

SUPPLEMENTARY MATERIALS

Use of real-world evidence in economic assessments of pharmaceuticals in the United States

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Supplement 1: Standardized Data Extraction Form (DEF)

PART1 – General information of an ICER report (6 items)

- Title of ICER report
- Date of publication
- Indication
- Interventions included in economic analyses
- Comparators included in economic analyses
- Goal of treatment (Extend life, improve symptoms or QoL, and others)

PART2 – Reason for RWE use (2 items)

- For which model input(s) RWE was used
 - Categories for model inputs (15 in total)
 - Non-drug specific clinical inputs
 - Disease progression/mortality rates
 - Incidence
 - Prevalence
 - Patient characteristics
 - Non-drug specific discontinuation rate
 - Other clinical inputs
 - Drug-specific clinical inputs
 - Effectiveness
 - Adverse drug event rates
 - Drug specific discontinuation rate
 - Utility inputs
 - Non-drug specific utility
 - Drug specific utility
 - Economic inputs
 - Healthcare costs
 - Non-healthcare costs
 - Treatment pattern/market share
 - Assumptions
 - To support assumptions
- Why RWE was used, not RCT?

PART3 – Characteristics of RWE (11 items)

- Title of RWE
- RWE publication date
- Drug(s) studied in RWE
- FDA approval year of drugs studied in RWE
- Noted as a pre-registered study
- Sponsorships
 - Categories for sponsorships
 - Industry
 - Non-industry (academia or others)
 - Unclear
- Types of RWE
 - Categories for types of RWE
 - Clinical studies
 - Economic studies
 - Utility studies
 - Diagnosis studies
 - Undetermined
- Study design
 - Categories for study design
 - Pragmatic controlled trial / Large simple trial
 - Quasi-experimental
 - Prospective cohort
 - Retrospective cohort
 - Cross-sectional
 - Cross-sectional for surveys
 - Meta-analysis / Network Meta-analysis
 - Systematic review
 - Utility study
 - Unidentifiable
- Data source
 - Categories for data source
 - Electronic health records
 - Administrative claims data
 - Registry data
 - Other observational data
 - Patient survey data / patient diary
 - Healthcare provider survey data

- Synthesis of multiple previous RWE studies
 - Inaccessible / Unidentifiable
- PICOTS (population, intervention, comparator, time, and setting)
- Sample size

PART4 – Model inputs (2 items)

- Model inputs
 - Base-case cost-effectiveness analysis
 - Sensitivity analysis and scenario analysis
 - Budget impact analysis
- Sources for each of the inputs
 - Completely informed by RWE
 - Partially informed by RWE
 - Not informed by RWE

Supplement 2: The consensus of reviewers on the data extraction

For some situations where reviewers need consensus, we made the following rules or decisions through discussion with other authors. The items of an agreement are as follows:

1. When an original study was not cited

When another economic evaluation study that used the same input was cited in an ICER report, instead of an original study from which the input was actually obtained or estimated, we identified the original study. If it is hard to identify the original study (e.g., when the input was based on estimates from multiple studies or when the input re-calculated or calibrated and thus it is hard to find the original study that they were based on, we indicated the cited study 'unclear source'.

2. When it was unclear whether or not a study should be counted as RWE

When a systematic review or meta-analysis was cited and its output was used to inform a model input, the study was counted as RWE if all studies included in the systematic review were real-world studies. Simulation or modeling studies were not counted as RWE.

In terms of studies used for utility inputs, studies in which patients who have a condition of interest were asked about their health status using validated tools were counted as RWE. Studies in which non-patients were asked to elicit their preference given hypothetical situations were not counted as RWE, based on the definition of RWE (i.e., data routinely collected regarding patient health status).

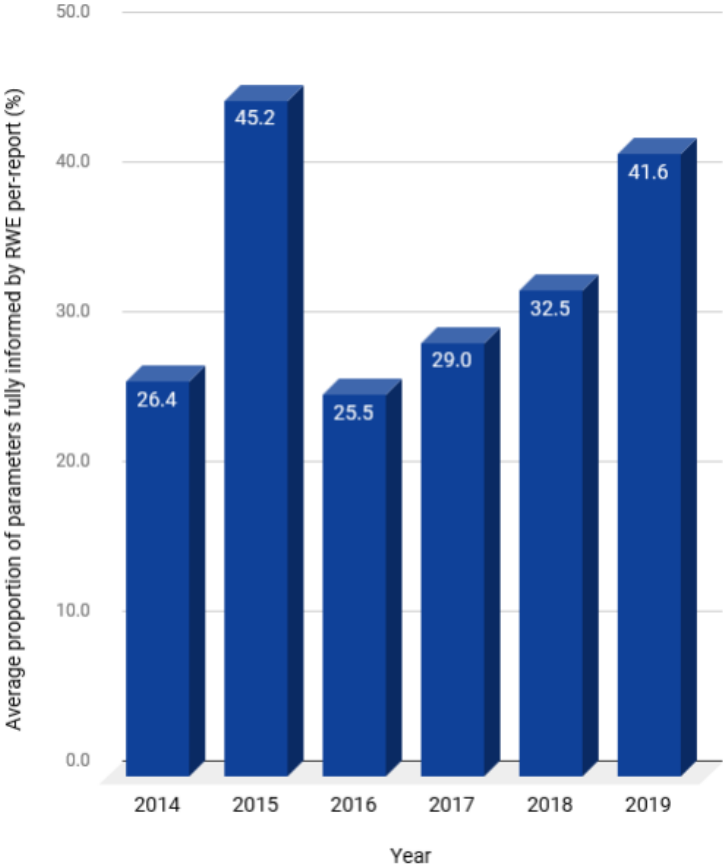
3. When it is unclear whether a study was used for economic assessments

Studies that were mentioned in an ICER report but did not have any role to inform any input in an economic model were not considered. Studies that were used to justify the decisions, make assumptions, determine cohort of patients or time horizon or calibrate obtained inputs were included even though they were not directly related to the model input.

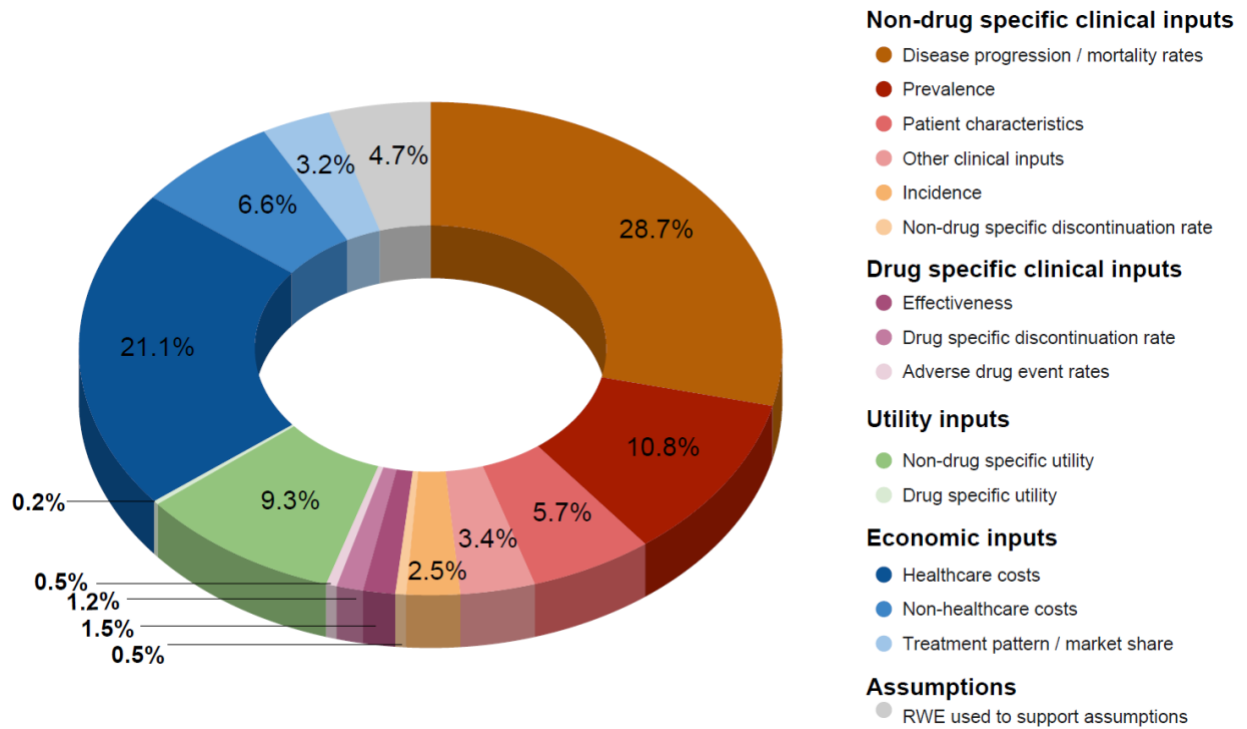
4. Counting the number of model inputs

All types of model inputs (e.g., cohort characteristics, clinical inputs, utility inputs, cost inputs, etc) that were used for base-case deterministic results, sensitivity analysis, scenario analysis, and budget impact analysis were counted. When an input obtained from the same study was stratified by subgroups of a study population (e.g., mortality stratified by age group) or used multiple times in a model, it was counted as one input. Uncertainty inputs that were obtained along with deterministic inputs (e.g., upper and lower bound of a deterministic input) were not counted separately.

Supplementary Figure 1. Annual mean proportion of inputs fully informed by RWE per-report

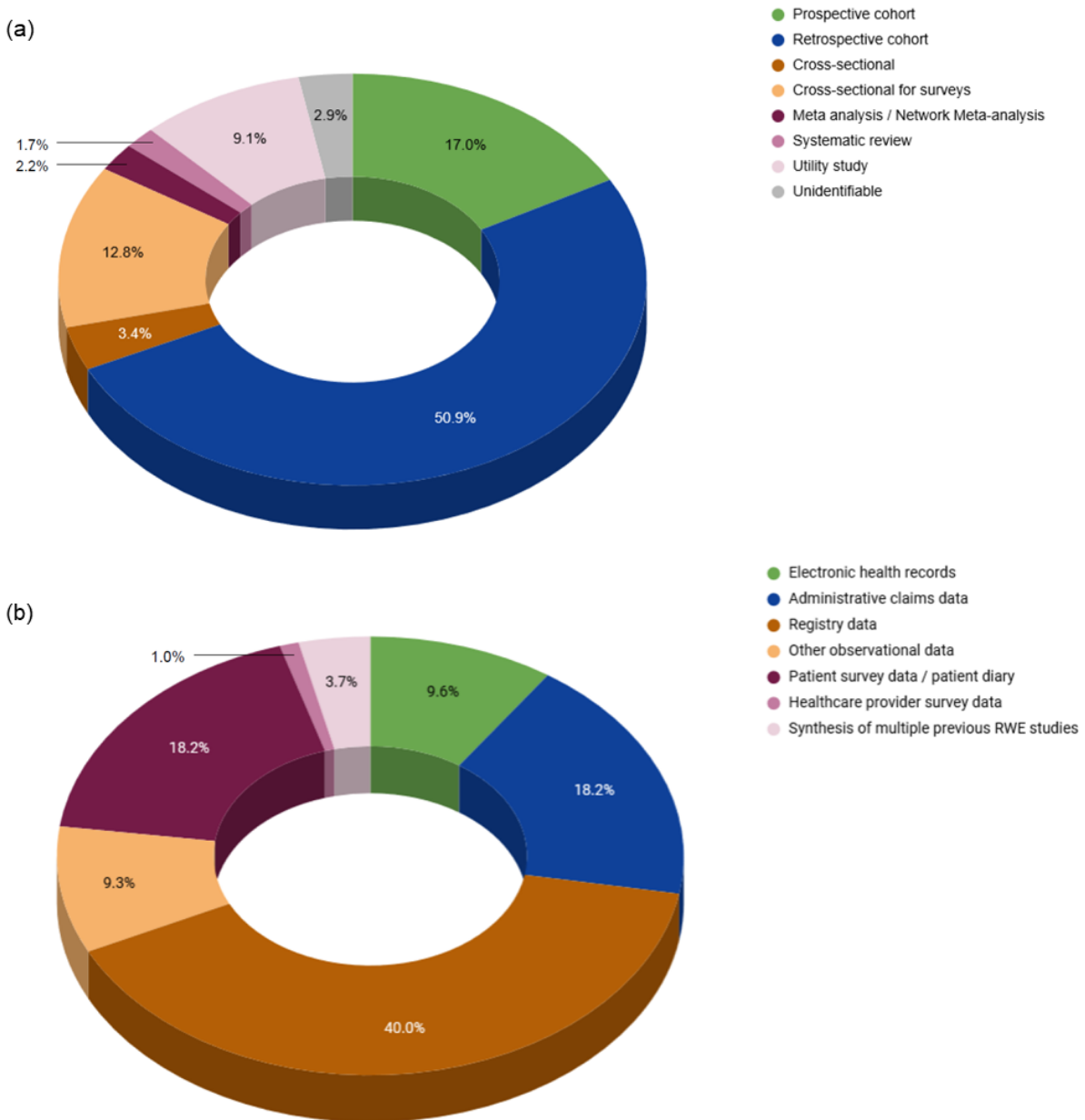


Supplementary Figure 2. The frequency distribution of types of inputs informed by RWE



The percentage of frequency was calculated by dividing the number of RWE uses for each input by the total number of RWE uses (n=407)

Supplementary Figure 3. Frequency distribution of study designs (a) and data sources (b) of RWE



The percentage of frequency was calculated by dividing the number of RWE uses with each study design or data source by the total number of RWE uses (n=407); Other observational data included US vital statistics, death and birth certificates, population estimates from US Census Bureau, survey with caregivers, employers and hospitals, data from prescription monitoring program, data from calls to the poison control center, hospital annual financial data, and a combination of multiple data sources.

SupplementaryTable 1. ICER reports included in the review

Title of ICER report	Date of publication	Interventions included in economic models^a
The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection	4/15/2014	Sofosbuvir, Simeprevir
The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection	1/30/2015	Simeprevir, Sofosbuvir, Ledipasvir, Daclatasvir, Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir
Controversies in Obesity Management	8/10/2015	Naloxone/bupropion sustained-release
PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks	11/24/2015	Ezetimibe, PCSK9 inhibitor
CardioMEMS HF System and Sacubitril/Valsartan for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks	12/1/2015	Lisinopril
Mepolizumab for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks	3/14/2016	Mepolizumab
Insulin Degludec for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks	3/14/2016	Insulin degludec
Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks	6/9/2016	Carfilzomib, Elotuzumab, Ixazomib, Panobinostat, Bortezomib
Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness, Value, and Value-Based Price Benchmarks	7/26/2016	Obeticholic Acid
Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis: Comparative Clinical Effectiveness and Value	7/26/2016	Obeticholic Acid
Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness, Value and Value-Based Price Benchmarks	11/1/2016	Afatinib, Erlotinib, Gefitinib, Atezolizumab, Nivolumab, Pembrolizumab

Disease-Modifying Therapies for Relapsing Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value	3/6/2017	Daclizumab, Glatiramer acetate, Interferon beta-1a, Interferon beta-1b, Peginterferon beta-1a, Dimethyl fumarate, Fingolimod, Teriflunomide, Alemtuzumab, Natalizumab, Ocrelizumab
Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value	4/7/2017	Adalimumab, Certolizumab pegol, Etanercept, Golimumab, Infliximab, Rituximab, Abatacept, Sarilumab, Tocilizumab. Tofacitinib, Baricitinib
Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value	6/8/2017	Dupilumab
Anabolic therapies for osteoporosis in postmenopausal women	7/17/2017	Abaloparatide, Teriparatide
Abuse-Deterrent Formulations of Opioids: Effectiveness and Value	8/8/2017	Abuse-deterrent formulations of Opioids
Poly ADP-Ribose Polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value	9/28/2017	Rucaparib, Niraparib, Olaparib
Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value	12/22/2017	Valbenazine, Deutetrabenazine
Voretigene Neparvovec for Biallelic RPE65 Mediated Retinal Disease: Effectiveness and Value	2/14/2018	Voretigene neparvovec
Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value	3/23/2018	Tisagenlecleucel Axicabtagene - ciloleucel
Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value	4/16/2018	Emicizumab
Modulator Treatments for Cystic Fibrosis: Effectiveness and Value	6/7/2018	Tezacaftor, Lumacaftor, Ivacaftor
Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value	7/3/2018	Erenumab, Fremanezumab, Galcanezumab
Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value	8/3/2018	Adalimumab, Etanercept, Infliximab, Certolizumab pegol, Secukinumab, Ixekizumab, Brodalumab, Ustekinumab, Guselkumab, Tildrakizumab, Risankizumab, Apremilast

Elagolix for Treating Endometriosis	8/3/2018	Elagolix
Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value	10/4/2018	Apalutamide, Enzalutamide, Abiraterone Acetate
Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value	10/4/2018	Inotersen, Patisiran
Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value	11/15/2018	Lanadelumab, C1 inhibitors
Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value	12/3/2018	Monthly buprenorphine injection, Buprenorphine implant, Buprenorphine extended release injection
Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks	12/20/2018	Dupilumab, Omalizumab, Mepolizumab, Reslizumab, Benralizumab
Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value	4/3/2019	Onasemnogene abeparvovec, Nusinersen
Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value	6/20/2019	Esketamine
Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value	6/20/2019	Siponimod

SupplementaryTable 2. Number of RWE uses per-report

ICER report	CEA	BIA	Total
The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection	5	7	12
The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection	21	2	23
Controversies in Obesity Management	4	0	4
PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and ValueBased Price Benchmarks	26	0	26
CardioMEMS HF System (St. Jude Medical, Inc.) and Sacubitril/Valsartan (Entresto, Novartis AG) for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks	10	2	12
Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and ValueBased Price Benchmarks	6	2	8
Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks	9	3	12
Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks	3	3	6
Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness, Value, and Value-Based Price Benchmarks	17	1	18
Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis: Comparative Clinical Effectiveness and Value	20	0	20
Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness, Value and Value-Based Price Benchmarks	7	2	9
Disease-Modifying Therapies for Relapsing Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value	16	1	17
Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value	13	1	14
Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value	3	1	4
Anabolic therapies for osteoporosis in postmenopausal women	9	1	10
Abuse-Deterrent Formulations of Opioids: Effectiveness and Value	15	0 ^a	15

Poly ADP-Ribose Polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value	2	2	4
Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value	10	0	10
Voretigene Neparvovec for Biallelic RPE65 Mediated Retinal Disease: Effectiveness and Value	4	0	4
Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value	8	3	11
Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value	12	2	14
Modulator Treatments for Cystic Fibrosis: Effectiveness and Value	19	2	21
Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value	11	3	14
Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value	10	2	12
Elagolix for Treating Endometriosis	12	1	13
Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value	6	0	6
Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value	7	0	7
Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value	12	1	13
Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value	16	1	17
Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks	8	7	15
Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value	12	2	14
Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value	9	2	11
Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value	11	0 ^a	11

^a BIA was not conducted

Supplementary Table 3. Number of model inputs informed by RWE

ICER report	Number of inputs				Total
	Fully informed by RWE	Partially informed by RWE	Not informed by RWE	Unclear	
The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection	14	0	39	0	53
The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection	47	9	41	6	103
Controversies in Obesity Management	6	0	4	0	10
PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and ValueBased Price Benchmarks	44	4	28	1	77
CardioMEMS HF System (St. Jude Medical, Inc.) and Sacubitril/Valsartan (Entresto, Novartis AG) for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks	5	4	16	3	28
Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and ValueBased Price Benchmarks	12	2	29	1	44
Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks	20	0	86	2	108
Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks	9	0	68	0	77
Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness, Value, and Value-Based Price Benchmarks	17	30	29	2	78
Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis: Comparative Clinical Effectiveness and Value	43	3	17	3	66
Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness, Value and Value-Based Price Benchmarks	10	0	108	0	118
Disease-Modifying Therapies for Relapsing Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value	60	91	262	3	416

Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value	16	0	40	0	56
Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value	4	0	43	0	47
Anabolic therapies for osteoporosis in postmenopausal women	10	7	21	1	39
Abuse-Deterrent Formulations of Opioids: Effectiveness and Value	20	1	4	1	26
Poly ADP-Ribose Polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value	16	0	60	9	85
Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value	9	0	21	0	30
Voretigene Neparvovec for Biallelic RPE65 Mediated Retinal Disease: Effectiveness and Value	33	2	24	1	60
Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value	31	0	84	1	116
Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value	20	0	30	1	51
Modulator Treatments for Cystic Fibrosis: Effectiveness and Value	36	1	30	2	69
Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value	25	0	32	0	57
Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value	9	3	81	0	93
Elagolix for Treating Endometriosis	16	0	23	3	42
Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value	13	2	45	0	60
Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value	5	14	86	18	123
Prophylaxis for Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value	26	0	29	3	58
Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value	18	5	23	5	51
Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks	13	4	46	4	67

Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value	32	1	44	0	77
Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value	19	0	31	0	50
Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value	71	56	30	0	157

Supplementary Table 4. Year of FDA approval of drugs included in RWE

Year of FDA approval	Number of drugs		Number of RWE		Number of RWE per-drug
	Number	Percentage	Number	Percentage	
~1990	11	8.9	20	23.3	1.8
1991-1995	2	1.6	1	1.2	0.5
1996-2000	12	9.8	19	22.1	1.6
2001-2005	17	13.8	28	32.6	1.7
2006-2010	9	7.3	9	10.5	1.0
2011-2015	31	25.2	9	10.5	0.3
2016~	41	33.3	0	0.0	0.0
Total	123	100.0	86	100.0	0.7