Preliminary Evaluation of an Internet-Assisted Cognitive Behavioral Intervention for Targeted Therapy Fatigue

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PROTOCOL TITLE: Preliminary Evaluation of an Internet-Assisted Cognitive Behavioral Intervention for Targeted Therapy Fatigue

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A. SPECIFIC AIMS

Targeted therapies are a new generation of cancer drugs designed to interfere with molecular targets critical for tumor growth and progression. One of the first and most successful examples is the oral medication imatinib (Gleevec®), a tyrosine kinase inhibitor (TKI) developed for chronic myelogenous leukemia (CML). Following its introduction, 8-year survival rates for CML improved from <20% to >85%. Several second-generation TKIs have since been approved for CML, and other oral medications targeting TKI pathways have been or are being developed for many other forms of cancer. Although imatinib and similar TKIs are much better tolerated than the regimens they replaced, these medications do possess side effects that are bothersome to patients, interfere with quality of life (QoL), and contribute to problems with adherence. Since TKI therapy typically continues on a daily basis for many years and may be life-long, effective management of side effects is critically important. Research consistently shows that fatigue is the most common symptom in CML patients taking TKIs and the main factor adversely affecting their QoL. It is highly surprising then that there are no published trials of interventions addressing targeted therapy-related fatigue (TTF).

Research has shown cognitive behavior therapy (CBT) is effective against fatigue in disease-free cancer survivors who have completed treatment. Based on this evidence, CBT was among the interventions recommended in guidelines recently developed by the American Society of Clinical Oncology (ASCO) for addressing fatigue in clinically disease-free cancer survivors, including CML patients on maintenance TKI therapy. CBT for Post-Cancer Fatigue (CBT-PCF), an intervention developed by the Consultants in the Netherlands, was specifically cited as an example of an effective strategy based on a randomized trial showing it produced clinically significant improvements maintained over an extended period of time in disease-free cancer survivors who were initially experiencing heightened fatigue following treatment completion.

We propose to build on CBT-PCF, with assistance from its developers, to create a new Internet-assisted form of CBT to address TTF (CBT-TTF). CBT-PCF's conceptual basis is the precipitating-perpetuating model of symptom evolution. Research shows that, once a cancer treatment (e.g., chemotherapy) has precipitated fatigue, certain cognitive and behavioral responses (e.g., catastrophizing and reduced physical activity) then perpetuate it in the posttreatment period. Consistent with this model, CBT-PCF has been delivered in-person in clinic settings using a tailored approach in which up to 6 modules are administered to address perpetuating factors assessed as operative. Unlike chemotherapy patients, CML patients continue to take a medication that can precipitate fatigue. However, research shows that many of the same factors that perpetuate fatigue in the posttreatment period also serve to exacerbate it while patients are on treatment.

Accordingly, the first step is to adapt CBT-PCF, an intervention based on the precipitating-perpetuating model and designed for fatigued cancer patients who completed treatment, to develop CBT-TTF, an intervention based on a revised precipitating-exacerbating model and designed for fatigued patients on maintenance oral targeted therapy. Adopting the tailored modular approach, the team recently completed qualitative research with fatigued CML patients on maintenance TKIs and CML care providers to determine which CBT-PCF modules to retain and adapt and to identify potential new modules to develop based on the conceptual model. In addition, the team has completed formatting the intervention for real-time face-to-face videotelephony delivery via 4G equipped computer tablets (FaceTime via iPads) to minimize travel burden and maximize convenience for participants and to enhance dissemination potential. Now that initial development work has been completed, we propose to evaluate CBT-TTF with fatigued CML patients on TKIs for feasibility, acceptability and potential efficacy relative to usual care only in a small-scale randomized controlled trial.

The specific aims of this protocol are to: 1) Evaluate CBT-TTF and related methods for feasibility and acceptability; 2) Explore the efficacy of CBT-TTF in reducing fatigue (primary outcome); 3) Explore the efficacy of CBT-TTF in improving quality of life and oral medication adherence (secondary outcomes); and 4) Explore the efficacy of CBT-TTF in modifying factors identified as intervention targets (tertiary outcomes).

B. BACKGROUND

B.1. Advent of Targeted Cancer Therapies. Targeted therapies are a new generation of drugs designed to interfere with molecular targets that play a critical role in tumor growth and progression. One of the first and most successful examples was in treatment of chronic myelogenous leukemia (CML). With ~5000 cases diagnosed annually in the U.S.[1], CML accounts for 20% of new adult leukemias. Based on research showing the cause to be formation of the *BCR-ABL* oncogene that produces a constitutively active tyrosine kinase[2], the oral medication imatinib (Gleevec®) was evaluated because it is a potent inhibitor of this enzyme[3]. Clinical trials confirmed its efficacy[4,5] and demonstrated clinically significant differences in quality of life (QoL) favoring imatinib[6] over the existing regimen. Eight-year survival rates for CML patients have since improved from <20% historically to 87% in the imatinib era[7]. The success of imatinib is widely considered a model for development of other targeted cancer therapies[8]. Several second-generation tyrosine kinase inhibitors (TKIs) have since been approved for use against CML[8] and other oral medications targeting tyrosine kinase pathways have been or are being developed for many other forms of cancer[9].

B.2. Fatigue Reports in CML Patients Prescribed TKIs. Due to high potential for recurrence[10-12], daily use of TKIs in CML typically continues for many years and may be life-long. This situation necessitates effective management of TKI side effects. Although imatinib and similar TKIs are better tolerated than many regimens they replaced[6], evidence suggests they possess bothersome side effects that interfere with QoL and contribute to nonadherence[13-16]. Moreover, several studies indicate fatigue is the most problematic symptom experienced by CML patients. Efficace et al[13] found that among 422 CML patients on imatinib an average of 5 years and assessed with a 9-item TKI-specific checklist, fatigue was most common; it was present in 82% of patients and rated as "quite a bit" or "very much" bothersome by 29%. Williams et al[17] found that among 152 CML patients (93% on TKIs) who rated 20 symptoms (0-10) with the MDASI-CML[17], fatigue had the highest severity rating ($\underline{M}$=2.67) and the highest percentage of moderate-severe ($\geq$5) ratings (21%). Differences among TKIs were not significant. Efficace et al[18] asked 236 CML patients on TKIs and 59 CML care providers to identify from among 74 QoL issues a "top 10" list; fatigue was most frequently nominated by each group. Another report speaks to clinical significance. Efficace et al[19] evaluated the relationship of symptoms, clinical features, and demographics to QoL (SF-36[20]). Fatigue (FACIT-F[21]) was independently associated with worse QoL on all SF-36 scales ($p<.05$) and had the highest inclusion frequency of all variables examined. The presence of fatigue was also associated with greater symptom burden, a factor related to poorer TKI adherence in CML patients[16]. These findings led the authors to conclude, "*… fatigue is the main factor limiting the [health-related] QOL of CML patients who receive long-term imatinib therapy*"[19].

B.3. Interventions to Address Targeted Therapy-Related Fatigue (TTF). Despite its importance, we could not identify any published intervention trials for TTF. In the absence of understanding TTF's pathophysiology[19], recently issued clinical practice guidelines for addressing fatigue in cancer survivors[22] suggest promising strategies. The guidelines state they are applicable to patients off-therapy as well as patients on maintenance therapies such as TKIs for CML[22]. While evidence was insufficient to recommend pharmacologic therapies, it was sufficient to recommend physical activity interventions and cognitive behavior therapy (CBT). With regard to the latter, an intervention developed by the Consultants was cited as a prime example[23]. This intervention (CBT for Post-Cancer Fatigue or CBT-PCF) was designed for disease-free patients who completed treatment but were experiencing elevated fatigue. Its conceptual basis, the precipitating-perpetuating symptom model, has been applied successfully to chronic pain and sleep problems[24,25]. We have shown the model to be applicable to cancer-related fatigue in that treatments (e.g., chemotherapy) routinely function as precipitating factors, while certain cognitive responses (e.g., catastrophizing) and behavioral responses (e.g., reduced physical activity) to fatigue contribute to its persistence and worsening over time[26,27]. Based on this model and relevant research, CBT-PCF focuses on 6 possible perpetuating factors: insufficient coping with cancer; fear of disease recurrence; dysfunctional fatigue-related cognitions; sleep dysregulation; activity dysregulation; and low social support/negative social interactions. An innovative feature is use of a modular approach in which the intervention is tailored based on those perpetuating factors assessed as operative. To test it, 112 fatigued cancer survivors in the Netherlands were randomized to CBT-PCF or a wait-list control condition[23]. The intervention ($\underline{M}$=12.5 1-hour sessions) was delivered in-person in clinic settings by trained and supervised therapists. Fatigue (primary outcome) was assessed at baseline and 6 months later using the CIS[28]. At 6 months, CBT-PCF patients showed a greater decrease in fatigue than control patients ($p<.001$); clinically

significant improvement (based on reliable change index) was evident in 54% of CBT-PCF patients vs. 4% of control patients ($p<.001$)[23]. At a follow-up a median of 2 years after therapy completion, fatigue remained lower than at baseline ($p<.05$) and similar to levels seen at the 6-month assessment among patients offered CBT-PCF[29].

B.4. Adaptation of CBT-PCF. As noted earlier, the team recently completed the process of adapting CBT-PCF for use with fatigued patients on maintenance oral targeted therapy. This work, which was accomplished under another IRB-approved protocol, involved conducting in-depth interviews with 10 CML patients at Moffitt prescribed a TKI who were experiencing heightened fatigue and 4 health care professionals at Moffitt (two MDs, two ARNPs) who provide care to patients with CML. In general, patients and providers felt that all the existing modules were relevant and had potential to improve fatigue in patients on maintenance oral targeted therapy. Suggested changes focused on modifying reference to fear of cancer recurrence (an issue more relevant to patients who have completed treatment for early stage solid tumors) to instead refer to fear of increasing disease activity (an issue more relevant to patients who are on maintenance therapy to control their disease). Interviews also suggested that patients would benefit from psychoeducation designed to review understanding of their disease and its treatment, provide basic factual information their disease and its treatment, and identify discrepant beliefs about their disease and treatment that could be addressed as part of other modules (e.g., the helpful thinking module). Based on feedback, a number of minor changes were made to the therapy manual and an additional psychoeducation module was created. Finally, feedback about the proposed delivery channel for the intervention (i.e., FaceTime using iPads) from patients and providers was generally positive.

C. APPROACH

C.1. Approach Overview. A pilot RCT will be conducted in which fatigued CML patients taking TKIs are randomized to a CBT-TTF intervention condition (CBT-TTF) or a wait-list control condition (WLC). As part of trial initiation, we will seek to recruit and obtained informed consent for up to 3 patients per treating therapist and provide them with CBT-TTF and administer all study measures so the therapists can gain experience in administering the intervention per protocol before they are assigned patients randomized to receive the intervention. Data for these patients will not be included with data based on randomization of study participants. As noted below, therapists will have already studied the intervention and practiced it before this activity takes place and will be closely supervised by senior clinicians with considerable relevant experience.

C.2. Eligibility Criteria. Participants must: 1) be $\geq$18 years old; 2) be able to speak/read English; 3) be diagnosed with chronic phase CML; 4) not have been treated for other cancer (except non-melanoma skin cancer) in the past 5 years; 5) be under the care of a MCC physician; 6) be on the same oral TKI for $\geq$3 months; 7) new onset or worsening of fatigue since starting TKI; 8) report moderate-severe fatigue in past week (FSI average rating $\geq$4 of 0-10)[30]; and 9) have no clinical history of disease (e.g., multiple sclerosis, fibromyalgia) that could account for their fatigue presentation. Patients must not: 1) be scheduled to discontinue their TKI under medical supervision within the next 3 months.

C.3. Recruitment. Participants will be identified via review of medical records compliant with HIPAA guidelines or through the cancer registry. Those identified will be telephoned by the Study Coordinator (SC), at which time the study will be described and they will be screened for fatigue (eligibility criteria #7-8 above). Those who meet all eligibility criteria and express interest in participating will be sent a secure email link to an online informed consent form (if they have Internet access) or will be mailed a paper copy of an IRB-approved consent form along with a postage-paid return envelope (if they do not have Internet access) to review. The SC will re-contact the patient by telephone to see if he/she has any questions and to see if he/she wishes to participate.

C.4. Baseline Assessment. Those patients providing informed consent will be asked to complete a baseline (T1) questionnaire using a secure weblink (if they have Internet access) or a scanable form mailed to them along with a postage-paid return envelope (if they do not have Internet access). See below for content of this 40-minute questionnaire. The Study Coordinator (SC) will be available via a toll-free telephone number to

answer any questions and provide any needed assistance. Participants will be paid $25 for completing this assessment.

C.5. Randomization. A randomization schedule will be prepared by the MCC Biostatistics Core under Dr. Small's supervision and transferred to a secure intranet application. As noted below (C.10.5), participants will be randomized to CBT-TTF or WLC on a 2:1 basis. Randomization will be stratified by gender. After completion of the baseline questionnaire, the SC will use it to assign patients in a 2:1 ratio to CBT-TTF or WLC. The SC with then notify the participant by telephone of his/her intervention assignment and describe next steps based on intervention assignment (see C.6 and C.7).

C.6. Wait-List Control Condition (WLC). Participants randomized to this condition will continue to receive care under direction of their MCC physician. Physicians will be informed by email of patients' participation on the basis of elevated fatigue and their randomization to WLC. Chart review and a patient self-report form will be used at baseline and follow-up assessments to determine what, if any, services or interventions participants received in the preceding 18 weeks that might address fatigue. Similar data will be collected for CBT participants for services and interventions unrelated to study participation. Upon completion of the follow-up assessment (see below), participants randomized to WLC will be offered the opportunity to receive CBT is the same manner as described below (see. C.7). Follow-up questionnaire data will be collected from WLC participants who elect to receive CBT as described in Tables 1 and 2.

C.7. Cognitive Behavior Therapy for Targeted Therapy-related Fatigue (CBT-TTF)

C.7.1. Content and Delivery. CBT-TTF retain CBT-PCF's basic format of assessing perpetuating/exacerbating factors and selecting modules based primarily on factors determined to be operative[23]. The assessment of these factors will occur as part of the baseline assessment. See below for details on assessment of these factors. Consistent with CBT-PCF, therapists will introduce the intervention and its rationale in an initial in-person session held at Moffitt. The therapist will also present results of the assessment of perpetuating/exacerbating factors during this session and will outline the therapy plan based on the modular approach. This initial session is expected to last 90 minutes. Determination of the ordering of modules will be decided during therapist supervision (see below). Each CBT-TTF module (with the exception of psychoeducation) follows a basic format of problem recognition, solution generation, implementation, and progress evaluation. Subsequent sessions will initially be held weekly for approximately 45 minutes each using FaceTime (see below) at a time mutually agreed upon by the participant and therapist. Depending on participant progress in meeting therapy goals, therapists will have the option of scheduling some sessions at 1-2- or 3-week intervals. As with CBT-PCF, participants who completed all planned therapy sessions prior to week 18 will receive one or more booster sessions at 1-, 2- or 3-week intervals. These booster sessions are designed to monitor participant's continued used of recommended strategies to address fatigue. As with CBT-PCF, a final session will summarize progress and ways to maintain therapeutic gains. Participants will be given the option of conducting this final session in-person at Moffitt or via FaceTime. A complete description of CBT-TTF is provided in the Therapy Manual included as an Appendix.

C.7.2. Therapist Training and Supervision. Therapists are students admitted to the USF Clinical Psychology Doctoral Program. As part of their study-related activities, therapists will participate in training, supervision, and treatment fidelity oversight as described below. Dr. Jim, licensed psychologist with considerable experience in providing CBT, has already trained two therapists in collaboration with the Consultants (Drs. Knoop and Gielissen), developers of CBT-PCF. Training involves the therapists reviewing the CBT-TTF therapy manual and then rehearing intervention elements in modeling and role-playing sessions. As part of this protocol, each therapist will be assigned up to 3 patients who meet all eligibility criteria and provide informed consent in order to gain experience delivering the intervention per protocol before they are assigned participants on the basis of randomization. Throughout the time they provide interventions to participants, the therapists will meet weekly with Dr. Jim for supervision. Dr. Jim will use audio recordings of therapy sessions and therapist observations to ensure CBT-TTF is administered effectively and consistent with the manual. Dr. Knoop will participate in the supervision sessions via videconference during initial months of each therapist's activity to address any new issues that may not have arisen during training.

C.7.3. Intervention Fidelity. Audio recordings will be made of all therapy sessions; 25% of each therapist's sessions will be selected randomly on an ongoing basis for fidelity rating. Using checklists specific to each

module, Dr. Jim will rate adherence to key intervention elements and describe instances of nonadherence. This information will be shared with the therapist and Dr. Jim and used in supervision sessions to promote continued fidelity. It will also be summarized for reporting purposes.

C.7.4. Use of Videotelephony. Following the initial in-person session, CBT-TTF will be delivered in real time and face-to-face via an encrypted videotelephony application (FaceTime) using iPads (Model A1454), an approach that meets HHS standards for security and privacy and is HIPAA compliant (healthit.gov/mobiledevices). The rationale for this approach over in-person clinic-delivered sessions is to minimize travel burden, maximize convenience, and foster greater dissemination potential, while maintaining key elements of face-to-face therapeutic interactivity. iPads programmed and modified by the MCC Survey Methods Core will be 4G equipped so individuals without Internet access can participate and for security purposes. Each device will be WPA-2 password enabled and loaned to a participant for the duration of participation. Restrictions will be set to protect iPads from virus contamination, including not allowing Wi-Fi access since many networks are not encrypted or password secured. As part of intervention assignment notification, the SC will demonstrate iPad use, place a practice FaceTime call to the participant, and arrange regular and convenient times for FaceTime sessions. Participants will also be provided with the name and telephone number of a contact in the MCC Survey Methods Core who can provide any needed technical assistance.

C.8. Follow-up Assessments. Based on the once weekly format, we estimated that the maximum number of modules can be completed within 18 weeks. Accordingly, all participants will be asked to complete the follow-up (T2) questionnaire approximately 19 weeks post randomization (see below for content). Participants will be asked to complete the form online using a secure weblink (if they have Internet access) or on paper using a form mailed to them by the SC along with a postage-paid return envelope. The SC will telephone and or email participants to remind them to complete the form up to 3 times if it is not completed and returned within 5 business days of being made available to participants. Waitlist control participants who elect to receive the intervention will complete a T3 questionnaire after they complete the intervention. The T3 questionnaire will be identical to the T2 questionnaire. Participants will be paid $25 for completing each follow-up questionnaire.

C.9. Study Measures.

C.9.1. Demographic and Clinical Characteristics. Demographic information (e.g., age, gender, race, ethnicity, marital status, education, occupation, income, alcohol use, tobacco use, prescription and non-prescription medication use, history of fatigue and self-reported comorbidities[31] will be collected via a self-report form at T1. Clinical information (e.g., height, weight, Sokal group, CML diagnosis date, current TKI start date, dosing instructions for current TKI, previous TKI [if applicable], current additional targeted therapy [if applicable], current hematologic response [complete, incomplete, none], date of current hematologic response, current cytogenetic response [complete, partial, minor, minimal, none], date of current cytogenetic response, current molecular response [complete, major, none), and date of current molecular response] will be collected via chart review at T1 and T2.

C.9.2. Primary and Secondary Outcomes. The primary outcome (fatigue) and secondary outcomes (QoL, adherence) outcomes will be assessed via self-report at T1 and T2 (see Table 1). CBT-TTF participants will also be asked at follow-up to rate their satisfaction with the intervention using items used previously to evaluate Internet-assisted interventions.[32]

Table 1. Primary and Secondary Outcomes and Associated Measures
Fatigue will be assessed with the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue)[21] v.4, a 13-item self-report measure yielding total score with demonstrated reliability, validity, sensitivity to change[21] and an identified Minimally Clinically Important Difference (MID)[33]
Quality of life will be assessed with the Functional Assessment of Cancer Therapy General Scale (FACT-G)[34] v.4, a 27-item measure yielding total score and scores for physical, social/family, emotional, and functional well-being of demonstrated reliability, validity, and sensitivity to change[34]
Medication adherence will be assessed with the self-report Morisky Medication Adherence Scale (MMAS), an 8-item self-report measure of demonstrated reliability and validity[35] used previously with CML patients[36]
Symptom burden and impact on daily functioning will be assessed with the M.D. Anderson Symptom Inventory for Chronic Myelogenous Leukemia (MDASI-CML)[17], a 26-item self-report measure yielding total

score with demonstrated reliability, validity, and sensitivity to change.

C.9.3. Perpetuating/Exacerbating Factors. As described above, CBT-TTF participants will be assessed for perpetuating/exacerbating factors at T1 in order to determine the selection of certain therapy modules. They will be reassessed for the same factors at T2. WLC participants will also be assessed on these factors at T1 and T2. These data will be used to explore whether intervention assignment was related to changes on factors identified as therapeutic targets. See Table 2 for descriptions of factors to be assessed and measures to be used to assess those factors. Please note that for some factors there is more than one measure to be used for assessment purposes. Should scores on any measure for a factor exceed the cut-off, that measure will be included in CBT-TTF. All CBT-TTF participants will receive the Psychoeducation module; therefore, there is no measure associated with this module.

Table 2. Perpetuating/Exacerbating Factors (Tertiary Outcomes and Associated Measures
The Sickness Impact Profile (SIP) sleep-rest subscale is a 7-item measure assessing sleep-rest patterns.[37,38] Respondents are asked to check a box next to the symptoms that apply to them. Higher scores are indicative of more dysregulated sleep-rest patterns. Based on previous research,[23] a cutoff of ≥60 will be used to determine whether participants should receive the Disturbed Sleep/Wake Rhythm module of CBT-TTF.
The Daily Sleep Diary is an 8-item assessment of sleep-wake patterns administered daily.[39] Daily ratings are averaged together to yield a total score with higher scores indicating poorer sleep. An average weekly rating of 5 or higher will be used to indicate poor sleep and to determine whether participants should receive the Disturbed Sleep/Wake Rhythm module of CBT-TTB.
The Checklist for Individual Strength (CIS) is a 20-item measure that assesses subjective fatigue and related behavioral components of fatigue.[28] This study will focus on the concentration scale which is a 5-item measure that assesses the extent to which patients are experiencing concentration problems in the last two weeks. Each item is rated on a 7-point response scale ranging from “yes, this is true” to “no, that is not true”. Concentration scores can range from 5 to 35 with higher scores indicating more concentration problems. A cutoff of 16 will be used based on prior research[23] to determine whether participants should receive the Activity Regulation module of CBT-TTF.
The Sickness Impact Profile (SIP) social interaction subscale is a 20-item measure that assesses negative social interactions.[37,38] Respondents are asked to check a box next to the items that apply to them. Higher scores are indicative of more dysfunctional social interactions. A cutoff of 150 will be used based on prior research[23] to determine whether participants should receive the Activity Regulation module of CBT-TTF.
The International Physical Activity Questionnaire (IPAQ) Short Form is a 7-item measure assessing health-related physical activity.[40] Items are assessed in 4 generic domains including moderate and vigorous physical activity, walking, and sitting. Respondents are asked to rate how many days per week they engage in the activity and for how much time per day. Physical activity is then classified into low, moderate, or high levels with higher classifications indicating greater activity. American Cancer Society guidelines[41] recommend 150 minutes of moderate intensity activity or 75 minutes of vigorous intensity activity each week (or a combination of these). These guidelines will be applied to IPAQ reports and participants who do not meet this threshold will be administered the Activity Regulation module of CBT-TTF.
The Impact of Events Scale (IES) is a 15-item measure assessing psychological stress.[42] Both the intrusion and avoidance subscales of the IES will be used for this study. Items are rated on a 4-point response scale (0=no bother/avoidance; 3=often bothered/avoids). Based on prior research,[23] scores of 10 or above are indicative of significant psychological stress and will be used to determine whether participants should receive the Insufficient Processing module of CBT-TTF.
The Illness Cognition Questionnaire (ICQ) is an 18-item measure that assesses favorable and unfavorable ways of adjusting to chronic illness.[43] Each item is rated on a 4-point response scale (1=does not agree at all; 4=completely agrees). The ICQ groups cognitions into three dimensions including acceptance, helplessness, and perceived benefit. This study will focus on acceptance for which a cutoff of ≤12 will be used and helplessness for which a cutoff of >14 will be used based on prior research[23] to determine whether participants should receive the Dysfunctional Thinking module of CBT-TTF.
The Self-Efficacy Scale 28-Fatigue (SES28) is a 5-item measure assessing the extent to which a respondent feels they have control over their fatigue.[44] Items are rated on a 5-point scale ranging from “no, out of the

question" to "yes, I'm sure". Higher scores are indicative of a greater sense of control over fatigue symptoms. Based on previous research,[23] a cutoff of ≤19 will be used to indicate low self-efficacy in this study and to determine whether participants will receive the Dysfunctional Thinking module of CBT-TTF.
The Fatigue Catastrophizing Scale (FCS), a 10-item measure that assesses catastrophizing thoughts about fatigue.[27] Each item is rated on a 5-point response scale ranging from "never true" to "all of the time true". A total score is derived by averaging the 10 ratings. Higher scores on the FCS are indicative of greater catastrophizing thoughts. A cutoff of ≥16 will be used based on prior research[23] to indicate whether or not a patient is having catastrophizing thoughts about their fatigue and to determine whether participants should receive the Dysfunctional Thinking module of CBT-TTF.
The Illness Management Questionnaire-Focusing on Symptoms (IMQ--factor III) is a 9-item subscale of the Illness Management Questionnaire that assesses the extent to which patients are preoccupied by their symptoms and appraise their life as dominated by their symptoms.[45] Items are rated on a 6-point response scale ranging from "never" to "always." Higher scores are indicative of greater preoccupation with symptoms. Based on previous research,[23] a cutoff of ≥10 will be used in this study to determine whether patients should receive the Dysfunctional Thinking module of CBT-TTF
The Social Support List-Negative Interactions (SSL-N) is a 14-item measure that assesses perceptions of negative social interactions. The SSL was developed in the Netherlands and was validated with an English-language sample.[46] Items are rated on a 4-point scale ranging from "seldom or never" to "very often" with higher scores indicating that the respondent experiences more negative interactions. Based on prior research,[23] a cutoff of ≥10 will be used to determine whether participants should receive the Social Support and Interactions module of CBT-TTF.
The Social Support List-Discrepancy (SSL-D) is a 8-item measure that assesses discrepancy between perceived and desired social support. The SSL was developed in the Netherlands and was validated with an English-language sample.[46] Items are rated on a 4-point scale ranging from "I miss it, I would like it to happen more often" to "It happens too often, it would be nice if it happened less often". Higher scores are indicative of a greater discrepancy between perceived and desired social support. Based on prior research,[23] a cutoff of ≥53 will be used to determine whether participants should receive the Social Support and Interactions module of CBT-TTF.
The Cancer Worry Scale (CWS), an 8-item measure that assesses concerns about developing cancer or experiencing a cancer recurrence[47] has been adapted for use in the current study. Each item is rated on a 4-point response scale (1="never"; 4="almost always"). Higher scores indicate that the respondent experiences more frequent worries about their cancer. A cutoff of ≥14[47] will be used to determine whether participants should receive the Heightened Fear of Increase in Disease Activity module of CBT-TTF.

C.10. Statistical Analyses.

C.10.1. Preliminary Analyses. Descriptive and graphical statistics will be used to check distributional assumptions and appropriate transformations or non-parametric methods will be applied as necessary. Analyses will be conducted to evaluate if randomization was successful in yielding groups equivalent with regard to demographic and clinical characteristics. If even marginally significant differences ($p<.1$) are observed, the characteristic will be included as a covariate in subsequent multivariable analyses.

C.10.2. Analyses Related to Aim 1. To calculate the participation rate, the number of individuals who consent will be divided by the number of individuals who meet all eligibility criteria and provide an informed consent. The study will be considered acceptable if this rate is ≥50%. To calculate the retention rate, the number of individuals who complete baseline and follow-up assessments will be divided by the number of individuals who provide informed consent and are not discontinued due to ineligibility. To calculate the CBT-TTF completion rate, the number of sessions participants in this condition are expected to complete will be divided by the number of classes actually completed. The study will be feasible if these two rates are ≥70%.

C.10.3. Analyses Related to Aims 2, 3 and 4. FACIT-F scores at baseline and follow-up (primary outcome) will be treated two ways. First, they will be used as continuous variables in a repeated measures analysis (SAS PROC MIXED) to evaluate longitudinal changes as a function of group assignment (CBT-TTF vs. UCO). Although data will be evaluated for statistical significance, the primary purpose is to compute the effect size (Cohen's d) at follow-up (i.e., difference between the groups divided by pooled standard deviation). CBT-TTF will be considered potentially efficacious if $d \geq 0.5$ (i.e., medium sized effect) favoring CBT-TTF. A similar strategy will be applied to continuous FACT-G and MARS scores (secondary outcomes) and scores for

measures of perpetuating/exacerbating factors (tertiary outcomes). Second, we will classify each participant's change on the FACIT-F for whether or not it meets a minimal clinically important difference of ≥3 points of positive change[33]. This dichotomous score will then be used as the outcome in a logistic regression analysis with intervention group as the predictor. Finally, we will conduct exploratory analyses to evaluate if the number of sessions of CBT-TTF moderates changes in FACIT-F scores using a residualized change regression approach.

C.10.4. Missing Data and Protection of Type I Error. Multiple imputation will be used for sporadic missing data[48]. To protect against Type I error, principal analyses for Aims 2-3 are designed to answer well-defined questions about potential efficacy based on well-specified primary and secondary outcome variables. All tests will be two-tailed at alpha=.05.

C.10.5. Sample Size. Because this is an exploratory study, we seek a sample size that will provide reliable estimates of feasibility and acceptability. Accordingly, we will enroll 48 participants allocated on a 2:1 ratio to the intervention arm (n=32) and the control (n=16). Nevertheless, these sample sizes allow us to detect between group differences of .88 SD units at follow-up with power=.80 at alpha=.05 (two-tailed), a difference smaller than that observed by Gielissen et al.[23] for CBT-PCF at the 6-month point (d = 1.04). Moreover, the within group sample sizes used here allow us to detect a change of .51 SD units, which corresponds to the threshold for potential efficacy described above. Pharmacy data indicate MCC physicians care for ~370 CML patients on TKIs. If only 40% are eligibility criteria and agree to participate (n=148), numbers are still sufficient to complete the proposed work.

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