| Project InitiationThis Section must be Completed Prior to Project Dataset(s) Creation |
| --- |
| **Project Title:** | Examining Systemic Scleroderma with Interstitial Lung Disease (SSc-ILD) in Canada's Largest Province: An Estimate of the Prevalence and Incidence of SSc-ILD in Ontario |
| **Project TRIM number:** | 2019 0970 147 000 |
| **Research Program:** | DAS |
| **Site:** | ICES Central |
| **Project Objectives:** | *Insert Project Objectives as listed in the approved ICES Project PIA* |
| This study will allow us to get a better understanding of the market for OFEV® (nintedanib). This research will be conducted in anticipation of the Canadian approval of a subsequent indication for the treatment of systemic scleroderma (SSc) in the presence of interstitial lung disease (ILD) in late 2019. The Canadian Patient Access team would like to conduct a real-world evidence study to determine the prevalence and incidence (if possible) of SSc-ILD in Ontario, Canada. Systemic sclerosis (SSc) is an autoimmune disease that is characterised by skin thickening and fibroblast dysfunction that leads to excessive collagen accumulation in extra-cellular matrix and internal organ damage. SSc is associated with conditions such as renal failure, pulmonary fibrosis/interstitial lung disease, and gastrointestinal disorders, with the highest rates of mortality among patients with SSc-associated interstitial lung disease (SSc-ILD).To date, no published study has generated population based estimates of prevalence and incidence SSc-ILD in Canada. This primary objective of the current study, which will be described further below, is to develop prevalence and incidence estimates of SSc-ILD in Ontario.This study is intended to be used to fulfil a requirement of health technology assessments submissions in Canada to CADTH and INESSS. It is also likely to be used to develop public payer budget impact models (BIAs) for the SSc-ILD indication of OFEV®. It could be used in pan- Canadian Pharmaceutical Alliance (pCPA) and/or individual public payer negotiations for listing. This is critical a step to allow the payers to have a better sense of the patient characteristics and potential size of the patient population that could be eligible for OFEV® treatment for SSc-ILD. •Estimate the prevalence of SSc and SSc-ILD in Ontario •Estimate the incidence rate of SSc and SSc-ILD in Ontario •Estimate the prevalence and incidence of SSc and SSc-ILD by age, gender and region within Ontario •Describe the demographic profile of patients with SSc and SSc-ILD diagnoses in Ontario Brief Summary (Purpose)The purpose of this study is to estimate the prevalence of SSc and SSc-ILD. This will allow payers to have an idea of the number of patients that could be eligible for treatment when a drug for this disease becomes available. It may also let them know how many new patients there will each year. |
| **ICES Project PIA Initial Approval Date:** | *The ICES Employee or agent who is responsible for creating the Project Dataset(s) is responsible for ensuring there is an approved ICES Project PIA and verifying the date of approval prior to creating the Project Dataset(s)* |
| yyyy-mon-dd |
| **Principal Investigator (PI):** |  |
| **Check the applicable box if the PI is an ICES Student/Trainee** | [ ]  ICES Student [ ]  ICES Fellow [ ]  ICES Post-Doctoral Trainee [ ]  Visiting Scholar |
| **Responsible ICES Scientist:** | *Name the Responsible ICES Scientist if the PI is not a Full Status ICES Scientist* |
|  |
| **Project Team Member(s) Responsible for Project Dataset Creation and/or Statistical Analysis and date joined (list all):** | *All person(s) (ICES Analyst, Appointed Analyst, Analytic Epidemiologist, PI, and/or Student) responsible for creating the Project Dataset(s) and/or statistical analysis on the Research Analytics Environment (RAE) and the date they joined the project must be recorded* |
| Kobina QuansahRefik Saskin | yyyy-mon-dd |
| **Other ICES Project Team Members and date joined (list all):** | *All other Research Project Team Members (e.g., Research Administrative Assistants, Research Assistants, Project Managers, Epidemiologists) and the date they joined the project must be recorded* |
| TBD | yyyy-mon-dd |
| **Confirmation that DCP is consistent with Project Objectives:** | *The following individuals must confirm that the ICES Data provided for in this DCP is relevant (e.g., with respect to cohort, timeframe, and variables) and required to achieve the Project Objectives stated in the ICES Project PIA prior to initial Project Dataset creation: 1) PI; 2) Responsible ICES Scientist if the PI is not a Full Status ICES Scientist, or a second ICES Scientist or the Scientific Program Lead if the PI is creating both the DCP and the Project Dataset[s]; 3) ICES Research and Analysis Staff creating the DCP; and 4) ICES Analytic Staff (ICES Employee or agent responsible for creating the Project Dataset[s]). This may be delegated either verbally or via e-mail.* |
| ***Principal Investigator*** | [ ]  | yyyy-mon-dd |
| ***Responsible ICES Scientist or Second ICES Scientist/Lead*** | [ ]  | yyyy-mon-dd |
| ***ICES Research and Analysis Staff Creating the DCP*** | [ ]  | yyyy-mon-dd |
| ***ICES Analytic Staff*** | [ ]  | yyyy-mon-dd |
| **Designated ICES Research and Analysis Staff accountable for Project Documentation:** | *The person named (ICES staff) is accountable for ensuring that the approved ICES Project PIA, ICES Project PIA Amendments, and DCP are saved on the T Drive, ensuring ICES Project PIA Amendments are submitted as required, ensuring DCP Amendments are documented, and sharing the final DCP with the PI/Responsible ICES Scientist at project completion* |
|  |
| **DCP Creation Date and Author:** | *Date DCP was finalized prior to Project Dataset(s) creation* | *Name of person who created the DCP* |
| ***Date*** | ***Name*** |
| 2018-Dec-14 | RS |

| ICES DataThis Section must be Completed Prior to Project Dataset(s) Creation |
| --- |
| *The ICES Employee or agent who is responsible for creating the Project Dataset(s) must ensure that this list includes only data listed in the ICES Project PIA**Changes to this list after initial ICES Project PIA approval require an ICES Project PIA Amendment* | *Mandatory for all datasets that are available by individual year* |
| ***General Use Datasets – Health Services*** | ***Years (where applicable)*** |
| CIHI DAD | 2008-2018 |
| CIHI SDS | 2008-2018 |
| NACRS | 2008-2018 |
| See list |  |
| ***General Use Datasets – Care Providers*** |  |
| See list |  |
| ***General Use Datasets – Population*** |  |
| RPDB |  |
| See list |  |
| ***General Use Datasets – Coding/Geography*** |  |
| LHIN |  |
| See list |  |
| ***General Use Datasets – Facilities*** |  |
| See list |  |
| ***General Use Datasets – Other*** |  |
| See list |  |
| ***Controlled Use Datasets*** |  |
| See list |  |
| ***Other Datasets*** |  |
|  |  |

| Project Amendments and Reconciliation |
| --- |
| **ICES Project PIA Amendment History (add additional rows as needed):** | *Privacy approval date* | *Person who submitted amendment* | *Note that any changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment* |
| ***Date*** | ***Name*** | ***Amendment*** |
| yyyy-mon-dd |  |  |
| **DCP Amendment History (add additional rows as needed):** | *Date DCP amended* | *Person who made the DCP amendment* | *Note that any DCP amendments involving changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment* |
| ***Date*** | ***Name*** | ***Amendment*** |
| yyyy-mon-dd |  |  |
| **Date Programs/DCP reconciled** | *The person(s) creating the dataset and/or analyzing the data are responsible for ensuring that the final DCP reflects the final program(s) when the project is completed* |
| yyyy-mon-dd |

| Project Cohort |
| --- |
| **Study Design** | [x]  Cohort study [ ]  Matched cohort study [ ]  Case-control study[ ]  Cross-sectional study [ ]  Other (specify):  |
| **Index Event / Inclusion Criteria** | SSc patients will be identified via the following inclusion and exclusion criteria **Inclusion Criteria- Ontario:*** Age greater than 18 years of age
* with a valid health card on the first day of the fiscal year (s) of interest (April 1)
* Date of last contact with the health care system within 7 years prior to the first day of the fiscal year of interest (April 1)
* Eligible for the provincial insurance plan on the first day of the fiscal year (s) of interest (April 1)
* Patient identified with a diagnosis (defined below) between April 1, 2008 to March 31, 2018:
	+ Prevalent SSc:
		- M34 Systemic Sclerosis all categories:
		- M34.0 Progressive systemic sclerosis
		- M34.1 CR(E)ST Syndrome (includes combination of calcinosis, Raynaud's phenomenon, (o)esophageal dysfunction, sclerodactyly, telangiectasia)
		- M34.2 Systemic sclerosis induced by drugs and chemicals
		- M 34.8 Other forms of systemic sclerosis
		- M34.9 Systemic sclerosis, unspecified
	+ Prevalent SSc-ILD:
		- Any Systemic Sclerosis (all M34 codes-see above) **only if followed by either of the following:**
		- J99.1 – Respiratory disorders in the other diffuse connective tissue disorders at point following any M34 diagnoses codes within the study period

**or*** + - J84.1- other interstitial pulmonary diseases with fibrosis

or* + - J84.9 Interstitial pulmonary disease, unspecified

**or*** J84.8 Other specified interstitial pulmonary diseases

NOTE: As a sensitivity analysis, please include only patients with at least 2 years of follow-up to determine ILD status following SSC diagnosis. For example, the last cohort of SSC patient that could be identified would be (2015-16) and followed up until the end of (2017-2018)* + Incident SSc:
		- Any Systemic Sclerosis (all M34 codes-see above)
		- First occurrence only
	+ Incident SSc-ILD:
		- Any Systemic Sclerosis (all M34 codes-see above) **only if followed by either**
		- J99.1 (any diagnosis type) – Respiratory disorders in the other diffuse connective tissue disorders (at point following M34.8 diagnosis within the study period)

**or*** + - J84.1- other interstitial pulmonary diseases with fibrosis

**or*** + - J84.9 Interstitial pulmonary disease, unspecified

**or*** J84.8 Other specified interstitial pulmonary diseases
	+ - First occurrence only (of both codes together e.g. M34.8 diagnosis and J99.1, J84.1, J84.9 or J84.8)

NOTE: As a sensitivity analysis, please include only patients with at least 2 years of follow-up to determine ILD status following SSC diagnosis. For example, the last cohort of SSC patient that could be identified would be (2015-16) and followed up until the end of (2017-2018) |
| **Estimated Size of Cohort** **(if known)** | Unknown |
| **Exclusions (in order)** | *Step* | Description |
| 1 | Invalid ikn, missing age, sex |
| 2 | Non-Ontario resident |
| 3 | Death date before index date |

| Project Time Frame Definitions |
| --- |
| Look-back WindowObservation Window(in which to look for outcomes)**Index Event Date**Accrual WindowMax Follow-up Date |
| **Accrual Start/End Dates** | 2008-2017 |
| **Max Follow-up Date** | 31Mar2018 |
| **When does observation window terminate?** | 31Mar2018 |
| **Lookback Window(s)** | 2 years  |

| Variable Definitions (add additional rows as needed) |
| --- |
| **Main Exposure or Risk Factor** |  |
| **Primary Outcome Definition** | 1. **Crude rate of prevalence and incidence of SSc-ILD**
* **Overall and annual prevalence of SSc and SSc-ILD**

Annual prevalence rates will be calculated using the following methodology: For each of the 10 fiscal years of the study, the denominator of eligible patients will be calculated. From this pool of eligible patients, those with the specific diagnosis code(s) of interest in a given fiscal year will be flagged (SSc or SSc-ILD). The number of patients flagged will be divided by the denominator of eligible patients and converted to a prevalence rate out of 100,000 people.Similarly, a 10-year period prevalence will be calculated using the below methodology: Patients who have the condition at any time from 2008-2018All adults who live in the province with a valid health card at any time from 2008-2018* **Overall and annual incidence of Ssc and SSc-ILD**

Annual incidence rate will be defined as no diagnosis of the condition in the previous year based ICD coding in the province of interest and be calculated with the following formula:Incident patients during the fiscal yearAll adults with a valid health card person-time during the fiscal yearOverall incidence rate will be calculated with the following formula:$$\frac{Incident Patients date ^{\*}2008-2018}{All enrollees person-time 2008-2018}$$Incidence rate and prevalence will in addition be presented by:* Age
* Sex
* LHIN

Statistical analysis:Descriptive analyses will be conducted to report the results of this study. Continuous variables (e.g., age) will be presented as mean values, medians, ranges, and standard deviations and categorical variables will be presented as absolute and relative frequencies (e.g., sex). Rates will include a 95% confidence interval. |
| **Secondary Outcome Definition(s)** | 1. **Survivial Analysis for SSc and SSc-ILD**

Please use the Kaplan and Meier method to determine to estimate survivalSurvivalprobability= Number of patients living at the start- number of patients diedNumber of patients living at the startPlease report the numbers at risk n(%), death n(%) and censored n(%) Please create Kaplan Meier Curves for SSc and SSc-ILDIf the SSc-ILD Kaplan Meier Curves is not possible, please explain the rationale/reasonFor SSc-ILD patients, please run a survival probability curve and generate a survival table looking at the survival from the point of ILD diagnosis.1. Time to ILD after SSc diagnosis

Please calculate time between diagnoses as in days report the median (range):Date of initial SSc diagnosis (all M34 categories)- Date of initial ILD diagnosis (codes J99.1, J84.1, J84,9 or J84.8)Time to ILD diagnosis (codes J99.1, J84.1, J84.9 or J84.8) after initial SSc diagnosis (all M34 categories) For both prevalent and incident patients |
| **Baseline Characteristics** | Age (18 to 29, 30 to 50, 51 to 64 and 65+)SexIncome quintileLHINUrban/ruralYearCharlson score (use 2 year lookback)Gastro-oesophageal reflux disease (K21)Raynaud’s Syndrome (I73.0)Primary pulmonary hypertension (I27.0)Sleep apnoea (G47.3 including G47,30, G47.31 ad G47.38)  |
| **Other Variables** |  |

Please delete tables 9 and 10 from the earlier version

| Analysis Plan and Dummy Tables (expand/modify as needed) |
| --- |
| **Descriptive Tables (insert or append dummy tables), e.g.:** |
|  **Table 1. Baseline characteristics according to primary/secondary exposure** |
|  **Table 2. Outcomes according to primary/secondary exposure** |
|  **Table 3. Covariates (baseline characteristics) according to outcomes**  |
| **Statistical Model(s)** |
|  **Type of model** |  |
|  **Primary independent variable** |  |
|  **Dependent variable** |  |
|  **Covariates** |  |
| **Sensitivity Analyses** |  |
|  **Type of model** |  |
|  **Primary independent variable** |  |
|  **Dependent variable** |  |
|  **Covariates** |  |
|  |

| Quality Assurance Activities  |
| --- |
| **RAE Directory of SAS Programs** |  |
| **RAE Directory of Final Dataset(s)** | *The* *final analytic dataset for each cohort includes all the data required to create the baseline tables and run all the models. It should include all covariates for all models such as patient risk factors, hospital characteristics, physician characteristics, exposure measures (continuous, categorical) and outcomes. It should include covariates that were considered but didn’t make the final cut. This would permit an analyst to easily re-run the models in the future.* |
|  |
| **RAE README file available:** [ ] Yes [ ] No |
| **Date results of quality assurance tools for final dataset shared with project team (where applicable):** |  |
|  | **%assign** | yyyy-mon-dd |
|  | **%evolution** | yyyy-mon-dd |
|  | **%dinexplore** | yyyy-mon-dd |
|  | **%track / %exclude** | yyyy-mon-dd |
|  | **%codebook** | yyyy-mon-dd |
| **Additional comments:** |  |