

HP-00048532

Safe Kidney Care Cohort Study
Research Protocol and
Statistical Analysis Plan

from CICERO 5.17.2018

Research Protocol

- 1 * Do you have a research protocol to upload?

Yes

- 2 If Yes, upload the research protocol:

Name	Created	Modified Date
SKC eHealth Literacy Tool	9/21/2012 3:52 PM	9/21/2012 3:52 PM
PI's Protocol Version 4_28Feb2012	2/28/2012 8:22 PM	2/28/2012 8:22 PM
PI's Protocol Version 4_28Feb2012_with track changes	2/28/2012 8:19 PM	2/28/2012 8:19 PM
PIs Protocol Version 3_7Nov2011_.docx	11/7/2011 2:56 PM	11/7/2011 2:56 PM
PI's Protocol Version 3_7Nov2011_with track changes.docx	11/7/2011 2:49 PM	11/7/2011 2:49 PM
Health Literacy Screen_CRF_v.2May2011	5/3/2011 3:01 PM	5/3/2011 3:01 PM
Eligibility_CRF_v.3May2011	5/3/2011 2:58 PM	5/3/2011 2:58 PM
Demographics Information Update_CRF_30Apr2011	5/3/2011 2:57 PM	5/3/2011 2:57 PM
Demographics Information_CRF_30Apr2011	5/3/2011 2:01 PM	5/3/2011 2:01 PM
Medical History - Update_CRF_v.30Apr2011	5/3/2011 1:59 PM	5/3/2011 1:59 PM
Medical History - Baseline CRF_v.30Apr2011	5/3/2011 1:12 PM	5/3/2011 1:28 PM
PI's Protocol Version 2, Dated: 2May2011	5/3/2011 1:10 PM	5/3/2011 1:10 PM
Appendix C Medical Safety Event Diary_v.9Mar2011	5/2/2011 4:53 PM	5/2/2011 4:53 PM
Appendix B Recruitment Brochure_v.2Feb2011	2/10/2011 2:48 PM	2/10/2011 2:48 PM

ID: VIEW4E00563F8D000
Name: v2_Research Protocol

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.

ID: VIEW4E02805225800
Name: v2_Risk Level

Type of Research

- 1 * Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):
Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).
Sample (Specimen) Collection and/or Analysis (including genetic analysis).
Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).

- 2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Yes No

ID: VIEW4E0280569E000
Name: v2_Type of Research

Lay Summary

- 1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

Chronic kidney disease not requiring dialysis (CKD) is common, but under-recognized, among patients who frequent the health care system, where improving patient safety is a high priority. Poor recognition of the disease and several other features unique to CKD make it a high-risk condition for adverse, patient-safety incidents (PSIs). In this context, PSIs refer to events of unintended harm or injury related to medications or medical care. These adverse safety events may include those usually cited for the general population (PSI), but also, CKD-specific unsafe practices (CKD-PSI) all of which, in turn, can lead to frequent hospitalization, accelerated loss of kidney function, increased risk of end-stage renal disease (ESRD), and death - all common outcomes in CKD. CKD-PSIs have been established in prior work by the PI with the help of an expert panel but it is not known how commonly PSIs or CKD-PSIs occur or how to possibly measure these reliably in the CKD population. Furthermore, it is not known what role poor disease recognition plays in the occurrence of such safety events. Finally, it remains to be determined whether CKD-PSIs contribute to the high frequency of adverse outcomes so common in this disease. If CKD-PSIs are common and account for a significant portion of the adverse events so common in this population, then it is possible that by reducing the incidence of CKD-PSIs, through increased disease recognition, outcomes can be improved in this patient population.

In this study, volunteers were enrolled from the population with pre-dialysis CKD for the purpose of observing the frequency of CKD-PSI in the target population detected over time. The participants were assessed every 6 months via 1 annual clinic visit and 1 mid-year brief telephone follow-up for events that relate to CKD-PSI. The first 100 participants (Phase I) were provided with a standard medical alert accessory (bracelet or necklace) which is commonly used to alert doctors and other providers of a patient's disease state. In this case the medical alert accessory stated "Decreased Kidney Function. For My Care, Please Visit www.safekidneycare.org" Participants were asked to log onto a website using a unique 4-digit ID assigned by the PI to track their use of the website and to further improve the website. Since all information on the website was available to the public, participants are not required to use the ID to access the content of the website. The website did not collect or store patient health

information, except for the IP address which provides limited information on the location of the computer used to access the website (city, state, zip, and area code).

The volunteers in Phase I were tracked over time as to whether they accept and tolerated the medical alert bracelet/necklace and for their incidence of CKD-PSI. Enrollment continued after Phase I into Phase II (n = 250) with Phase II participants tracked on an identical study schedule for detection of CKD-PSI. All study procedures are the same for Phase II except for the medical alert accessory. The overall goal of this study will be to determine the frequency of CKD-PSI in the target population, the acceptability of an alert device (Phase I only) intended to increase the recognition of CKD, and the contribution of CKD-PSI to the high incidence of adverse outcomes in CKD.

Due to limited funding, beginning July 1, 2016, annual clinic visits stopped and study procedures were reduced to one, brief annual telephone follow-up to continue capture

- Self-reported safety events leading to hospitalizations/ER visits,
- Death and cause of death,
- Onset of end-stage renal disease requiring renal replacement therapy (dialysis and/or kidney transplant), and
- Updated contact information
- Frequency and severity of hypoglycemic episodes for participants with diabetes

Annual data collection of above-noted elements will continue for an additional 5 years through December 2021.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

View: v2_Justification, Objective, & Research Design

Justification, Objective, & Research Design

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 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

In this study, 371 individuals with pre-dialysis CKD were consented to achieve a cohort of 350 that proceeded to study procedures with the following objectives:

1) Assess the Tolerability and Efficacy of a Commonly-used Medical Alert Accessory Designed to Increase Recognition of Chronic Kidney Disease (CKD) in a Pilot Sample of Participants from the SAFE KIDNEY CARE COHORT

The first 108 subjects of the Safe Kidney Care cohort (Phase I) were provided a medical alert accessory (choice of bracelet or necklace, stainless steel or sterling silver). Regular contacts were made with Phase I participants to monitor tolerance of medical alert accessory along with the use of a supplemental informational website on best safe practices for patients with CKD, and to measure the frequency of newly-developed Patient Safety Indicators specific to CKD (CKD-PSI).

2) Validate Established CKD-PSIs in a Cohort of Individuals with CKD Tracked Longitudinally

After enrollment in Phase I has concluded, an additional 242 volunteers from the target population were enrolled into the Safe Kidney Care cohort (Phase II) for a total of 350 participants tracked longitudinally to detect the incidence of established CKD-PSIs, assess their measurability, and exam the relationship between the occurrence of these safety events and adverse renal outcomes.

- 2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

Study design: Observational cohort study. Study population: Persons with Stage III – V, pre-dialysis CKD enrolled from a single center (n = 350). The first 108 participants (Phase I) were provided a medical alert accessory (choice of bracelet or necklace).

Study Measurements: Participants in both Phase I and II underwent baseline and annual in-center visits for medical history and medication review, anthropometric measures, measurement of renal function (serum Cr for estimation of GFR); other laboratory measures, measures of physical function and health literacy, and other questionnaires. Additionally, they had a follow-up telephone call between annual visits to review medications, update contact information, assess for medical events and hospitalizations. Phase I participants also had an assessment of medical alert accessory acceptance and tolerance. The expected duration of study allows up to 4 annual clinic visits and up to 4 mid-year telephone follow-up visits through June 30, 2016. Beginning, July 1, 2016, annual clinic visits stop and will be replaced with just the annual telephone visit up to December 2021. The mid-year telephone follow-up will stop.

Primary outcomes: CKD-PSIs including medication errors (such as NSAIDs, improperly dosed meds), toxic exposures (such as contrast agents), and medical events (such as hyperkalemia or hypoglycemia); Secondary outcomes: including changing renal function, hospitalization, ESRD, and death. Phase I participants were followed for acceptance and tolerance of medical alert accessory.

- 3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:
Refer to Protocol item 5. BACKGROUND

- 4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Chronic kidney disease (CKD) is common, but under-recognized, among patients in the health care system, where improving patient safety is a high priority. Poor disease recognition and several other features of CKD make it a high risk condition for adverse safety events. These adverse safety events may include those usually cited for the general population (PSI), but also, CKD-specific poor outcomes including unsafe practices and errors (CKD-PSI) specific to the unique care that CKD patients receive. These in turn, have the potential to lead to frequent hospitalization, accelerated loss of renal function, increased risk of end-stage renal disease (ESRD), and death. Our overall hypothesis is that poor disease recognition leads to an increased occurrence of CKD-PSI which in turn contributes to the high rate of adverse events seen in this population. This study proposes to address key elements of this overall hypothesis. These include determining the frequency of previously established CKD-PSI (see HP00042985) in the target population and determine the extent that these CKD-PSIs contribute to adverse disease outcomes. Furthermore, it will evaluate the longitudinal acceptance and tolerance of a commonly-used medical alert accessory intended to alert providers to a disease state and increase CKD recognition with supplemental information on the safe care of patients with CKD (www.safekidneycare.org).

ID: VIEW4E02805EA0C00
Name: v2_Justification, Objective, & Research Design

View: v2_Supporting Literature

Supporting Literature

- 1 * Provide a summary of current literature related to the research: **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 box below.**

Previous work by the PI has described the unique risk for safety events among in patients with CKD. Additional studies have shown the risk associated with hyperkalemia and hypoglycemia which are common in CKD.

Seliger SL, Zhan M, Hsu VD, Walker L, Fink JC. Chronic Kidney Disease Adversely Influences Patient Safety. J Am Soc Nephrol. 2008 Dec;19(12):2414-9.

Fink JC, Brown J, Hsu VD, Seliger SL, Walker L, Zhan M. CKD as an under-recognized threat to patient safety. Am J Kidney Disease; 2009 53(4): 681-8.

Moen MF, Zhan M, Hsu VD, Walker L, Einhorn LM, Seliger SL, Fink JC. The frequency and significance of hypoglycemia in chronic kidney disease. Clin J Am Soc Nephrol 2009 4: 1121-1127.

Einhorn LM, Zhan M, Hsu VD, Walker L, Moen MF, Seliger SL, Weir MR, Fink JC. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med 2009; 169(12):1156-1162.

Chapin E, Zhan M, Hsu VD, Seliger SL, Walker LD, Fink JC. Adverse safety events in chronic kidney disease: the frequency of "multiple hits". Clin J Am Soc Nephrol; 2010 5: 87-94.

Fink JC, Chertow GM. Medication errors one piece to the patient safety puzzle. Kidney Int; 2009 76: 1123-1125.

2 If available, upload your applicable literature search:

Name	Created	Modified Date
There are no items to display		

3 * Provide a list of 3 keywords or search terms (1 per line) relevant to your research that would help potential participants find your study using search engines:

Keyword 1: patient safety

Keyword 2: chronic kidney disease

Keyword 3: medical errors

ID: VIEW4E02805A7E400
Name: v2_Supporting Literature

View: v2_Study Procedures

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:

Beginning July 1, 2016, Mod 11 replaces the annual clinic visit with a 10-15 minute telephone call and eliminates the mid-year telephone follow-up visit. In addition, study procedures were also drastically reduced and are now restricted to the following data collection at the annual telephone visit:

- Self-reported safety events leading to hospitalizations/ER visits,
- Death and cause of death,
- Onset of end-stage renal disease requiring renal replacement therapy (dialysis and/or kidney transplant), and
- Updated contact information

Mod 12 adds the Clarke Hypoglycemia Index_Questionnaire_6.20.2016 to the above data collection to measure frequency and severity of hypoglycemic episodes.

Every effort will be made to complete all visits within target range; however, we anticipate that some participants will miss some annual telephone visits due to unforeseen circumstances, such as illness or family events. At each encounter with the participant, we will attempt to collect all information on events that have occurred since the last encounter and complete data collection. Outlined below are the study procedures and questionnaires.

Participant and Designated Proxy Contact Information - participants will be asked to provide their preferred methods to be contacted, such as mailing address, telephone numbers, and email address. In addition, we will request that the participant provide the contact information of someone we can contact in case we have been unable to reach them, who can provide information to the participant's status, such as moved, ill, hospitalized, or deceased. This information is collected at each annual telephone follow-up visit.

Self-Reported Safety Events Questionnaire - this questionnaire tracks symptoms or medical problems that might be related to self- or medically-directed care and the frequency of hospitalizations.

Clarke Hypoglycemia Index_Questionnaire -Mod 12 adds one additional questionnaire, the Clarke Hypoglycemia Index_Questionnaire. This instrument will be administered beginning July 1, 2016 at the annual, telephone follow-up. Patients with diminished kidney function and diabetes are at risk for hypoglycemic episodes. The Clarke Hypoglycemia Index will provide information about the level of "unawareness" and ability to self-recover and avoid a patient safety event.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):

No procedures are being performed for diagnostic or treatment purposes.

3 * Describe the duration of an individual participant's participation in the study:

Mod 11 Changes to be initiated July 1, 2016: Length of participant may extend up to 10 years for those enrolled in 2011 and up to 7 years for the last participants enrolled in 2014.

4 * Describe the duration of the entire study:

Mod 11 Changes to be initiated July 1, 2016: Duration may extend to end of 2021.

5 * Describe any additional participant requirements:

Mod 11 Changes to be initiated July 1, 2016: Participants will no longer need to retain medication containers/packaging; attend an annual follow-up clinic visit; wear the medical alert bracelet/necklace, or maintain a diary.

ID: VIEW4E0280585B400
Name: v2_Study Procedures

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:

From PI's Protocol, Section 9.I.4, page 30:

9.I.4. Sample Size Considerations

For this study, the key aim of the power calculations will be to ensure adequate precision in the detected estimates of CKD-PSIs. In order to conduct such power calculations it is important to make reliable assumptions about the expected incidence rate of key disease-specific safety indicators.

The preliminary data presented offers evidence of the expected incidence rate of selected events. The estimated incidence of various CKD-specific safety events reported by PI range from 14.8% of participants, with an episode of hypoglycemia (glucose \leq 60 mg/dl) in a given year, to 30% with a medication error in a given year. When considering a composite of a series of prospective, disease-specific safety indicators, one can see that the expected incidence rate could be substantial. Yet, to determine the precision of incidence estimates of CKD-PSIs in the validation cohort, we varied the presumed baseline rate from a conservative low frequency to a range closer to what is suggested by our preliminary data (Table 4 on page 31 of PI's protocol and below). Choosing the sample size for Phase II cohort of 250 (final n 242), achieved confidence interval, across our projections for a baseline incidence rate, assures a high degree of precision in measured event rates for CKD-PSIs.

The additional sample of 110 (final n 108) participants for piloting the medical alert accessory (Phase 1) will provide a reasonable estimate of the acceptance and tolerability of the alert accessory.

Table 4

Precision (95% Confidence interval for varying baseline incidence of safety indicators and different sample sizes)

Baseline incidence rate per year of (CKD-PSIs)

Sample size 10% 20% 30% 40%

100 \pm 6% \pm 8% \pm 9% \pm 10%

200 \pm 4% \pm 5.5% \pm 6.5% \pm 7%

250 \pm 3.6% \pm 4.8% \pm 5.6% \pm 6%

300 \pm 3.3% \pm 4.7% \pm 5.3% \pm 5.7%

- 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:

From Protocol:

9.I.3. Statistical Analysis

The purpose of this analysis will be to measure the incidence of the CKD-PSIs in the study cohort and to determine the adjusted incidence rates across key factors which relate to safety in CKD. Event ascertainment will begin 4 months (with first telephone follow-up) after enrollment at which time individual events will be recorded longitudinally and cumulatively.

We will consider each specific type of event as an endpoint, but the primary analysis will be based on a composite endpoint of all CKD-PSIs endorsed for inclusion in the trial. The incidence of the events will be expressed per patient-months accrued for all participants in the study cohort and cumulative incidence rates will be determined for both the composite and individual events. Each event will be recorded per individual at the time of the event. For example, if there was an episode of hypoglycemia documented in April for a participant enrolled in January, and an exposure to NSAID in December, then that individual will have 2 CKD-PSI events per 12 patient-months.

As outlined previously, events will be ascertained from several sources including study visits, medical history review, medication review, and retrieval of hospitalization records. The source of events will be accordingly labeled. Poisson regression will be employed to determine key measured factors which predict the incidence of patient safety events. For this analysis, there will be no predetermined primary exposure to be tested in the regression analysis; however, a key analysis will be the relationship between entry GFR and incidence of CKD-PSIs. Other exposures of interest will be examined. The Poisson regression will assume the number of events for each subject follows a Poisson distribution with mean being a product of the length of the follow-up period and the rate of events, where the logarithm of the expected rate of events (per patient-month), is the linear combination of the covariates. We will check whether data display any over-dispersion and may use negative-binomial regression model if over-dispersion is present.

The data will also be structured such that it is possible to explore the relationship between the incidence of CKD-PSIs and key renal endpoints (secondary outcomes). The key adverse secondary outcomes measures to be examined will be 1) hospitalization and, 2) rate of change in renal function, as measured by estimated GFR. For hospitalization, the primary measure will be incidence of unique hospitalizations over the observed patient-months in each group. Comparisons groups will be the patient-months labeled by the prior incidence or absence of CKD-PSIs in a given patient. While an individual without any CKD-PSI during study observation has a hospitalization, that event occurs in the non-PSI group, another individual with at least one CKD-PSI in the study period who has two hospitalizations – one before and the other after the incidence of the CKD-PSI – will contribute two hospitalization events to the data set. The first will be assigned to the non-CKD-PSI group and corresponding to the period from entry to the occurrence of the first CKD-PSI, the second event will be assigned to CKD-PSI group and corresponding to the period from the occurrence of the first CKD-PSI to last follow up time or the end of the study.

Generalized estimating equations (GEE) with log link function will be employed for examination of the relationship between incidence of CKD-PSIs and hospitalization. GEE will allow for joint modeling of the repeated measures and the incorporation of such a time-varying covariate based in the detection of a CKD-PSI. The effect of ever experiencing CKD-PSI during the study period on the frequency of hospitalization will be displayed by the rate ratio and its 95% confidence interval of hospitalization in PSI group versus non-PSI group.

Estimated GFR will be determined at baseline and at all annual follow-up visits. Since enrollment will be planned to ensure at least one follow-up visit per individual, it will be possible to generate slope estimates for change in renal function in all study participants. Measurement of serum creatinine will be done at a single laboratory to minimize variation in calibration across laboratories, and GFR will be estimated with the modified MDRD equation. Proper transformation will be performed as needed if the distribution of GFR values is skewed. Random effects models will be used to compare change in GFR between those with and without a CKD-PSI. To employ random effects models as a means to compare change in renal function between those participants with and without the incidence of a CKD-PSI and adjust for multiple covariates, the following assumptions will be made:

Each individual will have a separate slope β_i , with an independent intercept α_i , and an error term ϵ_i with mean 0 and a Normal distribution. The residual variance of each slope is assumed to be the same across all individual slopes and the distribution of β_i for participant time assigned to each group is assumed to be a Normal distribution with a mean of b_1 or b_2 corresponding to the two groups (without or with the bracelet/necklace). Similarly, the distribution of individual intercept α_i is assumed to be a Normal distribution with an equal variance across all individuals, and a mean of a_1 or a_2 corresponding to the two groups.

The random effects model will allow for inclusion of both baseline and time-varying covariates which would include timing of the incidence of the CKD-PSI. In comparison of change in renal function across the two groups (CKD-PSI vs never CKD-PSI), we will test whether the mean slopes b_1 and b_2 are equal, and construct a 95% confidence interval for $d = b_2 - b_1$. For these analyses, we will employ PROC MIXED in SAS V9.1 (SAS Institute Inc., Cary, NC, USA), building on the research group's substantial prior experience using such models and examining changes in renal function.