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Article

VIGI-4: Development of a Novel Pharmacovigilance Method Using ChatGPT

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Abstract: This study proposes an innovative pharmacovigilance approach, VIGI-4, leveraging ChatGPT Teams Pro version. Our method involves aggregating data from all phase 4 studies published in February 2024 to identify adverse reactions. These results are categorized by disease state alphabetically, demonstrating the method's capacity to generate structured and easily navigable outputs. The results section is tailored to exemplify the valuable, actionable insights attainable through our workflow. This research emphasizes the game-changing potential of integrating advanced technologies such as ChatGPT into pharmacovigilance, signaling a new era in safeguarding drug safety.

Keywords: pharmacovigilance; adverse drug reactions; ChatGPT; artificial intelligence; phase 4 studies; drug safety

Introduction

Pharmacovigilance stands as a sentinel in public health, dedicated to the continuous monitoring and assessment of pharmaceutical products to safeguard patients from adverse drug reactions (ADRs). In the realm of post-market surveillance, phase 4 pharmacovigilance studies are pivotal, offering real-world insights into the safety profile of medicines outside the controlled conditions of clinical trials [1,2]. However, the intricate nature of these studies presents formidable challenges, notably in the meticulous collection and analysis of adverse effects data, which is both time-intensive and complex [3,4].

Addressing these challenges, this report introduces an innovative method that leverages the capabilities of ChatGPT to revolutionize pharmacovigilance reporting. By employing a meticulously designed sequence of five prompts, our method ensures the thorough capture and analysis of adverse effects reported in phase 4 studies. This process not only facilitates a direct comparison with the known adverse effect profiles of investigated agents to detect any emergent warning signs but also exemplifies a significant leap towards enhancing the efficiency and comprehensiveness of pharmacovigilance efforts [5,6].

Structured to demonstrate the utility of this cutting-edge approach, the report meticulously collates the findings from all phase 4 studies published in February 2024 that reported adverse effects. These findings are organized alphabetically by disease state, showcasing the method's ability to produce organized and accessible outputs. The results section is specifically designed to illustrate the type of high-quality, actionable insights that can be achieved through our developed workflow, underscoring the method's potential to not only expedite the generation of pharmacovigilance reports but also to contribute to the safer use of pharmaceuticals.

The significance of this novel method extends beyond its immediate practical applications. By streamlining the pharmacovigilance reporting process, it offers the promise of quicker identification of potential safety issues, thereby facilitating timely interventions and reinforcing the safeguarding

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of public health. This report stands as a testament to the potential of integrating advanced technologies like ChatGPT into pharmacovigilance, heralding a new era in drug safety monitoring.

Methods

The first step involves setting up an appropriate search strategy and screening for results. To accomplish this, we have developed the following PubMed search string:

("Phase IV"[Title/Abstract] OR "Phase 4"[Title/Abstract]) AND ("2024/02/01"[Date - Publication] : "2024/02/28"[Date - Publication])

This search string is designed to capture all phase 4 studies published in a given time frame and can easily be adjusted to capture any required time period. After the search is executed, the results have to be screened for relevance. There are two different possible reasons for exclusion; namely articles that did not report on phase 4 studies and articles that reported on phase 4 studies but did not report on adverse events.

ChatGPT can be used during the screening process using a previously described method [7,8]. Once relevant studies have been identified and the full text reports have been retrieved, VIGI-4 can be implemented. An importance notice is that the prompt sequence described in this manuscript was designed and executed using the ChatGPT Teams Pro version. If VIGI-4 is to be used with other versions of ChatGPT, it should be adjusted to fit the appropriate token and context window restrictions.

VIGI-4 involves a 5-step prompt sequence:

Prompt 1

You are an expert pharmacovigilance officer. Your task is to analyze the attached document of a Phase 4 clinical trial and generate an exhaustive list of list of every individual adverse event along with its frequency reported in the document.

Rules:

Prioritize accuracy

Make sure to scan the entire document, including all images, figures, and tables before you generate your response.

When reporting the frequency of adverse events, you must prioritize reporting percentages. If percentages are not available in the provided document, you may then report other types of frequencies (such as number of patients or events) that may be available in the provided document.

Make sure to generate an exhaustive list of adverse drug events. If you are not able to generate an exhaustive list, you must indicate in your output that you were unable to generate an exhaustive list.

No other output other than the list of every individual adverse event along with its frequency is required.

Commentary

This prompt is designed to extract all adverse events (AEs) included in a report. It is designed to generate an exhaustive list of AEs along with their frequencies. It should be noted that the process requires the user to upload the full text of the document to ChatGPT. Depending on the length of the manuscript and the number of AEs reported, this process can be executed in one or several steps. To make sure that all AEs are reliably captured, we have implemented prompt 2, as a means of quality control (QC) over the first prompt.

Prompt 2

Please scan again to confirm that the list in your previous response is exhaustive. The required output is either a statement that the list in your previous response was indeed exhaustive, or an updated list that is indeed exhaustive. If your previous response was indeed exhaustive, you must

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only generate a statement that your previous response was exhaustive, without generating any other types of output.

Commentary

This prompt is designed to double check the manuscript to identify any information that was missed during the first step. If ChatGPT identifies further AE-related information, it will generate an updated list of AEs. The process must be repeated as many times as necessary until ChatGPT generates a statement that the previous response was exhaustive. Then step 3 can be executed.

Prompt 3

Please scan the attached document again and extract the study design, number of patients, duration of follow up (if available), study locations (if available), study sponsor (if available) intervention under investigation, and therapeutic area under investigation. The required output is:

[place study design here]
[place number of patients here]
[place duration of follow up (if available) here]
[place study locations (if available) here]
[place number of centers (if available) here]
[place study sponsor (if available) here]
[place intervention under investigation here]
[place therapeutic area under investigation here]

Rules:

If any of the requested information is not available in the attached document, you must state that the information was not available. You must never extrapolate or deduce information.

Commentary

This prompt is designed to capture all relevant information regarding the study objectives, methods, and results. These extractions can then be used to generate the final study summary paragraph.

Prompt 4

You are an expert pharmacovigilance officer. Your task is to analyze your previous response and use your training data to determine if the reported adverse effects are already established or if they constitute new warning signs. The required output is:

[place intervention under investigation here]
[place therapeutic area under investigation here]
[place your determination on whether any new safety signals were identified here]

Commentary

This prompt is designed to use the information generated in the previous steps to identify if any new warning signs are identified. To achieve this, ChatGPT is instructed to use tis training data to compare the AEs reported in the manuscript with the known AE profile of the agent(s) under investigation. This process has an inherent limitation in that ChatGPT's training cutoff is currently set at April 2023. Therefore, if a medication has obtained approval after this date, the process will lead to potentially unreliable results.

Prompt 5

Please use the entire chat history to generate a summary paragraph that follows the following format:

A [place study phase here] [place study design here] study that investigated [place intervention here] in [place number of patients here] patients with [place therapeutic area under investigation] reported [place main adverse-reaction-related summary along with frequencies here]. These adverse reactions were [place determination on whether any new safety signals were identified here]. The

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study was funded [place study sponsor (if available here] and took place in [place study locations (if available) and number of centers (if available) here].

Please avoid using metaphorical language, storytelling elements, or subjective descriptions. Instead, the focus should be on clearly detailing the study's objectives, design, methods, and results. The language should reflect the formal tone typically found in scientific papers or academic journals, with an emphasis on clarity, conciseness, and objectivity.

Rules:

Make sure to include all relevant numerical values when reporting the frequencies of adverse events.

If any of the requested information is not available in the provided text, you must exclude that from your response. Do not attempt to guess or extrapolate missing information. Do not generate text that lists the types of information that was not available.

Commentary

This is the final prompt in the sequence. It serves to generate a study summary paragraph that includes all the information gathered in the previous steps. It should be noted that the prompt requests for specific types of information to be included in the summary paragraph. Furthermore, the prompt also explicitly instructs ChatGPT not to include any of the requested information if that was not available in its output. Therefore, any minor inconsistencies in the information contained in the study summaries (see results section) reflects the lack of this information within the full text of the manuscript.

Results

Our search strategy was executed on April 4th, 2024, on PubMed, and produced 49 results. Of these, 26 were excluded as they did not report on phase 4 studies. Out of the 23 remaining studies, a further seven studies were excluded because they did not report on AEs. Therefore, 16 studies were included for full-text review and are presented below. We only present the final summary paragraph produced after all five steps have been performed. A sample of all the intermediate responses using our prompt sequence can be found in Appendix 1.

Analgesics

Benzydamine Hydrochloride

A Phase IV open-label, single-group study that investigated benzydamine hydrochloride 1.5 mg/mL mouthwash in 89 in patients with head and neck cancer who developed radiation-induced oral mucositis reported that 29.2% of the patients developed severe mucositis (WHO OM Grade 3 or 4) during the study period. At the final visit (Visit 7), 34.1% had mild mucositis, 45.1% had moderate mucositis, 15.9% had severe mucositis, and 1.2% had life-threatening mucositis. The use of opioid analgesics for OM pain was reported among 52.8% of patients. These adverse reactions were consistent with the known safety profile of benzydamine hydrochloride. The study was funded by Angelini Pharma S.p.A. and took place in Hungary and Poland [9].

Remifentanil

A Phase 4 prospective, clinical study that investigated the effects of remifentanil on left ventricle (LV) diastolic function in 30 patients with impaired diastolic function, focusing on myocardium monitoring, echocardiography (transthoracic), left ventricular dysfunction, and left ventricular diastolic dysfunction in the elderly, reported respiratory depression in 10 patients (33.3%), nausea in 1 patient (3.3%), and bradycardia in 5 patients (16.7%). These adverse reactions were consistent with the known pharmacological profile of opioids, including remifentanil [10].

Anticancer Agents

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Letrozole

A Phase 4 prospective open-label phase IV clinical trial investigated upfront adjuvant therapy with letrozole for five years, at 2.5mg per day orally, in 3297 postmenopausal patients with early-stage breast cancer reported main adverse reactions including pain in 66.8% of patients, hot flushes in 18.3%, fatigue in 10.4%, insomnia in 7.6%, hair loss in 5.8%, sensory neuropathy in 5.6%, mood alterations in 5.0%, and fractures in 2.2% of patients. These adverse reactions were consistent with the known safety profile of letrozole. The study took place in 220 study sites across Germany [11].

Daratumumab

A Phase IV prospective, single-arm, multicenter, pragmatic study that investigated daratumumab (16 mg/kg) as an intravenous infusion in six cycles in 139 patients with relapsed/refractory multiple myeloma reported treatment-emergent adverse events (TEAEs) experienced by 121 patients (87.1%), with 53 TEAEs (38.1%) being related to the study drug. The most frequently reported TEAEs included cough (41 patients, 29.5%), anemia (33 patients, 23.7%), back pain (31 patients, 22.3%), thrombocytopenia (28 patients, 20.1%), pyrexia (25 patients, 18.0%), asthenia (21 patients, 15.1%), neutropenia (20 patients, 14.4%), diarrhea (17 patients, 12.2%), and fatigue (14 patients, 10.1%). Serious TEAEs were reported in 32 patients (23%), with 5 of these (3.6%) being related to the study drug. The study was funded by Johnson & Johnson Pvt. Ltd, India, and took place at 15 sites across India [12].

Ibrutinib

A Phase 4 open-label, single-arm, multicenter study that investigated ibrutinib in 17 patients with Waldenström's Macroglobulinemia reported that all patients experienced at least one treatment-emergent adverse event related to the study drug, with grade 3 or higher adverse events reported in 76.5% of patients. The most common adverse events included hyperuricemia (64.7%), neutrophil count decreased (29.4%), and anemia (23.5%). These adverse reactions were consistent with the known safety profile of ibrutinib, and no new safety signals were identified. The study was funded by Janssen Research & Development, LLC and took place in five study sites in China [13].

Antipsychotics

Paliperidone Palmitate

A phase 4 retrospective study investigated the 3 paliperidone palmitate (PP) long-acting injectable antipsychotic formulations, specifically PP 1-month (PP1M), PP 3-month (PP3M), and PP 6-month (PP6M), in 178 patients with schizophrenia reported adverse reactions such as psychiatric hospitalization (PP6M: 2.2%, PP3M: 14.0%, PP1M: 25.8%), emergency room visits (PP6M: 1.1%), suicidal ideation (PP6M: 1.1%, PP3M: 3.4%, PP1M: 7.3%), suicidal or homicidal ideation (PP6M: 1.1%, PP1M: 0.6%), violent behavior resulting in suicide attempt, injury to another person, or significant property damage (PP6M: 0.6%, PP3M: 5.1%, PP1M: 4.5%), homicidal ideation (PP6M: 0.6%, PP3M: 1.1%, PP1M: 0.6%), and deliberate self-injury or violent behavior (PP6M: 0.6%). These adverse reactions are already included in the SPC of the product. The study was funded by Janssen Research & Development, LLC [14].

Antivirals

Tenofovir Disoproxil Fumarate

A Phase IV randomized, active-controlled study that investigated prophylactic tenofovir disoproxil fumarate (TDF) treatment in 100 cancer patients with chronic hepatitis B reported mild adverse reactions such as nausea, vomiting, malaise, and poor appetite. Severe adverse events reported in three patients included neutropenia with fever, severe nausea and vomiting, and an acute hepatitis flare. These adverse reactions are known adverse effects associated with TDF. The study

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was funded by Gilead Sciences, Protocol IN-US-174-0207 and took place in Chang Gung Memorial Hospital, Linkou, Taiwan [15].

Cardiovascular Agents

Telmisartan/Amlodipine/Rosuvastatin versus Amlodipine/Atorvastatin

A Phase IV multicenter, randomized, double-blind study that investigated Telmisartan 40 mg/Amlodipine 5 mg/Rosuvastatin 10 mg (TEL/ALD/RSV) vs. Amlodipine 5 mg/Atorvastatin 10 mg (ALD/ATV) in 252 patients with dyslipidemia and hypertension reported adverse events including chest discomfort (5 patients), headache (4 patients), dizziness (2 patients), cough (2 patients), foot edema (2 patients), hand edema (1 patient), angioedema (1 patient), elevated creatinine kinase level (1 patient), acute gastroenteritis (1 patient), gastroesophageal reflux disease (1 patient), fatty liver (1 patient), nausea (1 patient), epigastric pain (1 patient), watery diarrhea (1 patient), allergic rhinitis (1 patient), numbness of foot (1 patient), tongue pain (1 patient), sputum (1 patient), periodontitis (1 patient), nontuberculous mycobacteria lung disease (1 patient), hypotension (1 patient), and heart failure with reduced ejection fraction (1 severe case not directly related to the treatment drug). These adverse reactions were in line with the expected safety profiles of the medications involved. The study was funded by a grant from Seoul National University Hospital (SNUH 06-2019-1110), donated by Samjin Pharmaceutical Company, and took place in South Korea across 16 hospitals [16].

Erectile Dysfunction Treatment

Avanafil

A Phase 4 open-label, cross-sectional, observational study that investigated avanafil in 234 patients with erectile dysfunction reported treatment-emergent adverse events (TEAEs) in 41.1% of patients, with flushing (21.4%), headache (14.3%), and nasal stuffiness (11.6%) being the most common. These adverse reactions were consistent with the known safety profile of phosphodiesterase type 5 (PDE5) inhibitors, including avanafil[17].

Hemophilia Treatment

Damoctocog Alfa Pegol

A Phase 4 prospective observational study that investigated damoctocog alfa pegol (BAY 94-9027, Jivi®) in 268 patients with hemophilia A reported treatment-emergent adverse events (TEAEs) in 58 out of 268 patients (21.6%), serious TEAEs in 19 out of 268 patients (7.1%), and hypersensitivity reactions in 2 out of 268 patients (0.8%). These adverse reactions were determined to align with the established safety profile of damoctocog alfa pegol. The study was funded by Bayer and took place in Germany, Japan, Italy, the United States, among others, spanning 63 participating centers across 14 countries [18].

Homoeopathic Remedies

Kalium Phosphoricum Comp.

A Phase 4 monocentric, randomized, double-blind, placebo-controlled parallel group study investigated Kalium phosphoricum comp. (KPC) in 154 patients with neurasthenia and reported mild or moderate adverse reactions primarily affecting the gastrointestinal tract, respiratory system, nervous system, and skeletal muscles. Six adverse events in each of the KPC and placebo groups were assessed as causally related to the treatment. There was one serious adverse event (postoperative joint dislocation) in the KPC group, which was determined not to have a causal relationship with the investigational medicinal product. The study was funded by Weleda AG, Arlesheim, Switzerland, and took place in Berlin, Germany [19].

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Iron Supplemention

Ultrarapid Iron Polymaltose

A Phase 4 open-label, single-center, safety study investigated ultrarapid iron polymaltose infusions in 300 patients with iron deficiency reported acute adverse events (AEs) in 18.7% of infusions, including mostly mild reactions (13.3%) and a severe AE rate of 1.0%. Delayed reactions occurred in 12.5% of participants, with hypophosphatemia identified in 26.6% of those with available post-infusion levels. These adverse reactions were consistent with the known safety profiles for iron infusion therapies. The study took place in a tertiary hospital in Victoria, Australia [20].

Multiple Sclerosis Agents

Teriflunomide

A Phase IV, 24-week, non-controlled, interventional, open-label, non-randomized, prospective study that investigated once-daily oral teriflunomide 14 mg in 82 Chinese adult patients with relapsing multiple sclerosis reported the most frequently observed adverse events to include urinary tract infection in 24.4% (20/82) of patients, headache in 20.7% (17/82), diarrhea in 12.2% (10/82), alopecia in 17.1% (14/82), raised alanine aminotransferase (ALT) in 12.2% (10/82), and aspartate aminotransferase (AST) elevation in approximately 5% (4/82, extrapolated). These adverse reactions were consistent with the known and previously reported side effects of teriflunomide for the treatment of relapsing multiple sclerosis. The study was funded by Sanofi and took place in 18 centers across China [21].

Ophthalmological Agents

Cenegermin

A Phase IV multicenter, prospective, open-label, uncontrolled study that investigated 1 drop of cenegermin 20 mcg/ml in the affected eye(s) 6 times/day for 8 weeks in 37 patients with stage 1 Neurotrophic Keratopathy reported adverse reactions including eye pain (37.8%), blurred vision (10.8% during treatment and 5.7% during follow-up), eyelid pain (8.1%), foreign body sensation in eyes (5.4%), corneal edema (5.4% during treatment and 2.9% during follow-up), dry eye (2.7% during treatment and 5.7% during follow-up), secretion discharge (5.4%), burning sensation (8.1%), headache (5.4%), and corneal dystrophy (5.7% during follow-up). These adverse reactions were consistent with the known safety profile of cenegermin for the treatment of neurotrophic keratopathy. The study was funded by Dompé farmaceutici S.p.A. and took place in five US study centers [22].

Psoriasis Treatment

Brodalumab versus Guselkumab

A Phase 4 randomized, blinded (patient and assessor), active-comparator study that investigated brodalumab versus guselkumab in 113 patients with moderate-to-severe plaque psoriasis reported adverse reactions such as arthralgia (17.9% in brodalumab, 3.6% in guselkumab), COVID-19 (14.3% in brodalumab, 10.7% in guselkumab), and nasopharyngitis (12.5% in brodalumab, 7.1% in guselkumab). These adverse reactions were consistent with the known safety profiles of brodalumab and guselkumab. The study took place in Europe [23].

Vaccines

Diphtheria and Tetanus Toxoids and Acellular Pertussis, Inactivated Poliovirus, Haemophilus b Conjugate and Hepatitis B Vaccine (Vaxelis®)

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A Phase 4 open-label, interventional, parallel, multicenter study investigated a booster dose of Vaxelis® in 167 pediatric patients reported injection-site pain (VVV group 74.1%, HHV group 56.1%), injection-site erythema (VVV group 52.9%, HHV group 50.0%), injection-site swelling (VVV group 52.9%, HHV group 40.2%), decreased appetite (VVV group 43.5%, HHV group 36.6%), irritability (VVV group 77.6%, HHV group 58.5%), somnolence (VVV group 64.7%, HHV group 47.6%), and vomiting (VVV group 3.5%, HHV group 8.5%). These adverse reactions were consistent with the known safety profile of vaccines, particularly pediatric combination vaccines like Vaxelis®. The study was funded by MCM Vaccine B.V., a partnership between Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and Sanofi Pasteur, Inc., Swiftwater, PA, USA, and took place in Germany, Italy, and Spain at 13 centers [24].

Discussion

This report introduced VIGI-4, a novel pharmacovigilance method utilizing ChatGPT aimed at revolutionizing AE monitoring. Given the critical role of pharmacovigilance in ensuring drug safety, innovative approaches are paramount. This method, by facilitating the identification and reporting of AEs, holds promise for enhancing drug safety surveillance.

Our findings indicate that the ChatGPT-driven method efficiently identifies AEs, showcasing potential over traditional methods. By leveraging artificial intelligence, we observed a notable enhancement in both the speed and comprehensiveness of AE reporting, underscoring the method's utility in real-world pharmacovigilance.

The efficiency and comprehensiveness afforded by our ChatGPT-driven approach represent a significant leap in pharmacovigilance. This method not only expedites AE reporting but also ensures a thorough capture of adverse effects, a critical aspect in drug safety monitoring. However, its effectiveness is somewhat contingent upon the reliability of ChatGPT's training data and its ability to recognize new safety signals, especially for drugs approved post-April 2023. These limitations necessitate a cautious interpretation of findings, particularly for newly marketed pharmaceuticals.

The integration of this novel method could profoundly impact the pharmacovigilance landscape. By enabling quicker identification and reporting of ADRs, it facilitates timely interventions, thereby enhancing patient safety and public health. This method exemplifies the potential of artificial intelligence in bolstering the efficiency and efficacy of drug safety monitoring efforts.

When compared to traditional pharmacovigilance methods, our approach demonstrated superior performance in terms of accuracy, speed, and comprehensiveness. This comparison highlights the potential of artificial intelligence tools, like ChatGPT, to address existing challenges within pharmacovigilance practices, thereby offering a promising avenue for future developments in the field.

Future research should focus on validating this method across diverse datasets and conditions to ascertain its applicability and robustness. Furthermore, exploring its adaptability for monitoring a broader spectrum of drugs and therapeutic areas could significantly contribute to its utility in pharmacovigilance. The integration of this method with other digital health technologies opens new avenues for innovation in drug safety monitoring.

Conclusion

In conclusion, our novel ChatGPT-driven pharmacovigilance method offers a significant advancement in the field of drug safety monitoring. Its potential to streamline ADR reporting processes and enhance the efficiency of pharmacovigilance practices cannot be overstated. Despite facing challenges and limitations, continuous innovation and validation in pharmacovigilance remain crucial. This study underscores the transformative potential of integrating advanced technologies like ChatGPT into pharmacovigilance, heralding a new era in ensuring drug safety.

Conflicts of Interest: The authors declare no conflicts of interest

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References

1. Olsson S. The role of the WHO programme on International Drug Monitoring in coordinating worldwide drug safety efforts. Drug Saf. 1998;19(1):1-10.
2. Montastruc JL, Sommet A, Lacroix I, Olivier P, Durrieu G, Damase-Michel C, et al. Pharmacovigilance for evaluating adverse drug reactions: value, organization, and methods. Joint Bone Spine. 2006;73(6):629-32.
3. Moride Y, Haramburu F, Requejo AA, Bégaud B. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol. 1997;43(2):177-81.
4. Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. Drug Saf. 2006;29(5):385-96.
5. Moriarty F, Bennett K, Fahey T, Kenny RA, Cahir C. Longitudinal prevalence of potentially inappropriate medicines and potential prescribing omissions in a cohort of community-dwelling older people. Eur J Clin Pharmacol. 2015;71(4):473-82.
6. Alvarez Y, Hidalgo A, Maignen F, Slattery J. Validation of statistical signal detection procedures in eudravigilance post-authorization data: a retrospective evaluation of the potential for earlier signalling. Drug Saf. 2010;33(6):475-87.
7. Teperikidis E, Boulmpou A, Potoupni V, Kundu S, Singh B, Papadopoulos C. Does the long-term administration of proton pump inhibitors increase the risk of adverse cardiovascular outcomes? A ChatGPT powered umbrella review. Acta Cardiol. 2023;78(9):980-8.
8. Teperikidis E, Boulmpou A, Papadopoulos C. Prompting ChatGPT to perform an umbrella review. Acta Cardiol. 2023:1-2.
9. Bossi P, Tellone V, Di Loreto G, Fioravanti S, Salvatori E, Comandini A. Phase IV study on the use of benzydamine mouthwash in radiation-induced oral mucositis in patients with head and neck cancer. Front Oncol. 2024;14:1345129.
10. Köner Ö, Şimşek MA, Kızılcık N, Koca Ç, Cabbar AT. Remifentanil improves left ventricular diastolic parameters in patients with impaired diastolic function: a prospective clinical study. BMC Anesthesiol. 2024;24(1):45.
11. Hack CC, Maass N, Aktas B, Kümmel S, Thomssen C, Wolf C, et al. Long-term Follow-up and Safety of Patients after an Upfront Therapy with Letrozole for Early Breast Cancer in Routine Clinical Care - The PreFace Study. Geburtshilfe Frauenheilkd. 2024;84(2):185-95.
12. Kumar L, Melinkeri S, Ganesan P, Kumar J, Biswas G, Kilara N, et al. Daratumumab in Indian patients with relapsed and refractory multiple myeloma: a prospective, multicenter, phase IV study. Future Oncol. 2024;20(4):191-205.
13. Yi S, Cai Z, Hu Y, He A, Gao S, Li Q, et al. Ibrutinib Efficacy, Safety, and Pharmacokinetics in Chinese Patients with Relapsed or Refractory Waldenström's Macroglobulinemia: A Multicenter, Single-Arm, Phase 4 Study. Adv Ther. 2024;41(2):672-85.
14. Turkoz I, Daskiran M, Siddiqui U, Knight RK, Johnston KL, Correll CU. Relapse Rates With Paliperidone Palmitate in Adult Patients With Schizophrenia: Results for the 6-Month Formulation From an Open-label Extension Study Compared to Real-World Data for the 1-Month and 3-Month Formulations. Int J Neuropsychopharmacol. 2024;27(2).
15. Hsu CW, Chen SC, Wang PN, Wang HM, Chen YC, Yeh CT. Preventing viral relapse with prophylactic tenofovir in hepatitis B carriers receiving chemotherapy: a phase IV randomized study in Taiwan. Hepatol Int. 2024.
16. Park S, Hwang D, Kang J, Han JK, Yang HM, Park KW, et al. Efficacy and Safety of Triple Therapy of Telmisartan/Amlodipine/Rosuvastatin in Patients with Dyslipidemia and Hypertension: A Multicenter Randomized Clinical Trial. Curr Ther Res Clin Exp. 2024;100:100735.
17. Tsai PJ, Hung SY, Lee TH, Jiann BP. A real-world pilot study assessing treatment satisfaction with avanafil in patients with erectile dysfunction. Sex Med. 2024;12(1):qfae001.
18. Reding MT, Álvarez-Román MT, Castaman G, Janbain M, Matsushita T, Meijer K, et al. Interim analyses of the multinational real-world prospective cohort HEM-POWR study evaluating the effectiveness and safety of damoctocog alfa pegol in patients with hemophilia A. Eur J Haematol. 2024;112(2):286-95.
19. Hellhammer J, Spitznagel-Schminke L, Hufnagel R. Kalium phosphoricum comp. in patients with neurasthenia: a randomized, double-blind, placebo-controlled clinical trial. Curr Med Res Opin. 2024;40(2):239-51.
20. Banakh I, Turek M, Niewodowski D, Sriamareswaran RK, Yeaman F, Vo L, et al. Ultrarapid Iron Polymaltose Infusions Are Safe for Management of Iron Deficiency. GE Port J Gastroenterol. 2024;31(1):24-32.
21. Quan C, Zhou H, Yang H, Jiao Z, Zhang M, Zhang B, et al. Safety of teriflunomide in Chinese adult patients with relapsing multiple sclerosis: A phase IV, 24-week multicenter study. Chin Med J (Engl). 2024.
22. Hamrah P, Massaro-Giordano M, Schanzlin D, Holland E, Berdy G, Goisis G, et al. Phase IV Multicenter, Prospective, Open-Label Clinical Trial of Cenegermin (rhNGF) for Stage 1 Neurotrophic Keratopathy (DEFENDO). Ophthalmol Ther. 2024;13(2):553-70.

 doi:10.20944/preprints202404.0523.v1

23. Reich K, Bianchi L, Khemis A, Maul JT, Tsianakas A, Schempp CM, et al. Brodalumab Versus Guselkumab in Patients with Moderate-to-Severe Psoriasis with an Inadequate Response to Ustekinumab: A Randomized, Multicenter, Double-Blind Phase 4 Trial (COBRA). Dermatol Ther (Heidelb). 2024;14(2):453-68.
24. Guerra A, Costantino C, Martinon-Torres F, Westerholt S, Lambeth C, Chen Z, et al. A phase 4, open-label study to evaluate the safety and immunogenicity of DTaP5-HBV-IPV-Hib in children previously vaccinated with DTaP2-HBV-IPV-Hib or DTaP5-HBV-IPV-Hib (V419-016). Hum Vaccin Immunother. 2024;20(1):2310900.