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Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology**

**Biologics Effectiveness and Safety (BEST) Contract 1:  
Data Tools and Infrastructure for Surveillance of Biologics Task Order 1 (TO1)**

**Final Draft Report**  
Syncope Case Algorithm  
Version 6.0

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<b>List of Acronyms</b>
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AFHSB	United States Armed Forces Health Surveillance Branch
BEST	Biologics Effectiveness and Safety Sentinel Initiative
CBER	Center for Biologics Evaluation and Research
CPT	Current Procedural Terminology
ED	Emergency department
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
LOINC	Logical Observation Identifiers Names and Codes
MeSH	Medical Subject Headings
NDC	National Drug Code
NPV	Negative predictive value
PICO	Population, Intervention, Comparator, Outcome
PPV	Positive predictive value

## Defining Syncope Using Administrative Claims Data: A Case Algorithm

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### A Summary

Administrative claims datasets can be a useful resource in supporting efforts to monitor safety and assess effectiveness of therapeutics. The FDA BEST Initiative is working to expand their capacity to conduct such analyses. In support of this, a literature review was conducted to identify validated methods for ascertaining cases of syncope in large administrative healthcare databases. Several relevant studies were identified, with three providing measures of diagnostic accuracy performance.

Two studies assessed the validity of International Classification of Diseases, Ninth Revision (ICD-9) code 780.2, which corresponds to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 780.2 (syncope and collapse).<sup>1,2</sup> An Italian study reported a positive predictive value (PPV) of 83% (95% confidence interval [CI] 79–87%), a negative predictive value (NPV) of 95% (95% CI 94–95%), a sensitivity of 63% (95% CI 58–67%) and a specificity of 98% (95% CI 98–99%). Meanwhile, a U.S. study reported a PPV of 92% and an NPV of 100% among a cohort of 100 patients.<sup>2</sup>

A Danish validation study employed chart review to assess the validity of International Classification of Diseases, Tenth Revision (ICD-10) code R55.9, which translates to International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code R55 (syncope and collapse).<sup>3</sup> Among a cohort of patients seen or admitted to the emergency department (i.e., use of R55.9 in the emergency department setting), authors reported a PPV of 93%. Among the cohort of patients admitted to the hospital, authors reported a PPV of 95.6%, an NPV of 99.5%, a sensitivity of 62.7% and a specificity of 99.9%.

While there are some ICD codes that incorporate information on the etiology of syncope, there is a single, all-encompassing code in both the ICD-9-CM (780.2 – syncope and collapse) and ICD-10-CM (R55 – syncope and collapse) that refers to the clinical event of syncope. These codes do not include information on etiology, although they can be paired with other diagnosis codes that suggest the etiology of the syncopal event. Other studies using administrative claims databases to identify potential cases of syncope corroborate this finding.<sup>2,4-6</sup>

The proposed case definition combines ICD-9-CM code 780.2 and ICD-10-CM code R55, and is identical to a case definition developed independently by the United States Armed Forces Health Surveillance Branch (AFHSB) to support routine surveillance of ‘syncopal events’.<sup>7</sup> Previous studies suggest that these codes have a moderate-to-high PPV but a low sensitivity; this may be due to the availability of other, more specific codes that specify the etiology of syncope (e.g., heat syncope).<sup>1,3</sup> The BEST Initiative team then tested this algorithm using a dataset of insured U.S. patients in the IBM® MarketScan® Research Databases, using the Treatment Pathways 4.0 analytic platform, generating descriptive statistics on the frequency of syncope occurrence and reporting.

## **B Background**

Among other responsibilities, the U.S. Food and Drug Administration (FDA) is mandated to protect public health by ensuring the safety and efficacy of drugs, biologics and medical devices.<sup>1</sup> In support of this charge, the FDA Center for Biologics Evaluation and Research (CBER) has a mission to conduct policy and regulatory reviews of biologics and related products, including blood products, vaccines, allergenics, tissues, and cellular and gene therapies. CBER assesses the risks and benefits of new biologic products, as well as previously approved products that have been proposed for new indications. The CBER process emphasizes the pursuit of the maximum public benefit with the minimum risk to public safety associated with each biologic product. The Biologics Effectiveness and Safety (BEST) Sentinel Initiative is a program initiated by CBER with the objective of assessing the safety and effectiveness of biologic products using large datasets of administrative claims and clinical data.

A joint report by the American College of Cardiology/American Heart Association Taskforce on Clinical Practice Guidelines and the Heart Rhythm Society provides the following case definition of syncope:

*A symptom that presents with an abrupt, transient, complete loss of consciousness, associated with inability to maintain postural tone, with rapid and spontaneous recovery. The presumed mechanism is cerebral hypoperfusion... There should not be clinical features of other nonsyncope causes of loss of consciousness, such as seizure, antecedent head trauma, or apparent loss of consciousness (i.e., pseudosyncope) (p. e30).<sup>8</sup>*

While transient loss of consciousness (TLOC) is one of the defining features of syncope, it can also be associated with nonsyncopal events, including neurological (e.g., seizures), medical (e.g., hypoglycemia), and other conditions (e.g., concussion associated with head trauma).<sup>9</sup> Syncope is due to decreased perfusion of blood to the brain, whereas these nonsyncopal events are related to other mechanisms. Identification of syncope is often challenging, especially when cases are not medically attended, as symptoms of syncope are self-resolving, by definition, and may not be medically evaluated.

In the United States, more than 1.3 million episodes of syncope occur each year, which account for approximately 440,000 hospital admissions and more than \$2.4 billion in healthcare costs.<sup>10</sup> Across North America, syncope results in an estimated 1.2 million emergency department (ED) visits per year.<sup>11,12</sup> Although syncope is generally uncomplicated in otherwise healthy individuals, it can be associated with serious medical conditions and increased morbidity and mortality, including from sudden cardiac death.<sup>13-15</sup> An ED visit for syncope has been associated with a 9% risk of 10-day mortality and with a 5.7–15.5% 1-year mortality rate.<sup>16,17</sup> While this rate will be affected by other factors such as age, comorbidities and etiology, the costs and risks associated with syncope point to the importance of reliable methods for identifying and studying the condition.

The objective of this review was to assess the state of knowledge regarding validated methods of using administrative claims databases to identify cases of syncope. These methods could draw on a variety of standardized code sets, including the ICD, the Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT®), National Drug Codes (NDCs) and Logical Observation Identifiers Names and Codes (LOINC).

A comprehensive literature review of methods for identifying potential cases of syncope using administrative claims data was conducted, leveraging findings from U.S. and international studies to inform the development of a code-based outcome definition (hereafter referred to as an “algorithm”). The draft algorithm was then subject to review by clinical subject matter experts and testing in a large administrative claims dataset using a cloud-based analytic tool, the IBM MarketScan Treatment Pathways platform. **Sections C and D** summarize the literature review methodology and findings, respectively; **Section E and F** present the algorithm and its associated assumptions and decisions, respectively;

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<sup>1</sup> U.S. Food and Drug Administration. What We Do. March 28, 2018. <https://www.fda.gov/aboutfda/whatwedo/>

**Section G** presents the results of the initial characterization of the algorithm in a claims database; and **Section H** provides discussion and concluding thoughts.

## C Methodology

The BEST Initiative developed a literature review search strategy based upon a Population, Intervention, Comparator, Outcome (PICO) framework. The PICO framework for this review can be summarized as follows:

- **Population:** *any population group (human)*
- **Intervention:** *any intervention or no intervention*
- **Comparator:** *any comparator, placebo*
- **Outcome:** *syncope, transient loss of consciousness*
- **Setting:** *any clinically-observable setting (led individual to seek care)*

Briefly, the review process began with conducting systematic searches of existing publications available in the FDA Sentinel databases<sup>ii</sup> (no articles were retrieved from either). Next, a structured review of the academic literature was conducted, using PubMed, Medline, and Google Scholar to identify relevant resources. The PubMed search strategy is summarized below:

- Search 1 used keywords (syncope [MeSH Major Topic]) AND (diagnos\* [Title/Abstract]): retrieved 2,063 articles
- Search 2 used keywords (syncope [MeSH Major Topic]) AND (cardiac [Title/Abstract] OR cardiovascular [Title/Abstract]): retrieved 1,969 articles
- Search 3 used keywords (syncope [MeSH Major Topic]) AND (noncardiac [Title/Abstract]): retrieved 35 articles

Relevant gray literature, including clinical guidelines and reports from organizations such as the AFHSB and the Agency for Healthcare Research and Quality, was also identified through *ad hoc* and targeted searches. In addition, data repositories such as the NDC repository were searched.<sup>iii</sup> A snowballing technique was also applied, wherein the bibliographies of relevant studies were scanned for additional resources. The literature search was conducted between January 25, 2019, and February 13, 2019.

All abstracts were reviewed, and 25 articles were reviewed in full text. All screening was conducted by a single reviewer (PSH) with a doctoral degree in Public Health and seven years of professional experience conducting similar reviews. A Microsoft® Excel spreadsheet was developed to extract relevant data. The data elements collected are provided in **Figure 1**. A relevance ranking was assigned based on the judgement of the reviewer and the available information on study location (“Group/Country”), the algorithm specifications (“Algorithm/Criteria”), and the measures of validity and diagnostic accuracy (such as PPV and NPV). The scale ranged from 1 (most relevant) to 3 (least relevant), with publications being ranked as follows:

- Relevance Rank 1: U.S. study that defines algorithm and provides measures of validity
- Relevance Rank 2: EITHER a U.S. study that defines the algorithm but does not provide measures of validity OR an international study that defines the algorithm and provides measures of validity

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<sup>ii</sup> U.S. Food and Drug Administration. Science & Research (Biologics). March 28, 2019.

<https://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/default.htm>

Sentinel. Publications and Presentations. <https://www.sentinelinitiative.org/communications/publications>

<sup>iii</sup> U.S. Food and Drug Administration. National Drug Code Directory. November 9, 2017.

<https://www.fda.gov/drugs/informationondrugs/ucm142438.htm>

- Relevance Rank 3: EITHER a U.S. study that does not define the algorithm OR an international study that defines the algorithm but does not provide measures of validity.

Publications receiving a “1” or “2” were subject to full data extraction. Those receiving a “3” were not extracted in full but were reviewed for potential inclusion in the Discussion section.

Title	Author	Year	Group/Country	Summary	Relevance	Disease Definition	Algorithm/Criteria	Validity	Comments
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**Figure 1. Data elements recorded in the extraction spreadsheet.**

## D Results

Following title and abstract screening, full-text review and data extraction, three publications were identified as being particularly relevant (Relevance Ranking 1–2); each reported measures of diagnostic accuracy associated with administrative claims codes for syncope.

An Italian study by Furlan and colleagues sought to validate the use of ICD-9 code 780.2 to identify cases of syncope.<sup>1</sup> The study was conducted in two teaching hospitals among 32,586 patients who were admitted to the ED. Of these patients, authors sought to identify those with a diagnosis possibly related to syncope, defined on the basis of (1) the use of ICD-9 780.2, (2) an ED assessment of syncope, or (3) admission as a consequence of “loss of consciousness (i.e. presyncope, syncope, lipothymia, pre-lipothymia, fall, trauma, vertigo, dizziness, wound, hypotension, epilepsy, transient ischemic attack, absence, loss of consciousness, sickness, malaise” (p.578).<sup>1,iv</sup> Authors cast a broad net in their search for potential cases, prioritizing sensitivity over specificity. Out of 3,357 patients with a diagnosis potentially related to syncope, medical record review identified 441 (13%) cases of syncope. An ICD-9 code of 780.2 was reported in 277/411 (63%) cases. Authors reported a PPV of 83% (95% CI 79–87%), an NPV of 95% (95% CI 94–95%), a sensitivity of 63% (95% CI 58–67%) and a specificity of 98% (95% CI 98–99%) associated with ICD-9 code 780.2.

A U.S. study seeking to identify clinical predictors of syncope used ICD-9-CM code 780.2 to retrieve suspected syncope cases from medical records.<sup>2</sup> Although the main objective of the study was not to assess the diagnostic accuracy of the code, study authors performed a small (n=100) validation analysis using blinded clinician chart review. They reported a PPV of 92% and an NPV of 100% associated with ICD-9-CM code 780.2. The small study population size would suggest that the diagnostic accuracy measures reported may not be as reliable as those from the other two studies. However, this study does support the single-code approach used for identifying syncope, which was also observed in a U.S. study of serious events in the 30 days following syncope<sup>4</sup> and in two studies by the AFHSB to assess syncope among military trainees and active service members.<sup>5,6</sup>

Similarly, a Danish study by Ruwald and colleagues described an approach for using the ICD-10 code R55.9 to identify cases of syncope in Danish administrative databases.<sup>3</sup> This publication was part of a broader series of articles describing the epidemiology, etiology and prognosis of syncope.<sup>18-21</sup> The study authors retrospectively reviewed all patient charts that contained the ICD-10 diagnosis code for syncope (R55.9) in the principal position,<sup>v</sup> validating cases via chart review and guided by the European Society of Cardiology case definition for syncope. A total of 750 charts from patients with the diagnosis code for syncope were reviewed, including 150 ED charts and 600 inpatient charts. The ICD-10 code R55.9 had a PPV of 93% in ED patients. Among the cohort of patients admitted to the hospital, authors reported a PPV of 95.6%, an NPV of 99.5%, a sensitivity of 62.7% and a specificity of 99.9% associated with ICD-10

<sup>iv</sup> Lipothymia refers to faintness that generally is not associated with loss of consciousness; pre-lipothymia is a milder manifestation of this feeling or condition. Both could be considered as “pre-syncope”.

<sup>v</sup> This study was the only one to specify that the code should be in the principal position. The other studies either did not report whether diagnosis position was considered or searched for codes in any position.

code R55.9; this code does not exist in ICD-10-CM but corresponds to ICD-10-CM code R55 (syncope and collapse).

## E Syncope Code Algorithm

As informed by previously published studies, the BEST Initiative has developed an algorithm that includes the diagnosis codes for general syncope events. While there are other syncope codes available that specify a given etiology (e.g., heat syncope, carotid sinus syncope), the ICD-9-CM code 780.2 and ICD-10-CM code R55 are all-encompassing codes that include syncope related to various (or unknown) etiologies, as well as presyncope (which can be viewed as severe lightheadedness without loss of consciousness and is not included in the clinical case definition for syncope). These general codes for syncope are commonly used in clinical practice, as the etiology is often specified in combination with other diagnosis codes.

The proposed algorithm for identifying syncope using administrative claims codes is presented in **Table 1**. This algorithm may need to be adjusted for specific research questions that arise in the future. Annual counts of patients with individual diagnosis codes are provided in **Appendix A (Table A1)**.

Briefly, the proposed algorithm can be summarized as follows:

**INCLUDE: ANY** (“either–or” logic) of the codes listed in **Table 1**, regardless of health care setting or coding position (only one code required).

**Table 1. Syncope algorithm.**

Code	Description	Code Category	Code Type
780.2	Syncope and collapse	DX	09
R55	Syncope and collapse	DX	10

Abbreviation: DX, ICD-CM diagnosis.

The case definition for syncope (included in **Section B**) does not necessarily align with typical coding practices. For example, the general codes for syncope include pre-syncope, which is not part of the case definition. Given this, the BEST Initiative has sought an approach that is consistent with those reported in the published literature; this involved selecting the general, all-encompassing codes for syncope while excluding those that are either expressly inclusive of an etiology unlikely to be useful in measuring associations between a biologic exposure and syncope outcomes (e.g., heat syncope) or do not meet the clinical definition for syncope (e.g., other somatoform disorders, psychogenic syncope). This approach supports alignment and comparability with past studies and reflects current coding practices but may impact diagnostic accuracy performance if assessed against the typical case definition for syncope. Excluded codes related to syncope are listed in **Table 2**.

The algorithm and exclusions proposed in **Tables 1** and **2** are consistent with approaches identified in the peer-reviewed literature, and are identical to those developed independently by the AFHSB<sup>7</sup> for use in a peer-reviewed article on syncope.<sup>22</sup> The AFHSB case definition was originally developed in 2014 and was based on a review of the published literature, ICD-9-CM codes and internal analyses.<sup>7</sup> It was updated to include ICD-10-CM codes in 2016.

**Table 2. Excluded codes relevant to syncope.**

Code	Description	Code Category	Code Type
300.89	Other somatoform disorders	DX	09
337.01	Carotid sinus syndrome	DX	09
992.1	Heat syncope	DX	09
F48.8	Psychogenic syncope	DX	10

Code	Description	Code Category	Code Type
G90.01	Carotid sinus syncope	DX	10
T67.1	Heat syncope	DX	10

Abbreviation: DX, ICD-CM diagnosis.

## F Assumptions and Decisions

The algorithm presented in **Section E** was reviewed internally as well as with CBER stakeholders and partners. Decisions and assumptions related to algorithm construction are summarized below. Some of these assumptions may be adjusted for future research questions.

- As informed by approaches in the published literature and on the basis of clinical consultation, it was decided that methods for diagnosing and treating syncope — as would be reflected in procedural and prescription coding standards — were too variable and general to be included in the code-based definition. The proposed algorithm has therefore been restricted to ICD diagnosis codes.
- The restriction of queries based on diagnosis coding position (e.g., principal position codes only), varied across studies reviewed. Such an approach may be appropriate but will likely depend on the research question. A “principal diagnosis” is the condition primarily responsible for hospital admission, while a “secondary diagnosis” is a “condition also present on admission, that developed during the hospital stay, or that influences the care of the patient or length of stay (p.3).<sup>23</sup> A position-unspecified code, meanwhile, would represent cases where position is not reported.
- Risk windows used to determine the association of syncope with a particular exposure should be determined on the basis of the particular research question and exposure of interest.

## G Algorithm Characterization

To summarize the epidemiology of syncope among a an insured population in the United States (including commercial insurance and Medicare), the BEST Initiative used the IBM MarketScan Research Databases, accessed via the Treatment Pathways<sup>vi</sup> platform, to query and analyze the ICD codes for syncope and collapse (ICD-9-CM code 780.2; ICD-10-CM code R55). The Treatment Pathways platform supports customizable analyses of data stored on IBM Watson Health servers. The BEST Initiative used the 100% Treatment Pathways sample of data from January 1, 2011 through December 31, 2017.

Age- and gender-specific data on MarketScan enrollment and syncope case counts were collected. The figures presented below have been drawn from the study period of January 1, 2014–December 31, 2017. For all analyses, ICD-9-CM codes were only queried for January 1, 2014–September 30, 2015 and ICD-10-CM codes were only queried for October 1, 2015–December 31, 2017, because the United States transitioned from ICD-9-CM to ICD-10-CM on October 1, 2015, and the BEST Initiative sought to exclude codes that were reported in error.

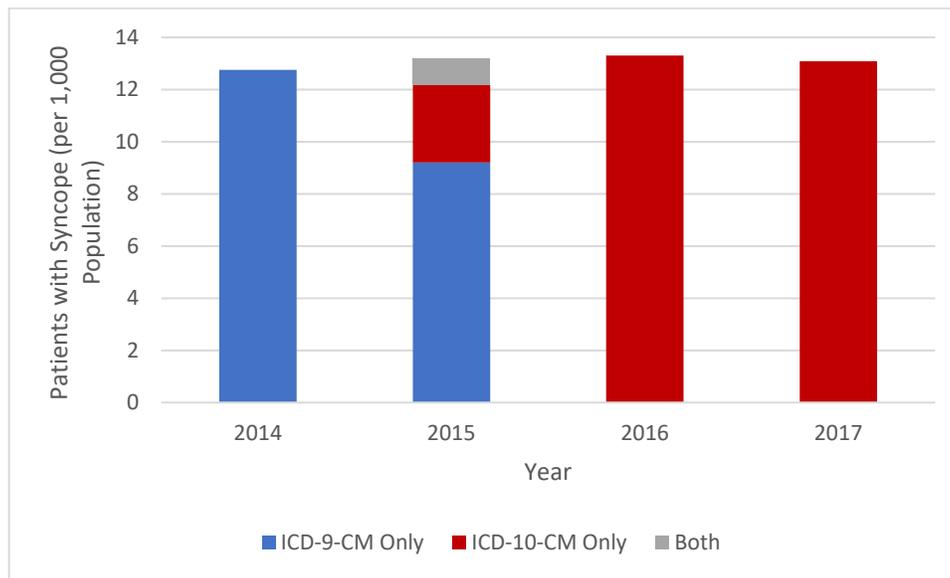
Individuals had to be continuously enrolled in any enrollment category to be included in the analysis for a particular year. For example, patients had to be continuously enrolled from January 1 to December 31, 2014, to be included in the 2014 dataset. From 2014–2017, there were 41,172,696 unique individuals that were enrolled for at least one calendar year. Age was calculated at the end of each calendar year (i.e., age in 2014 was calculated as of December 31, 2014). Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under one year old), this

<sup>vi</sup> IBM MarketScan Research. Insight for Better Healthcare. <https://marketscan.truvenhealth.com/marketscanportal/Portal.aspx>

population group has been left out of the charts depicting the proportions of individuals with syncope by age.

It is important to note that the BEST Initiative reviewed counts of individual patients that had a diagnosis code related to syncope, rather than counts of syncope cases. As such, counts relate to the first diagnosed syncope event for an individual during a given surveillance period (e.g. January 1–December 31, 2014), and individuals could only be counted once per surveillance period.

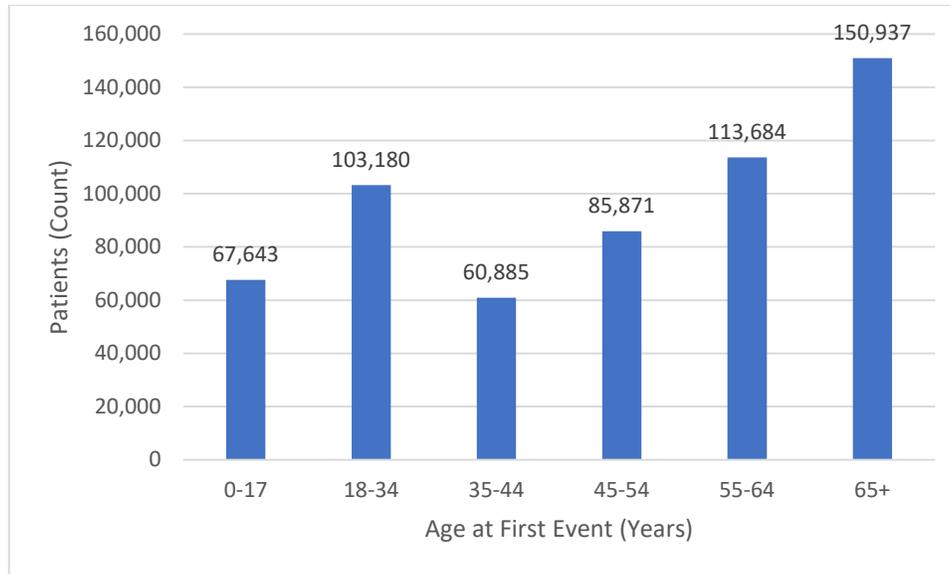
The BEST Initiative sought to assess whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of syncope. **Figure 2** illustrates the proportion of the enrolled population with a syncope diagnosis and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a syncope diagnosis.



**Figure 2. Proportion of patients with syncope per 1,000 enrolled, by year (2014–2017).**

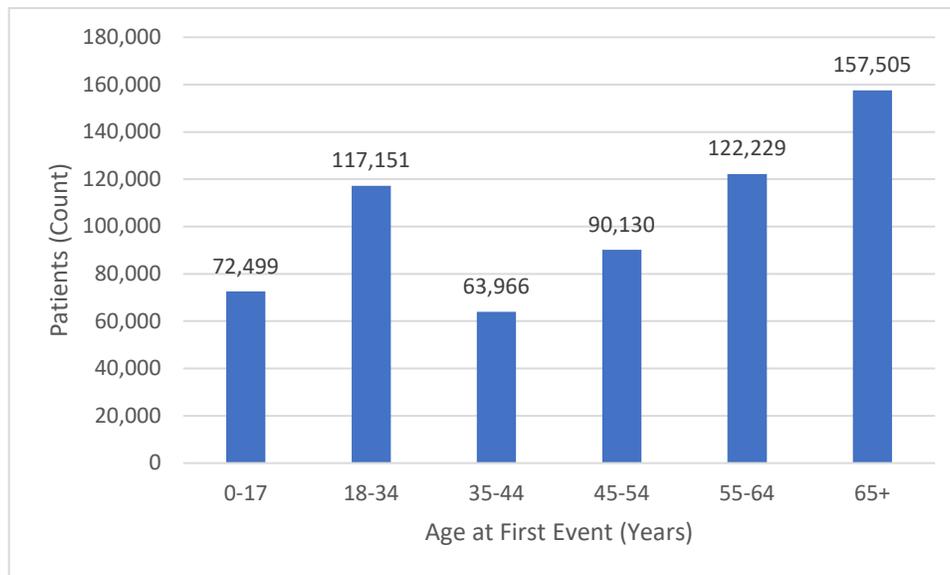
Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

**Figure 3** presents counts of patients with syncope, defined by ICD-9-CM code 780.2 and stratified by age category. Counts were calculated using a combined cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year in 2014 or 2015. There were 582,200 individuals with at least one ICD-9-CM code for syncope between January 1, 2014, and September 30, 2015, with an average age (calculated at the first event) of 49 years.



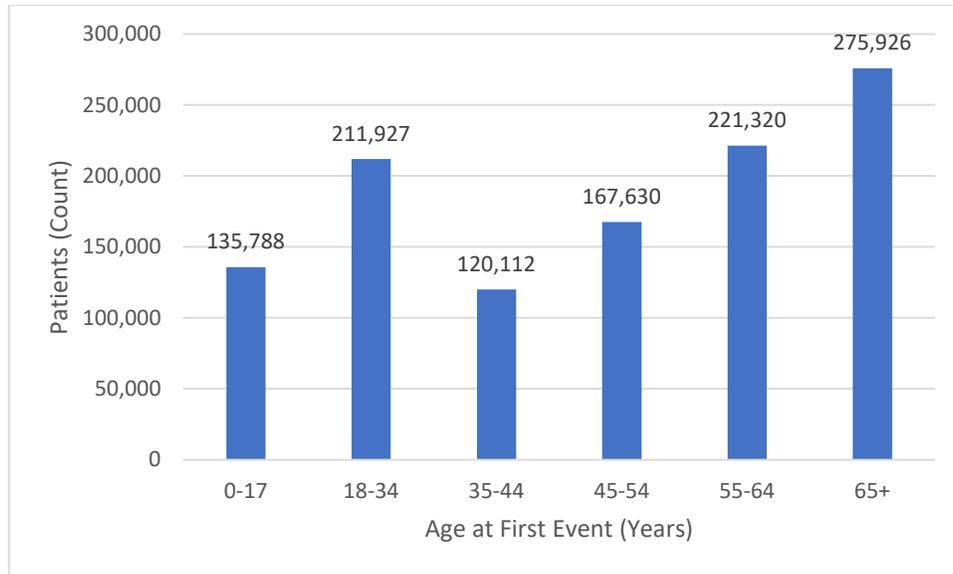
**Figure 3. Patients with at least one diagnosis code for syncope (ICD-9-CM code 780.2), January 1, 2014–September 30, 2015, stratified by age.**

**Figure 4** presents counts of patients with syncope, defined by ICD-10-CM code R55 and stratified by age category. Counts were drawn from a cohort of 30,319,401 patients who were enrolled for at least one calendar year between 2015 and 2017. Among 623,480 individuals with at least one ICD-10-CM code for syncope between October 1, 2015, and December 31, 2017, the average age at first event was 48 years.



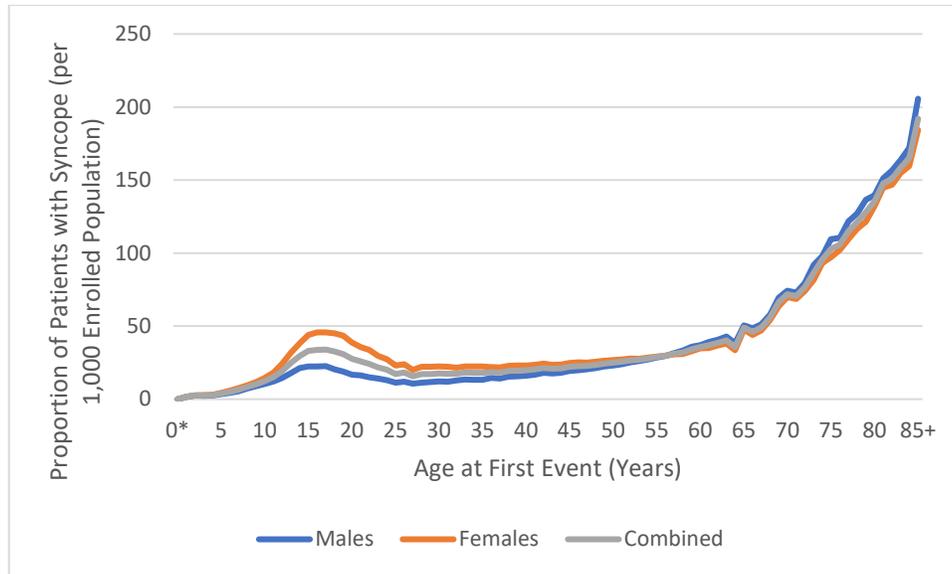
**Figure 4. Patients with at least one diagnosis code for syncope (ICD-10-CM code R55), October 1, 2015–December 31, 2017, stratified by age.**

**Figure 5** presents counts of patients with either an ICD-9-CM or ICD-10-CM code for syncope among a cohort of 41,172,696 individuals who were continuously enrolled for at least one calendar year between 2014 and 2017. Among 1,132,703 individuals (2.8% of entire cohort) who received a diagnosis code for syncope between January 1, 2014, and December 31, 2017, the average age at the first event was 48 years. Absolute patient counts were highest in the 65+ years age category.



**Figure 5. Patients with at least one diagnosis code for syncope (ICD-9-CM or ICD-10-CM), January 1, 2014–December 31, 2017, stratified by age.**

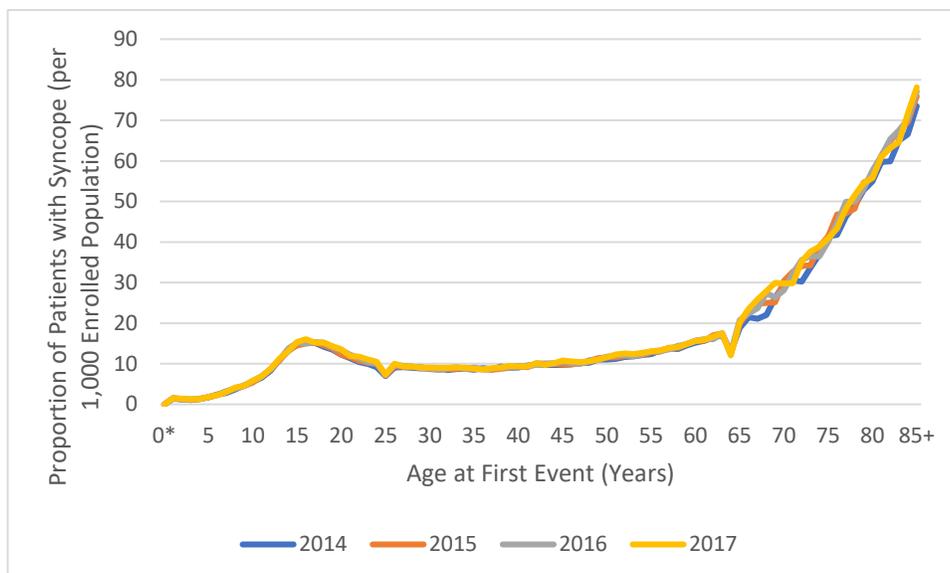
The BEST Initiative also gathered age- and gender-specific counts of individuals experiencing syncope as well as the size of the enrolled population by age (between 1 and 100 years) and gender, using these figures to calculate age- and gender-specific proportions of individuals with syncope. Patients 85 years or older were grouped together in order to minimize the effect of unstable estimates due to the smaller enrolled population sizes available in this age range. The 41 million-patient cohort was used for this analysis and individuals were not required to be enrolled for the full four-year period to be included in the calculations. **Figure 6** summarizes the proportion of the population with at least one ICD-9-CM or ICD-10-CM code for syncope (per 1,000 population enrolled in MarketScan Research Databases) between January 1, 2014, and December 31, 2017, by age and gender. Results suggest that the proportion of patients with syncope increases with age and is distributed evenly between males and females, with a peak in late adolescence (15–20 years of age) that is followed by a slow increase to about 65 years of age. After this, there is a marked increase in the proportion of individuals experiencing syncope.



**Figure 6. Proportion of patients with at least one diagnosis code for syncope (ICD-9-CM code 780.2 or ICD-10-CM code R55) per 1,000 population, by gender (January 1, 2014–December 31, 2017).**

\* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing syncope has been excluded from the chart and marked as zero.

The BEST Initiative also sought to assess whether there was notable variation in the proportion of patients with syncope by calendar year of diagnosis. **Figure 7** presents the annual proportions of patients with a diagnosis code for syncope for ages 1–85+ years. Results suggest that proportions were fairly consistent across calendar years. It should be noted that the proportions presented in **Figure 7** are substantially lower than those in **Figure 6**, where syncope encounters were queried for the entire 2014–2017 period instead of for a single year.



**Figure 7. Proportion of patients with at least one diagnosis code for syncope (ICD-9-CM 780.2 or ICD-10-CM R55) per 1,000 population, by calendar year (January 1, 2014–December 31, 2017).**

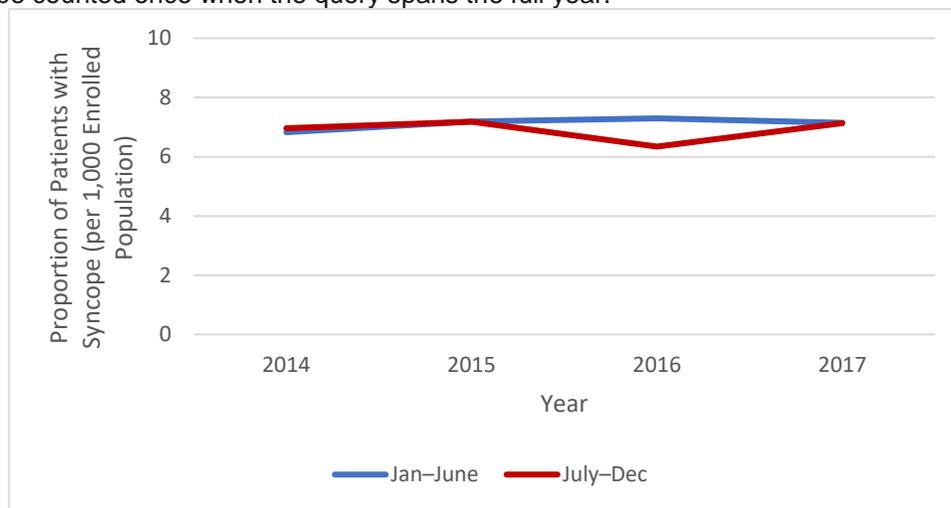
\* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing syncope has been excluded from the chart and marked as zero.

Analyses were also conducted to test whether there was a temporal association in the occurrence or reporting of syncope according to the time of the year, possibly as a result of an association with weather patterns or vaccination schedules. To test this, enrollment and syncope encounter data for January 1–June 30 and July 1–December 31 were queried for each year. As presented in **Table 3** and **Figure 8**, there did not appear to be a substantial difference in the proportion of patients experiencing syncope between the first and second halves of the year. The one exception was 2016, where the proportion of patients experiencing syncope was lower in the second half of the year. A separate analysis (presented in **Appendix B**) based on seasonality suggested that rates may be higher in the Spring/Summer (April–September) than in the Fall/Winter (January–March and October–December), though it is not clear whether this difference is significant.

**Table 3. Counts and proportions of patients experiencing syncope\*, defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2017).**

Description	Calendar year			
	2014	2015	2016	2017
January–June patient count	212,336	173,197	171,663	154,692
July–December patient count	214,872	170,609	150,671	150,672
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
<b>January–June proportion (per 1,000 enrolled)</b>	<b>6.83</b>	<b>7.19</b>	<b>7.29</b>	<b>7.14</b>
<b>July–December proportion (per 1,000 enrolled)</b>	<b>6.96</b>	<b>7.18</b>	<b>6.34</b>	<b>7.14</b>

\* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.



**Figure 8. Proportion of patients with at least one diagnosis code for syncope (ICD-9-CM code 780.2 or ICD-10-CM code R55), stratified by time of year (2014–2017).**

## H Discussion and Conclusion

The objective of this review was to assess and describe validated methods of identifying cases of syncope in administrative databases. The BEST Initiative found three published studies that reported measures of validity associated with general ICD codes for syncope.<sup>1-3</sup> Studies reported a moderate-to-high PPV associated with the diagnosis codes but noted a low sensitivity (i.e., increased chance of missing true cases). This may be due to the common approach of excluding more specific syncope codes

associated with a particular etiology (e.g., heat syncope) and the decision by Ruwald and colleagues to restrict searches to syncope codes in the principal diagnosis position. A case algorithm was developed based on these findings and refined through consultation with clinical subject matter experts.

Using the specified case algorithm, descriptive analyses were conducted using MarketScan commercial and Medicare claims data, accessed via Treatment Pathways, to test the feasibility of algorithm use and conduct initial analyses describing the epidemiology of syncope in a U.S. database of insured patients. Findings suggest that approximately 12.76–13.30 individuals per 1,000 population experienced at least one syncope event each year (**Appendix A**). It should again be emphasized that only one case per person could be counted per query time period, and that a single individual might have experienced multiple episodes of syncope. The average age for those diagnosed with syncope was approximately 48 years. This is younger than the average age of 64.6 years reported by Ruwald and colleagues.<sup>18</sup> This may be due to a higher number of events per individual in older age groups. However, it may also be the case that the two population cohorts differed, and additional analyses would be required prior to drawing conclusions with confidence.

The proportion of patients experiencing syncope was similar between males and females, with a peak in young adults and sharp increase with advancing age. The observed age distribution is similar to the trimodal distribution reported previously, wherein peaks were observed around 20, 60 and 80 years old.<sup>18,24</sup> Also, the proportion of patients experiencing syncope did not seem to vary substantially between the first and second halves of the calendar year, though analyses suggested that there may be some variation across seasons.

A limitation of this review is the low sensitivity that has previously been associated with the proposed algorithm, which may be explained in part by the exclusion of more specific syncope diagnosis codes and the decision by Ruwald and colleagues to restrict their analysis to codes in the principal diagnosis position. The BEST Initiative decided that any efforts to improve sensitivity by making the algorithm more inclusive (i.e., relaxing eligibility criteria) could introduce more problematic risks of bias and have proposed an approach that is consistent with previous studies. Meanwhile, the analyses conducted using MarketScan data should be viewed as exploratory, and additional studies would be required to validate the results and observations stemming from these queries. Selection bias in the cohort of individuals with observed syncope is also possible, as most cases of syncope are not medically attended or reported. Lastly, care-seeking behavior and the absence of universal diagnostic and coding practices could result in under-ascertainment of cases, and results for the algorithm characterization analyses should be considered conservative estimates.

Some potentially interesting avenues for future research were also noted. These include analyses of medications associated with the onset of syncope, drug–drug interactions causing syncope, vulnerable subpopulations (such as pregnant women and those with cardiac arrhythmia or heart failure), and treatments and prognosis following syncope. The hope is that the syncope algorithm proposed herein will facilitate future research in these important areas.

## I Acknowledgements

Development of the syncope algorithm and review report benefitted from significant engagement with the FDA CBER team members and their partners. We thank them for their contributions and feedback. Additional feedback on the proposed algorithm and draft report was provided by IBM Watson Health, Acumen and Epi Excellence LLC. MarketScan is a registered trademark of IBM Corporation in the United States, other countries or both.

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## Appendix A. Counts of Patients with Specific Codes Proposed for the Algorithm

As an initial test of the proposed algorithm, the BEST Initiative ran code-specific queries in a large U.S. administrative claims dataset. Researchers used the MarketScan Research Databases, accessed via the Treatment Pathways analytic platform, to query the past four full years of available data. Results are presented in **Table A1**. Because the transition between International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM to ICD-10-CM) occurred on October 1, 2015, ICD-9-CM codes were queried for January 1, 2014–September 30, 2015, and ICD-10-CM codes were queried for October 1, 2015–December 31, 2017.

**Table A1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in syncope algorithm (January 1, 2014–December 31, 2017).**

Code	Code Description	Calendar Year			
		2014	2015*	2016	2017
ICD-9-CM 780.2	Syncope and collapse	362,412	226,004		
ICD-10- CM R55	Syncope and collapse		88,161	287,499	258,991
780.2 OR R55	Syncope and collapse	362,412	291,691	287,499	258,991
	MarketScan Research Databases enrollment	28,407,959	22,117,235	21,616,367	19,802,253
	Proportion of patients with syncope per 1,000 enrolled population	12.76	13.19	13.30	13.08

\* In 2015, queries combining 780.2 OR R55 returned lower patient counts than when codes were queried individually. This is because of cases where both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–October and October–December timeframe, respectively. This overlap is due to the transition from ICD-9-CM to ICD-10-CM in 2015 and resulted in 22,476 duplications (i.e., individuals that were counted in both the ICD-9-CM and ICD-10-CM query).

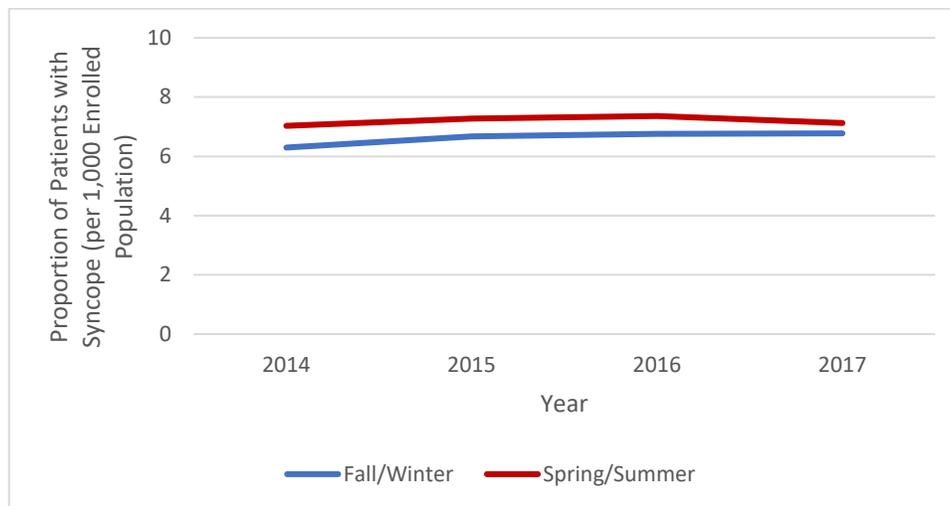
**Appendix B. Counts of Patients with Syncope by Season**

Analyses were also conducted to test whether there was a seasonal association in the occurrence or reporting of syncope, possibly as a result of an association with weather patterns or vaccination schedules. To test this, enrollment and syncope encounter data for Fall/Winter (January 1–March 31 and October 1–December 31) and Spring/Summer (April 1–September 30) were queried for each year. As presented in **Table B1** and **Figure B1**, the proportion of patients receiving a syncope diagnosis appeared to be higher in the Spring/Summer period. It is not clear whether the difference between seasons (<1 person per 1,000 enrollees for each year queried) is clinically or statistically significant.

**Table B1. Counts and proportions of patients with at least one diagnosis code for syncope\* (defined by ICD-9-CM and ICD-10-CM codes), stratified by season (2014–2017).**

Description	Calendar year			
	2014	2015	2016	2017
Fall/Winter Patient Count	229,542	185,178	182,842	167,304
Spring/Summer Patient Count	216,310	172,981	172,147	152,364
Fall/Winter Enrollment	36,459,990	27,751,531	27,071,490	24,695,788
Spring/Summer Enrollment	30,773,308	23,767,603	23,390,113	21,380,134
Fall/Winter	6.30	6.67	6.75	6.77
Spring/Summer	7.03	7.28	7.36	7.13

\* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.



**Figure B1. Proportion of patients with at least one diagnosis code for syncope (ICD-9-CM code 780.2 or ICD-10-CM code R55), stratified by season (2014–2017).**