



Computable Operational Definitions

Aaron Kamau MD MS MPH
aaron@navidence.com

ISPOR
May 2024

Confidential

Computable Operational Definitions

Key Take-away Messages

- Operational Definitions are essential for stakeholder submissions/reports/publications
- Computable Operational Definitions (CODefs) ensure consistency, transparency & simplicity in RWE
- “Small differences in the choice of operational definition ... may have a large impact on study results.”

Computable Operational Definitions

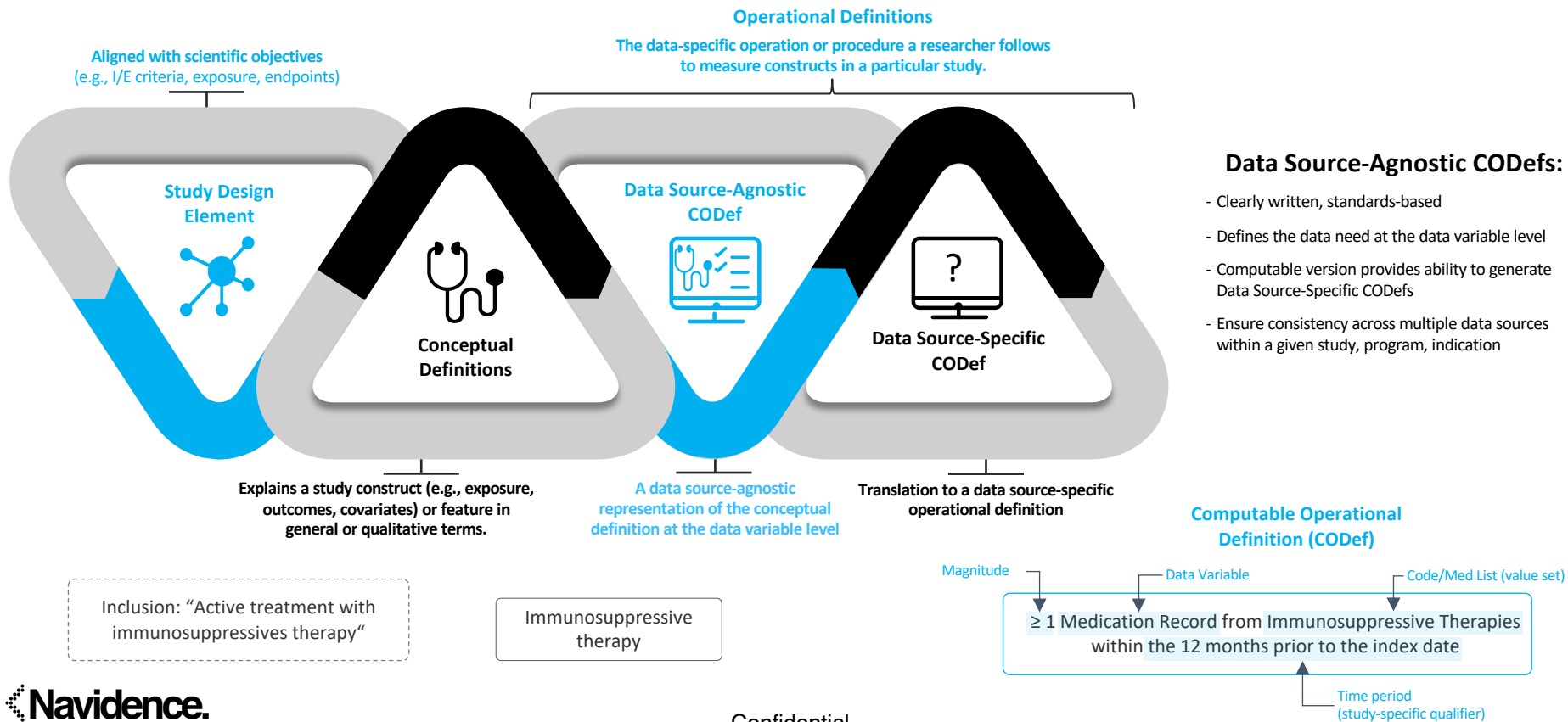
The Challenge

- Implementing Computable Operational Definitions (CODEfs) from concept to operation is hard
 - Developing / selecting the best fit CODEf for your study elements; having a complete set of options to select from & understanding the impact of each CODEf on your study
 - Managing code lists & value sets, and ensuring updates to code standards are managed over time; while maintaining an accurate representation of past studies
- No consistent practice
 - How CODEfs are represented *
 - Re-use of updated CODEfs is challenging (e.g., stored in Word, PDF, Excel files across convoluted folder systems)
 - Standard set of CODEfs to use across studies, programs, organizations or the industry
- There is value in leveraging advancements in **technology** to provide simplicity, consistency, that is compliant with stakeholder expectations

* Kamau AWC. Clear, Consistent, and Computable Operational Definitions: Defining the Purpose and Data Needs for Real-World Evidence Generation. Presented at SCOPE 2023, Orlando, Florida, February 2023.

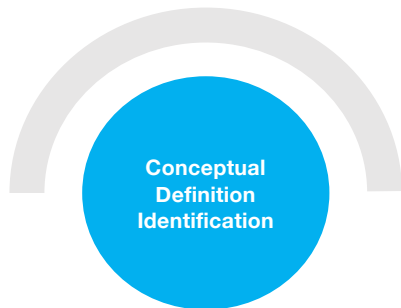
Definition Journey: Clinical & Data Relevance

Matching Protocol Design Elements to CODEfs



Operational Definitions Development

Literature-driven CODEf Development

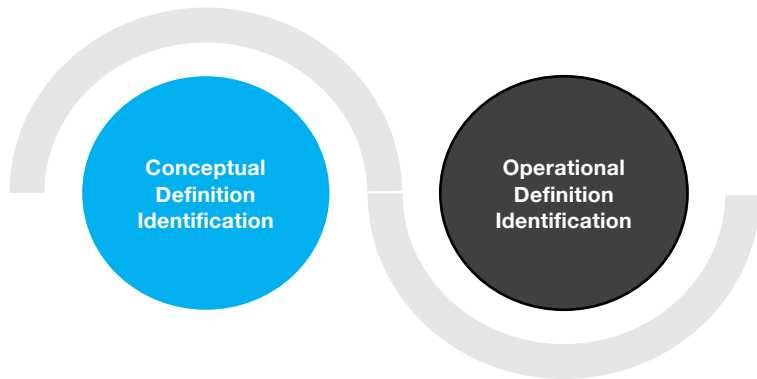


Conceptual Definition Identification

- Determine relevant conceptual definitions
 - sources: study elements from public references, publications, study protocols (including I/E criteria, exposure, endpoints, covariates, etc.), and clinical expertise

Operational Definitions Development

Literature-driven CODEf Development

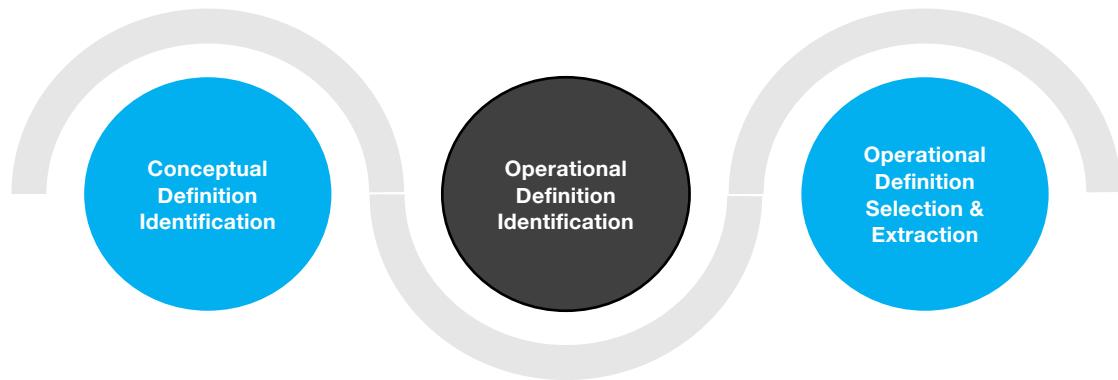


Operational Definition Identification

- Identify potentially relevant operational definitions for each conceptual definition
 - optimize search terms
 - tag info in publications (including definitions/algorithms, code lists, data sources, validation metrics & gold standard, etc.)

Operational Definitions Development

Literature-driven CODEf Development

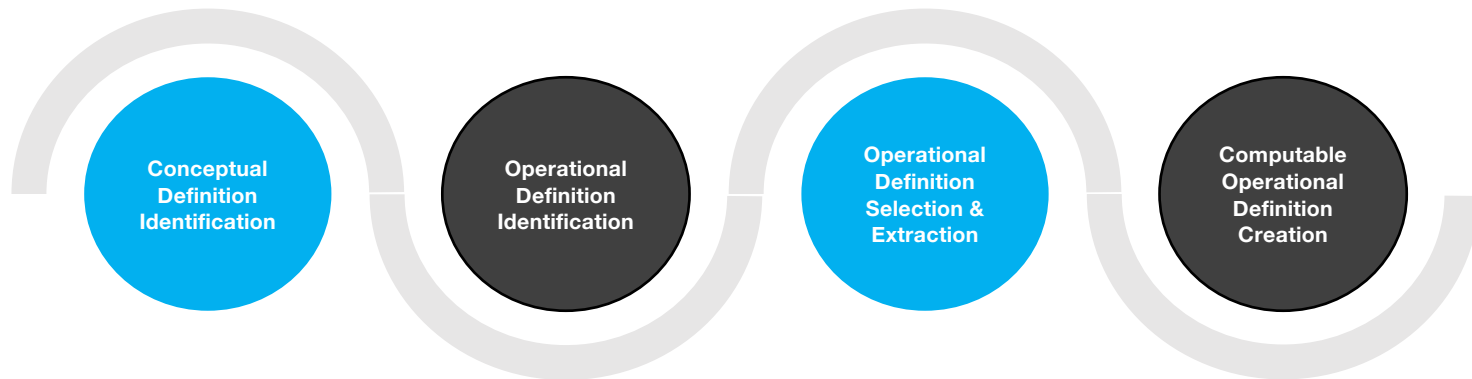


Operational Definition (OpDef) Selection and Extraction

- Determine the relevant operational definitions & code lists
 - review by medical informatics and content engineering experts
 - select relevant definitions and extract tagged information w/ references

Operational Definitions Development

Literature-driven CODEf Development



Computable Operational Definitions (CODEfs) Creation

- Load & organize CODEfs
 - parse information from the literature into granular data variable-level components, consistent with the stakeholder expectations
 - organize by indication / study

Computable Operational Definitions

CODef examples with code lists, references & validation metrics

Element	Conceptual Definition	Operational Definition	Justifications, Algorithms, Limitations, & Notes	Value Sets
Heart Failure (≥ 1 dx)	Diagnosis of heart failure (HF)	≥ 1 Diagnosis Record from Heart Failure Diagnoses (any time in the past AND any encounter type AND any diagnosis position)	Algorithms ≥ 1 ICD-9-CM diagnosis for HF [Tison 2018] Limitations This broad definition may have the potential for false positives	Heart Failure Diagnoses
Source Wording Heart failure				
Normalized Wording N/A				

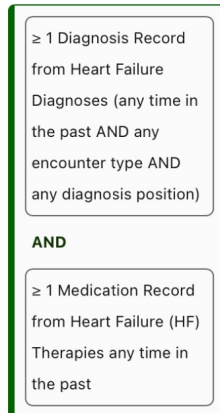
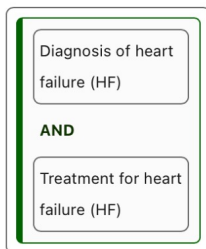
Heart Failure (≥ 1 dx) and Treatment for Heart Failure (≥ 1 rx)

Source Wording

Heart failure with pharmacologic treatment

Normalized Wording

N/A



Algorithms

≥ 1 ICD-9-CM diagnosis for HF and HF-specific treatment [Tison 2018]

[Heart Failure \(HF\) Therapies](#)

[Heart Failure Diagnoses](#)

2 example CODefs for identifying people with Heart Failure

Computable Operational Definitions

CODef examples with code lists, references & validation metrics

Element	Conceptual Definition	Operational Definition	Value Set Detail																												
Heart Failure (≥1 dx)	Diagnosis of heart failure (HF)	≥ 1 Diagnosis Record from Heart Failure Diagnoses (any time in the past AND any encounter type is position)	<div>Heart Failure Diagnoses</div> <div>Value Set Detail</div> <div>Heart Failure Diagnoses (ICD-10-CM)</div> <div>Details</div> <div>Description</div> <div>Type</div> <div>Status</div> <div>VSAC OID</div> <div>References</div> <div>Notes</div> <div>Subsets</div> <div>Value Set Label</div> <div>Heart Failure Diagnoses (ICD-10-CM)</div> <div>Heart Failure Diagnoses (ICD-9-CM)</div> <div>Concepts</div> <table><thead><tr><th>System</th><th>Code</th><th>Label</th><th>Notes</th></tr></thead><tbody><tr><td>ICD-10-CM</td><td>I50</td><td>Heart failure</td><td></td></tr><tr><td>ICD-10-CM</td><td>I50.1</td><td>Left ventricular failure, unspecified</td><td></td></tr><tr><td>ICD-10-CM</td><td>I50.2</td><td>Systolic (congestive) heart failure</td><td></td></tr><tr><td>ICD-10-CM</td><td>I50.20</td><td>Unspecified systolic (congestive) heart failure</td><td></td></tr><tr><td>ICD-10-CM</td><td>I50.21</td><td>Acute systolic (congestive) heart failure</td><td></td></tr><tr><td>ICD-10-CM</td><td>I50.22</td><td>Chronic systolic (congestive) heart failure</td><td></td></tr></tbody></table>	System	Code	Label	Notes	ICD-10-CM	I50	Heart failure		ICD-10-CM	I50.1	Left ventricular failure, unspecified		ICD-10-CM	I50.2	Systolic (congestive) heart failure		ICD-10-CM	I50.20	Unspecified systolic (congestive) heart failure		ICD-10-CM	I50.21	Acute systolic (congestive) heart failure		ICD-10-CM	I50.22	Chronic systolic (congestive) heart failure	
System	Code	Label	Notes																												
ICD-10-CM	I50	Heart failure																													
ICD-10-CM	I50.1	Left ventricular failure, unspecified																													
ICD-10-CM	I50.2	Systolic (congestive) heart failure																													
ICD-10-CM	I50.20	Unspecified systolic (congestive) heart failure																													
ICD-10-CM	I50.21	Acute systolic (congestive) heart failure																													
ICD-10-CM	I50.22	Chronic systolic (congestive) heart failure																													

2 example CODefs for identifying people with Heart Failure ... displaying code lists

Verify Code Lists: DuVall SL, Parker CG, Shields AR, Alba PR, Lynch JA, Matheny ME, Kamauu AWC. Toward Real-World Reproducibility: Verifying Value Sets for Clinical Research. Stud Health Technol Inform. 2024 Jan 25;310:164-168. [PMID: 38269786] Presented at MedInfo23, Sydney, Australia, July 2023.

Computable Operational Definitions

CODef examples with code lists, references & validation metrics

“Small differences in the choice of operational definition ... may have a large impact on study results.”

Element	Conceptual Definition	Algorithm Details	Algorithm Validation
Heart Failure (≥1 dx)	Diagnosis of heart failure (HF)	≥1 ICD-9-CM diagnosis for HF	
Source Wording			
Heart failure			
Normalized Wording			
N/A			
Heart Failure (≥1 dx) and Treatment for Heart Failure (≥1 rx)	Diagnosis of heart failure (HF) AND Treatment for heart failure (HF)	≥1 ICD-9-CM diagnosis for HF and HF-specific treatment	
Source Wording			
Heart failure and HF-specific treatment			
Normalized Wording			
N/A			

Algorithm Details		Algorithm Validation				
Geography	USA	Sensitivity	Specificity	PPV	NPV	Sample Size
Data Source(s)	The provider-linked medical records from each institutionOlmsted County, Minnesota	78.7	98.9	68.5	99.4	76254
Gold Standard	Manual medical record review					
Citation	Tison GH, et al. Identifying heart failure using EMR-based algorithms. Int J Med Inform. 2018 Dec;120:1-7. doi: 10.1016/j.ijmedinf.2018.09.016. [PMID: 30409334]					

Algorithm Details		Algorithm Validation				
Geography	USA	Sensitivity	Specificity	PPV	NPV	Sample Size
Data Source(s)	The provider-linked medical records from each institutionOlmsted County, Minnesota	67.2	99.2	72.3	99	76254
Gold Standard	Manual medical record review					
Citation	Tison GH, et al. Identifying heart failure using EMR-based algorithms. Int J Med Inform. 2018 Dec;120:1-7. doi: 10.1016/j.ijmedinf.2018.09.016. [PMID: 30409334]					

Reference	
Citation	Tison GH, et al. Identifying heart failure using EMR-based algorithms. Int J Med Inform. 2018 Dec;120:1-7. doi: 10.1016/j.ijmedinf.2018.09.016. [PMID: 30409334]

2 example CODefs for identifying people with Heart Failure ... displaying published validation metrics

CODef examples with code lists, references & validation metrics

“Small differences in the choice of operational definition ... may have a large impact on study results.”

Element	Conceptual Definition	Operational Definition	Justifications, Algorithms, Limitations, & Notes
Heart Failure (≥1 dx)	<p>Diagnosis of heart failure (HF)</p>	<p>≥ 1 Diagnosis Record from Heart Failure Diagnoses (any time in the past AND any encounter type AND any diagnosis position)</p>	<p>Algorithms</p> <p>≥ 1 ICD-9-CM diagnosis</p> <p>Limitations</p> <p>This broad definition may include...</p>
<p>Source Wording</p> <p>Heart failure</p>	<p>AND</p> <p>Treatment for heart failure (HF)</p>	<p>AND</p> <p>≥ 1 Medication Record from Heart Failure (HF) Therapies any time in the past</p>	<p>Algorithm Details</p> <p>≥ 1 ICD-9-CM diagnosis</p> <p>Sensitivity</p> <p>78.7</p> <p>Geography</p> <p>Data Source</p> <p>Gold Standard</p> <p>Citation</p>
Heart Failure (≥1 dx) and Treatment for Heart Failure (≥1 rx)	<p>Diagnosis of heart failure (HF)</p>	<p>≥ 1 Diagnosis Record from Heart Failure Diagnoses (any time in the past AND any encounter type AND any diagnosis position)</p> <p>OR</p> <p>≥ 2 Diagnosis Record from Heart Failure Diagnoses (on different dates AND any encounter type AND any diagnosis position)(any time in the past AND any encounter type AND any diagnosis position)</p>	<p>Algorithms</p> <p>≥ 1 ICD-9-CM diagnosis</p>
<p>Source Wording</p> <p>Heart failure with pharmacologic treatment</p>			
<p>Normalized Wording</p> <p>N/A</p>			
Heart Failure (≥1 inpt or ≥2 any dx)	<p>Diagnosis of heart failure (HF)</p>	<p>≥ 1 Diagnosis Record from Heart Failure Diagnoses hospitalization/inpatient encounter type)(any time in the past AND any diagnosis position)</p> <p>OR</p> <p>≥ 2 Diagnosis Record from Heart Failure Diagnoses (on different dates AND any encounter type AND any diagnosis position)(any time in the past AND any encounter type AND any diagnosis position)</p>	<p>Algorithms</p> <p>≥ 1 inpatient or ≥ 2 outpatient ICD-9-CM diagnosis</p>
<p>Source Wording</p> <p>Heart failure</p>			
<p>Normalized Wording</p> <p>N/A</p>			
Heart Failure (≥2 dx) and Elevated NT-proBNP		<p>≥ 1 Diagnosis Record from Heart Failure Diagnoses (any time in the past AND any encounter type AND any diagnosis position)</p> <p>AND</p> <p>≥ 1 Medication Record from Heart Failure (HF) Therapies any time in the past</p>	<p>Algorithms</p> <p>≥ 2 ICD-9-CM diagnosis for HF (≥30 days apart) [Tison 2018]</p>
<p>Source Wording</p> <p>Heart failure with pharm proBNP</p>			
<p>Normalized Wording</p> <p>N/A</p>			

There are 9 published CODEfs for identifying people with Heart Failure ... here are 4 examples

Algorithm Details		Algorithm Validation			
≥1 ICD-9-CM diagnosis for HF		Sensitivity	Specificity	PPV	NPV
		78.7	98.9	68.5	99.4
				Sample Size	
				76254	

Algorithm Details		Algorithm Validation			
≥1 ICD-9-CM diagnosis for HF and HF-specific treatment		Sensitivity	Specificity	PPV	NPV
		67.2	99.2	72.3	99
				Sample Size	
				76254	

Algorithm Details		Algorithm Validation			
≥1 ICD-9-CM diagnosis for HF and HF-specific treatment					
Sensitivity	Specificity	PPV	NPV	Sample Size	
67.2	99.2	72.3	99	76254	

Algorithm Details		Algorithm Validation			
≥1 inpatient or ≥2 outpatient ICD-9-CM diagnosis for HF (≥30 days apart)					
Sensitivity	Specificity	PPV	NPV	Sample Size	
73.3	99.2	74.1	99.2	76254	

Algorithm Details

≥1 inpatient or ≥2 outpatient ICD-9-CM diagnosis for HF (≥30 days apart)

Algorithm Validation

Sensitivity	Specificity	PPV	NPV	Sample Size
73.3	99.2	74.1	99.2	76254

Geography

Data Source(s)

Gold Standard

Algorithm Details

≥2 ICD-9-CM diagnosis for HF (≥30 days apart) and HF-specific treatment and elevated NT-proBNP

Algorithm Validation

Sensitivity	Specificity	PPV	NPV	Sample Size
41.6	99.8	86.5	98.3	76254

Citation

Geography USA

Data Source(s)

The provider-linked medical records from each institutionOlmsted County, Minnesota

Gold Standard

Manual medical record review

Reference

Citation

Tison GH, et al. Identifying heart failure using EMR-based algorithms. Int J Med Inform. 2018 Dec;120:1-7. doi: 10.1016/j.ijmedinf.2018.09.016. [PMID: 30409334]



Computable Operational Definitions

CODef examples with code lists, references & validation metrics

Element	Conceptual Definition	Operational Definition	Justifications, Algorithms, Limitations, & Notes	Value Sets
Inclusion 2: Prostate Cancer	<div>Diagnosis of prostate cancer</div>	<div>> 1 Diagnosis Record from Prostate Cancer Diagnoses (within the patient identification period AND any encounter type AND any diagnosis position)</div>	<div>Algorithms</div> <div>≥1 diagnosis ICD-10 code (primary, admit, or "most resource-consuming" encounter) for prostate cancer (61) [Fujiwara 2022]</div> <div>≥1 diagnosis ICD-10 code for prostate cancer [Fujiwara 2022]</div> <div>Limitations</div> <div>This broad definition may have the potential for false positives; this is less likely a problem given the nature of this medical condition</div> <div>Notes</div> <div>Patient Identification Period: 01 January 2019 - 31 December 2023</div>	<div>Prostate Cancer Diagnoses</div>
Inclusion 3: Androgen Deprivation	<div>Androgen deprivation - medical castration</div> <div>OR</div> <div>Androgen deprivation - surgical castration</div> <div>AND</div> <div>Low testosterone</div>	<div>≥ 1 Medication Record from Androgen Deprivation Therapies any time on or after the index date</div> <div>OR</div> <div>≥ 1 Procedure Record from Androgen Deprivation Procedures any time on or after the index date</div> <div>AND</div> <div>Testosterone Free/Testosterone.total in Serum or Plasma < 50 ng/dL within the 1 month after the treatment</div>	<div>Notes</div> <div>Index Date: Date of the first documented diagnosis for prostate cancer during the patient identification period</div>	<div>Androgen Deprivation Procedures</div> <div>Androgen Deprivation Therapies</div>
Inclusion 4: Prostate Cancer Progression	<div>Progressive disease</div> <div>OR</div> <div>Progressive disease</div>	<div>RECIST v1.1 Result:progressive disease (PD) any time after the treatment</div> <div>OR</div> <div>Prostate specific Ag [Mass/volume] in Serum or Plasma by Immunoassay ≥ 2 ng/ml any time after the treatment</div> <div>AND</div> <div>Prostate specific Ag [Mass/volume] in Serum or Plasma by Immunoassay ≥ 2 ng/ml (higher value than previous result AND ≥ 1 week between results)(any time after the treatment AND multiple values: two separate distinct values)</div>		

Example CODEfs for identifying a cohort of people with Castration-Resistant Prostate Cancer (CRPC)

Computable Operational Definitions

CODef examples with code lists, references & validation metrics

Element	Conceptual Definition	Operational Definition	Justifications, Algorithms, Limitations, & Notes	Value Sets
---------	-----------------------	------------------------	--	------------

Immunosuppressive
Therapy (≥ 1 rx, ≤ 12 mo)

Treatment with
immunosuppressive
therapy

≥ 1 Medication Record
from Immunosuppressive
Therapies within the 12
months (1 year) prior to
the index date

Justifications

"Active" treatment is defined as within the 12 months prior to the query as they may have impact c
after tre

Immunosuppressive
Therapies

Source Wording

Active treatment with
immunosuppressive or
immunomodulatory
therapy

An example CODef for identifying
people treated with an
Immunosuppressive therapy
... displaying med/code lists *

Value Set Detail

Immunosuppressive Therapies

Details

Description	List of immunosuppressive therapies
Type	grouping
Status	active
VSAC OID	n/a

References

Master Protocol Development: COVID-19 Natural History. Sentinel Initiative. 2020. Available from: <https://www.sentinelinitiative.org/methods-data-tools/methods/master-protocol-development-covid-19-natural-history>. [Accessed 5 April 2022]

Kamau AW, Parker CG, Shields A, Glaser L, DuVall S, Haidar G, Lynch J, Kamau AG, Taylor S, Talarico C. Development of a Comprehensive List of Immunosuppressive Therapies to Enable a Multi-Data Source Global Real-World Effectiveness (RWE) Program of Immunocompromised Patients. The Professional Society for Health Economics and Outcomes Research (ISPOR); ISPOR Europe 2023. Copenhagen, Denmark; Nov 2023.

Notes

Adapted from a list of therpaies from a few specific health systems in U. S.

Subsets (Value sets within this grouping value set)

Value Set Label	Type
Immunosuppressive Therapies (ATC)	extensional
Immunosuppressive Therapies (NDC)	extensional
Immunosuppressive Therapies (Name)	extensional
Immunosuppressive Therapies (RxNorm)	extensional

* Kamau AWC, Parker CG, Shields AR, Glasser L, DuVall SL, Haidar G, Lynch JA, Kamau AG, Taylor S, Talarico C. Development of a Comprehensive List of Immunosuppressive Therapies to Enable a Multi-Data Source Global Real-World Effectiveness Program of Immunocompromised Patients. Presented at ISPOR EU 2023, Copenhagen, Denmark, November 2023.

Computable Operational Definitions

CODef examples with code lists, references & validation metrics

Element	Conceptual Definition	Operational Definition	Justifications, Algorithms, Limitations, & Notes	Value Sets
Adequate Liver and Renal Function	<div><div>Adequate liver function</div><div>AND</div><div>Adequate renal function</div></div>	<div><div>Bilirubin.total [Mass/volume] in Serum or Plasma ≤ 1.5 ULN (within the 12 months (1 year) prior to the index date AND most proximal documented value to the index date)</div><div>AND</div><div>Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma ≤ 3.0 ULN (within the 12 months (1 year) prior to the index date AND most proximal documented value to the index date)</div><div>AND</div><div>Alanine aminotransferase [Enzymatic activity/volume] in Serum or Plasma ≤ 3.0 ULN (within the 12 months (1 year) prior to the index date AND most proximal documented value to the index date)</div><div>AND</div><div>Creatinine renal clearance predicted by Cockcroft-Gault formula ≥ 45 ml/min (within the 12 months (1 year) prior to the index date AND most proximal documented value to the index date)</div></div>		<div>LOINC code: 1975-2</div> <div>LOINC code: 1920-8</div> <div>LOINC code: 1742-6</div> <div>LOINC code: 35591-7</div>
Source Wording	Adequate liver & renal function			
Normalized Wording	N/A			

Example lab-based CODefs for determining adequate liver & renal function
... using LOINC codes to define the lab tests of interest

Computable Operational Definitions

Key Take-away Messages

- Operational Definitions for each study element in studies generating real-world evidence (RWE) is essential for internal purposes as well as external stakeholders
- Computable Operational Definitions (CODEfs) are **compliant** with stakeholder expectations, with added benefits:
 - Data source-agnostic CODEfs support **fit-4-purpose** data qualification and ensure **consistency** across multi-data source / multi-country RWE programs *
 - Data variable level CODEfs with code lists provide **transparency** of standards-based definitions for data queries / collection, case ascertainment, cohort stratification, analyses, results reporting and publications, etc.
 - Data source-specific CODEf translations afford **simplicity** for data partners and data analysts, without ambiguity
- “Small differences in the choice of operational definition ... may have a large impact on study results.”

* Kamau AWC, Parker CG, Shields AR, Glasser L, Dube S, Talarico C, Taylor S. Development of Computable Operational Definitions to Maximize Comparability & Consistency Across a Multi-Data Source Global Real-World Effectiveness Program. Presented at ICPE 2023, Halifax, Canada, August 2023.

 **Mahalo nui loa!**

Aaron Kamau MD MS MPH
aaron@navidence.com

ISPOR
May 2024

Confidential