

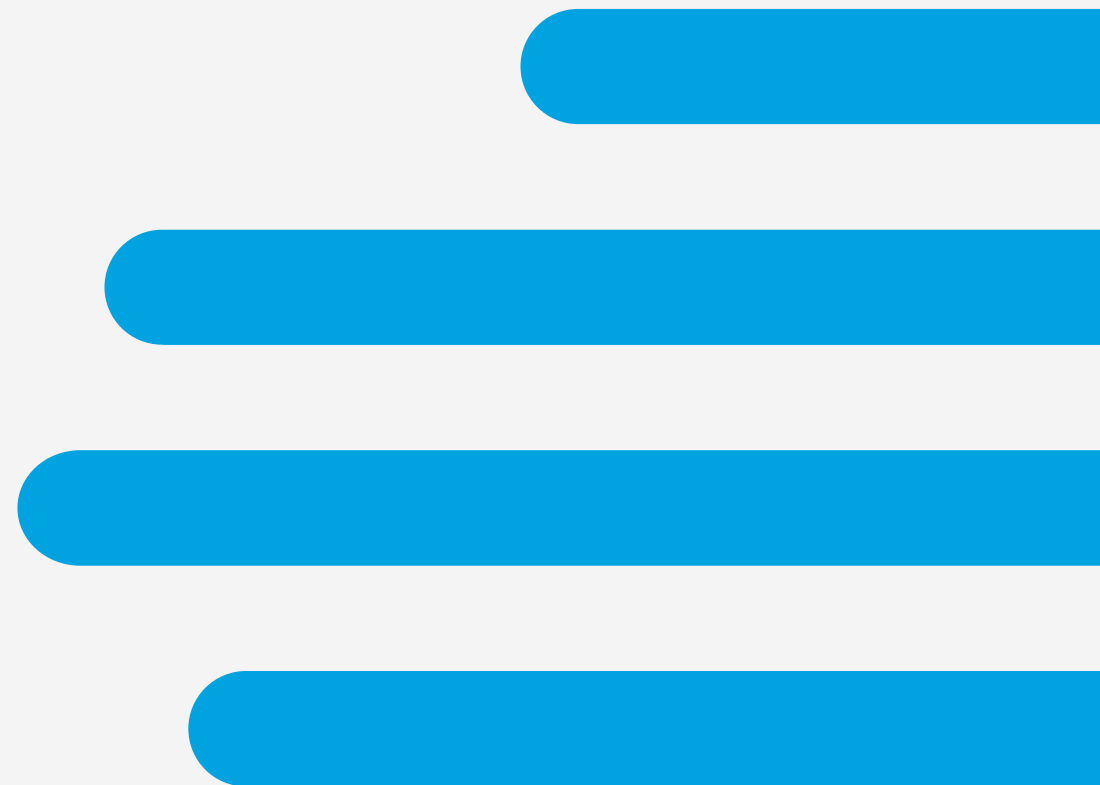
医療情報DB推進コンソーシアム

海外のアウトカムバリデーション 研究結果の共有方法 - 調査結果の共有 -

2023年2月14日

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調査の背景



昨年度の振り返り

バリデーション結果の共有と再利用、および環境構築の更なる検討が有用となった。

これらの事項を検討していくことが有用

- ・バリデーション結果の共有のあり方
- ・バリデーション実施の代替としての既存のバリデーション研究の活用
- ・医療機関のバリデーションへの協力推進に向けた環境構築

課題/要望

(製薬企業/DB事業者)

- ・ 先行研究の再利用の許容
- ・ 必須シーンや必要指標の明確化
- ・ 実施タイミングの具体化

- ・ 結果の共有方法の具体化
- ・ 結果の妥当性判断の基準設定
- ・ 結果が不十分だった際の対応の明確化

- ・ 施設の協力を得やすい環境づくり
- ・ カルテレビュー方法の標準化 (調査票/実施体制 等)

バリデーションの
計画策定

バリデーションの
実施

バリデーションの
結果解釈

課題解決の 参考事例

(海外事例/国内事例)

[国内事例]

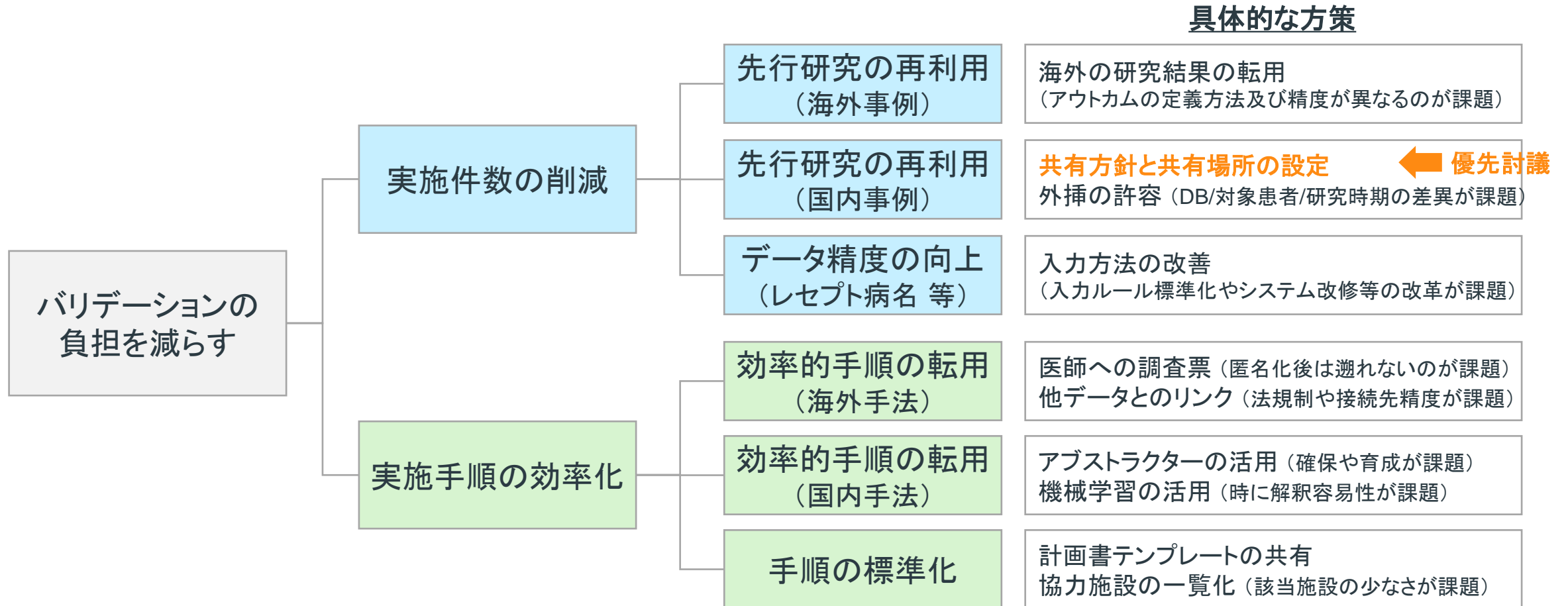
- ・ 機械学習を活用したアウトカム定義作成の効率化 (陽性的中率と感度のバランス良い定義)
- ・ PMDAによるバリデーションの基本方針の発出 (令和2年7月31日薬機レギ長発第0731002号及び薬機審長発第0731002号)

[海外事例]

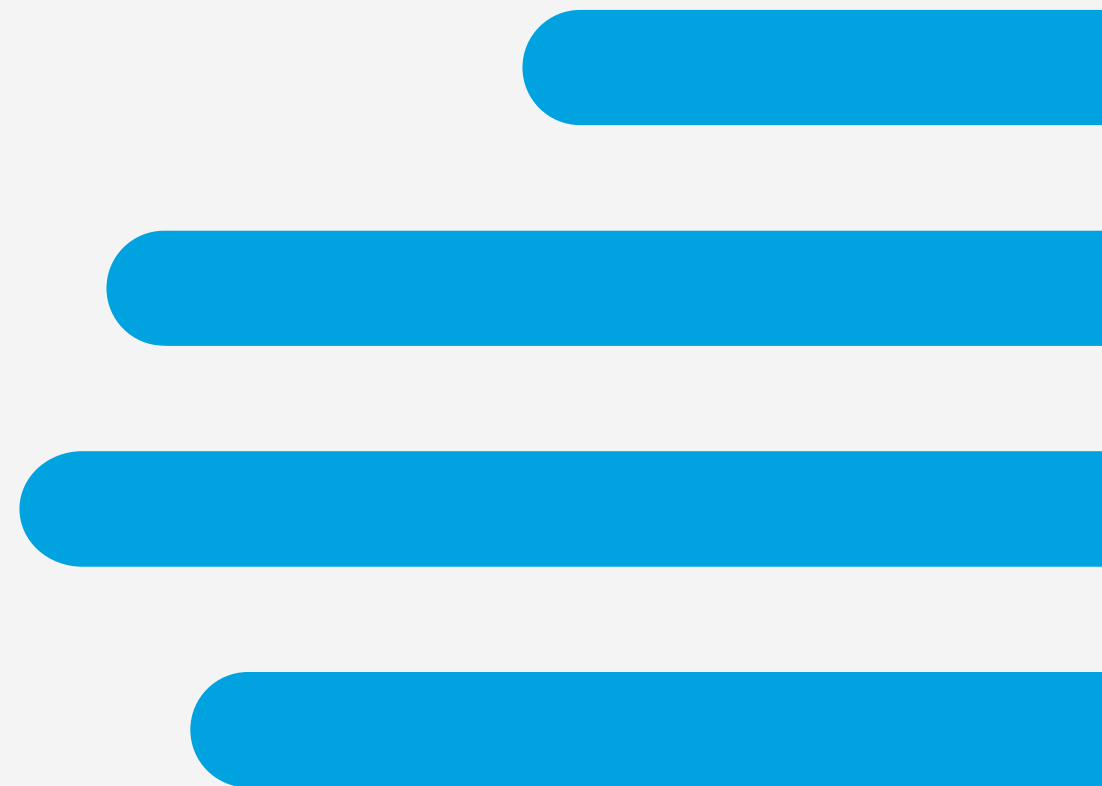
- ・ バリデーション結果の蓄積と活用
- ・ 多様なバリデーション方法 (医師への調査票送付 等)

今年度(第1回)の振り返り

第1回会議での発表と討議を通じて方策が網羅的に洗い出された。昨年度の結論もふまえ、第2回会議では「バリデーション研究結果の再利用」を優先的に討議することとなり、その参考として海外事例を調査する。



調査の結果



調査対象/方法と結果

日本の規制当局WEBサイトでのバリデーション研究結果の共有方針を検討するために、海外の規制当局主導のWEBサイトにおける事例共有方法を簡易調査した。

		米国 (FDA)	欧州 (EMA)
		Sentinel	RMP (1/2/3)
		Drug Assessments Sentinel Initiative	EU PAS Register (encepp.eu)
事例まとめ (一覧表)	掲載場所	Health Outcomes of Interest	-
	掲載内容	Systematic review結果 - Sentinel以外のDBのバリデーション研究 - アウトカム別に研究を一覧でまとめている - 研究内容/結果および文献情報等を要約	-
個別事例	掲載場所	各PASSの要約サイト内 (掲載ない場合も有り)	各PASSの要約サイト内 (掲載ない場合も有り)
	検索方法	① 「Search Health Outcomes of Interest」で該当PASS/Validationをフィルタリング (TitleとOutcomesが検索対象でタグ付き) ② 検索先の「Additional Information」タブ内の格納を確認	① 「Search Study」で該当PASS/Validationを検索 (Titleが検索対象) ② 検索先の「Document」タブ内の格納を確認 (格納ない場合はPASS Protocolの中身を確認)

調査対象/方法と結果

今回は第1回会議で紹介した「脳梗塞」のバリデーション研究調査を実例として調査した。

脳梗塞（アウトカムバリデーション研究の比較）

		日本	イギリス	イギリス	デンマーク	スペイン	米国	
		MID-NET	THIN	CPRD	DNRP	SIDIAP	Sentinel	
情報元 (DOI)		Tanigawa (10.1002/pts.5423)	Ruigomez (10.1002/pts.1919)	Hill (10.1212/01.wrl.000011 0312.36909.7f)	Krarup (10.1159/000102143)	Indacaterol/ Glycopyrronium Bromide	Ammann (10.1087/MD.000000000 0008440)	Coding Trend Fung
種類		acute ischemic stroke	ischemic stroke /TIA	stroke	ischemic stroke	stroke	acute ischemic stroke	ischemic stroke
定義	概要	傷病名+入院 +検査+薬剤 (Algorithm B)	傷病名+入院 +フリーテキスト (Read Code)	傷病名 (Read/OXMIS Code)	傷病名+入院 (ICD10)	傷病名 (ICD10)	傷病名+入院 (ICD9)	傷病名 (ICD9/ICD10)
	詳細	ESX/G08 CT/MRI/MRA 抗血栓薬	G63-G67 /F423600	NA	ESX	I50-I59 /G46/Z86	433.x1/434.xx/436	433.x1/434.xx/436 ↓ I53.X
方法	対象	一般集団	一般集団	片頭痛患者	一般集団	OOPD患者	XIV投与者	-
	手順	カルテレビュー (3施設) ①Possible Caseから サンプリング (366例) ②2人の医師による 真偽判定 ③11種類の定義別 でPPV算出 (1施設で感度算出)	医師への調査票 ①アウトカム定義群 からサンプリング (245例) ②医師に調査票を 送付して真偽判定 (161例の回答) ③PPV算出	データリンク (Written recordsと) ①アウトカム定義群 からサンプリング (339例) ②Written recordsの 取得(215例) ③Computerized recordsとの比較で 真偽判定 ④PPV算出(76/86)	データリンク (コホート研究と) ①アウトカム定義群 をCopenhagen City Heart Study とクロスリンクし、 詳細な情報を入手 (236例) ②2人の評価者による 真偽判定 ③PPV算出(32/33)	データリンク (入院情報と) ①アウトカム定義群 を抽出(144例) ②リンクした入院情報 で真偽判定 ③リンク無し症例 (は医療記録を マニュアルレビュー ④PPV算出	カルテレビュー (13のSDD Partner) ①アウトカム定義群 からサンプリング (126例) ②数名の医師による 真偽判定 ③病名ポジション別 (principal/secondary) にPPV算出	2015年10月の ICD9からICD10 への移行を機に そのマッピング方法 および移行状況を 解析 (胎産中の発生率 推移を解析した所 移行前後での差異 はなかった)
結果	PPV	84.3% (Algorithm B)	85.7%	89%	>97%	75.7%	60% (Principal position)	-
	感度	88.9% (Algorithm B)	-	-	-	-	-	-

米国（事例まとめ）

Sentinel以外のDBのバリデーション研究のLiterature Reviewsの結果が掲載されている。
定期的な更新は実施されていない模様。

The screenshot shows the Sentinel HP website interface. The top navigation bar includes links for About, Studies, Methods, Data, & Tools, News & Events, Featured, and Engage with Sentinel, along with a search bar. The left sidebar contains a menu with items like Methods, Sentinel Common Data Model, Signal Identification in the Sentinel System, Routine Querying Tools, Software Packages & Toolkits, Health Outcomes of Interest (circled in orange), FDA-Catalyst Projects, and Sentinel as a National Resource. The main content area is titled 'Health Outcomes of Interest' and features a sub-heading 'Health Outcome Algorithm Inventory' (circled in orange). Below this, there are tabs for 'Details' and 'Contributors'. The 'Details' tab is active, showing a 'Date Posted' of Monday, May 23, 2016, a 'Status' of COMPLETE, and a list of 'Health Outcome(s)'. The list includes various medical conditions such as Achilles tendon rupture (ATR), Bell's palsy, Guillain-Barré syndrome, Hemoch Schönlein purpura (HSP), acute intracranial hemorrhage, acute ischemic stroke, acute pancreatitis, acute respiratory failure, acute stroke (ischemic or hemorrhagic), agranulocytosis, aplastic anemia, asthma exacerbation, attempted suicide, erythema multiforme major, febrile seizure, gastrointestinal (GI) bleed, hip fracture, hypertensive emergency, idiopathic thrombocytopenic purpura, inflammatory bowel disease (IBD), juvenile rheumatoid arthritis, neutropenia, peripheral neuropathy, premature delivery, pulmonary fibrosis, pulmonary hypertension, rhabdomyolysis, sepsis, severe acute liver injury (SALI), spontaneous abortion (SAB), stillbirth, sudden cardiac death, sudden or rapidly-progressing hearing loss, suicide, systemic lupus erythematosus (SLE), thrombocytopenia, thrombotic thrombocytopenic purpura, toxic epidermal necrolysis, tuberculosis (TB), type 1 diabetes mellitus, and venous thromboembolism (VTE). The 'Study Type' is listed as Literature Reviews.

米国（事例まとめ）

エクセル形式で、アウトカム別に該当研究の要約が一覧化されている。
 要約項目は「Study characteristics」「Algorithm performance」から構成されている。

Algorithm performance													Study characteristics		
PUBMED	Article Experi	1st Author/ Exp name	Year	HOI	Algorithm	N	PPV	SE	NPI	SPE	Other Findi	Count	Data date	Data Source	Expert opi
22262598; 12105309	Article	Andrade SE; Williams LS	2012 (Andrade systematic review); 2002 (Williams)	Acute Ischemic Stroke	ICD-9 code 434.X or 436.X in principal position on an inpatient claim	N=671 (Williams)	Several studies of acute stroke events presented PPV for individual codes with PPV>85% for first position 434 and >80% for first position 436. PPV 98% in Williams et al)	UNK	UNK	UNK		US (Williams)	July 1993 - June 1999 (Williams)	4 studies specific to ischemic stroke, one VA, One Canadian, One Seattle hospitals, Regenstrief. One study used the exact algorithm. This was the largest of the 4 studies (Williams et al, n=671) used 434 and 436 first position with very high PPV but unclear outcome confirmation criteria. From Williams et al - "Data were obtained from the Regenstrief Medical Record System (RMRS), an electronic medical record system that captures patient level laboratory, clinical, and utilization data for inpatient and outpatient encounters at Wishard Hospital, an inner-city public teaching hospital in Indianapolis, IN. 14 Patients admitted to the hospital with acute ischemic stroke between July 1, 1993 and June 30, 1998 were identified using primary position discharge ICD-9 codes 434 and 436. 15 stroke diagnosis was confirmed by chart review in all patients, and follow-up data were collected through June 30,	
22262598; 12364739	Article	Andrade SE; Tirschwell DL	2012 (Andrade systematic review); 2002 (Tirschwell)	Acute Ischemic Stroke	ICD-9 code 433.X1, 434.X1, or 436 in principal position on an inpatient claim	N=206 (Tirschwell)	88-90% or greater	UNK	UNK	UNK		US (Tirschwell)	1990-1996 (Tirschwell)	Tirschwell et al examined the exact algorithm with PPV 88-90% in Seattle, WA hospitals	
9707200	Article	Goldstein LB	1998	Acute Ischemic Stroke	ICD-9 diagnosis code 433.X or 434.X or 436 in principal position	N=175	61%	UNK	UNK	UNK		US	May 1995 - June 1997	Durham VA acute ischemic stroke identified in principal position on hospital discharge abstract	
NA	Protocol	Chrischilles EA	2015	Acute Ischemic Stroke	Any of the following ICD-9 diagnosis codes: 433.X1, 434.X, or 436 in any position on an inpatient encounter	NA	UNK	UNK	UNK	UNK		US		Mini-Sentinel	
NA	Protocol	Carnahan RM	2015	Acute Ischemic Stroke	Any of the following ICD-9 diagnosis codes: 433.X1, 434.X1, or 436 in a principal or unspecified position on an inpatient encounter	NA	UNK	UNK	UNK	UNK		US		Mini-Sentinel	
NA	Protocol	Go AS	2015	Acute Ischemic Stroke	Any of the following ICD-9 codes: 433.X1, 434.X1, 436 in a principal position on an inpatient encounter	NA	UNK	UNK	UNK	UNK		US		Mini-Sentinel	

米国（個別事例）

「Search Health Outcomes of Interest」で該当PASS/バリデーション研究のフィルタリングが可能。

Search Health Outcomes of Interest

validation stroke

Filter by

Displaying 1 to 1 of 1 results Sort by: Date Display: 25 Export as

Title	Outcomes	Date
Thromboembolic Events After Immunoglobulin Administration Validations Supported by Traditional Medical Chart Review	acute myocardial infarction (AMI) ischemic stroke thromboembolic events (TEE) ...	07/13/2017

次頁

米国（個別事例）

検索先の「Additional Information」タブ内にバリデーション研究へのリンクが格納されている。

Thromboembolic Events After Immunoglobulin Administration

Details	Additional Information	Contributors
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FDA Center: CBER
Time Period: 2006 - 2012
Study Type: Protocol/Surveillance Plan
Assessment Type: Safety Analyses
HOI Study Type: Validations Supported by Traditional Medical Chart Review
Population / Cohort: All individuals who are immunoglobulin users
Data Sources: Sentinel Distributed Database (SDD)

Related Links:

- [Chart Validation of Inpatient ICD-9-CM Administrative Diagnosis Codes for Ischemic Stroke Among IGIV Users in the Sentinel Distributed Database](#)
- [Chart Validation of Inpatient ICD-9-CM Administrative Diagnosis Codes for Acute Myocardial Infarction \(AMI\) Among Intravenous Immune Globulin \(IGIV\) Users in the Sentinel Distributed Database](#)
- [Chart Validation of Inpatient ICD-9-CM Administrative Diagnosis Codes for Venous Thromboembolism among Intravenous Immune Globulin Users in the Sentinel Distributed Database](#)

欧州（個別事例）

「Search Study」で該当PASS/バリデーション研究の検索が可能。

ENePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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Standards & Guidances
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Public Consultation
Glossary of terms

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EU PAS Register

About EU PAS Register

Search Studies

The search criteria are non-mandatory. Therefore, not specifying any search criteria will return all database entries.

EU PAS Register Number: EUPAS

Status of Study: Planned
 Ongoing
 Finalised

Title of Study:

Acronym:

Study type: Active surveillance
 Observational study
 Clinical trial
 Other

Lead investigator: Last Name
First Name

Study requested by a regulator:

Risk Management Plan:

Other registration numbers:

Coordinating Study entity: All
 AEMPS
 AIBILI
 AMSP
 ANFOMED GmbH
 ARS
 ASSR Emilia-Romagna
 AII-ADA
 Other

Research Network: All
 ACRPV
 AMSP
 BIOBADASER
 BIOREG
 CARING
 COVIDRIVE



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Home Sitemap Q & A Notice Board Links Contact Us

Home > Search results

News
About Us
ENCePP Documents
Training in PhEpi and PV

Code of Conduct
Standards & Guidances
ENCePP Study Seal
Public Consultation
Glossary of terms

Resources Database

Partners forum

EU PAS Register

About EU PAS Register

16 Studies found

Status	EU PAS Register number	Official Title	Last Updated
Finalised	EUPAS21574	Cohort study of cardiovascular events in patients with chronic obstructive pulmonary disease initiating olodaterol or other long-acting beta2-agonists	19/09/2022
Finalised	EUPAS8205	Risk of subsequent cardiovascular events in patients discharged after myocardial infarction - Perseus	17/05/2022
Finalised	EUPAS20546	Cohort Study of the Incidence of Major Cardiovascular Events in New Adult Users of Mirtazapine and Remote Adult Users of Other ADHD Treatments	23/09/2021
Finalised	EUPAS9200	Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort	06/0
Finalised	EUPAS16302	A retrospective analysis of pre-existing and acquired major adverse cardiovascular events (MACE) in a real world cohort of multiple myeloma (MM) patients treated with proteasome inhibitors (20160154)	02/06/2020
Finalised	EUPAS16282	Post-authorization Safety Study Evaluation of Cardiovascular Events in Users of Mirabegron and Other Treatments for Overactive Bladder	28/04/2020
Finalised	EUPAS7545	The risk of ischemic cardiovascular events associated with oxycodone/naloxone use	21/03/2019
Finalised	EUPAS4700	Risk of stroke and other cardiovascular events among warfarin-treated atrial fibrillation patients - a nationwide cohort study in Finland	25/04/2017
Ongoing	EUPAS36734	VALIDATION STUDY PROTOCOL (OP0007) FOR THE EUROPEAN NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY RELATED TO SERIOUS CARDIOVASCULAR EVENTS OF MYOCARDIAL INFARCTION AND STROKE AND ALL-CAUSE MORTALITY FOR ROMOSUZUMAB BY THE EU-ADR ALLIANCE (OP0004) AND EUROPEAN NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY RELATED TO SERIOUS INFECTIONS FOR ROMOSUZUMAB BY THE EU-ADR ALLIANCE (OP0006)	29/10/2020
Ongoing	EUPAS35881	European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke, and all-cause mortality for romosozumab by the EU-ADR Alliance	29/10/2020

次頁

Source :EU PAS Register ([Search Studies \(encepp.eu\)](https://encepp.eu))

欧州（個別事例）

検索先の「Document」タブ内にバリデーション研究へのリンクが格納されている。

The screenshot shows the ENCePP website interface. The top navigation bar includes 'Home', 'Sitemap', 'Q & A', 'Notice Board', 'Links', and 'Contact Us'. The main content area has a breadcrumb 'Home > View Study' and a set of tabs: 'Administrative Details', 'Targets of the Study', 'Methodological Aspects', and 'Documents' (which is selected). The 'Documents' tab shows a list of documents, including 'SPD555-802 protocol_final 30May2014_to Shire .pdf' and 'Study SPD555-802 Final Report Addendum 2.0_24Jan2019_abstract.pdf'. Below this, there is a section for 'Reference' with a table of publications. A red dashed circle highlights the following reference entry:

Reference	Link to web-publication
Gilsenan A, Fortuny J, Cainzos-Achirica M, Cantero AF, Flynn RWV, Garcia-Rodriguez L, et al. Cardiovascular safety of prucalopride in patients with chronic constipation: a multinational population-based cohort study. <i>Drug Saf.</i> 2019. https://doi.org/10.1007/s40264-019-00835-0 .	https://link.springer.com/article/10.1007%2Fs40264-019-00835-0
Fortuny J, Gilsenan A, Cainzos-Achirica M, Cantero AF, Flynn RWV, Garcia-Rodriguez L, et al. Study design and cohort comparability in a study of major cardiovascular events in new users of prucalopride versus polyethylene glycol 3350. <i>Drug Saf.</i> 2019. https://doi.org/10.1007/s40264-019-00836-z .	https://link.springer.com/article/10.1007%2Fs40264-019-00836-z
Ruigómez Á, Plana E, Gilsenan A, et al. Identification and Validation of Major Cardiovascular Events in the United Kingdom Data Sources Included in a Multi-database Post-authorization Safety Study of Prucalopride. <i>Drug Saf.</i> 2021;44(5):541-551. doi:10.1007/s40264-021-01044-4	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8653159/pdf/40264_20

Source :EU PAS Register ([Search Studies \(encepp.eu\)](https://encepp.eu))