Statistical Methods

Specific Aim 1: Examine the effectiveness of iCBT in improving community reintegration and overall quality of life. Community reintegration will be measured using the 3 subscales of the CRIS-CAT: extent of participation, perceived limitations, and satisfaction with participation. Quality of life will be measured by the SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Although our quantitative analyses will be intention-to-treat, we will provide information on the number of and characteristics of any participants who did not receive the treatment as allocated or who did not complete the study. We will tabulate baseline characteristics, such as age, race, gender, disease severity, comorbidities, and psychotropic medications. Based on recommendations of the CONSORT group,[81] we will adjust analyses for variables we have decided *a priori* may be important to control (i.e., depression, period of service [OEF/OIF/OND, Gulf War, and other] concomitant psychotropic medication use, and the primary diagnosis stratification variable). Results from both an intent-to-treat and treatment completer analyses will be compared.

Hypothesis 1a: *iCBT and sCBT will significantly improve community reintegration and quality of life relative to TAU at 3-and 6-month follow-ups. To compare changes between the iCBT, sCBT, and TAU groups at all time periods in a single regression, we will use a hierarchical mixed-model analysis. Because the number of patients randomized to the 3 groups is not equal, we will test for unequal variances and if necessary, will account for this in our regression models. For outcomes with unequal variances, in the mixed model, we will estimate the variances separately and adjust the degrees of freedom for the unequal variances. The model will contain terms for the intercept, treatment, time period and interaction between time and treatment. A priori covariates as well as the stratification variable of anxiety disorders will also be included in the model. A significant time-by-treatment interaction will be followed by pairwise contrasts to determine whether the active interventions differed from TAU and whether the active treatments differed from each other. We will report the p-values and adjust p-values post-hoc using multiple comparisons procedures (e.g., Bonferroni) as recommended in the literature.*[82]

Hypothesis 1b: *iCBT will result in improved reintegration/quality of life measures relative to sCBT at 1-month follow-up. Only patients in the iCBT and sCBT groups will be used in the analyses. For each outcome, we will run a hierarchical linear regression model using the baseline and 1 month data and with the a priori covariates and anxiety disorder stratification variables. Patients will be nested within therapist. The models will contain the 1 month value as the outcome variable and the baseline value of the outcome as an additional covariate.* A significant value for the parameter estimate for the intervention will indicate that the iCBT and sCBT groups differed at 1 month.

Specific Aim 2: ***Examine the effectiveness of iCBT in reducing anxiety/depression symptoms relative to sCBT and TAU***. **Hypothesis 2a***: iCBT and sCBT will significantly reduce anxiety and depression symptoms relative to TAU at 3-and 6- month follow-ups. The analyses described for hypothesis 1a will be repeated for this hypothesis using the secondary outcomes. Anxiety will be measured using the BAI and depression measured using the BDI-II.*

Hypothesis 2b*: iCBT will result in improved anxiety/depression measures relative to sCBT at 1-month follow-up. The analyses described for hypothesis 1b will be repeated for this hypothesis using the secondary outcomes.*

Specific Aim 3 (Exploratory): Hypothesis 3a: Compare rates of psychotherapy engagement in iCBT relative to sCBT. We will use hierarchical logistic regression models to test if the iCBT and sCBT groups differed on treatment engagement (defined as the percentage of randomized patients who participated in 12 or more treatment hours). The outcome will be whether or not

the patient completed 12 or more treatment hours. The a priori variables to be included as independent variables in the treatment engagement model will be selected based on the SOTA Access model described earlier. Items comprising the subscales of geographical, temporal, financial, and cultural barriers will be selected from the PB-SMHS measure for inclusion. The model will also include intervention group and our primary diagnosis stratification variable. To account for clustering, we will nest patients within therapist. **Hypothesis 3b**: Examine heterogeneity of treatment effects on 3- and 6-month outcomes. Because our sample size may not be adequate to substantiate sources of heterogeneity of treatment effects (HTE), exploratory analyses will allow us to describe patterns that can be examined in future larger trials. We will assess HTE on 3-and 6- month effectiveness outcomes through examining potential moderators collected at baseline including demographics, geographic region, co-occurring depression, psychiatric comorbidity, and medication use. Examining the role of potential moderator variables will provide a better understanding of how individuals vary in their response to iCBT and the conditions under which iCBT may be optimal. Following the approach suggested by Kent et al[83] for assessing HTE, we will use a multivariable prediction tool to report how relative and absolute risk reduction varies by baseline risk. We will use an internally-developed model from a regression analysis of data from the active treatment arms. Per Brookes et al[84], we will test the interaction terms in the models as the most statistically robust approach to assessing HTE. Missing Data for quantitative analyses: To assess impact of missing data, we will conduct sensitivity analyses using tests for missing completely at random and tests for nonrandom missingness using approaches suggested by Molenberghs and Kenward.[85] These will allow us to evaluate whether the reasons for loss to follow-up at the various time periods are related to the observed values of the outcome variables. We will also plot the data over time to visually assess changes in outcomes from baseline to 3 and 6 months and to indicate whether additional terms are needed in the models to account for nonlinearity over time*. We will also follow recommendations provided by Sterne et al.[86] regarding multiple imputation methods for missing data in clinical research. In performing our imputation techniques, we will assess non-normality of the data and transform variables as needed to approximate normality before imputation and then transform the imputed values back to the original scale. We will attempt to avoid bias in the imputation analyses by including all variables in the substantive analyses and when computationally feasible, all variables predictive of the missing values and all variables influencing the cause of the missing data, even if they are not of interest in the substantive analysis.*

Initial analyses will be intention-to-treat. We will use the PROC MI in SAS software for multiple imputation of the missing data. The Markov chain Monte Carlo method will be used for imputation if the dataset has arbitrary missing data patterns. PROC MIANALYZE will subsequently be used to combine the results of the analyses of imputation to generate valid statistical inferences. In addition to the analyses of imputed data, we will conduct completer analyses on the observed data. *If the results of the completer analyses and analyses based on imputed values differ, we will look for possible reasons and report this in our publications. Sensitivity analyses will investigate the robustness of the findings to be assumed missing not at random (NMAR).[87,88]*