Sick-Day Protocol to Improve Outcomes in Chronic Kidney Disease

Study Protocol and Statistical Analysis Plan

NCT03141905

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Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

Consented participants will undergo the following procedures:

1) Baseline Visit:
All study participants will be surveyed via telephone or in person for medical history, demographics, co-morbidities, and recent medical events. Medication ascertainment will include VA and non-VA, prescribed or OTC drugs per protocols employed in Safe Kidney Care (SKC). All study participants will be provided an in-service over the phone describing the features of a sick-day event (e.g, vomiting, diarrhea, fever, and poor fluid intake) and the potential health consequences of a sick day including volume depletion. Participants will be instructed on signs of volume depletion including thirst, weight change, fatigue, lightheadedness, and the significance of such events should they persist more than a day.

Intervention participants (Sick-Day Protocol): They will be provided with detailed instructions on the elements of the protocol to be initiated in the event of a sick-day which include holding of RAS blocker and diuretic (or NSAID or metformin) during the sick-day and resumption upon resolution of illness. Participants will be asked to obtain pre-ordered laboratories at their home clinic during the sick-day or as soon after the event as possible (unless they have need for ER visit or admission). The study coordinator and or study-associated staff in the Renal Inter-Disciplinary Safety Clinic (RISC) (described below) will monitor laboratory values in conjunction with primary care staff for alert findings.They will be provided with a tutorial and demonstration on use of the IVSRDS (described below). Sick-day protocol participants will have a weekly IVSDRS assessment of the frequency of sick-day events, and will be tracked for their use of the self-management protocol in the event of a sick-day event They will have the option for the IVSDRS to call their usual care provider if needed or in the event the sick-day is protracted. RISC will also monitor participants for requests for follow-up call or prolonged illness.

Usual Care participants: The participants will be provided a card identifying the sick day features only. They will be provided with instruction to call their usual care provider, or study-associated RISC staff in the event of a sick-day event. Participants will be asked to obtain pre-ordered laboratories at their home clinic during the sick-day or as soon after the event as possible (unless they have need for ER visit or admission). The study coordinator and RISC staff will monitor laboratory values in conjunction with primary care staff for alert findings.

2) 6 month Study visit: (+ or - 2 weeks to accommodate scheduling conflicts. Note : This is our target visit range. Due to the disease burden of this populations and hospitalizations, scheduling conflicts may occur, in which case, study visit will be completed as soon as possible.)
All participants will have a medical history update, medication profile update, and confirmation of final laboratory testing. IVSDRS satisfaction survey will be administered to participants in the active arm. All study participants will be surveyed as to the occurrence of sick-days over the prior six months (the responses of the active arm participants will be compared to their IVSDRS results).

IVSDRS procedure: Upon participant randomization to the active Sick-Day Protocol arm, the coordinator will request a designated telephone number (wireless or ground line) and preferred times for weekly IVSDRS calls. The automated voice-driven protocol will be delivered weekly to active arm participants. With each IVSDRS call, participants will verify identity with a unique study identifier. The initial query menu will elicit whether a sick-day event is ongoing or occurred during the prior 7-day interval. In respondents with no sick-day occurrence, the call will end with the next call in 7 days. In participants who register a sick-day event in the previous 7 days, a follow-up query algorithm will determine self- initiated actions in response to the sick-day and whether the actions are consistent with the self- management Sick-Day Protocol to hold high risk drugs (RAS blocker, diuretic, metformin, or NSAID) and whether these drugs were resumed. In participants with an ongoing sick-day at the time of the call, a follow-up call will be initiated in 3 days to determine the participants, status and whether all drugs have been resumed. The IVSDRS has capability for participant to request speaking to a provider with an urgent incident, and providers are notified via text when an urgent or frequent event is detected. All IVSDRS responses are stored centrally and are accessible to research staff. Entries that require timely attention will be flagged, reviewed by staff and decision-support team, and communicated to the usual care team where appropriate. Note: study participants will be tracked in an intent-to-treat manner and not considered loss-to-follow-up unless unreachable at 6-month close-out visit.

Clinical measures: With the plan for all encounters in this protocol to be conducted remotely to accommodate recruitment of a large sample size, there will be no in-center collection of vital sign or anthropometric measures. However, clinical encounter in the VAMHCS include EHR recording of several important variables which can be utilized for this study including weight, calculated BMI, automated blood pressure, pulse, and temperature (with the latter protocol-pertinent). Point-of-care measures of glucose, pulse oximetry, hemoglobin, and glycosylated hemoglobin readings are also available, and laboratory readings including those for hemoglobin, lipids, and urinalysis are prevalent. For this study, readings will be utilized within 90 days or less following registration of a prescription of RAS blocker and diuretic, with summary measures including mean, median, high and low values utilized for those with repeated measures.

Laboratory assessment: All participants will have baseline and end-of-study measurement of renal chemistry panel (including serum sodium, potassium, bicarbonate, BUN, creatinine, Ca, and P04) through VAMHCS laboratory services. The blood drawl will be no more than 3 teaspoons or 14.8 ml at each visit. They will also be instructed to obtain serum chemistry tests proximate to a sick-day incident to identify acute kidney injury and electrolyte disturbances, with standing orders at participants' home clinic laboratory. VAMHCS laboratory services use CKD-EPI equation for automated reporting of estimated GFR.

Decision-support for Renal Inter-disciplinary Safety Clinic (RISC): The VA RISC is a referral clinic with a multi-disciplinary staff dedicated to assessment of CKD patients with adverse safety events. The RISC staff will be available to all study participants who elect to call providers for guidance on self-management of a sick-day event. Primary care providers of all study participants will be provided with contact information and services available through the RISC. For usual care participants this will be on a consultative basis in conjunction with primary care providers when their assigned patients are sick per standard clinical protocol. For Sick-Day Protocol participants, RISC staff will review all IVSDRS entries for alerts that require phone evaluation (e.g, failure of participants to pick up 3-day post sick-day call, failure to resume RAS inhibitor or diuretic after sick-day, and additional medication starts or cessation). RISC staff will monitor labs obtained on all study participants over duration of the protocol for necessary recommendations.

COVID-19 Update: Study laboratory assessments will not be completed during this time to limit unnecessary travel and human-to-human contact. Participants currently enrolled will be contacted by phone at the timepoints indicated by protocol. Telephone phone visits will be conducted by the study coordinator remotely. Survey data will be recorded on paper forms. The only identifiable information on these forms are the patient's name and date of the phone visit. Once the UMB telework period has ended, study coordinator will file the forms in the Baltimore VAMC research office and enter them electronically. We will add specific data entries to our electronic data capturing system (REDCap) for information such as missed study visits or study discontinuations due to current state of emergency with COVID-19 status.

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:

With change in renal function as our primary outcome, we utilized a VAMHCS data sample to determine a baseline rate of renal function loss. From CKD patients taking a RAS blocker and diuretic, and with a documented sick-day ICD-9 code, we selected the most proximate measure of renal function ≥ 2 weeks preceding the sick-day incident as an index measure. Renal function trajectories were then tracked up to 1 year after the sick day. The median rate of GFR change was -0.02 per ml/min/1.73m2 per month in the pilot sample, and 41% were designated as rapid progressors defined by a GFR loss of 0.2ml/min/1.73 m2 or greater per month (2.4 ml/min/.73 m2 or more annually). The sample data also showed that 27% of participants on a RAS blocker and diuretic experienced an ICD-9 code documented sick-day in 2014, but we assert this is an under-estimation of all sick-days since it only accounts for events linked to a hospitalization or clinic/ER visit. Of note: only about 10% of SKC participants reporting a GI illness at a study visit notified a provider or went to the ER/hospital. Therefore, we estimate the proportion of participants experiencing a sick-day during the study period to be 33%.

We also examined detectable rate differences in urgent service utilization between the usual care vs sick-day protocol arm (with the latter set with lower rates of utilization) across a range of sample sizes. The SKC study results reveal at initial 6-month telephone follow-up, > 30% of SKC participants had one or more hospitalization since enrollment for a rate of 8.8 hospitalizations per 100 patient-months. Using this count data as the presumed rate for the usual care group we can estimate a median hospitalization rate of .528 hospitalization over 6 months ((8.8/100 patient-months) x(6 months)).

Anticipating 33% of enrollees will experience a sick-day during the protocol a sample size of 800 participants is feasible to be enrolled given the inclusion criteria and the proposed 2 year period. This sample size provide the power to detect difference in effect of Sick-Day Protocol on frequency of rapid renal function losers and incidence of hospitalization. We view this sample size to be achievable given the PI and SKC program's enrollment success, the target VAMHCS population, the plan for phone-based study visits, and the low burden remote data capture protocol.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

This trial's analysis will adhere to the principle of intention-to-treat based on participant group assignment. Additional analyses will be conducted with restriction to those reporting sick-days within each assigned group. Expected causes of drop-out include ESRD, death, and loss to follow-up (at last clinical entry for usual care group, and last IVSDRS entry for active group) if not contacted at final 6-month visit.

Aim 1: The null hypothesis for Aim 1 is there is no difference in the rate of renal function loss, AKI episodes, or urgent service utilization between the sick-day protocol vs usual care arms. For examination of change in renal function from baseline to 6-months in estimated GFR, we will employ linear regression, which accommodates continuous measure outcomes and adjusts for other covariates, and any difference in GFR at baseline. Note: the model will permit an indicator for use of RAS blocker and diuretic individually if required due to expanded enrollment of individuals taking RAS blocker AND/OR diuretics (see Enrollment). To determine difference in count of AKI episodes between the groups, whether defined by health system encounters with diagnostic codes, or by incidental measures of renal function during a sick-day, we will use repeated-measures Poisson regression containing an indicator variable for group assignment (even when restricted to only those participants reporting a sick-day). With the potential for repeated events, we will employ generalized linear mixed models (SAS PROC GLIMMIX), which performs repeated measures analyses allowing for one of everal covariance structures (e.g. unstructured, compound symmetry, etc) to account for the correlation inherent in repeated measures data. We will select the best covariance structure using AICC, a modified version of Akaike's Information Criteria. We anticipate that our data may be over-dispersed and GLIMMIX can be programmed to use a negative binomial or Poisson distribution – both methods allowing analysis of over-dispersed data[69]. Since follow-up time may vary from individual to individual (if subjects are lost to follow-up prior to the final 6-month visit) we will use the offset parameter (capturing person-months) to convert the number of events for each subject to an event rate, and compare event rates in the two groups. Similar analysis method will be employed to determine differences in urgent service use between the sick-day protocol and usual care arms.

Aim 2: The objective of Aim 2 will be to determine the rate of sick-day events in high-risk CKD patients, who are tracked by IVSDRS or by survey. We will use descriptive methods to evaluate the incidence rate of this discrete event. GLIMMIX with a Poisson distribution will be employed to accommodate the potential for repeated events within individuals and also variable follow-up time given the possibility of ESRD, death of loss to follow-up. GLIMMIX can also accommodate the introduction of covariates defined such that difference in AKI rates can be examined across pertinent strata (e.g, diabetics, older patients, use of RAS blocker AND/OR loop diuretic). Similar analyses will be conducted using survey responses regarding of sick-day events obtained on all participants at study completion.

Aim 3: The objective of Aim 3 is to assess the adherence of active-arm participants to the sick-day protocol. The analysis will be restricted to the active (IVSDRS) arm participants with determination of protocol adherence conditioned on the recording of a sick-day. Descriptive statistics will be employed to determine the proportion of participant sick-days during which RAS blockers and/or diuretics are ceased, and then the proportion of participant sick-days after which these agents are resumed. We will examine what factors determined at baseline are predictive of adherence vs non-adherence. We will also examine frequency of urgent service utilization following a sick-day due to failure to resume RAS blockers and/or diuretics (e.g urgent CHF or hypertension admissions).

Covariates: Several variables are clinically available and will be included in the multivariate analyses along with covariates ascertained as part of the study protocol. As described in Study Procedures, EHR vital sign and anthropometric measures along with several biochemical measures (e.g, HbA1C, hemoglobin, electrolytes) will be collected, summarized and updated during study interval. Measures of co-morbidity, case-mix, and pharmacotherapy will also be ascertained at baseline and 6 months, and included in analyses.