Project Initiation This Section must be Completed Prior to Project Dataset(s) Creation	
Project Title:	Real World Evaluation of Access-driven Canadian Treatment Sequences in Progressive Prostate Cancer
Project TRIM number:	2020 0970 192 000
Research Program:	Cancer
Site:	ICES Central
Project Objectives:	*Insert Project Objectives as listed in the approved ICES Project PIA* The purpose of this study is to inform policy and practice on the optimal use of Ra-223 as part of treatment sequences for mCRPC by evaluating clinical outcomes and healthcare resource utilization using real-world data. The **primary objective** is to determine the effects of Ra-223 placement (no Ra-223 received; early Ra-223 received; late Ra-223 received). The **primary endpoint** is overall survival. The **secondary endpoints** are: a. **Event-free survival (EFS)**, a composite of time to change in life-prolonging therapy or death from any cause. b. Use of **External Beam Radiation Therapy (EBRT).** c. Real-world **Healthcare Resource Utilization (HCRU)**. The **exploratory endpoints** are: a. Time from Ra-223 completion to initiation of next life prolonging therapy **Secondary objectives** The secondary objective is to evaluate the correlation between **changes in biochemical markers (PSA, ALP)** during treatment with Ra-223 and clinical response (primary and secondary endpoints) in patients with mCRPC.
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 *(Not applicable)*
Principal Investigator (PI):	Louis Rogers
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* Refik Saskin
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* Refik Saskin, Stefana Jovanovska, Josephine Hsieh, Bo Zhang — 2019-Nov-21 *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*

Project Initiation
This Section must be Completed Prior to Project Dataset(s) Creation

Other ICES Project Team Members and date joined (list all):	Lisa Ishiguro		2021-Feb-18
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 (Louis Rogers)	☒	2021-May-13
	Responsible ICES Scientist or Second ICES Scientist/Lead	☒	2021-May-13
	ICES Research and Analysis Staff Creating the DCP	☒	2021-May-13
	ICES Analytic Staff	☒	2021-May-13
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*		
	Bo Zhang		
DCP Creation Date and Author:	*Date DCP was finalized prior to Project Dataset(s) creation*	*Name of person who created the DCP*	
	Date	***Name***	
	2020-Mar-01	Bo Zhang	

ICES Data This 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	2006 -2019
CIHI SDS	2006 -2019
NACRS	2006 -2019
ODB	2006 -2019
OHIP	2006 -2019
General Use Datasets – Care Providers	
See list	
General Use Datasets – Population	
RPDB	2006 -2018
See list	
General Use Datasets – Coding/Geography	
LHIN	2006-2018
PCCF	2006-2018
General Use Datasets – Facilities	
See list	
General Use Datasets – Other	
OLIS	1992-2019
Controlled Use Datasets	
OCR	2006 -2018
NDFP	2006 -2019
ALR	2006 -2019
ONMARG	2006, 2011, 2016
Other Datasets	
NMS	2012 -2019
ESAS	2007-2019

Project Amendments and Reconciliation			
	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*

Project Amendments and Reconciliation

ICES Project PIA Amendment History (add additional rows as needed):	***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***
	2020-Sep-15	Bo Zhang	Double checking proportion(s) of patients who used any of the 5 PC life-proloinging therapies between 01Jan2013 and 31Dec2017 could be found in the OCR data.
	2020-Sep-25	Bo Zhang	Added a sensitivity analysis for EFS2 among patients who used at least 3 lines of life-prolonging therapies.
	2021-Jan-10	Bo Zhang	Added adjusted survival curves for overall survival, EFS2, ED visit, and hospitalization by the two radium use groups.
	2021-Feb-26	Bo Zhang	Added new analysis by changing the index date from 2nd line to 1st line therapy to examine if the results would be changed on the overall survival.
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*		
	2021-Apr-21		

Project Cohort

Study Design	☒ Cohort study ☐ Matched cohort study ☐ Case-control study ☐ Cross-sectional study ☐ Other (specify):
Index Event / Inclusion Criteria	Start of second life-prolonging systemic therapy for metastatic castrate resistant prostate cancer (mCRPC)/ Men with mCRPC and at least 2 lines of life-prolonging therapy initiated between 01 Jan 2012 to 31 Dec 2017. The index date is the date of initiation of the 2nd life prolonging therapy for mCPRC. The 2nd line of life-prolonging therapy was initiated between 01 Jan 2012 to 31 Dec 2017. Use OCR with CURR_TOPOG_CD in: 'C61' to get patients with prostate cancer. OCR time period: 01Jan1992-31Dec2017 mCRPC: the first line therapy can be any time before the 2nd line of treatment Due to challenges in identifying mCRPC (versus 'prostate cancer') as a diagnosis consistently across all provinces, the use of life-prolonging therapy typically prescribed for mCRPC will be used to identify the study population. A line of therapy could be: (1) androgen receptor axis targeted (ARAT) therapy: abiraterone acetate and enzalutamide (2) chemotherapy: docetaxel and cabazitaxel or (3) targeted alpha therapy: Ra-223

Project Cohort

A line of therapy is the eligible mCRPC life-prolonging therapy plus any other drugs within 28 days of starting the first agent in that line setting https://www.sciencedirect.com/science/article/pii/S1558767319303921?via%3Dihub); while for radium223 use, a new line of therapy must occur after the end date of current radium223 use as well (generally all cycles of radium223 should be within 6 months), apart from the above criterion.

3 data sources should be used to find the 5 life prolonging therapies for prostate cancer:
Time period: 01Jan1992-31Aug2019

1. ALR-Systemic based on cco_regimen
1.1 Abiraterone acetate [index(cco_regimen,'ABIR')>0 in ALR-systemic data, including: '*ABIRPRED', 'ABIRPRED' and *ABIRDEXA']
1.2 Enzalutamide [index(cco_regimen,'ENZ')>0 in ALR-systemic data, inclinding: '*ENZL', 'ENZL', and '*ENZLDENO')
1.3 Docetaxel [cco_regimen in ('*DOCEPRED', '*DOCETAXEL-PREDNISONE', '*DOCE(W)PRED', 'DOCE(W)PRED', 'DOCEPRED', 'DOCE(W)PRE', 'DOCE(W)+PRED', , '*DOCE(W)', 'DOCE', 'DOCE(W)', '*DOCETAX-75', '*DOCETAXWK', '*CRBPDOCE')]
1.4 Cabazitaxel [index(cco_regimen,'CABA')>0; including '*CABAPRED']
1.5 Radium223 [index(cco_regimen,'RAD223')>0; including '*RAD223']

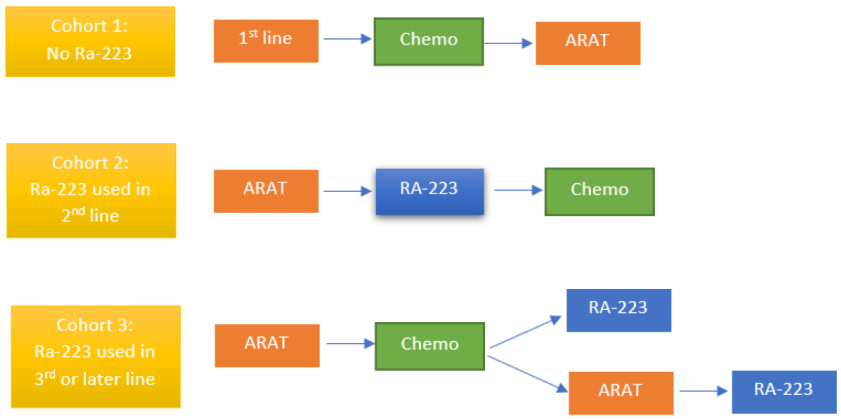
2. NDFP: drug_name in ('Cabazitaxel' 'Docetaxel' 'Radium-223 Dichloride'); no other life-prolonging therapies for PC were found in NDFP.

3. ODB
3.1 Abiraterone acetate: din in ('02371065, '02457113')
3.2 Cabazitaxel: din in ('02369524')
3.3 Docetaxel: din in ('02177080', '02177099', '02412225', '02177080', '02361957')
3.4 Enzalutamide: din in ('02407329')
3.5 Radium223: din: 02418398; not available in ODB

Early use of RA-223: 2nd line (or 1st line)
Late use of RA-223 (3rd or later line)

Project Cohort

Figure 6. Most common sequences included in each cohort



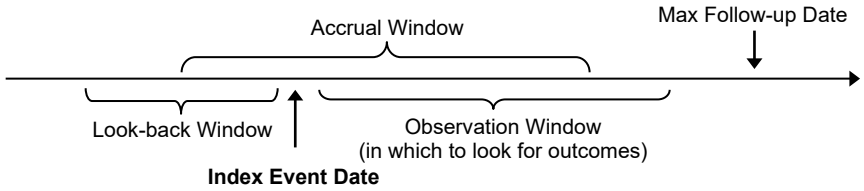
Note: This diagram does not cover all possible variations to the sequence of agents used.

Estimated Size of Cohort (if known)

Exclusions (in order)

Step	Description
1	Invalid ikn
2	Missing age, sex, sex=F, non-Ontario residents
3	Death date before index date

Project Time Frame Definitions



Accrual Start/End Dates	2012/2018 (01Jan2012-31Dec2017)
Max Follow-up Date	31Aug2019
When does observation window terminate?	31Aug2019
Lookback Window(s)	2 years prior to 1st line for Charlson Index

Variable Definitions (add additional rows as needed)

Main Exposure or Risk Factor	Metastatic castrate resistant prostate cancer (mCRPC) with no Ra-233; early Ra-233 (second line) or late Ra-233 (third or later placement). In the main analysis, we need to exclude those who used Ra-223 as first line. Use early Ra-233 as reference category so we can can make three-way comparison: Early vs none, Late vs none, Early vs Late

Variable Definitions (add additional rows as needed)	
Primary Outcome Definition	Overall survival: The length of time from the date of initiation of second line life-prolonging treatment to death due to any cause.
Secondary Outcome Definition(s)	Event-free survival (EFS): The length of time from the start of second line life prolonging treatment to the earliest occurrence of one of the following: (1) A change in life-prolonging treatment (2) Death from any cause EFS will be measured from the start of the second line of life-prolonging treatment (index date) to 1. the start of the 3rd line of life-prolonging treatment or death (**EFS1**), and 2. the start of the 4rh line of life-prolonging therapy or death (**EFS 2**), (need to breakdown on the EFS endpoint into line of therapy and deaths in absolute number) Time to External beam radiotherapy (EBRT): will be measured from the start of the first second life-prolonging treatment (index date) until the first use of EBRT Total incidence of EBRT: will be measured as the total number of EBRT treatments received over the course of the patient's journey starting from the initiation of 2nd line life-prolonging treatment (index date) until death. All cause Hospitalizations: (1) Number of overnight hospital stays (do not use SDS data) from the initiation of second-line life prolonging therapy (index date) until death. (2) Average length of hospital stays (number of days) from the initiation of second-line life prolonging therapy (index date) until death. All cause Emergency Room visits (do NOT include not seen or scheduled): Number of visits to the ER, irrespective of duration, from the initiation of second-linelife prolonging therapy (index date) until death. Time from Ra-223 completion to initiation of next line of therapy Variables needed: • Date of administration of the 6th (or last) cycle of Ra-223 • Date of initiation of next line of therapy Change in ALP: The percentage change in ALP from baseline (Refik indicated on the April 23, 2020 the meeting: Data for ALP are not readily available for analysis; You may have an update to use ALP data next year.) Change in PSA: The percentage change in PSA from baseline For Ra-223 users only: PSA1 is the value within 30 days (before or after) of the first dose of Ra-223. When more than one lab value is available within this window, the lab value on the date closest to the first dose date will be used. PSA2 is the value within 60 days following the 3rd cycle of Ra-223. When more than one lab value is available within this window, the lab value on the date closest to the 3rd cycle will be used. The percentage change in PSA from baseline, computed as: $\left(\frac{PSA2 - PSA1}{PSA1}\right) \times 100$
Baseline Characteristics	• 1. Age (years), at baseline (1st line) • 2. ethnicity, (onMarg): there are four dimensions, including residential instability, material deprivation, ethnic concentration, and dependency;

Variable Definitions (add additional rows as needed)

- We will use quintiles (1 least to 5 most marginalized) to report results

Table 1. Dimensions of marginalization and their respective indicators

	DIMENSIONS			
	Residential instability	Material deprivation	Dependency	Ethnic concentration*
INDICATORS	Proportion of the population living alone	Proportion of the population aged 20+ without a high-school diploma**	Proportion of the population who are aged 65 and older	Proportion of the population who are recent immigrants (arrived in the 5 years prior to census)
	Proportion of the population who are not youth (aged 16+)***	Proportion of families who are lone parent families	Dependency ratio (total population 0-14 and 65+ /total population 15 to 64)	Proportion of the population who self-identify as a visible minority
	Average number of persons per dwelling***	Proportion of the population receiving government transfer payments	Proportion of the population not participating in labour force (aged 15+)***	
	Proportion of dwellings that are apartment buildings	Proportion of the population aged 15+ who are unemployed		
	Proportion of the population who are single/ divorced/widowed***	Proportion of the population considered low-income****		
	Proportion of dwellings that are not owned***	Proportion of households living in dwellings that are in need of major repair		
	Proportion of the population who moved during the past 5 years			

* Aboriginal indicators did not load on any of the factors.

** For the 2006 index, the indicator is the proportion of the population aged 25+ without a certificate, diploma or degree. This is due to a change in the Statistics Canada definition.

*** Indicators were reverse coded, meaning they were coded opposite of the measure (e.g. % married/common law becomes %single/divorced/separated/widowed).

**** "Low income" is defined as below the low income cutoff (LICO), a Statistics Canada measure that is adjusted for community size, family size and inflation.

- 3. treatment facility type (academic/non academic): using DADSDS (+/-90 days of 1st line), or OCR data (on PC diagnosis date); treat this varaiable as 'teacing' if any one of the hospital type is teaching from the two data souces; else as 'non-teaching'

- 4. use of bone health agents (yes/no): (+/- 90 days of 1st line)

Data should be created using data from ODB, ALR-systemic (cco_regimen) and NDFP;

DINs are listed below:
Denosumab: 02343541; 02343568; 02368153
Zoledronic acid: 02269198; 02408449; 02408325; 02482525; 02403056; 02415100; 02415186; 02426414; 02421720; 02401606; 02304007; 02424894; 02407639; 02421550; 02434458; 02444739; 02472805; 02413701; 02420961; 02422425; 02408082; 02422433; 02479311; 02248296; 02242725
Alendronate: 02401118, 02401126, 02401134, 02381478, 02381486, 02381494, 02258102, 02258110, 02485168, 02485176, 02485184, 02299712, 02302004, 02343916, 02343924, 02352966, 02303078, 02405717, 02405725, 02248727, 02248728, 02248729, 02248730, 02454467, 02454475, 02388545, 02388553, 02365057, 02365065, 02365073, 02365081, 02282763, 02308398, 02201011, 02201038, 02233055, 02245329, 02248625, 02276429, 02314940, 02270110, 02385015, 02385023, 02385031, 02394855, 02394863, 02394871, 02270129, 02286335, 02282771, 02273179, 02284006, 02372304, 02384698,

Variable Definitions (add additional rows as needed)

02384701, 02384728, 02275279, 02270870, 02270889, 02476398, 02476401, 02288079, 02288087, 02288095, 02288109, 02429160, 02247373, 02248251, 02261715, 02403633, 02403641, 02428717, 02428725, 02428733

Risedronate: 02239146, 02242518, 02246896, 02297787, 02316838, 02370417, 02279657, 02285541, 02353687, 02377721, 02406284, 02406292, 02406306, 02442760, 02309831, 02368552, 02357984, 02397773, 02358883, 02358891, 02358905, 02427354, 02309874, 02302209, 02424177, 02362414, 02377446, 02319861, 02347474, 02352141, 02370239, 02370247, 02370255, 02411407, 02341077, 02327295, 02298376, 02298384, 02298392, 02413809, 02326981

Etidronate: 02263866, 02248686, 02248687, 02276844, 02276852, 02176017, 01908480, 01997629, 02347989, 02353210, 02347962, 02347970, 02247323, 02245330, 02324199,

Need to have 2-subcategories:
- Denosumab and zoledronic acid
- Oral bisphosphonates (risedronate, alendronate and etidronate)

- 5. number of lines of treatment before mCRPC diagnosis: median (min; max); This is use of something other than the life-prolonging therapies, so all the other drugs (bicalutamide, Lupron, zoladex, etc) BEFORE starting life-prolonging therapies (i.e. BEFORE mCRPC). Each one would be considered a line (regardless of stopping and starting the SAME drug which is historical usage of intermittent dosing, if it is the same drug consider it the same line); '*DOCE' from cco_regimen should also be included.

Get the following drugs from ODB and ALR-systemic (need to use all DINs, even those not listed in ON, because some of these drugs are found in ODB). Note: NDFP does not have these drugs.

GnRH agonists:

- Leuprolide Gel (listed AB, not listed ON)
  7.5 mg : DIN: 02248239
  22.5 mg DIN: 02248240
  30 mg DIN: 02248999
  45 mg DIN: 02268892

- Lupron Depot :
  7.5 mg DIN: 00836273
  22.5 mg DIN: 02230248
  30 mg DIN: 02239833
  ON also lists:
  3.75mg DIN 00884502
  11.25mg DIN 02239834

- Buserelin (not listed in ON, but is listed in AB)
  6.3 mg DIN: 02228955
  9.45 mg DIN: 02240749

Variable Definitions (add additional rows as needed)

- Goserelin
  3.6 mg DIN: 02049325
  10.8 mg DIN: 02225905

- Triptorelin (not listed in AB; but is listed in ON)
  3.75 mg/vial DIN:02240000

- Histrelin (not listed in AB or ON)
  50mg DIN:02278383

- Cyproterone (not listed in AB or ON, not sure about QC or BC)
  50mg DIN:02245898

GnRH antagonist:

- Degarelix
  80 mg DIN- 02337029
  120 mg DIN- 02337037

1st generation NSAA:

- Bicalutamide
  50 mg DIN- TEVA: 02270226 (AB listing)
  50 mg DIN- PMS: 02275589 (AB listing)
  50mg DIN- Casodex Brand 02184478 (ON listing)

- Flutamide (listed in AB, not ON)
  250 mg DIN: 02238560

- Nilutamide (listed in AB, not ON)
  50mg DIN: 02221861

All DIN list for ADT (incl. GnRH agonists, GnRH antagonist and NSAA)

Drug	TradeName	DIN
Leuprolide Acetate	Eligard 7.5mg	02248239
Leuprolide Acetate	Eligard 22.5mg	02248240
Leuprolide Acetate	Eligard 30mg	02248999
Leuprolide Acetate	Eligard 45mg	02268892
Leuprolide Acetate	Lupron 5mg	00727695
Leuprolide Acetate	Lupron Depot 7.5mg	00836273
Leuprolide Acetate	Lupron Depot 3.75mg	00884502
Leuprolide Acetate	Lupron Depot 22.5mg	02230248
Leuprolide Acetate	Lupron Depot 30mg	02239833
Leuprolide Acetate	Lupron Depot 11.25mg	02239834
Leuprolide Acetate	Zeulide Depot 3.75mg	02429977
Leuprolide Acetate	Zeulide Depot 22.5mg	02462699
Buserelin Acetate	Suprefact 100mcg	02225158

Variable Definitions (add additional rows as needed)

Buserelin Acetate	Suprefact 1mg	02225166
Buserelin Acetate	Suprefact Depot 6.3mg	02228955
Buserelin Acetate	Suprefact Depot 9.45mg	02240749
Buserelin Acetate	Suprefact Inj 1mg/mL	00680028
Buserelin Acetate	Suprefact Intranasal solution	00680036
Buserelin Acetate	Suprefact Liq	01989669
Goserelin acetate	Zoladex 3.6mg	02049325
Goserelin acetate	Zoladex LA 10.8mg	02225905
Triptorelin	Decapeptyl 0.1mg	02389282
Triptorelin	Trelstar 3.75mg	02240000
Triptorelin	Trelstar 11.25mg	02243856
Triptorelin	Trelstar 22.5mg	02412322
Histrelin acetate	Vantas 50mg	02278383
Cyproterone	Alti-CPA 50mg	02229449
Cyproterone	Androcur 50mg	00704431
Cyproterone	Androcur Depot 100mg/mL	00704423
Cyproterone	Cyproterone	02237253
Cyproterone	Cyproterone	00245898
Cyproterone	Med-cyproterone	02390760
Cyproterone	Mylan-cyproterone	02229723
Cyproterone	Novo-cyproterone	02232872
Cyproterone	Riva-cyproterone	02395797
Cyproterone	Riva-cyproterone	02242127
Degarelix	Firmagon 80mg	02337029
Degarelix	Firmagon 120mg	02337037
Bicalutamide		02270226
Bicalutamide		02275589
Bicalutamide		02184478
Flutamide		02238560
Nilutamide		02221861

ADT data from ALR:
From cco_regimen, including '*BICA', '*BICAGOSE', '*BICALPRL', '*BICALU', '*BICATRIP', '*BUSERELIN', '*CYPR', '*CYPROTERONE', '*FLUT', '*GOSE', '*GOSE-BICALU', '*GOSER', '*LEUPBICALU', 'LEUPFLUT', '*LEUPRO', '*NILUT' , '*TRIP', '*TRIPTORELIN', '*GOSE', 'LEUP'

- 6. number of Ra cycles: median (min;max);
  - Number of cycles of Ra-223 used in any line (the cohorts will be early (1st and 2nd line) vs late (3rd line or later).
  - Just to clarify terminology, a "line" of therapy is the entire time a patient is on the same drug. A "cycle" is often a single dose (when not a daily drug), but could be a dosing schedule over a particular (2-3 week time frame). In prostate cancer it's straightforward:

Variable Definitions (add additional rows as needed)

- Abiraterone is a daily oral medication. No "cycles", and the "line" is the entire time the patient was on it.
- Enzalutamide – same as abiraterone
- Docetaxel is given every 3 weeks, so that 1 dose in a 3 week period = a "cycle"; while the line of therapy is the entire time the patient was on it (first dose to start of new treatment, even if there is a gap between last dose of doce and next line of therapy, it's still considered part of that "line"
- Cabazitaxel is same as docetaxel (3 week cycle with one dose administered)
- Ra-223 is similar to docetaxel and cabazitaxel in concept, but the cycle is 4 weeks (one dose every 28 days)

- Count the cycles of first Ra-223 use if Ra-223 was used more than once

- 7. use of nonsteroidal agents
- Anti-androgen (NSAA) treatment prior to index date (yes/no);
  - Anytime (majority will be prior to 1st line mCRPC, but we should differentiate any usage after 1st line mCRPC although it is not standard and there is really no evidence it still happens)
  - Note that use of NSAA would be considered a line of therapy prior to mCRPC. We may end up lumping all these together and not care what one the patient got, but we may want to call out use of NSAA so it's good to be able to separate the lines easily if needed (not just how many they got).

- 8. number of lines of therapy prior to index date: median (min;max),
- This is the same as for the 2nd line of PC cancer treatment; For the number of lines of other cancer drug use

- 9. time from prostate cancer diagnosis to mCRPC: median (min;max);
  To the 1st line of the 5 life-prolonging therapies.
  Some patients might start their first line of therapies before their PC diagnosis date (a negative value for time from PC diagnosis to mCRPC). Keep these patients in the cohort (may treat their time from PC diagnosis date to 1st (and to 2nd) line as missing).

- 10. duration of response to Androgen deprivation therapy (ADT): median (min;max);
  - This would be from time they started the first ADT, to mCRPC – 1st line
  - The DINs are in the word document (Drug list with DINs) – GnRH angonists and antagonists and 1st generation NSAA. (listed above for question 5)

- 11. stage of disease at initial prostate cancer diagnosis (digital rectal exam [DRE], prostate specific antigen [PSA], Gleason score or TNM);
  - For stage of disease at diagnosis there are two things normally identified for patients: TMN is a standard grading system for cancer and tells you if the cancer is local or has spread, and how extensive the disease is. Gleason score is specific to prostate cancer. This would be determined at the time of biopsy at diagnosis of prostate cancer. Patients who opt to

Variable Definitions (add additional rows as needed)

not get a biopsy may not have this grading/classification done. Time period could be anytime, but it would be only once for each patient and around the time of diagnosis of prostate cancer.
    - For DRE – it's an exam that can be done to screen for prostate cancer. If not easily identifiable, I don't think it will add much value to the baseline characterstics. The goal is to get as many baseline characteristics related to prostate cancer as possible, so that we can determine how well balanced the groups are. (Note: DRE not available with ICES data)

- 12. PSA: First to check if PSA data are available 30 days before the 1st line of therapy (use the closest date data to 1st line); if not, check to see if PSA data are available 30 days after the 1st line for the baseline information. This would apply to the other lines as well. Refik and Bo will check data to see if 30 days are a good estimate for time gap between 2 lines of therapies.
- LOINC codes =10886-0 12841-3 19197-3 2857-1 35741-8

- 13. Gleason score: from CSSSF7 (Gleason's Primary Pattern and Secondary Pattern Values on Needle Core Biopsy/Trnaurethral Resection of Prostate (TURP); CSSSF8 (Cleason's Score on Needle Core Biopsy/Transurethral Resection of Prostage (TURP), from cstage_2018 data (based on PC diagnosis date; whatever is available).
  http://web2.facs.org/cstage0205/prostate/Prostateschema.html
- TNM: cs_drvd_ajcc_m_cd, cs_drvd_ajcc_n_cd, cs_drvd_ajcc_t_cd from beststage_2018 data (based on PC diagnosis date; whatever is available). Tumour size: http://web2.facs.org/cstage0205/prostate/Prostate_apa.html

- 14. alkaline phosphatase [ALP] and hemoglobin (Hb)
    - This is a lab results, we'd like to see baseline level at the time of starting 1st line mCRPC therapy (one of our 5 PC drugs)
    - Keep in mind for lab values, that we have an exploratory endpoint that is more detailed on ALP, so more ALP datapoints will need to be captured. Just if it matters in the way you pull the data – for the baseline characteristic we only need the one, but we'll need other results later.

  Notes:
  - ALP: not available as of September 2020; may be able to get update next year;
  - Hb: data are available; using the same approach as for PSA.
  - Hb: LOINC 718-7 and 20509-6 for hemoglobin in blood

- 15. Pain score (standardized) and
    - Some provinces use fairly standardized pain scores, like ESAS (Edmonton Symptom Assessment Scale) or BPI (Brief Pain Index) more readily than others, and some capture it in the data. Performance Status is another common one in cancer. Time would be at baseline – i.e. start of 1st line mCRPC therapy.

  Notes:

Variable Definitions (add additional rows as needed)	
	- Use the closest data to the 1st line (baseline) within +/- 90 days - Present results as mean (SD), median (IQR), and min-max - Data from ESAS (variable: esas_value) • 16. opioid use (yes/no) ○ At baseline – time of starting 1st line mCRPC. ○ DIN list for opioid use (in Appendices 1 and 2). Notes: - Use the data within +/- 90 days to the 1st line (baseline) • 17. Charlson Comorbidity Index (CCI), ○ Baseline characteristic – so at the time of starting 1st line mCRPC therapy. Notes: - 2 years prior to the 1st line mCRPC, based on both DADSDS (all sources) and NACRS (all sources) data; The standard Charlson Co-morbidity Index is generally created based on hospitalization data (DAD data) 2 years prior to index date (thus sometimes it is called # of hospitalizations). Because the standard way may result in many missing data, we use the alternative way to get this variable. • 18. Eastern Co-operative Oncology Group (ECOG) score. Notes: - Use the closest data to the 1st line (baseline) within +/- 90 days - Present results as 0, 1, and 2+ - Use the variable ecog_value • 19. Proportion of patients who used any of the 5 life-prolonging therapies, regardless of lines - Follow-up time by cohort - Recalcuate the percetages using the number of patients that had previous treatment to the primary as the denominator to get the information about the patients with the primary treated and the type they received. • 20. Treatment Patterns - Explore the treatment patterns based on the 5 life-prolonging therapies, e.g., Abiraterone – docetaxel – radium 223 Docetaxel – radium 223 – enzalutimate This should be done by lines of therapies, 2 lines only, 3 lines only and 4+ lines
Other Variables (time dependent)	Previous treatment, prostate specific antigen (PSA), alkaline phosphatase (ALP), hemoglobin (Hb) and Charlson Comorbidity Index (CCI) . Previous treatment of radiation therapy 1. Radiation (**EBRT**): >=20+ sessions (one day as one session; from all data sources) (between PC diagnosis date and 1st line of life-prolonging therapy) DADSDS and NACRS: CCI code ‘1QT27’ (radiation, prostate); CCP code ‘0621’ ‘0622’ ‘0624’ ‘0631’ ‘0632’

Variable Definitions (add additional rows as needed)	
	OHIP feecode: 'X310, X311, X312, X313 (X310-X313: treatment planning), X302 (thera. radiol.-teleradiotherapy-x-ray,radium,cobalt etc.), X304 (thera. radiol.-teleradiotherapy-minor), X322 (thera. radiol.-radium-sealed source-treat. planning), X324 (thera. radiol.-radium-sealed source-interstitial application) Need 20+ fractions to define RT, we will need to use treatment (**Radiotherapy fractions:** The full dose of **radiation** is usually divided into a number of smaller doses called **fractions**. This allows healthy cells to recover between treatments. You have the **fractions** as a series of treatment sessions that make up your **radiotherapy** course.) 2. **Brachytherapy** (between PC diagnosis date and 1st line of life-prolonging therapy) CCI code '1QT26' (CCP code '0634') from DADSDS or NACRS and ohip feecode 'S640' 3. Radical prostatectomy (**RP**) (before 1st line therapy) OHIP feecode: 'S645' 'S646' 'S647' 'S650' 'S651 and S653 4. **Cryotherapy** (before 1st line therapy): DADSDS and NACRS: CCI code '1QT59BAAD' (Destruction, prostate endoscopic per orifice approach using cryosurgery; CCP: '721') '1QT59HAAD' (destruction, prostate, percutaneous approach using cryosurgery; CCP: '7252')
Outcome	EBRT (after 2nd line therapy) DADSDS and NACRS: CCI code '1QT27' (radiation, prostate; no CCP code found); OHIP feecode: X310, X311, X312, X313 (X310-X313: treatment planning), and dxcode '185' (prostate) and specialty code '34' (therapeutic radiology); ALR-radiation NHPIP code: 534, 535, 549, 575, 592, 594, 597 Note: One course of EBRT should be completed within 14 days and a gap of at least 14 days should be applied from one course to next. Double checking proportion(s) of patients who used any of the 5 PC life-proloinging therapies between 01Jan2013 and 31Dec2017 could be found in the OCR data.

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	
Using counting-process data for all figures below:	
Figure 1. Survival curve for overall survival (cohort)	
Figure 2. Survival curve for overall survival (adjusted)	
Figure 3. Survival curve for EFS1 (cohort)	
Figure 4. Survival curve for EFS1 (adjusted)	
Figure 5. Survival curve for EFS2 (cohort)	
Figure 6. Survival curve for EFS2 (adjusted)	
Figure 7. Survival curve for EBRT (cohort)	
Figure 8. Survival curve for EBRT (adjusted)	
Statistical Model(s)	
Type of model	Cox regression models, using counting process data
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Overall survival**
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), and time-dependent covariates of PSA and HB; to deal with immortal time bias for Ra223, late use group should be identified after patients received Ra223 in the modeling analysis, treating Ra223 use as a time-varying variable.
Statistical Model(s)	
Type of model	Cox regression models, using counting process data
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Event free survival (EFS1 and EFS2)**
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), and time-dependent covariates of PSA and HB; to deal with immortal time bias for Ra223, late use group should be identified after patients received Ra223 in the modeling analysis, treating Ra223 use as a time-varying variable.
Statistical Model(s)	
Type of model	Cox regression models, using counting process data
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Time to EBRT (to the first EBRT)**, using counting process data
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), and time-dependent covariates of PSA and HB; to deal with immortal time bias for Ra223, late use group should be identified after patients received Ra223 in the modeling analysis, treating Ra223 use as a time-varying variable.

Analysis Plan and Dummy Tables (expand/modify as needed)	
Statistical Model(s)	
Type of model	Cox regression models, using counting process data
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Time to Hospitalization (to the first Hospitalization)**, using counting process data
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), and time-dependent covariates of PSA and HB; to deal with immortal time bias for Ra223, late use group should be identified after patients received Ra223 in the modeling analysis, treating Ra223 use as a time-varying variable.
Statistical Model(s)	
Type of model	Cox regression models, using counting process data
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Time to Emergency Room (ER) visits (to the first ER Visit)**, using counting process data
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), and time-dependent covariates of PSA and HB; to deal with immortal time bias for Ra223, late use group should be identified after patients received Ra223 in the modeling analysis, treating Ra223 use as a time-varying variable.
Statistical Model(s)	
Type of model	Poisson Regression Modeling with link of negative binomial
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Incidence of EBRT**
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), baseline PSA and Hb; offset = time to last EBRT or censored date
Statistical Model(s)	
Type of model	Poisson Regression Modeling with link of negative binomial
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Incidence of hospitalisation**
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), baseline PSA and Hb; offset = time to last hospitalization or censored date
Statistical Model(s)	
Type of model	Descriptive Analysis
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Duration of hospitalisation**
Covariates	Not applicable

Analysis Plan and Dummy Tables (expand/modify as needed)	
Statistical Model(s)	
Type of model	Poisson Regression Modeling with link of negative binomial
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Incidence of Emergency Room (ER) visits**
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), baseline PSA and Hb; offset = time to last ER visit or censored date
Statistical Model(s)	
Type of model	Descriptive Analysis
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Time from Ra-223 completion to initiation of next line of therapy**
Covariates	Not applicable
Statistical Model(s)	
Type of model	Not applicable
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Percent change in ALP (no data)**
Covariates	Not applicable
Statistical Model(s)	
Type of model	Descriptive Analysis
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	**Percent change in PSA**
Covariates	Not applicable
Sensitivity Analyses	
Type of model	Cox regression models, using counting process data among overall cohort, including those who used Ra223 as first line
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	Overall survival (sensitivity analysis), including those who used Ra223 as first line
Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), and time-dependent covariates of PSA and HB; to deal with immortal time bias for Ra223, latek use group should be identified after patients received Ra223 in the modeling analysis.

Sensitivity Analyses	
Type of model	Cox regression models, using counting process data, among patients who used 3+ lines of life-prolonging therapies
Primary independent variable	Radium -233 placement (none, early or late)
Dependent variable	EFS2 among patients who used 3+ lines of life-prolonging therapies

Covariates	Age (years), use of bone health agents (yes/no), prior systematic treatments (yes/no), response to ADT (before, missing vs. after PC diagnosis), stage of cancer at initial PC diagnosis (Gleason score and TNM scores in categories), standardized pain score (-4 to 4), comorbidities (Charlson Comorbidity Index, in categories), and time-dependent covariates of PSA and HB; to deal with immortal time bias for Ra223, late use group should be identified after patients received Ra223 in the modeling analysis.

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:

For the purposes of the **Bayer DAS P2019-053 / 2020 0970 192 000** project titled, "***Real World Evaluation of Access-driven Canadian Treatment Sequences in Progressive Prostate Cancer***," we have taken the following steps in order safeguard the quality of the research outputs / deliverables produced:

- **A DAS Staff Scientist** (Refik Saskin) has been assigned to the project.
  The Staff Scientist provides ongoing feedback on the Dataset Creation Plan (DPC), reviewes the code (cohort creation and analysis) and coding practices, checkes research outputs/ deliverables, and ensures that the DCP is accurately followed by the analysts.

- **A primary DAS Senior Analyst** (Bo Zhang) has been assigned to work on the project.
  The primary analyst ensures that the established Dataset Creation Plan (DCP) was accurately followed in order to create the cohort and research outputs/ deliverables. The analyst maintains an ongoing communication with the project team and ensures all questions are addressed and resolved and the DCP changes are tracked and documented.
  The primary analyst double checks the coding and results and confirms that inclusion and exclusion criteria are applied when creating the cohort.
  As this is a private sector project, %dinexplore is not permitted for use. Coding is used to replace the above macro programs with the same function. Table of contents is created.

- **A secondary DAS Senior Analyst** (Erind Dvorani) has been assigned to double code the cohort creation.
  The secondary analyst works individually to a new code the cohort creation based on the established Dataset Creation Plan (DCP).
  If there are differences in the outcomes, the Staff Scientist, and the primary and secondary DAS Analysts, will methodically go over the code together to determine where and why it differentiates .
  Bayer will be notified of all updates.

To learn more about the Data Strategy at ICES you may access the following report .

Appedix 1. Opiod DIN list for Marketed

Drug	Trade Name	DIN
Morphine	Doloral 1	00614491
	Doloral 5	00614505
	Kadian	02184435
	Kadian	0218443
	Kadian	02184451
	Kadian	02242163
	M-Eslon	02019930
	M-Eslon	02019949
	M-Eslon	02019957
	M-Eslon	02019965
	M-Eslon	02177749
	M-Eslon	02177757
	Morphine HP 50-50mg/mL (SC/IM)	00617288
	Morphine SR	02350815
	Morphine SR	02350890
	Morphine SR	02350912
	Morphine Sulfate Inj	00392588
	Morphine Sulfate Inj	00392561
	Morphine Sulfate Inj BP	02474980
	Morphine Sulfate Inj SDZ	02382997
	Morphine Sulfate Inj USP	00636908
	Morphine Sulfate Inj USP	02242484
	Morphine Sulfate Inj USP	02482681
	Morphine Sulfate Inj USP	02482746
	Movapo	02459132
	MS Contin SRT	02014319
	MS Contin SRT	02015439
	MS Contin SRT	02014327
	MS Contin SRT	02014297
	MS Contin SRT	02014300
	MS.IR	02014203
	MS.IR	02014211
	MS.IR	02014238
	MS.IR	02014254
	Sandoz Morphine SR	02244790
	Sandoz Morphine SR	02244791
	Sandoz Morphine SR	02244792
	Sandoz Morphine SR	02478889
	Sandoz Morphine SR	02478897
	Statex Suppositories	00596965
	Statex Suppositories	00639389

	Statex Suppositories	00632228
	Statex Suppositories	00632201
	Statex Tab	00594644
	Statex Tab	00594652
	Statex Tablet	00594636
	Statex Tablet	00675962
	Teva-Morphine SR	02302764
	Teva-Morphine SR	02302772
	Teva-Morphine SR	02302780
	Teva-Morphine SR	02302799
	Teva-Morphine SR	02302802
Hydromorphone	Apo-Hydromorphone	02364115
	Apo-Hydromorphone	02364123
	Apo-Hydromorphone	02364131
	Apo-Hydromorphone	02364158
	Apo-Hydromorphone CR	02476614
	Apo-Hydromorphone CR	02476622
	Apo-Hydromorphone CR	02476630
	Apo-Hydromorphone CR	02476649
	Apo-Hydromorphone CR	02476657
	Apo-Hydromorphone CR	02476665
	Apo-Hydromorphone CR	02476673
	Apo-Hydromorphone CR	02476681
	Dilaudid	00125083
	Dilaudid	00125121
	Dilaudid	00705438
	Dilaudid	00786543
	Hydromorph Contin	02359502
	Hydromorph Contin	02359510
	Hydromorph Contin CR CAP	02125366
	Hydromorph Contin CR CAP	02243562
	Hydromorph Contin CR CAP	02125382
	Hydromorph Contin CR CAP	02125390
	Hydromorph Contin CR CAP	02125323
	Hydromorph Contin CR CAP	02125331
	Hydromorphone HP 10	02145928
	Hydromorphone HP 20	02145936
	Hydromorphone HP 50	02146126
	Hydromorphone HP Forte Inj	02244797
	Hydromorphone Hydrochloride Inj	02460602
	Hydromorphone Hydrochloride Inj HP 10	02460602
	Hydromorphone Hydrochloride Inj HP 50	02469413

	Hydromorphone Hydrochloride Inj HP Forte	02468468
	Hydromorphone Hydrochloride Inj USP	02145901
	Hydromorphone Hydrochloride Inj USP	02382636
	Hydromorphone Hydrochloride Inj USP	02485532
	Hydromorphone Hydrochloride Inj USP	02485540
	PMS-Hydromorphone Sirop 1mg/mL	01916386
	PMS-Hydromorphone Suppositoire 3mg	01916394
	PMS-hydromorphone tab 1mg	00885444
	PMS-hydromorphone tab 2mg	00885436
	PMS-hydromorphone tab 4mg	00885401
	PMS-hydromorphone tab 8mg	00885428
	Teva-hydromorphone	02319403
	Teva-hydromorphone	02319411
	Teva-hydromorphone	02319438
	Teva-hydromorphone	02319446
Oxycodone	ACT Oxycodone CR	02394170
	ACT Oxycodone CR	02394189
	ACT Oxycodone CR	02394197
	ACT Oxycodone CR	02394200
	ACT Oxycodone CR	02306530
	Apo-Oxycodone CR	02306530
	Apo-Oxycodone CR	02366746
	Apo-Oxycodone CR	02366754
	Apo-Oxycodone CR	02366762
	Apo-Oxycodone CR	02366789
	Apo-Oxycodone CR	02394766
	Apo-Oxycodone CR	02394774
	Apo-Oxycodone CR	02394782
	Oxy.Ir	02231934
	Oxy.Ir	02240131
	Oxy.Ir	02240132
	OxyNeo	02372525
	OxyNeo	02372533
	OxyNeo	02372541
	OxyNeo	02372568
	OxyNeo	02372576
	OxyNeo	02372584
	OxyNeo	02372797
	PMS-Oxycodone	02319977
	PMS-Oxycodone	02319985
	PMS-Oxycodone	02319993
	PMS-Oxycodone CR	02309882

	PMS-Oxycodone CR	02309890
	PMS-Oxycodone CR	02309904
	PMS-Oxycodone CR	02309912
	Supeudol	02262983
	Supeudol 10	00392480
	Supeudol 10	00443948
	Supeudol 20	00392472
	Supeudol 5	00789739
	Targin	02339609
	Targin	02339617
	Targin	02339625
	Targin	02387425
Oxycodone/Acetaminophen	Apo-Oxycodone/Acet 5mg	02324628
	Rivacocet	02242468
	Sandox-Oxycodone/Acetaminophen	02307898
	Teva-Oxycocet	00608165
Oxycodone/ASA	Teva-Oxycodan	00608157
Fentanyl	Fentanyl citrate inj SDZ	02384124
	Fentanyl citrate inj USP	02240434
	Fentanyl citrate inj USP	02385406
	Fentora	02408007
	Fentora	02408015
	Fentora	02408023
	Fentora	02408031
	Fentora	02408058
	PMS-Fentanyl MTX	02341379
	PMS-Fentanyl MTX	02341387
	PMS-Fentanyl MTX	02341395
	PMS-Fentanyl MTX	02341409
	PMS-Fentanyl MTX	02341417
	Sandox Fentanyl Patch	02327112
	Sandox Fentanyl Patch	02327120
	Sandox Fentanyl Patch	02327139
	Sandox Fentanyl Patch	02327147
	Sandox Fentanyl Patch	02327155
	Sandox Fentanyl Patch	02327163
	Teva-Fentanyl	02282941
	Teva-Fentanyl	02282968
	Teva-Fentanyl	02282976
	Teva-Fentanyl	02282984

	Teva-Fentanyl	02311925
Codeine	Codeine 15	02009889
	Codeine 30	02009757
	Codeine Contin 100mg CR tab	02163748
	Codeine Contin 150mg CR tab	02163780
	Codeinte Contin 200mg CR tab	02163799
	Codeine Conton 50mg CR tab	02230302
	Codeine phosphate inj USP	00544884
	Codeine phosphate syrup	00050024
	Linctus Codeine Blanc	00380571
	Teva-Codeine	00593435
	Teva-Codeine	00593451
	Teva-Cotridin	02169126
	Teva-EMTEC-30	02053403
Codeine/Acetaminophen/Caffeine	Teva-Lenoltec NO.2	00653241
	Teva-Lenoltec NO.3	00653276
	Tylenol w. Codeine NO 2	02163934
	Tylenol w. Codeine NO 3	02163926
Codeine/Acetaminophen	Teva-Lenoltec NO.4	00621463
	Tylenol w. Codeine NO 4	02163918
	Triatec-30	00789828
Codeine/ASA/Butalbital/Caffeine	Fiorinal-C 1/2	00176206
Codeine/ASA/Butalbital/Caffeine	Fiorinal-C 1/4	00176192
Codeine/ASA/Butalbital/Caffeine	Teva-Tecnal C 1/2	00608181
Codeine/ASA/Butalbital/Caffeine	Teva-Tecnal C 1/4	00608203
	Trianal C 1/4	02242406
	Trianal C 1/2	01971387
Codeine/ASA/Methocarbamol	Robaxisal C 1/2	01934783
Codeine/ASA/Methocarbamol	Robaxisal C 1/4	01934740
Tramadol	Apo-Tramadol	02426153
	Auro-tramadol	02479672
	Durela	02373017
	Durela	02373025
	Durela	02373033
	Mar-Tramadol	02480859
	Ralivia	02299194
	Ralivia	02299208
	Ralivia	02299216

	Taro-Tramadol ER	02450429
	Taro-Tramadol ER	02450437
	Taro-Tramadol ER	02450445
	Tridural	02296381
	Tridural	02296403
	Tridural	02296411
	Ultram	02349469
	Zytram XL	02286424
	Zytram XL	02286432
	Zytram XL	02286440
	Zytram XL	02286459
	Zytram XL	02360322
	Zytram XL	02360349
Tramadol/acetaminophen	Apo-Tramadol/Acet	02336790
	Auro-Tramadol/acetaminophen	0239050
	Jamp-Tramadol/acet	02388308
	Mar-Tramadol/acet	02388324
	Mint-Tramadol/acet	02389800
	PMS-Tramadol/acet	02401657
	Priva-Tramadol/acet	02391554
	Taro-Tramadol/acet	02388197
	Teva-Tramadol/Acet	02347180
	Tramacet	02264846
	Tramadol/Acet	02426803
Methadone	Cophylax	02224577
	Metadol	02241377
	Metadol	02247694
	Metadol	02247698
	Metadol	02247699
	Metadol	02247700
	Metadol	02247701
	Metadol-D	02244290
	Metadol-D	02247374
	Methadose	02394596
	Methadose	02394618
	Sandoz-Methadone	02481979
Buprenorphine	Butrans 10	02341212
	Butrans 15	02450771
	Butrans 20	02341220

	Butrans 5	02341174
	Probuphine	02474921
	Sublocade	02483084
	Sublocade	02483092
Buprenorphine/Naloxone	Act-buprenorphine/naloxone	02453908
	Act-buprenorphine/naloxone	02453916
	PMS-burprenorphine/naloxone	02424851
	PMS-burprenorphine/naloxone	02424878
	Suboxone	02295695
	Suboxone	02295709
	Suboxone	02468085
	Suboxone	02468093

Appedix 2. Opiod DIN list for Cancelled-PostMarket

Drug	Trade Name	DIN
Morphine	Diamorphine Hydrochloride Inj	00781460
	Diamorphine Hydrochloride Inj	00781479
	Homeopathic Remedy	02057093
	MOS 10 Syrup	00632503
	MOS 10 tabs	00690198
	MOS 20 Concentrate	00632481
	MOS SR tabs	00776181
	MOS SR tabs	00776203
	MOS Sulphate tab	02009765
	MOS Sulphate tab	02009749
	MOS Sulphate tab	02009706
	MOS Sulphate tab	02009773
	MOS syrup	00486582
	MOS syrup	00514217
	MOS 10	00624268
	MOS 20	00624276
	MOS 30	00636681
	MOS 20 tab	00690201
	MOS 40 tab	00690228
	MOS 50 concentrate	00690236
	MOS 60	00690244
	Morphine Extra-Fotre	00869325
	Morphine Fore	00869317
	Morphine SR	02350920
	Morphine SR	02350947
	Morphine Sulfate Inj	00649619
	Morphine Sulfate Inj	00850322
	Morphine Sulfate Inj	00850330
	Morphine Sulfate Inj	00885509
	Morphine Sulfate Inj	02137232
	Morphine Sulfate Inj	02137240
	Morphine Sulfate Inj	02137267
	Morphine Sulfate Inj	02022672
	Morphine Sulfate Inj	02022680
	Morphine Sulfate Inj	02003759
	Morphine Sulfate Inj	02010380
	Morphine Sulfate Inj	02009897
	Morphine Sulfate Inj	02010364
	Morphine-EPD	01949047
	Morphine-EPD	01949055
	MS Contin Supp	02146827

	MS Contin Supp	02145952
	MS Contin Supp	02145960
	MS Contin Supp	02145944
	MS IR SUP	02014173
	MS IR SUP	02014246
	MS IR SUP	02014262
	Opium Tincture	00094277
	Oramorph SR	01988743
	Oramorph SR	01988727
	Oramorph SR	01988735
	PMS-morphine sulfate	02245287
	PMS-morphine sulfate	02245284
	PMS-morphine sulfate	02245288
	PMS-morphine sulfate	02245285
	PMS-morphine sulfate	02245286
	Ratio-morphine	00607762
	Ratio-morphine	00607770
	Ratio-morphine	00690783
	Ratio-morphine	00690791
	Statex DPS	00705799
	Statex drops	00621935
	Statex syrup	00647217
	Statex syrup	00591467
	Statex syrup	00591475
Hydromorphone	Dilaudid	00125105
	Dilaudid	00786535
	Dilaudid	02085895
	Dilaudid-HP-plus	02146118
	Dilaudid-XP	02145863
	Hydromorph IR	02245703
	Hydromorph IR	02245704
	Hydromorph IR	02245705
	Hydromorphone	02192101
	Hydromorphone	02192144
	Hydromorphone	02249928
	Hydromorphone	02249936
	Hydromorphone HCL	01916289
	Hydromorphone HCL sup	01916270
	Jurnista	01979914
	Jurnista	02337266
	Jurnista	02337274
	Jurnista	02337282

	Palladone XL	02337290
	Palladone XL	02243160
	Palladone XL	02243161
Oxycodone		
	Oxycodone	02325950
	Oxycodone	02325969
	Oxycodone	02325977
	Oxycontin	02323192
	Oxycontin	02323206
	Oxycontin	02323214
	Oxycontin	02202441
	Oxycontin	02202468
	Oxycontin	02202476
	Oxycontin	02258129
	Oxyontin	02202484
Oxycodone/Acetaminophen	Endocet	01916548
	Oxycodone-Acet	0232171
	Percocet	01916475
	Pms-Oxycodone-Acet	02245758
	Percocet-Demi	01916491
	Roxicet	01916327
Oxycodone/ASA	Endodan	01916483
	Percodan	01916572
	Percodan-Demi	01916556
Fentanyl	Abstral	02364174
	Abstral	02364182
	Abstral	02364190
	Abstral	02364204
	Abstral	02364212
	Abstral	02364220
	Apo-Fentanyl matrix	02314630
	Apo-Fentanyl matrix	02314649
	Apo-Fentanyl matrix	02314657
	Apo-Fentanyl matrix	0234665
	Co Fentanyl	02386844
	Co Fentanyl	02386852
	Co Fentanyl	02386879
	Co Fentanyl	02386887
	Co Fentanyl	02386895

	Duragesic	02275813
	Duragesic	02275821
	Duragesic	02275848
	Duragesic	02275856
	Duragesic	02334186
	Duragesic	01937413
	Duragesic	02280345
	Duragesic	01937383
	Duragesic	01937391
	Duragesic	01937405
	Fentanyl citrate inj	02126648
	Fentanyl citrate inj	00888346
	Fentanyl citrate inj	01988778
	Fentayl patch	02395657
	Fentayl patch	02395665
	Fentayl patch	02395673
	Fentayl patch	02395681
	Fentayl patch	02395703
	Innovar Inj	00554243
	Mylan-Fentanyl matrix patch	02396696
	Mylan-Fentanyl matrix patch	02396718
	Mylan-Fentanyl matrix patch	02396726
	Mylan-Fentanyl matrix patch	02396734
	Mylan-Fentanyl matrix patch	02396742
	Onsolis	02350661
	Onsolis	02350688
	Onsolis	02350696
	Onsolis	02350718
	Onsolis	02350726
	Ran-Fenanyl matrix patch	02330105
	Ran-Fenanyl matrix patch	02330113
	Ran-Fenanyl matrix patch	02330121
	Ran-Fenanyl matrix patch	02330148
	Ran-Fenanyl matrix patch	02330156
	Ran-Fenanyl transdermal system	02249391
	Ran-Fenanyl transdermal system	02249413
	Ran-Fenanyl transdermal system	02249421
	Ran-Fenanyl transdermal system	02249448
	Sublimaze Inj	00751251
Codeine	Broncodeine syr	00779539
	Codeine phosphate inj	00497282
	Codeine phosphate inj	00497290

	Codeine phosphate syrup	00093114
	Codeine phosphate tab	00093122
	Codeine phosphate tab	00093130
	Codeine phosphate tab	00093149
	Codeine tab	00779458
	Codeine tab	00779466
	PMS-codeine	00243978
	PMS-codeine	02243979
	Ratio-codeine	00779474
	Stanley syrup w codeine	00470651
Codeine/Acet	Acet 2	00706515
	Acet 3	00706523
	Acet Codeine 30	01999648
	Acet Codeine 60	0199656
	Atasol 15	00293504
	Atasol 30	00293512
	Empracet-30	00666130
	Empracet-60	00666149
	Exdol 15	00372358
	Exdol-30	00372323
	Exdol-15	02232388
	Exdol-30	02232389
	Novogesic C15	00687200
	Novogesic C30	00687219
	Paveral liq 10mg/ml	00779482
	Phl-acet-codeine 30	02254271
	Phl-acet-codeine 60	02254263
	Procet-30	02232658
	Rounox avec	00440809
	Rounox codeine	00477664
	Ruonox codeine	00477672
	Routec and codeine	02209748
	Tylenol w codeine NO2	00425370
	Tylenol w codeine NO3	00425389
	Tylenol w codeine NO4	00396516
	Tylenol w codeine elixir	00685143
	Tylenol w codeine elixir	02163642
Codeine/ASA	Coryphen 325 Codeine 30	00406112
	Coryphen 650 Codeine 30	00406104
	Painex tab	00294942
	Painex tab	00295124

Codeine/ASA/butalbital	Pronal C1/2	02229734
	Pronal C1/4	02229735
Codeine/ASA/phenobarbital	Phenaphen No 2	01909290
	Phenaphen No 3	01909312
	Phenaphen No 4	01909304
	Phenaphen No 2	02042851
	Phenaphen No 3	02042878
	Phenaphen No 4	02042886
Codeine/ASA/Methocarbamol	Methoxisal-C 1/2	01966375
	Methoxisal-C 1/4	01966367
Tramadol/Acet	Act-tramadol/acet	02383209
	Mylen-tramadol/acet	02425599
	NRA-tramadol/acet	02469650
	Pat-tramadol/acet	02389274
	Riva-tramadol/acet	02424959
	Tramadol/Acet	02429969
	Tramadol-Acet	02417502
	Tramaphen-Odan	02388294
Methadone	Cophylac	00116343
	Cophylax drops	01987577
Buprenorphine	Belbuca	02465221
	Belbuca	02465248
	Belbuca	02465256
	Belbuca	02465264
Buprenorphine/naloxone	Mylan-buprenorphine/naloxone	02408090
	Mylan-buprenorphine/naloxone	02408104

Appendix 3. TNM and Gleason Score

1. TMN
    a. Each of the T,M, N are reported separately and T is (0,1,2,3,4,TX, Unknown); N is 0, 1, NX, Unknown; M is (0,1 (including a,b,c), Unknown). TX/NX is tumor or lymph nodes could not be assessed.
    b. If more detailed data are not available or the sample size is too small for each catetory, we may just report T,M,N as yes/no.

2. Gleason score:
    a. We may report the score in three categories: 6-7, 8-10 and unknown.
    b. If more detailed data are not available or the sample size is too small for each catetory, we may just report the score as yes/no.