SUPPORTING STATEMENT - PREVALENCE & CLINICAL COURSE OF DEPRESSION AMONG PATIENTS WITH HEART FAILURE, VA HSR&D, NURSING RESEARCH INITIATIVE # 05-209-3
VA FORM 10-21085a,b,c,d,e(NR)
OMB-2900-XXXX

II. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS:

1. Provide a numerical estimate of the potential respondent universe and describe any sampling or other respondent selection method to be used. Data on the number of entities (e.g. households or persons) in the universe and the corresponding sample are to be provided in tabular format for the universe as a whole and for each strata. Indicate response rates. If the collection had been conducted previously, include the actual response rate achieved.

a. The number of respondents for the entire period of the research study is N=218. These respondents are patients with heart failure (HF). The sample selection method is as follows:

(1) The primary inclusion criterion will be admission to the hospital with the primary diagnosis of HF. The diagnosis of HF will be determined on admission using Ho's HF epidemiologic criteria in which patients meet either 2 major criteria or 1 major criterion and 2 minor criteria.[1] Major criteria include: paroxysmal nocturnal dyspnea, neck vein distension, rales, radiographic evidence of cardiomegaly, acute pulmonary edema, S_3 gallop, increased central venous pressure (right atrial pressure = > 16 cm), and circulation time $\geq$ 25 seconds. Minor criteria include: bilateral ankle edema, nocturnal cough, exertional dyspnea, hepatomegaly, pleural effusion and tachycardia (rate > 120/minute).[1] Other inclusion criteria are: 1) left ventricular ejection fraction (LVEF) $\leq$ 45% by echocardiogram, 2) New York Heart Association (NYHA) Class I-IV, and 3) literate in English. For those HF patients admitted with a higher acuity (i.e. cardiogenic shock requiring intraaortic balloon pump and/or intubated with or without a respirator) enrollment will be deferred until the patient is stable enough to participate as indicated by the attending medical doctor (MD). Exclusion criteria will be: 1) admission with primary diagnosis of myocardial infarction and/or coronary artery bypass surgery with subsequent development of HF; 2) previous enrollment in this study (i.e., hospital readmission for any causes after study participation); 3) acute infection, and 4) autoimmune disease, such as rheumatoid arthritis, Raynaud's disease, etc. 5) major psychiatric disorder other than depression (i.e., schizophrenia, bipolar disorder, and current substance abuse), and 6) documented cognitive impairment (i.e. dementia or Alzheimer's). In the absence of documented dementia, exclusion based on cognitive impairment will be determined by a mini-mental state (MMSE) score of 12.[2]. In the study of Ruckdeschel et al, the Minimum Data Set mood disturbance items can be reliably and validly administered via self-report in patients with a $\geq$12 MMSE score.[2] Since both anxiety disorders and post-traumatic stress syndromes (PTSD) are highly comorbid with depression, HF Veterans with these disorders will not be excluded from the study.

(2) Every effort will be made to recruit women and minorities into the study. The VA Greater Los Angeles Health Care System [VA GLAHS] has a robust research program and has not experience difficulty recruiting participants of different ethnic distribution. Hence, recruitment of minorities will not be a significant problem. Because most Veterans are male, an attempt will be made to oversample women, which will be very difficult. From 1997 to 1999, women accounted for only 1.6% of Veterans with HF nationally.[3] This study will oversample women with a target of 5% (N=13), which may be achievable in the proposed 2.25 years of enrollment. However, oversampling women by 5% will not yield enough power to evaluate depression among Veteran women with HF

b. <u>Data on the number of respondents:</u> Based on the research objectives of the research study, each respondent (patient) will respond to the same information (questionnaires) about 4-6 times in a period of 1 year. Overall, the total data collection time points will be N=1308.

c. Response Rates: This is a new application; therefore, the response rates for this research study are unknown. In the PI's previously funded research study (VA HSR&D, NRI # 96.031.1), the response rates of those who complete the study are quite high (about 80%).[4] However, there are respondents who dropout prior to the completion of the study (either voluntary withdrawal or death). These dropout influences the response rates. For this reason, the research team accounted for dropout rates and non-response bias in the calculation of study sample size (see response below #2).

2. Describe the procedures for the collection of information, including: 1) Statistical Methodology for stratification and sample selection; 2) Estimation procedure; 3) Degree of accuracy needed; 4) Unusual problems requiring specialized sampling procedures; and 5) Any use of periodic less frequent than annual data collection to reduce burden.

a. The statistical methodology employed to determine sample size is explained below. Dropouts (a potential problem in any longitudinal research study) were accounted for in the estimation of sample size. The proposed sample size will be 218 Veterans admitted with a primary diagnosis of HF at VA GLAHS. Initially, the sample size was calculated based on effect sizes derived from related non-VA studies.[5-7] A sample of 80 HF patients was sufficient to yield a trend toward a positive correlation of depression and physical functioning (r= .21, p= .06) when a less sensitive measure of depression, the Multiple Affect Adjective Checklist, was used. Further sample size calculations were based on prevalence reports of hospitalized and community-dwelling HF patients with depression and with ages comparable to those of Veterans with HF. The rate of major depression in hospitalized HF patients was 36.5%[8] compared to 11% among community dwellers.[6] Differences of this magnitude yield a large effect size (w= .53). Using α = .05 and power = .80, a sample of 28 patients would be sufficient to identify group differences. To be conservative, the plan was for a more modest medium-sized effect (w= .30). Under the same conditions, a sample size of 88 will be sufficient to yield statistically significant differences (medium effect size of .30, α= .05, and power= .80) between hospitalized and community dwelling Veterans. For the proposed third aim of the study, effect sizes were calculated using the limited data currently available regarding correlations between cytokines and depression in HF patients (Table 1).[7] Where data was not available, medium effects were assumed. Based on these calculations and assuming a maximum of 10 covariates in multiple regression analyses, it's estimated a final sample size of 118 will be needed to show statistical significance for a particular predictor with α= .05, and power= .80.

Table 1. Effect Sizes for Biomarkers and Sample Size to obtain 80% power with α = 0.05

Outcome Variable	R	R^2	Effect Size	Total Required Sample
TNF-α (pg/ml)	.47	.21	.266	71
Interleukin-6 (pg/ml)	.36	.13	.150	118
Interleukin-10 (pg/ml)	.64	.41	.695	34
TNF-α/ Interleukin-10	-.56	.31	.449	47

b. Since this is a 1-year longitudinal study, potential dropouts were accounted for in the calculation of the total sample size. VA summed mortality and non-mortality related dropout from other HF studies. First, the mortality rate was evaluated of HF up to 1 year after index admission (Table 2); the most appropriate study indicated mortality rate of 28% (in males). Second, in the applicant's pilot work, the non-mortality dropout rate was 18%. Summed together, these rates support a proposed total dropout rate of 46%. Thus, based on the formula: 118/(1-.46), a final sample size of 218 is anticipated.

Table 2. 30-Day, 3-, 6- and 12-month mortality after HF Hospitalization

Author, Year	Sample Size	30-day	3-month	6-month	12-month
Deswal et al, 2004[3]	Veterans (N = 21,994)	7%	-	-	23%
Jiang et al, 2001[9]	Non-Veterans (N=374)	-	7.9%	-	16.2%
Levy et al, 2002[10]L	Non-Veterans (N=323)				28% (Male)
Smith et al, 2003[11]	Non-Veterans (N = 413)	-		21%	

c. The collection of information (data collection via questionnaires) is more frequent than annually because of the stated objectives of the research study. Currently, evaluation of depression is not a standard of practice among patients with HF. Eventually, this study may provide clinicians the appropriate timing and frequency necessary to evaluate depression in patients with HF; consequently, reducing respondent burden without compromising optimal care for Veterans with HF. The detailed statistical analysis for each of the study objectives is listed below:

AIM #1: Evaluate the prevalence of clinical depression (as measured by DSM-IV Diagnostic Interview and Structured Hamilton [DISH]- [VA Form 10-21085b NR]) and depressive symptoms (as measured by Beck Depression Inventory [BDI]- [VA Form 10-21085c NR]) among Veterans with HF during hospitalization and 2 weeks, 3 months, 6 months and 12 months post-discharge.

(1) At each time point during hospitalization and post-discharge, the prevalence of clinical depression will be determined by descriptive statistics:

Using the DSM-IV clinical depression criteria (DISH), the proportion of major, minor and no depression among Veterans with HF will be:

$$\textbf{Proportion (P)} = \frac{\text{\# of patients with DSM-IV major and/or minor depression}}{\text{\# of consented patients admitted with HF}}$$

Using the BDI depression score of ≥ 10, the proportions of depressive symptoms vs no depressive symptoms in Veterans with HF will be:

$$\textbf{Proportion (P)} = \frac{\text{\# of patients with depressive symptoms}}{\text{\# of consented patients admitted with HF}}$$

(2) The difference in sociodemographic (age, education, employment status, etc.) and clinical variables (i.e. HF duration, Functional class: NYHA and Specific Activity Scale (SAS) - (VA Form 10-21085d NR), LVEF, medications, medical and psychiatric comorbidities, etc.) among HF Veterans with DSM-IV diagnosis of major, minor and no depression will be compared using chi-square for categorical variables and analysis of variance (ANOVA) for continuous variables. Similarly, the sociodemographic and clinical characteristics of patients with depressive symptoms $\geq$ 10 BDI score vs. no depressive symptoms will be compared by chi-square for categorical variables and t-test for continuous variables. The change in proportions of clinical depression will be examined over time using a generalized linear model with a logit link function and adjusting for the various *confounding* variables. Missing data will be account for using multiple imputation techniques based on hot decking.

AIM # 2: Determine the temporal relationships of clinical depression (by DISH- [VA Form 10-21085b NR]) and physical functioning (by Functional class: NYHA and SAS- [VA Form 10-21085a NR]) among Veterans with HF at different time points from hospitalization through outpatient care (within 3 days of hospital admission, discharge day, and 2 weeks, 3 months, 6 months and 12 months post-discharge).

(1) At successive time points, chi-square tests will be used to determine the prevalence of major, minor and no depression among functional severity classes. For each time point, the correlation between changes in physical functioning status (Functional Class: NYHA and SAS- [VA Form 10-21085d NR]) and changes in depression status (DISH- [VA Form 10-21085b NR]) will be performed using the Spearman rank-order correlation. Controlling for the treatment status of depression and statin therapy, a multivariate ordinal logistic regression will be performed to determine the strength of the relationship between physical functioning and clinical depression status.

(2) The variation in these proportions over time will be evaluated using the same repeated measures methodology described in Aim #1.

AIM # 3: Determine the temporal relationships of clinical depression (by DISH [VA Form 10-21085b NR]) and biochemical markers associated with HF and/or depression such as Brain Natriuretic Peptide [BNP] and cytokines (i.e. tumor necrosis factor- α [TNF-α], Interleukin- 6 [IL-6] and Interleukin [IL-10], ratio of TNF-α/IL-10, and ratio of IL-6/ IL-10) among Veterans with HF at different time points from hospitalization through outpatient care (within 3 days of hospital admission, discharge day, and 2 weeks, 3 months, 6 months and 12 months post-discharge).

(1) At each time point, a one-way ANOVA will be used to determine if the levels of biomarkers (BNP, TNF-α, IL-6, TNF-α/IL-10, or IL-6/IL-10) differ by clinical depression groups (i.e. major, minor and no depression). Using Pearson R, correlations between changes in biochemical markers (BNP, TNF-α, IL-6, TNF-α/IL-10, or IL-6/IL-10) and changes in clinical depression status (DISH- [VA Form 10-21085b NR]) for each time points will be performed. Controlling for the treatment status of depression and statin therapy, a multivariate ordinal logistic regression will be performed to determine the strength of the relationship between biologic markers and clinical depression status at each time point.

(2) Evaluation of biochemical markers overtime for the depression groups will be based on a two-way repeated measures analysis of variance with the potential for data transformations of the outcomes (based on the Box-Cox family of transformations) in order to achieve Gaussian distributions where necessary. In addition, the assumption will be evaluated and the p-value adjusted, if needed using the Greenhouse-Geisser correction. Multiple imputations using hot decking will be employed.

AIM # 4: Determine the association of demographic variables (age, gender, socioeconomic status, etc.), clinical variables (i.e. type, etiology & duration of HF, smoking history, etc.), medical and psychiatric comorbid conditions, physical functioning (i.e. Functional Class: NYHA/SAS- [VA Form 10-21085d NR]), biochemical markers, and social support with clinical depression (i.e. absent, minor and major by DISH (VA Form 10-21085b NR) or BDI (VA Form 10-21085c NR) ≥ 10 [depression] vs. BDI < 10 [no depression*)* in Veterans with HF at index hospitalization and at 6 months post-hospitalization.

(1) For each time point, univariate and multivariate analyses will be performed:

a. Diagnosis of major, minor and no depression by DISH (VA Form 10-21085b NR): Univariately, chi-square tests (for categorical variables) and ANOVA (for continuous variables) will be performed to determined whether sociodemographic (i.e. age, gender, ethnicity, etc.), clinical variables (i.e. type, etiology & duration of HF, smoking history, etc.) medical and psychiatric comorbid conditions, physical functioning (measured by functional class), biochemical markers, and social support scores were different among clinical depression groups. Then, a multivariate ordinal logistic regression will be performed. In the multivariate analysis, the effects of depression treatment status and statin therapy will be controlled and variables that are univariately significant at $p \leq .10$ level will be included in the model. Model integrity will be evaluated using goodness-of-fit statistics.[12]

b. Depressed (BDI [VA Form 10-21085c NR] score ≥ 10) vs. Not Depressed (BDI score < 10): Univariately, chi-square tests (for categorical variables) and t-test (for continuous variables) will be performed to determined whether sociodemographic (i.e. age, gender, ethnicity, etc.), clinical variables (i.e. type, etiology & duration of HF, smoking history, etc.) medical and psychiatric comorbid conditions, physical functioning (measured by functional class) biochemical markers, and social support scores were different between depressed vs non-depressed BDI score. Then, a multivariate logistic regression will be performed. In the multivariate analysis, the effects of depression treatment status and statin therapy will be controlled and variables that are univariately significant at $p \leq .10$ level will be included in the model. Stepwise entry will be used, with standard cutoff points for variable entry and removal from the model. Model integrity will be evaluated using goodness-of-fit statistics.[12]

<u>Aim # 5:</u> Determine the sensitivity, specificity and positive predictive value of the BDI as a screening tool to identify clinical depression (DISH- [VA Form 10-21085b NR]) in Veterans with HF at index hospitalization and at 6 months post-hospitalization.

For data from index hospitalization and 6 months post-hospitalization, sensitivity, specificity, and positive and negative predictive value of BDI (VA Form 10-21085c NR)scores in relation to the diagnostic instrument (DISH- [VA Form 10-21085b NR]) to identify depression will be calculated using receiver operating curve analysis.

3. Describe methods to maximize response rate and to deal with issues of non-response. The accuracy and reliability of information collected must be shown to be adequate for intended uses. For collection based on sampling, a special justification must be provided for any collection that will not yield 'reliable' data that can be generalized to the universe studied.

a. The team conjured up a number of strategies to maximize response rates. First, the team will implement respondent-centered strategies that include providing: 1) a choice for respondents to decide the place (hospital clinic or home) where information can be collected (specifically for the outpatient data collection); 2) privacy, adequate rest periods and psychological support whenever necessary will be provided during the time of data collection, 3) a dedicated 800 number phone line for respondents to have ready access with members of the research team; and 4) the research team will contact the respondents frequently for respondents time and effort in participating with the collection of information. Second, a statistical strategy of increasing sample size was considered to account for potential patient dropouts (as explained in section II-1).

b. Despite all efforts to maximize response rates, issues of non-response are still likely to happen. To deal with issues of non-response, a statistical methodology for missing data will be employed by using multiple imputation techniques based on hot decking.

c. The accuracy and reliability of information collected is very important. Most of questionnaires that will be used for this study, has established validity and reliability. Hence, modifying or altering these questionnaires (to adjust for respondent burden) will compromise the validity and reliability of the instrument. Furthermore, the study team will perform reliability check of the questionnaires (identified above) on 5% of the sample on a regular annual basis.

4. Describe any tests of procedures or methods to be undertaken. Testing is encouraged as an effective means of refining collections of information to minimize burden and improve utility. Tests must be approved if they call for answers to identical questions from 10 or more respondents.

a. In response to the VA Health Services Research & Development (VA HSR&D) scientific reviewer recommendation, Dr. Corvera-Tindel conducted a very small pilot study to estimate the respondent burden of administering the necessary research questionnaires for obtaining information. The results of the pilot study are indicated below. Due to the amount of time to administer these questionnaires, the research team will implement strategies to address respondent burden during the collection of information (i.e. questionnaires), which is identified below.

b. The estimated time to administer the questionnaires (collect information) is about 60 minutes ± 15 minutes. Of the 7 patients in the pilot, only 1 required a break due to HF symptoms. Nonetheless, to minimize exacerbation of dyspnea or fatigue during data collection, the research team will reduce respondent burden by providing a quiet environment and ample time to respond to questions, and will offer rest periods every 15 minutes or whenever necessary. To address the potential risk of psychological and social distress, the research team will schedule data collection at a time and place that will ascertain the highest privacy and confidentiality. It will be scheduled at a time when visitors, other patients, and staff are absent or minimally present. In cases where patients are staying in a semi-private room during hospitalization, the research team will temporarily reserve or secure a private room. To insure that the research team is equipped to provide psychological support, Dr. Doering will train the research RN/LVN in purposive listening and empathic support. In addition to routine use of these skills during data collection, the research team will offer rest periods in the event of transient distress.

5. Provide the name and telephone number of individuals consulted on statistical aspects of the design and the name of the VA unit, contractor(s), grantee(s) or other person (s) who will actually collect and/or analyze the information for the agency.

The VA unit, grantee and the statistician for the identified research study are identified below:

VA Unit:	VA Greater Los Angeles Health Care System
Principal Investigator:	Teresita Corvera-Tindel, PhD, RN, Nurse Researcher (310) 268-3796

Statistician: Martin Lee, PhD,
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