures for inpatients. 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 eligible 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 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 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. The participant must receive a copy of the signed informed consent form.

Further screening might occur during a routine family information meeting and the nurse conducting this session will inform eligible families about the study. The research assistants will then approach the family, explain the study and obtain written informed consent, as described above.

If participants are not consented during the educational session, they may be enrolled in the study via telephone contact. The RSA will call potential patients excluding Calvary Hospital patients, (Calvary patient consents must be obtained in person) and family members and explain the study to them in full detail. For those expressing an interest in participating, the RSA will obtain verbal consent over the telephone.

The research investigators will approach eligible patients first, describe the nature of the study, solicit participation and obtain informed consent. Family members will then be approached through the patient. In the event that the index family member is too frail or declining to take part in the study, the family may participate without the index patient being involved.

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17.0 APPENDICES

Appendix A: Treatment/Therapy Session Calendar

Appendix B: Family Relationships Index Scale

Appendix C: Manual for Routine Family Informational Session

Appendix D: Family Focused Grief Therapy Manual for Therapist

Appendix E: Family Focused Grief Therapy Integrity Measure

Appendix F: Family Focused Grief Therapy coding Manual for Treatment Integrity

Appendix G: Baseline Economic and Medical information Assessment

Appendix H: Follow Up Economic and Medical information Assessment

Appendix I: Medical Assessment Form

Appendix J: Baseline Battery

- Beck Depression Inventory
- The Brief Symptom Inventory
- McMaster Family Assessment
- Family Crisis Orientation
- Family Environment Scale
- Social Adjustment Scale-Modified

Appendix K: 6 and 13 month questionnaire battery

- Beck Depression Inventory
- The Brief Symptom Inventory
- McMaster Family Assessment
- Family Crisis Orientation
- Family Environment Scale
- Social Adjustment Scale-Modified
- Complicated Grief Assessment Post-Loss
- Bereavement Phenomenology Questionnaire

Appendix L: Intervention Process Measures

Appendix M: Study summary

Appendix N: Quality of Life at the End of Life measure (QUALE-M)

Appendix O: Family Focus Grief Therapy Study Brochure/Flyer