TITLE: Giving Information Strategically and Transparently in Solid Tumor Cancer

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

ACP	Advanced Care Planning
AE	Adverse Event
CFR	Code of Federal Regulations
CwC	Coping with Cancer
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
EoL	End of Life
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIST	Giving Information Strategically and Transparently
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	Giving Information Systematically and Transparently in Solid Tumor Cancer
Short Title:	Oncolo-GIST
Principal Investigator:	Holly G. Prigerson, PhD
Study Description:	The study will develop, refine and pilot test the Oncolo-GIST clinician training intervention. The training is aimed at enhancing the clinician's communication with patients by teaching to relay information both sensitively and in simple terminology.
Sample Size:	Phase 1 Interviews: N=20 (N=10 clinicians, N=10 bereaved caregivers) Phase 2: N= 54 (N=50 patient subjects, N=4 clinician subjects)
Enrollment:	This study will enroll 74 subjects and screen up to 250 subjects.
Study Population:	Phase 1 Interviews: Bereaved Caregiver subjects will be caregivers of patients who died in the past year with a primary diagnoses of GI or lung cancers. Clinician subjects will be either oncologists, palliative care physicians, nurses, nurse practitioners, social workers and psychologists who care for patients with metastatic GI and lung cancers. Phase 2: Patient subjects will be adults (18+) diagnosed with lung, head and neck, or GI cancer, with a progression of their disease after one line of therapy. Clinician subjects will be Lung, Head and Neck, or GI oncologists. All subjects' primary language will be English and will have full mental capacity.
Enrollment Period:	Phase 1 (Interviews): 12 months Phase 2: 19 Months
Study Design:	Phase 1 (Interviews): Intervention manual development Phase 2: Intervention phase (two-group pilot randomized trial).
Participants:	Participants will be recruited at Weill Cornell Medical College/ New-York Presbyterian Hospital, at the Lung and GI Cancer centers.
Study Duration:	31 months **Start date:** Jan 22, 2020 **End date:** July 25, 2022 (end enrollment); January 25th, 2023 (end data analysis and all other activities)
Participant Duration:	Phase 1 Interviews: 2 hours Phase 2: 4 months (with patient status monitoring up to 12 months)
Primary Objective:	To assess the effectiveness of the Oncologist intervention by examining the patient's degree of prognostic understanding after discussing

prognosis with either Oncolo-GIST trained or non-Oncolo-GIST trained clinicians.

Secondary Objectives: To examine the effects on patients of having better prognostic understating, including its effect on their quality of life, the type of care they choose to receive and whether or not the care they received was consistent with the patient's preferences and values.

Endpoints: Outcome will be a training manual for clinicians that teaches the Oncolo-GIST methods of communication. The efficacy of the intervention will be determined by measuring the patient's prognostic understanding using our validated 4-item assessment. The assessment will determine if the patient understood the scan results as well as the expected outcomes of treatments offered. Outcomes will also include whether a DNR order was completed for the patient, the patients quality of life (McGill Quality of Life measure) , patient performance status (e.g., Eastern Cooperative Oncology Group, ECOG), as well as the type care received (e.g., anticancer, intensive, palliative care).

1.1 Study Objectives

1.1.1 Objectives

Objective 1*:* To develop and refine Oncolo-GIST*,* an intervention aimed at enhancing clinicians' communication with patients by teaching to relay information both sensitively and in simple terminology, by receiving feedback from clinicians as well from bereaved family members of cancer patients.

Objective 2: To determine feasibility and acceptability of Oncolo-GIST in a cluster trial in 50 patients with advanced cancer and 4 clinicians.

Objective 3*:* To test the preliminary efficacy of Oncologist on the 1) patients prognostic understanding 2) Other aspects of patient care including type of care, quality of life, and "value consistent" care.

1.1.2 Hypotheses / Research Questions

Hypothesis 1: The Oncolo-GIST intervention will be demonstrated to be feasible and acceptable to both clinicians and patients.

Hypothesis 2: The Oncolo-GIST intervention will be associated with advanced cancer patients' understanding of their scan results and prognosis (i.e., that they likely have months, not years, left to live).

2. Background and Significance

Informed consent requires an individual to have a clear understanding of the facts, implications, and consequences of an action.[1 2 3] Bioethical principles, rooted in a respect for human dignity, necessitate that patients have a basic understanding of their illness and the risks and benefits of treatments proffered. Patients cannot make informed decisions about their care in the absence of knowledge of their prognosis or expected outcomes of treatments under consideration. It is alarming how unaware of their prognosis the vast majority of patients in our NCI-funded Coping with Cancer (CwC) R01s proved to be. Among CwC advanced cancer patients with a median survival of 5 months from our baseline assessment, we found only 5% accurately understood that they had incurable cancer, were terminally ill, were at a late- or end-stage of their illness, and likely had months, but not years, left to live.[4] These findings highlight the ethical imperative of ensuring that patients have sufficient understanding of their prognosis, and expected risks/benefits of treatments being offered to them, for making informed choices. Preliminary evidence from CwC has shown that patients who get the gist that death is near are more likely to: a) engage in advance care planning (ACP) [5 6] b) receive less burdensome, intensive, and unbeneficial EoL care (e.g., fewer ICU stays, inappropriate palliative chemotherapy),[5 6 7 8] and c) more value-consistent EoL care.[6] Although we found that 71% of these patients state that they would want their oncologist to tell them their prognosis, only 17.6% stated that their oncologist had discussed their prognosis (i.e., life-expectancy) with them.[9] We find that patient prognostic understanding is improved by oncologist discussions of prognosis,[4 10 7] but that the manner of communication matters for patients to "get the gist" that death is near.[10]

These results suggest a compelling need for interventions that: a) promote oncologist discussions of prognosis with their advanced cancer patients, b) prove feasible to implement in clinic, c) are acceptable to oncologists, and d) improve patients' prognostic understanding. We believe that the Oncolo-GIST approach has enormous potential to address each of these needs. By enabling more patients to make informed medical choices, the Oncolo-GIST approach is expected to uphold bioethical principles by promoting patients' capacity to engage in truly informed medical decision-making which, based on prior findings, is also expected to result in better EoL outcomes (e.g., less intensive, more palliative and more value-consistent EoL care). [3 7 11]

3. Study Design and Methods

3.1 Overall Design

The overall goals are to refine and demonstrate the feasibility of implementing the Oncolo-GIST intervention, determine its acceptability to oncologists, and potential for improving advanced cancer patients' prognostic understanding. In pursuing these goals, this studyaims to determine the promise of the Oncolo-GIST approach for affecting the targeted outcomes and given positive results, to position us for a larger RCT. We, thus, propose to examine key aspects of intervention development, to evaluate the NIH's Stage I activities of the Stage Model of Behavioral Therapies (e.g., intervention refinement, adaptation, and pilot testing),[12 13] and to explore Oncolo-GIST's preliminary efficacy.

Both qualitative and quantitative methods will be used in Phase 1. During the Phase 1 interviews (Aim #1) we will obtain feedback from relevant stakeholders/key informants (bereaved caregivers and clinicians) on an early draft of the Oncolo-GIST manual and proposed approach using a version of the Delphi method [14] in which we interview bereaved family caregivers of advanced cancer patients (n=10) and oncology clinicians who care for patients with advanced gastrointestinal (GI) and thoracic (lung) cancers (n=10). The participants will have the option of completing a recorded phone interview or answering identical questions via a link to REDCap. Participants will also be asked demographic and oncology based communication questions specific to either clinicians or caregivers.

In Phase 2, for the pilot cluster RCT study (Aim #3), we will recruit adult patients (n=50) with metastatic GI, head and neck, or lung cancers with scan results that reveal progression (worsened disease) on an initial systemic treatment; that is, patients whose life-expectancy can reliably be estimated to be months, not years. [5 9] Medical oncologists (n=4) who care for these patients will also be consented for study participation and half (n=2) will be randomized to receive the brief "Oncolo-GIST communication" training. The Oncolo-GIST training will provide instruction in how to introduce the topic of prognosis, describe scan results as "worse," prognosis as "likely months, not years," and expected treatment outcomes (e.g., "not expected to be cured by treatment," and expected impact on quality of life – that is, whether the anticancer treatment is likely to make them feel overall better or worse). We expect 12-13 patients will be clustered within each of the 4 oncologists. Hierarchical Linear Modeling (HLM) techniques will be employed to address the non-independence of patient assessments within each cluster. Patients (n=25) will be seen by either an Oncolo-GIST trained oncologist or an oncologist not trained in the intervention; that is, usual care (n=25). Patients in both arms will have met the same eligibility criteria (i.e., have similar prognoses).

Thus, we will get initial feedback on the Oncolo-GIST intervention from relevant stakeholders and key informants, obtain information on the patient and oncologist experience with the intervention and evaluate its feasibility and acceptability. Finally, we will obtain preliminary effect size estimates

on the Oncolo-GIST Version 2.0's effect on our primary outcome – patient prognostic understanding – to inform the planning of a future larger scale efficacy randomized controlled trial (RCT). Patients will be assessed by trained research staff in the week prior to a scheduled meeting with their oncologist to discuss the scan results. This will provide patients' baseline levels of prognostic understanding and enable us to determine how the intervention relates to pre-post scan visit changes in prognostic understanding. Although the first scheduled scan after study enrollment may not reveal progressive disease, we have been assured by Drs. Epstein and Saxena that only exceptional cancer patients will not progress within 12 months of baseline. We thus propose to follow patients for 12 months or until a progression is detected in the scan, whichever comes first.

Patients will be assessed pre-scan, post-scan within a week of that progressive scan visit and after their two next scans, if applicable. [see Human Subjects section for Study Timeline & Assessment Schedule and details of assessment procedures]. Although not all patients are expected to die within the study observation period, given a median life expectancy of ~4-5 months from baseline,[9] we expect nearly half of the enrolled patients will die 4 months from baseline, and that the vast majority will die during the study observation period. Thus, for all patients enrolled in this study, the medical care that they receive can reasonably be considered end-of-life care, whether they die during the study observation period or not.

Informed consent of participants will occur in-person or will be conducted remotely by sending the participants the consent form by mail or secure file transfer (transfer.weill.cornell.edu) or via a REDCap Informed Consent form (see attached) The REDCap form will be implemented in the following manner to ensure informed consent: a research assistant will send the form to a participant prior to a scheduled phone call, go through the consent with the participant over the phone, and answer any questions. The participant will need to type the correct name of the person who recruited them in the REDCap form: a wrong answer will be counted as "not consented." REDCap has been automatically set up with the e-consent framework to auto-archive consents and email a PDF copy of the signed form to the participant. A research assistant will then call the participants to go over consent and answer any questions they may have prior to any assessments. Participants will keep one copy of the consent form and send one copy back by mail or secure file transfer prior to any assessments/data collection.

Phase 2 documents will be submitted upon completion of the Phase 1 Interviews and the Phase 1 Open Trial respectively. No participants will be enrolled without IRB approval of these documents.

3.2 Interviews, Focus Groups, Surveys, and/or Observations

A. Administration

- *Timing and Frequency*

  Phase 1 Interviews: Clinicians and bereaved caregivers will complete a one-time, 2 hour phone study session or REDCap survey (including embedded intervention manual) link.
  Phase 2: Patients will be assessed in the week prior to their scheduled scan, within 1 week of the clinic visit in which progressive scan results are discussed, and then after their next two scans, if they have them, to explore intervention effects on primary and secondary outcomes, respectively. Oncologists will be assessed in the week following that same clinic visit to obtain their impressions of the discussion of prognosis and the patient's prognostic understanding. All these assessments will take 20-30 minutes. Trained oncologists will complete a brief (5-minute) post-training quiz, and all oncologists will complete a brief (5-minute) survey on Oncolo-GIST at the end of the

study. Additionally, patients will be monitored via EPIC for progression of disease up to 12 months.

- *Location*
  Phase 1 interviews of caregivers and clinicians will take place at a location convenient to the participant over the phone or via REDCap. Assessments of patients and clinicians in the pilot stage will take place in-person in clinic, at a time convenient for the participant at a different appointment, or over the telephone. Patients in Phase 2 will also have the option of completing the surveys themselves via a secure web link if this is more convenient to them.
- *Person Identifiers*
  Co-investigators may review EPIC to identify potential participants who meet eligibility. Contact information and appointment information will also be collected for either in-person or letter (postal and email) recruitment. Only data from potential participants will be stored on secure servers. Patient subjects will also have data collected via medical chart abstraction including diagnoses, medications, advanced directives, and types of care received (e.g. hospice). These data will be deleted upon completion of the study.

B. Study Instruments

- Phase 1 Interviews for both clinician and bereaved caregiver subjects will consist of a survey including demographics and oncology based communication questions specific to either the clinicians or caregivers. After each section of the Oncolo-GIST manual, participants will answer open-ended questions about the module they just reviewed.
- Phase 2 patients will be screened with a mental status questionnaire and health literacy assessment. At the first visit they will answer an assessment battery including but not limited to questions about treatment and mental status prior to discussing their scan results. After the scan results, patients will answer questions to assess prognostic understanding and treatment preferences at 3 post-scan time points (1 week after initial scan, one week after second scan, one week after third scan from enrollment)). Trained co-investigators will also collect data via medical chart abstraction. Clinicians (Phase 2) will answer an initial demographic survey and surveys including prognosis questions, patient understanding, and patient medical status for each patient participant. Clinicians trained in Oncolo-GIST will also complete a short post-training quiz to assess their understanding of the Oncolo-GIST manual. All clinicians will complete a brief study completion questionnaire to assess the feasibility and acceptability of the Oncolo-GIST method.

- Referral information
  Data collected/received from participants will be reviewed within 24-48 hours and research study staff will be responsible for addressing elevated psychological symptoms/suicidality identified on the assessments so that timely and appropriate psychiatric assessment and care can be provided. If a participant at acute risk of self-harm or harm to others cannot be reached by the study team within 3 hours (after at least two phone call attempts and an email requesting a call back), the participant's emergency contact(s) will be contacted.

4. Study Design

4.1 Study Population

- Phase 1 Interviews: Bereaved Caregiver subjects will be caregivers of patients who died in the past year with a primary diagnoses of GI or lung cancers. Clinician subjects will be oncologists, palliative care physicians, nurses, nurse practitioners, social workers, or psychologists who care for patients with metastatic GI and lung cancers.
- Phase 2: Patient subjects will be adults (18+) diagnosed with lung or GI cancer, with a progression of their disease after one line of therapy. Clinician subjects will be Lung, Head and Neck, or GI oncologists. All subjects' primary language will be English and will have full mental capacity.

4.2 Inclusion Criteria

Phase 1 Interviews:

Bereaved Caregivers:

1. Caregivers of patients who died in the past year with a primary diagnoses of GI or lung cancer
2. Fluent in English

Clinicians:

1. Currently care for patients with metastatic GI and lung cancers as an oncologist, palliative care physician, nurse, nurse practitioner, social worker, or psychologist

Phase 2:

Patients:

1. Male or female ≥ 18 years of age.
2. Receiving ongoing care (≥ 2 visits) that includes regular scans
3. Progression on at least 1 line of systemic cancer therapy
4. Prognosis from an oncologist of less than 12 months
5. Receiving care from an oncologist participating in the Oncolo-GIST study
6. Fluent in English

Clinicians:

1. Specialize in Lung, Head and Neck, and GI cancers
2. Currently provide care at the WCM Lung, Head and Neck, and GI cancer clinics
3. Fluent in English

4.3 Exclusion Criteria

Phase 1 Interviews:

Bereaved Caregivers:

1. Caregivers of patients who died longer than 1 year from the time of enrollment
2. Caregivers of a patient that did not have a primary diagnoses of GI or lung cancer
3. Not fluent in English

Clinicians:

1. Does not currently care for patients with metastatic GI and lung cancers as either an oncologist, palliative care physician, nurse, nurse practitioner, social worker, or psychologist

Phase 2:

Patients:

1. Under 18 years of age
2. Not receiving ongoing cancer care (≥ 2 visits) that includes regular scans
3. Not progressing on at least 1 line of systemic cancer therapy
1. Prognosis from an oncologists of 12 months or more
4. Not receiving care from an oncologist participating in the Oncolo-GIST study
5. Not fluent in English
6. Cognitive impairment, as indicated by a score of <8 on the Short Portable Mental Status Questionnaire or a diagnosis of dementia or a related condition

Clinicians:

1. Does not specialize in Lung, Head and Neck, and GI cancers
2. Does not currently provide care at the WCM Lung, Head and Neck, and GI cancer clinics
3. Not fluent in English

4.4 Strategies for Recruitment and Retention

Phase 1 Interviews: Clinicians and bereaved caregivers will be recruited by targeted sampling. We will use WCM's EPIC system as well request referrals from Weill Cornell Medicine (WCM) clinicians to recruit 10 bereaved caregivers of GI and lung cancer patients who died within the past year. Trained research co-investigators will screen deceased patients using EPIC after referral. If deemed eligible, caregivers will be contacted by either phone or email by non-clinician co-investigators. Oncology clinicians including oncologists, palliative care physicians, nurses, nurse practitioners, social workers, and psychologists who care for patients with GI and lung cancer, will be identified for recruitment via convenience and snowball sampling by either phone or email. These clinicians are known by co-investigators and/or their affiliates. Recruitment emails will include an attached flyer. Flyers will also be distributed on WCM/NYP properties. Phone recruitment will be by script and will include information from the flyer. Participants will not be contacted more than twice if there is no response and if at any point, a potential participant asks not to be contacted, study staff members will thank them for their time, and be put on a do not contact list. Participants will receive $100 compensation via a ClinCard after the interview is completed.

Phase 2: Patients will be identified from weekly reviews of patient charts and discussions with the WCM GI, Head and Neck, and lung clinic staff working alongside Dr. Manish Shah and Dr. Ashish Saxena, respectively. Trained research assistants (RA) will screen patients at the Lung and GI Clinics for eligibility, using WCM's EPIC system. If deemed eligible (see eligibility and exclusion criteria), the research assistant will approach the patient in clinic, to explain the study, and the study procedures. Flyers will also be distributed on WCM/NYP properties. Patient subjects will receive $25 compensation via ClinCard after each interview is completed, with a possible total of $100 by the

end of the study.

- *Anticipated accrual rate*
  - Phase 1 Interviews
    - Recruit and enroll 10 oncology clinicians and 10 bereaved in the 1st 6 months of the study
  - Phase 2
    - Recruit and enroll 50 patients (3/month for ~ 18 months)

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Not Applicable

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events for Phase 1 Interviews (Bereaved Caregivers and Clinicians)

	Pre-study	Visit 1 (Interview)
Screening	X	
Informed Consent *(see note)*	X	
Review of Oncolo-GIST intervention		X
Demographics		X
Oncology Based Communication Questions		X
Semi-structured Interview		X

Table 2. Schedule of trial events for Phase 2

	Arm	Pre-Study	Pre-Scan	Post-Scan 1 (approx. 1 week)	Post-Scan 2	Post-Scan 3	Post-Scan 4 (up to 12 months)
Short Portable Mental Status Questionnaire[S]	P	X					
Health Literacy Assessment (REALM)[S]	P	X					
Informed Consent	B	X					
Oncolo-GIST Training (Clinicians)	C*	X					
Demographics	P		X				
4 Item Illness Understanding	P		X				
Treatment Intent	P		X				
Treatment Preferences	P		X				
CWC II Psychological questions	P		X				
NCCN Distress Thermometer	P		X				
The Human Connection Scale	P		X	X	X	X	
HADS	P		X	X	X	X	
McGill Quality of Life Questionnaire	P		X	X	X	X	
PSWQ-Ultra Brief	P		X				
PANAS	P		X				
Primary Appraisal Secondary Appraisal (PASA) items (Threat and Challenge subscales only)	P		X				
Post Scan Clinician Questionnaire	C			X			
Medical Chart Abstraction	C				X	X	X
Post Scan Patient Questionnaire	P			X	X	X	
Training Quiz	C*	X					
Post-Study Questionnaire	C						X

*C = Clinicians, P = Patients, B = Both, [S]= Screening, * = Intervention Arm Only*

Note: The Post-Scan 4 Chart Abstraction will occur when monitoring if progression of the disease is found after Post-Scan 3 or the patient is deceased; up to 12 months.

7.1 Data Reporting / Regulatory Considerations

7.2 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

7.2.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

7.3 Regulatory Considerations

7.3.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

7.3.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

7.3.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB/IEC requirements, applicable laws and regulations.

7.3.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

7.3.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

7.3.6 Data Safety and Monitoring Plan

Monitoring

A medical monitor is not appointed for this study as the risk level to participants is extremely low. Patients are only approached with the express approval of their treating oncologist. Furthermore, co-investigator Dr. Epstein will consult on the suitability of the study for individual patients, when this is in doubt, as well as any unexpected medical events that occur during patients' participation in the study. Participants' responses to study assessments will be monitored for severe psychological distress. Patients' participation will be discontinued if they experience severe distress attributable to the study, as determined by the co-investigators or their treating

physician. Participants may also withdraw from the study at any time with no effect on their treatment.

Reporting to DSMC

Due to the low clinical risk involved in this study, we propose reporting to the Weill Cornell DSMC on an **annual** basis. Annual reports will comprise: recruitment and retention totals, including voluntary patient withdrawals; a summary of progress since the previous DSMC report; and accounts of any and all adverse events (AEs). For the purpose of this study, an AE is defined as a participant experiencing severe psychological distress, regardless of attribution.

8. Statistical Considerations

8.1 Sample Size/Accrual Rate

Phase 1 Interview: Sample size will be 10 clinicians and 10 bereaved caregivers recruited over 6 months.

Phase 2: The pilot clustered RCT will enroll 4medical oncologists (2Oncolo-GIST Version 2.0 trained; 2usual care) and 50 patients (25 will receive care from an Oncolo-GIST Version 2.0- trained oncologist, 25 will receive usual care) within an 18-month recruitment period. Based on past recruitment yields in the GI and lung cancer clinics at WCM (e.g., recruitment of 60 advanced GI cancer patients alone in 18 months), we are confident that we can recruit this number of eligible patients within an 18- month period. Given this is an oncologist communication intervention, we expect the patient drop-out rate to be low. Fifty participants will ensure fairly stable estimates of intervention effects and confidence intervals and indicate if there is a "signal" that the intervention is helpful for promoting prognostic understanding. Using our validated 4-point prognostic understanding score[4] as a continuous outcome, if Cohen's d is large (0.8), with 48 patients and 4 oncologists, the power will be > 80%. If the effect size is medium (0.5), power will drop to 30%.

8.2 Stratification Factors

25 patients will be recruited to Oncolo-GIST trained clinicians, and 25 patients will be recruited to usual care clinicians in Phase 2.

8.3 Analysis of Endpoints

8.3.1 Analysis of Primary Endpoints

Phase 1 Interviews: We will obtain feedback on the current version of Oncolo-GIST (Version 1.0). Morse's guidelines[15] for rigorous qualitative research (e.g., audit trail, saturation) will be followed and Atlas.ti software used. [16] Themes emerging will be quantified (re: frequency, priority) and considered to inform revisions to the Phase 1 Open Trial Oncolo-GIST intervention.

Phase 2: We will generate preliminary effect size estimates to inform the planning of the larger, efficacy randomized controlled trial (RCT). Hierarchical Linear Modeling (HLM)[17] will be used to evaluate intervention effects. HLM is statistically appropriate because it accounts for the clustering of patients within oncologists, creating nonindependence of clustered assessments. HLM will model oncologists as a random effect as has been done in prior RCTs.[18] [19] Baseline covariates known to affect study outcomes (e.g., patient health literacy) will be included in models to increase the precision of effect size estimates.[20] This will provide a preliminary effect size estimate of Oncolo-GIST Version 2.0's ability to improve patients' prognostic understanding for a future, larger study. Linear and logistic regression models will estimate effects of the

Oncolo-GIST intervention on secondary and exploratory outcomes.

9. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of clinical research. Safety is monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

9.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. In the case of this study, which does not administer any drugs, the only potential AE is psychological distress. Any case of severe psychological distress, as indicated by regular study assessments (see Section 6.1) or by a participant's self-report, will be noted in the AE log, reported to the IRB, and included in the annual DSMC report. AEs will be reported regardless of attribution, which will be determined by the co-investigators according to the schedule below (section 9.1.1).

9.1.1 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- Attribution of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

9.1.2 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

9.1.3 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

9.1.4 Reporting Events to Participants

Not Applicable

9.1.5 Events of Special Interest

Not Applicable

9.1.6 Reporting of Pregnancy
Not Applicable

10. Unanticipated Problems Involving Risks to Subjects or *Others*
Not Applicable

10.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)
Not applicable

10.1.1 Unanticipated Problem Reporting
Not applicable

11. Safety Stopping Rules
We would stop the study if patients in the intervention arm became psychologically distressed and their distress was attributable to the way we are training oncologists to communicate, though it is our hypothesis and aim to demonstrate the emotional and cognitive benefits of our approach. Psychological distress is here defined as self-reported distress on the part of the subject or distress as evaluated by the researcher (defined as an AE in section 7.2.6). As we administer multiple psychometric assessments per interview and enquire about the patient's wellbeing, there is ample opportunity to catch and discuss psychological distress.

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