Electronic Supplementary Material 2

Development and Internal Validation of a Discrete Event Simulation Model of Diabetic Kidney Disease Using CREDENCE Trial Data

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AdViSHE Validation Assessment Tool:

The CREDENCE Economic Model of Diabetes Kidney Disease (CREDEM-DKD)
Version 1.1.1

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Part A: Validation of the Conceptual Model

- **A1:** Have experts been asked to judge the appropriateness of the conceptual model?

  Yes, the development of the conceptual model followed recommendations of the International Society of Pharmacoeconomic and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force-2 [1]. In addition to a literature review of economic models, expert clinicians were consulted to inform model design, objective, scope and key features, which was formally were documented in a conceptual model design. Consistent with the Task Force recommendations [1], the final conceptual design was not influenced by data availability. The final model conceptualization (and implementation) was examined by a multi-disciplinary NICE Scientific Advice Committee including a3 hours face-to-face meeting.

- **A2:** Has this model been compared to other conceptual models found in the literature or clinical textbooks?

  Yes, the conceptual model was designed in part based on an initial pragmatic targeted literature review of existing economic simulation models of CKD and subsequently reviewed when a literature review that identified 101 models that included CKD was published in 2019 [2].

Part B: Input Data Validation

- **B1:** Have experts been asked to judge the appropriateness of the input data?

  Yes. The model was been presented to an associate Professor at University of Manitoba as well as to an inter-disciplinary team of clinical and modelling experts. The appropriateness of inputs used in CREDEM-DKD were discussed and comments were subsequently incorporated. United Kingdom specific input data assumptions were reviewed by the NICE Scientific Advice Committee.

- **B2:** When input parameters are based on regression models, have statistical tests been performed?

  Yes. Regression models for the risk prediction equations are used in CREDEM-DKD. The regression models were first estimated with three parametric forms—exponential, Weibull, and Gompertz—and the functional form with best goodness-of-fit based on AIC was selected. Discrimination (C statistic) and calibration (ratio of predicted to observed cases at the study level, accounting for censoring on predictions using last outcome carried forward) were subsequently assessed, separately by study arm as well as overall.

Part C: Validation of the Computerized Model

- **C1:** Has the computerized model been examined by modeling experts?

  Yes. The model was been presented to an associate Professor at University of Manitoba as well as to an inter-disciplinary team of clinical and modelling experts. The appropriateness of the model was discussed and comments were subsequently incorporated.

- **C2:** Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?

  Yes. Every time a programing change is made to the model, implementation was tested systematically and debugged by both the programmer and other staff at the Swedish Institute for

Health Economics. Formal verification tests of CREDEM-DKD have been conducted and is presented as part of this publication (see ESM 1).

- **C3:** Have patients been tracked through the model to determine whether its logic is correct?

  Yes, CREDEM-DKD does not produce standard patient-level traces but health states and biomarker traces were generated and examined during model construction to confirm correct implementation.

- **C4:** Have individual sub-modules of the computerized model been tested?

  Yes. When model improvements were made to any sub-module, the modified sub-module was inspected thoroughly and tested with extreme sets of parameter values to isolate and investigate the effects of this sub-module on other parts of the model simulation.

Part D: Operational Validation

- **D1:** Have experts been asked to judge the appropriateness of the model outcomes?

  Yes. As part of developing of the conceptual design, a working group of health economists reviewed the evidence and met regularly with experts, conceptualizing the study problem and creating a preliminary statement of the study problem and the modeling objectives. In particular, CKD treatment guidelines, clinical evidence, and the CREDENCE study publications and data were consulted. Modeling guidelines were followed in the construction of the model, including the decision of what outcomes to report. The model was presented to a Professor at University of Manitoba as well as to an inter-disciplinary team of clinical and modelling experts. Furthermore, the final model conceptualization (and implementation) was examined by a multi-disciplinary NICE Scientific Advice Committee including a3 hours face-to-face meeting.

- **D2:** Have the model outcomes been compared to the outcomes of other models that address similar problems?

  No. As shown in the pragmatic literature review as well as the external model review, there are few models suitable for modeling the full set of kidney and macrovascular outcomes in T2DM patients with kidney disease. As such we have not been able to compare the model output to those of another model, but our aim is to cross-validate the model in the future when comparable models become available.

- **D3:** Have the model outcomes been compared to the outcomes obtained when using alternative input data?

  Yes. Model outputs generated using input data from a from the CANVAS Program study [3] with matching characteristics as the CREDENCE trial [4] have been assessed and the results are presented in this analysis. Furthermore, the formal verifications tests (see ESM 1) are all simulated using generic inputs.

- **D4:** Have the model outcomes been compared to empirical data?

  Yes. Internal validation of CREDEM-DKD was performed by loading the model to replicate the CREDENCE study [4] (patient populations, treatment effects, and time horizon) and comparing model predictions of the cumulative incidence of the outcomes with the Kaplan-Meier curves from the CREDENCE trial.

External validation of CREDEM-DKD was performed by loading the model to replicate a subgroup of the CANVAS Program [3] with patient characteristics matching those of the CREDENCE study [4] and comparing model predictions of the cumulative incidence of the outcomes with the Kaplan-Meier curves. The subgroup included a total of 567 patients and the baseline patient characteristics for the CANVAS Program subgroup with characteristics matching the CREDENCE trial are presented in Table S14 in ESM 1 and the treatment effects are presented in Table S15 in ESM 1. Note: as the CANVAS Program was designed to evaluate cardiovascular outcomes, start of maintenance dialysis was not recorded. Ideally, external validation would have been conducted comparing versus a renal outcome trial, but none are available at this time. Several trials will report in upcoming years.

Kaplan-Meier cumulative incidence curves describing internal model validation are presented in Figure 3. The model tended to overpredict the start of maintenance dialysis over the duration of the CREDENCE trial for both study arms, but the difference between arms was similar to that in the trial. The fit for the macrovascular and mortality outcomes were visually generally good.

The Kaplan-Meier results of the external validation using the subgroup of 567 patients in the CANVAS Program that met CREDENCE eligibility criteria [4] are presented in Figure 4. CREDEM-DKD overpredicted the incidence of doubling of serum creatinine in the CANVAS Program. Predictions for nonfatal myocardial infarction and hospitalization for heart failure visually matched CANVAS Program outcomes closely. The model also underpredicted all-cause mortality, especially after 1.5 years, and underpredicted the treatment effect.

Part E: Other Validation Techniques

- **E1:** Have any other validation techniques been performed?

  No

References

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