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SELECTING AN APPROPRIATE COMPARATOR GROUP IN VACCINE COHORT STUDIES OF OLDER ADULTS: RECOMBINANT ZOSTER VACCINE (RZV) AS AN EXAMPLE

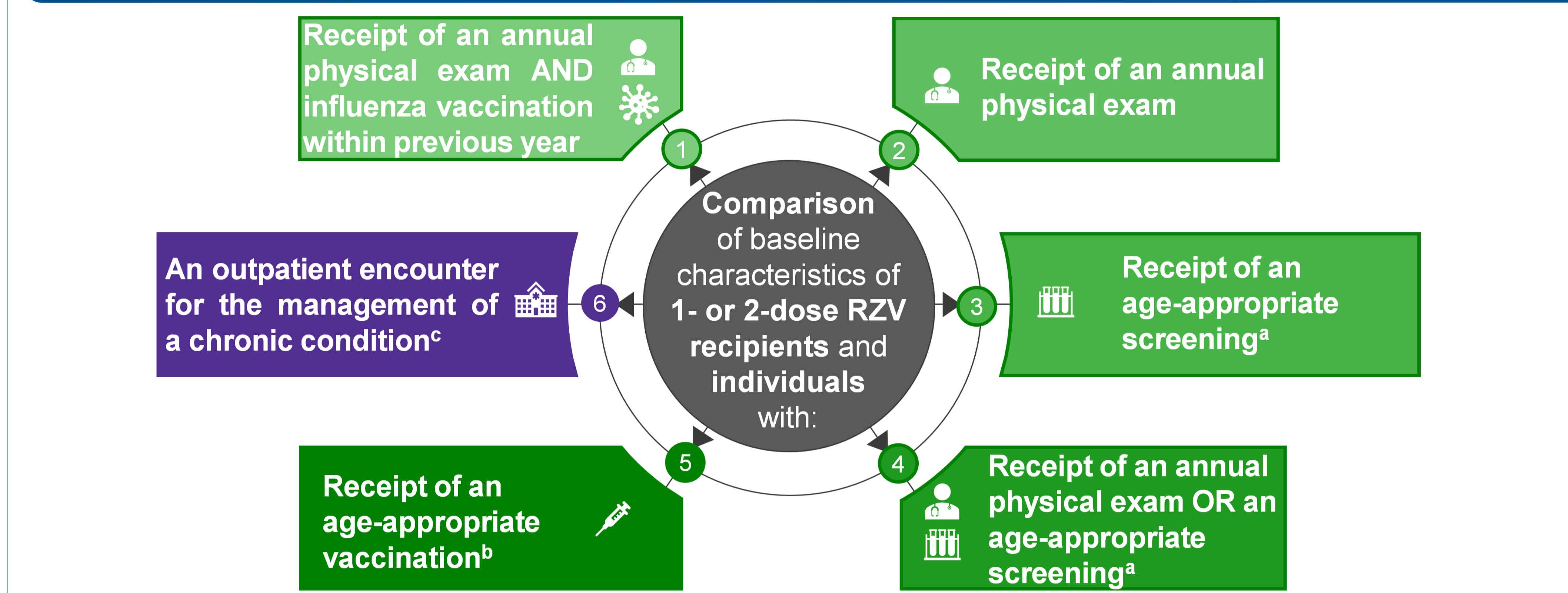
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BACKGROUND

- Observational studies are critical for assessing the effectiveness and safety of vaccines in the real-world setting.
- When comparing vaccinated versus unvaccinated individuals, substantive differences can lead to a number of biases. Notably, healthy-user bias is of significant concern when comparing outcomes between the two groups.^{1,2}
- Selection of an appropriate comparator group is an important study design consideration to help mitigate these biases; however, it can be particularly challenging in studies of older adults with multiple comorbidities and heterogeneous healthcare-seeking behaviors.
- The objective of this study was to identify the most appropriate comparator group for a cohort study assessing safety outcomes in recipients of the two-dose adjuvanted Recombinant Zoster Vaccine (RZV) in recipients aged ≥ 50 years.**

Algorithms using various combinations of "receiving at least one healthcare utilization service" were evaluated for comparability with RZV recipients



RZV, recombinant zoster vaccine. ^aIncluding screening for colon cancer, breast cancer, and osteoporosis; ^bIncluding receipt of at least one of the following vaccines: influenza; measles, mumps, rubella (MMR); measles, mumps, rubella, and varicella (MMRV); pneumococcal conjugate or polysaccharide; tetanus and diphtheria (Td); tetanus, diphtheria, and acellular pertussis (Tdap); ^cCurrent Procedural Terminology (CPT) codes 99211, 99212, 99213, 99214, 99215.

Comparison of baseline characteristics among RZV recipients and individuals in six unexposed groups: substantial variation in the prevalence of some comorbidities and healthcare-seeking behaviors

Baseline characteristic ^{a,b}	Receipt of 1 dose of RZV n (%) ^c	Receipt of 2 doses of RZV n (%) ^c	Algorithm 1 ^d n (%) ^e	Algorithm 2 ^d n (%) ^e	Algorithm 3 ^d n (%) ^e	Algorithm 4 ^d n (%) ^e	Algorithm 5 ^d n (%) ^e	Algorithm 6 ^d n (%) ^e
Age, mean (SD)	68 (9)	68 (9)	68 (9)	66 (9)	65 (8)	66 (8)	69 (9)	69 (10)
Female sex	147,475 (56.5)	75,224 (56.5)	982,930 (59.0)	1,974,596 (58.7)	2,066,731 (78.8)	2,684,334 (62.5)	1,147,344 (55.6)	3,690,952 (55.1)
Solid organ transplant	472 (0.2)	234 (0.2)	5,742 (0.3)	9,502 (0.2)	9,039 (0.2)	17,686 (0.2)	7,710 (0.3)	197,417 (0.5)
Hematopoietic cell transplant	225 (0.1)	104 (0.1)	1,789 (0.1)	2,963 (0.1)	2,777 (0.1)	5,399 (0.1)	3,842 (0.2)	79,296 (0.2)
Solid or hematologic malignancy or receipt of chemotherapy	38,833 (14.9)	20,550 (15.4)	318,098 (14.1)	562,083 (12.1)	433,435 (11.0)	938,117 (11.9)	324,824 (14.2)	8,134,454 (20.3)
Diabetes mellitus	59,800 (22.9)	30,705 (23.0)	621,978 (27.5)	1,100,563 (23.6)	931,709 (23.6)	1,909,801 (24.1)	700,663 (30.6)	13,787,110 (34.4)
Chronic kidney disease	46,268 (17.7)	23,978 (18.0)	547,536 (24.2)	933,289 (20.0)	715,602 (18.1)	1,556,104 (19.7)	574,515 (25.1)	12,532,709 (31.3)
Chronic lung disease ^f	29,543 (11.3)	15,062 (11.3)	350,458 (15.5)	589,039 (12.6)	482,868 (12.2)	1,007,931 (12.7)	379,092 (16.6)	8,673,956 (21.7)
Congestive heart failure	13,124 (5.0)	6,711 (5.0)	172,720 (7.6)	284,010 (6.1)	195,304 (5.0)	456,510 (5.8)	208,040 (9.1)	5,382,791 (13.4)
Ischemic heart disease	39,301 (15.1)	20,704 (15.5)	396,947 (17.6)	668,008 (14.3)	459,323 (11.6)	1,067,395 (13.5)	438,968 (19.2)	10,410,218 (26.0)
Dementia	4,950 (1.9)	2,416 (1.8)	74,601 (3.3)	124,816 (2.7)	61,011 (1.5)	177,744 (2.2)	89,906 (3.9)	1,799,403 (4.5)
Chronic liver disease	13,735 (5.3)	6,946 (5.2)	128,067 (5.7)	239,070 (5.1)	221,616 (5.6)	433,263 (5.5)	131,975 (5.8)	3,313,924 (8.3)
Stroke/transient ischemic attack	7,456 (2.9)	3,746 (2.8)	80,553 (3.6)	141,222 (3.0)	106,378 (2.7)	233,871 (3.0)	94,920 (4.1)	2,353,022 (5.9)
At least 1 dermatology visit	7,633 (2.9)	4,222 (3.2)	44,001 (1.9)	81,916 (1.8)	67,755 (1.7)	135,522 (1.7)	36,425 (1.6)	673,028 (1.7)
At least 1 optometry or ophthalmology visit	104,686 (40.1)	56,682 (42.5)	883,258 (39.1)	1,532,507 (32.9)	1,328,027 (33.7)	2,661,853 (33.7)	812,692 (35.5)	15,593,107 (39.0)

RZV, recombinant zoster vaccine; SD, standard deviation. ^aBaseline period defined as 365 days prior to the index date. Index date was defined as the date of vaccination for RZV recipients and the earliest date of meeting algorithm selection criteria for the comparator groups; ^bDefined using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes; ^cBased on total unique numbers of individuals; ^dSee Figure above for algorithm definition; ^eBased on total numbers of comparator algorithm episodes; ^fChronic obstructive pulmonary disease (COPD) or bronchiectasis. See supplementary materials for more details.

METHODS

- Curated administrative data in the Sentinel Common Data Model format from 4 health plan participants in the United States (US) Food and Drug Administration's Sentinel Initiative were used to select commercially-insured adults ≥50 years of age with medical and drug coverage from January 1, 2018 to January 31, 2019.³
- The exposed group was comprised of individuals who received at least one dose of the 2-dose RZV approved in the US for the prevention of herpes zoster in people aged ≥ 50 years.
- Demographics, certain healthcare-seeking behaviors, and the prevalence of specific comorbidities and immunosuppressive conditions for the RZV recipient groups and the comparator groups were descriptively compared.

RESULTS

- A total of 261,050 individuals received at least one dose of RZV during the study period. Of these, 133,256 individuals received the recommended two doses during the study period.
- The number of individuals with at least one comparator visit ranged from 1,666,326 to 6,698,184, depending on the definition used. The mean age for each of the comparator groups was similar to that of RZV recipients (68 years, standard deviation: 9 years).
- Adults unexposed to RZV who received a routine annual physical exam or an age-appropriate preventive screening measure (Algorithm 4) were comparable based on descriptive comparisons to RZV recipients.

CONCLUSIONS

- There were substantive differences in the prevalence of some comorbidities when comparing characteristics of RZV recipients to those of individuals in six different potential comparator groups of unexposed individuals.
- These differences highlight the importance of the rigorous selection of a comparator group in cohort studies evaluating vaccine effectiveness or safety, especially in older adults who have multiple comorbidities.
- By evaluating six different comparator group definitions, we identified an algorithm that would select unexposed individuals comparable to RZV recipients in this cohort study.

- When comparing outcomes among individuals who receive a vaccine of interest to those who do not, it is important that comparison-group individuals have similar characteristics to vaccine recipients.
- Defining an appropriate comparison group is critical for minimizing bias as much as possible when evaluating vaccine effectiveness and safety outcomes.

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SUPPLEMENTARY MATERIALS

List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, Current Procedural Terminology, Fourth Edition (CPT-4) codes, and Healthcare Common Procedure Coding System (HCPCS) codes used to define comparator groups

Code	Description	Code category	Code type
Annual physical exam			
Z00.00	Encounter for general adult medical examination without abnormal findings	Diagnosis	ICD-10-CM
Z00.01	Encounter for general adult medical examination with abnormal findings	Diagnosis	ICD-10-CM
99386	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 40-64 years	Procedure	CPT-4
99387	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 65 years and older	Procedure	CPT-4
99396	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	Procedure	CPT-4
99397	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 65 years and older	Procedure	CPT-4
G0438	Annual wellness visit; includes a personalized prevention plan of service (PPS), initial visit	Procedure	HCPCS
G0439	Annual wellness visit, includes a personalized prevention plan of service (PPS), subsequent visit	Procedure	HCPCS
G0468	Federally qualified health center (FQHC) visit, initial preventive physical exam (IPPE) or annual wellness visit (AWV)	Procedure	HCPCS
S5190	Wellness assessment, performed by nonphysician	Procedure	HCPCS
Age-appropriate preventive care screening			
Z12.11	Encounter for screening for malignant neoplasm of colon	Diagnosis	ICD-10-CM
Z12.31	Encounter for screening mammogram for malignant neoplasm of breast	Diagnosis	ICD-10-CM
Z12.39	Encounter for other screening for malignant neoplasm of breast	Diagnosis	ICD-10-CM
Z13.820	Encounter screening for osteoporosis	Diagnosis	ICD-10-CM
45378	Screening colonoscopy	Procedure	CPT-4
77067	Screening mammogram	Procedure	CPT-4
77080	Osteoporosis screening	Procedure	CPT-4
77081	Osteoporosis screening	Procedure	CPT-4
Receipt of influenza vaccine or age-appropriate vaccinations			
90661	Influenza virus vaccine, trivalent (cclIV3), derived from cell cultures, subunit, preservative and antibiotic free, 0.5 mL dosage, for intramuscular use	Procedure	CPT-4
90756	Influenza virus vaccine, quadrivalent (cclIV4), derived from cell cultures, subunit, antibiotic free, 0.5mL dosage, for intramuscular use	Procedure	CPT-4
90674	Influenza virus vaccine, quadrivalent (cclIV4), derived from cell cultures, subunit, preservative and antibiotic free, 0.5 mL dosage, for intramuscular use	Procedure	CPT-4
90653	Influenza vaccine, inactivated (IIV), subunit, adjuvanted, for intramuscular use	Procedure	CPT-4
90662	Influenza virus vaccine (IIV), split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use	Procedure	CPT-4
90656	Influenza virus vaccine, trivalent (IIV3), split virus, preservative free, 0.5 mL dosage, for intramuscular use	Procedure	CPT-4
90655	Influenza virus vaccine, trivalent (IIV3), split virus, preservative free, 0.25 mL dosage, for intramuscular use	Procedure	CPT-4
90657	Influenza virus vaccine, trivalent (IIV3), split virus, 0.25 mL dosage, for intramuscular use	Procedure	CPT-4
90658	Influenza virus vaccine, trivalent (IIV3), split virus, 0.5 mL dosage, for intramuscular use	Procedure	CPT-4
90689	Influenza virus vaccine quadrivalent (IIV4), inactivated, adjuvanted, preservative free, 0.25 mL dosage, for intramuscular use	Procedure	CPT-4
90686	Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.5 mL dosage, for intramuscular use	Procedure	CPT-4
90685	Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.25 mL, for intramuscular use	Procedure	CPT-4
90687	Influenza virus vaccine, quadrivalent (IIV4), split virus, 0.25 mL dosage, for intramuscular use	Procedure	CPT-4
90688	Influenza virus vaccine, quadrivalent (IIV4), split virus, 0.5 mL dosage, for intramuscular use	Procedure	CPT-4
90654	Influenza virus vaccine, trivalent (IIV3), split virus, preservative-free, for intradermal use	Procedure	CPT-4
90630	Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, for intradermal use	Procedure	CPT-4
90673	Influenza virus vaccine, trivalent (RIV3), derived from recombinant deoxyribonucleic acid (DNA), hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use	Procedure	CPT-4
90682	Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use	Procedure	CPT-4
90710	Measles, mumps, rubella, and varicella vaccine (MMRV), live, for subcutaneous use	Procedure	CPT-4
90707	Measles, mumps, and rubella virus vaccine (MMR), live, for subcutaneous use	Procedure	CPT-4
90670	Pneumococcal conjugate vaccine, 13 valent (PCV13), for intramuscular use	Procedure	CPT-4
90732	Pneumococcal polysaccharide vaccine, 23-valent (PPSV23), adult or immunosuppressed patient dosage, when administered to individuals 2 years or older, for subcutaneous or intramuscular use	Procedure	CPT-4
90714	Tetanus and diphtheria toxoids adsorbed (Td), preservative free, when administered to individuals 7 years or older, for intramuscular use	Procedure	CPT-4
90715	Tetanus, diphtheria toxoids, and acellular pertussis vaccine (Tdap), when administered to individuals 7 years or older, for intramuscular use	Procedure	CPT-4
Outpatient visit for management of a chronic condition			
99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are self-limited or minor. Typically, 10 minutes are spent face-to-face with the patient and/or family.	Procedure	CPT-4
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low complexity. Counseling and coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of low to moderate severity. Typically, 15 minutes are spent face-to-face with the patient and/or family.	Procedure	CPT-4
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A detailed history; A detailed examination; Medical decision making of moderate complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Typically, 25 minutes are spent face-to-face with the patient and/or family.	Procedure	CPT-4
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A comprehensive history; A comprehensive examination; Medical decision making of high complexity. Counseling and/or coordination of care with other physicians, other qualified health care professionals, or agencies are provided consistent with the nature of the problem(s) and the patient's and/or family's needs. Usually, the presenting problem(s) are of moderate to high severity. Typically, 40 minutes are spent face-to-face with the patient and/or family.	Procedure	CPT-4
99211	Office or other outpatient visit for the evaluation and management of an established patient, that may not require the presence of a physician or other qualified health care professional. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.	Procedure	CPT-4

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DISCLOSURES

- Business & Decision Life Sciences platform provided editorial assistance and publications coordination, on behalf of GSK. Carole Desiron coordinated publications development and editorial support.
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